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Supplementary Material Available: Figure S.1, showing an ORTEP diagram, and Tables S.I-S.V, listing respectively complete X-ray data, hydrogen atom positional parameters, thermal parameters, intramolecular atomic distances, and intramolecular angles for $TcCl_3(PC_{18}H_{15})(N_2C_{10}H_8)$ (7 pages); Table S.VI, listing calculated and observed structure factors for $TcCl_3(PC_{18}H_{15})(N_2C_{10}H_8)$ (41 pages). Ordering information is given on any current masthead page.

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(Malonato)bis[sulfinylbis[methane]-*S*']platinum(II) Compounds: Versatile Synthons for a New General Synthesis of Antitumor Symmetrical and Dissymmetrical (Malonato)platinum(II) Complexes

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New (malonato)platinum(II) compounds, *cis*-[Pt(OOCACOO)$(Me_2SO)_2$] (A = CH_2, cycloalkyl), have been prepared, and their reactions with various amines have led to a new general synthesis of antitumor symmetrical and dissymmetrical (malonato)platinum(II) complexes. Reaction of *trans*-(-)-1,2-cyclohexanediamine (CHDA*) with the cyclobutanedicarboxylate (CBDC) complex *cis*-[Pt(CBDC)$(Me_2SO)_2$] has been studied in detail, and crystallographic molecular structure determinations have been carried out on the Pt(CHDA*)(Me_2SO)(CBDC) intermediate and the Pt(CHDA*)(CBDC) product. Crystals of Pt(CHDA*)(Me_2SO)(CBDC) grown from aqueous solution form as unstable hydrates, which rapidly lose water molecules of crystallization upon removal from the crystallization solution at room temperature. X-ray data were collected on a crystal at -100 °C. The complex crystallizes in the noncentrosymmetric triclinic unit cell *P*1 with four independent Pt(CHDA*)(Me_2SO)(CBDC) molecules and thirteen independent water molecules per unit cell. Unit cell dimensions are a = 10.998 (3) Å, b = 13.946 (5) Å, c = 15.163 (5) Å, α = 65.39 (2)°, β = 88.21 (2)°, γ = 79.64 (2)°, and V = 2078 (1) Å^3. Complex molecules form as two independent hydrogen-bonded dimers, $[Pt(CHDA^*)(Me_2SO)(CBDC)]_2$, with hydrogen-bonded water molecules linking the two complex units. Platinum atoms of the complex are four-coordinate, bonded to the two nitrogens of the CHDA* ligand, the sulfur atom of the DMSO ligand, and one of the carboxylate oxygen atoms of the monodentate CBDC ligand. Crystals of Pt(CHDA*)(CBDC) obtained from aqueous solution form as hydrates in the noncentrosymmetric centered monoclinic unit cell *C*2. Unit cell dimensions are a = 24.889 (16) Å, b = 5.382 (2) Å, c = 11.426 (4) Å, β = 106.97 (2)°, and V = 1464 (1) Å^3, with one independent complex molecule and two half water molecules per asymmetric region of the unit cell. Displacement of the DMSO ligand of Pt(CHDA*)(Me_2SO)(CBDC) results in chelation of the CBDC ligand in Pt(CHDA*)(CBDC). The two half water solvate molecules are hydrogen bonded to oxygen atoms of adjacent complex molecules.

Introduction

cis-Diamminedichloroplatinum(II) (cisplatin)[1] is one of the most effective oncolytic agents against cancers of the testes, ovaries, bladder, and head and neck.[2-4] It is also an important adjunct for cancers of the cervix, lung, and breast.[2] Its most spectacular success has been in the treatment of testicular cancer,[3] a form of cancer previously resistant to any therapy but now considered to be curable in most cases. However, cisplatin has three drawbacks that limit its usefulness: (1) it has severe toxicities[5-7] such as nephrotoxicity, nausea/vomiting, myelosuppression, ototoxicity, and neurologic complications, (2) it only affects a narrow range of tumors, and (3) it causes the development of resistance in the tumor cell.

cis-Diammine(1,1-cyclobutanedicarboxylato)platinum(II) (carboplatin)[8-10] is the only clinically successful second-generation platinum complex. It does not exhibit significant nephrotoxicity and emesis, and its relatively lower toxicities as compared to those of cisplatin have been related to the greater pharmacokinetic stability of its 1,1-cyclobutanedicarboxylate ligand in solution.[11,12] Nevertheless, it still has two other drawbacks. Just like cisplatin, it only affects a narrow range of tumors and causes the development of resistance in the tumor cell.

In recent years, there has been an intense interest in developing third-generation platinum complexes with a broader spectrum of activity, improved clinical effectiveness, lack of cross-resistance to cisplatin, and enhanced water solubility. In our search for third-generation platinum complexes, we have encountered the following technical problems: (1) (malonato)platinum(II) complexes synthesized by literature procedures[13] were often contaminated with byproducts (sodium nitrate or silver chloride depending on the reaction employed and the solubility of the product), (2) no efficient synthesis of dissymmetrical platinum(II) complexes[14,15]

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has been reported in the literature, and (3) reaction of potassium tetrachloroplatinate with 2-hydrazinoazoles[16] gave a mixture of highly active polymeric platinum(II) complexes that could not be characterized. Consequently, the need for a better synthesis of antitumor platinum complexes has led us to develop a class of precursor complexes that can be conveniently synthesized from commercially available starting materials, can be stored over prolonged periods of time, and most importantly, can undergo stepwise selective substitution reactions with other ligands. We now report the synthesis of (malonato)bis[sulfinylbis[methane]-*S*]platinum(II) complexes and their application to a new general synthesis of antitumor symmetrical and dissymmetrical (malonato)platinum(II) complexes.

Experimental Section

1,1-Cyclobutanedicarboxylic acid (CBDCA), 1,1-cyclopropanedicarboxylic acid (CPDCA), malonic acid, *n*-propionic acid, *trans*-(-)-1,2-cyclohexanediamine (CHDA*), *trans*-(+)-1,2-cyclohexanediamine (CHDA), cyclohexanamine (CHA), 2,2-dimethyl-1,3-propanediamine (DMPDA), *n*-propylamine, benzylamine, and potassium tetrachloroplatinate were commercially available. *cis*-Dichlorobis[sulfinylbis[methane]-*S*]platinum[17] and tetrahydro-4*H*-pyran-4,4-dimethanamine (THPDMA)[18] were prepared according to the literature procedures. Silver salts of carboxylic acids were prepared by reactions of sodium carboxylates with an equimolar amount of silver nitrate at room temperature in the dark overnight.

All melting points were taken on a Mel-Temp apparatus. IR spectra were measured on a Nicolet 205XB FT-IR spectrophotometer. NMR spectra were determined with Nicolet NT-300 WB (^{1}H at 300 MHz, ^{13}C at 75 MHz) and a GN 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) spectrometers, and chemical shifts (δ) are in parts per million relative to internal tetramethylsilane.

All new platinum(II) complexes synthesized are summarized in Table I.

[1,1-Cyclobutanedicarboxylato(2-)-*O*,*O*']bis[sulfinylbis[methane]-*S*]-platinum(II) (3a). Typical Procedure for 3a–c. A mixture of 12.66 g (0.030 mol) of *cis*-[$PtCl_2(Me_2SO)_2$], 10.74 g (0.030 mol) of the disilver salt of 1,1-cyclobutanedicarboxylic acid, and 900 mL of water was stirred at room temperature in the dark for 22 h and then filtered. The filtrate was concentrated to ca. 25 mL and the precipitate collected, giving 14.5 g (90%) of **3a** as colorless crystals; mp 201 °C dec.

[1,1-Cyclobutanedicarboxylato(2-)-*O*,*O*'][*trans*-(-)-1,2-cyclohexanediamine-*N*,*N*']platinum(II) (4a). Method A. Typical Procedure for 4a–g. To a hot solution of 0.494 g (0.0010 mol) of *cis*-[$Pt(Me_2SO)_2$(CBDC)] (**3a**) in 10 mL of water was added a solution of 0.114 g (0.0010 mol) of *trans*-(-)-1,2-cyclohexanediamine in 3 mL of water. The mixture was kept at 100 °C for 6 h. After cooling, the solution deposited 0.361 g (80%) of **4a** as colorless crystals; mp 280 °C dec.

Method B. To a solution of 1.24 g (0.0025 mol) of *cis*-[$Pt(Me_2SO)_2$(CBDC)] (**3a**) in 40 mL of water at 40 °C was added 0.285 g (0.0025 mol) of *trans*-(-)-1,2-cyclohexanediamine. The reaction mixture was heated at 40 °C for 1 h. After removal of the water at 40 °C under reduced pressure, the solid residue was triturated with ethanol and then ether to give 1.23 g (90%) of **6a** as colorless crystals; mp 220 °C dec.

A solution of 0.20 g of **6a** in 5 mL of water was heated at 100 °C for 6 h. After cooling, the solution deposited 0.13 g (80%) of **4a** as colorless crystals; mp 280 °C dec.

[1,1-Cyclobutanedicarboxylato(2-)-*O*,*O*'](*n*-propanamine)[sulfinylbis[methane]-*S*]platinum(II) (7a). Typical Procedure for 7a,b. To a solution of 2.641 g (0.00535 mol) of *cis*-[$Pt(Me_2SO)_2$(CBDC)] (**3a**) in 80 mL of water was added a solution of 0.316 g (0.00535 mol) of *n*-propanamine in 10 mL of water. The reaction mixture was stirred at 40 °C for 2 h and concentrated under reduced pressure to ca. 8 mL. The precipitate was collected, giving 1.99 g (78%) of **7a** as colorless crystals; mp 212 °C dec.

[1,1-Cyclobutanedicarboxylato(2-)-*O*,*O*'](*n*-propanamine)platinum(II) (8a). Typical Procedure for 8a–c. To a slight suspension of 0.475 g (0.0010 mol) of **7a** in 15 mL of water at 100 °C was added slowly a solution of 0.099 g (0.0010 mol) of cyclohexanamine in 5 mL of water. After the addition, a clear solution was obtained. The reaction mixture was stirred at 100 °C for 4 h and then concentrated under reduced pressure to ca. 10 mL. The precipitate was collected, giving 0.350 g (71%) of **8a** as colorless crystals; mp 250 °C dec.

Kinetic Studies of the Conversion of 6a into 4a. A solution of 100 mg of **6a** in 3.0 mL of D_2O was divided and placed into five NMR tubes (0.6 mL each). The NMR tubes were heated in an oil bath at 80 ± 1 °C (or 100 ± 1 °C), withdrawn at intervals, cooled with ice–water, and finally diluted with 0.4 mL of D_2O for the ^{1}H NMR measurement with a GN 500 spectrometer. The **4a** produced was not all soluble in D_2O. The ^{1}H NMR spectra indicated that the slightly suspended reaction mixture consisted of **6a**, **4a**, and free DMSO. The rate of the conversion of **6a** into **4a** was based on the integrations of the signals at δ 3.38 and 3.37 of **6a** and δ 2.72 of free DMSO, assuming that the total amount of the S-bonded and free DMSO in the reaction mixture remained the same and that the rate of formation of **4a** and free DMSO is equal to the rate of disappearance of **6a**. The results of kinetic studies are summarized in Table II.

Crystallographic Structure Determination of 6a at −100 °C. Crystals of Pt(CHDA*)(Me_2SO)(CBDC) were grown by slow evaporation of an aqueous solution containing the complex. Crystals separated from the recrystallization solution were observed to deteriorate within seconds due to loss of hydrate solvent molecules of crystallization. Crystals were coated with various amorphous resins to prevent deterioration, but none were found to preserve crystallinity for more than the period of 1 h at room temperature. A crystal was removed from the solution at a temperature just above the freezing point of the solution (−10 °C), mounted, and placed in the cold N_2 stream of the diffractometer. During alignment and data collection, the crystal temperature was maintained at −100 (2) °C. No evidence of deterioration or variation in the intensities of standard reflections was observed during the time required for data collection. Unit cell dimensions are given in Table III, with details of procedures used for data collection and structure determination contained in a table included with the supplementary material.

Crystals of **6a** were found to form in the triclinic crystal system, and the presence of the chiral CHDA* ligand requires the noncentrosymmetric space group *P*1. A cell reduction procedure was used to assure that the unit cell chosen was a reduced cell. The crystal structure was found to consist of two independent dimeric [Pt(CHDA*)(Me_2SO)-(CBDC)]$_2$ units and thirteen independent water solvate molecules. Water molecules are hydrogen bonded to atoms of the ligands and bridge dimeric units. The structural features of the two dimers differ in the disposition of the uncoordinated carboxylate groups, and the environment formed by associated water molecules is different for the complex molecules. At the conclusion of refinement maximum residual electron density of 1.23 e/Å^3 was found to be 0.6 Å from Pt(3). Final cycles of refinement carried out with inverted atomic positions indicated that the chirality chosen was correct. Further, the chirality of the CHDA* ligands agrees with other structure determinations carried out on complexes containing this ligand in resolved form.[19] Final atomic positions for the structure are given in Table IV. Tables containing hydrogen atom positions, anisotropic thermal parameters, and structure factors are available as supplementary material.

Crystallographic Structure Determination of 4a at −100 °C. Crystals of **4a** were also grown by slow evaporation of an aqueous solution. Information on the structure determination is given in Table III. The complex was found to crystallize in a centered monoclinic unit cell with four molecules per unit cell. Systematic extinctions were consistent with space groups *C*2/*m*, *Cm*, or *C*2. Statistics provided by a Wilson plot suggested that the unit cell was noncentrosymmetric, and vectors that appeared on a three-dimensional Patterson map indicated that *C*2 was the likely choice of space group. The platinum atom was refined at the location indicated in Table V, and other atoms of the structure were located with the phases obtained from this refinement. Two half water molecules were found to be located at positions along crystallographic 2-fold axes of the space group, bridging adjacent complex molecules through hydrogen bonds to coordinated carboxylate oxygen atoms. Water O(20) is hydrogen bonded to O(1) oxygens and water oxygen O(21) is hydrogen bonded to two O(2) oxygen atoms of adjacent complex molecules. At completion of refinement, greatest residual electron density of 0.36 e/Å^3 appeared near the platinum atom. Final atomic positions are given in Table V; tables containing anisotropic thermal parameters are available as supplementary material.

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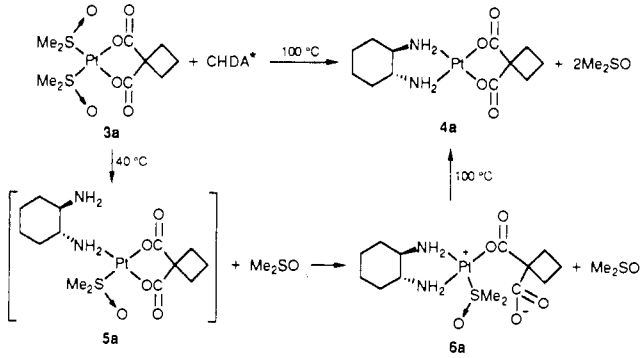
Scheme I[a]



[a] CHDA* = *trans*-(−)-1,2-Cyclohexanediamine.

Results and Discussion

I. (Malonato)bis[sulfinylbis[methane]-*S*]platinum(II) Complexes. Reactions of *cis*-$[PtCl_2(Me_2SO)_2]$ (**1**) with disilver salts of malonic acids (A = CH_2, cycloalkyl) **2** in water at room temperature gave new (malonato)platinum(II) compounds **3** in almost quantitative yield (Table I). Thus, reaction of **1** with the disilver salt of cyclobutanedicarboxylic acid (CBDCA) gave *cis*-$[Pt(Me_2SO)_2(CBDC)]$ (**3a**) in 90% yield.

$$\underset{\mathbf{1}}{cis\text{-}[PtCl_2(Me_2SO)_2]} + \underset{\mathbf{2}}{A(COOAg)_2} \rightarrow \underset{\mathbf{3}}{cis\text{-}[Pt(OOCACOO)(Me_2SO)_2]} + 2AgCl$$

The spectroscopic data for **3a** (Table I) are consistent with the proposed structure; for example, the ^1H NMR spectrum in D_2O shows a resonance for two S-bonded dimethyl sulfoxides at δ 3.58 ppm and the IR spectrum in KBr contains two strong ν(S–O) bands at 1150 and 1115 cm^{-1} due to two S-bonded dimethyl sulfoxide ligands in the cis structure.[17,20] The structures of the two other (malonato)platinum(II) compounds **3b–c** synthesized are also consistent with their analytical and spectral data.

The (malonato)platinum(II) complexes **3a–c** are remarkably stable and can be stored at room temperature without any appreciable decomposition for many years.

II. New Synthesis of Antitumor (Malonato)platinum(II) Complexes. Reactions of **3** with 1,2- or 1,3-diamines, or 2 equiv of monobasic amines in water at 100 °C, gave antitumor (malonato)platinum(II) complexes **4** in excellent yields (Table I). The reaction pathway of this new synthetic method is illustrated by the examples shown in Scheme I. Reaction of *cis*-$Pt(Me_2SO\text{-}S)_2(CBDC)$ (**3a**) with *trans*-(−)-1,2-cyclohexanediamine in water at 100 °C gave (cyclobutanedicarboxylato)platinum(II) complex **4a** in 80% yield. The same reaction at 40 °C afforded the transient intermediate **5a**, which quickly rearranged to give the intermediate **6a** in 90% yield. The intermediate **6a**, when heated in water at 100 °C, underwent cyclization to give **4a** in 80% yield with loss of the remaining dimethyl sulfoxide.

$$\mathbf{3} + 2R'NH_2 \rightarrow \underset{\mathbf{4}}{cis\text{-}[Pt(OOCACOO)(R'NH_2)_2]} + 2Me_2SO$$

We assigned **6a** rather than **5a** to the structure of the isolated intermediate on the basis of a comparison between its spectroscopic data and those of **7b**, whose structure closely resembled that of **5a**. The complex **7b** was obtained from reaction of **3a** with cyclohexylamine (described in the following section). The proton-decoupled ^{13}C NMR spectrum of **6a** in D_2O showed two carbon resonances for the carboxylates at δ 180.65 and 182.68 ppm, a difference of 2.03 ppm, whereas that of **7b** showed two carbon resonances at δ 178.79 and 178.87 ppm, a difference of only 0.08 ppm. The IR spectrum of **6a** in KBr contained a strong asymmetrical stretching band at 1570 cm^{-1} and a weaker symmetrical stretching band at 1380 cm^{-1} for the free carboxylate anion and a shoulder at 1630 cm^{-1} for the carboxylate ligand. The spectrum of **7b** contained two strong stretching bands for the carboxylate at 1638 and 1669 cm^{-1}. Furthermore, the intermediate **6a** has a solubility of >400 mg/mL in water at room temperature whereas **7b** has a solubility of only 20 mg/mL at 100 °C. The structure of the intermediate **6a** was further confirmed by a single-crystal X-ray analysis.

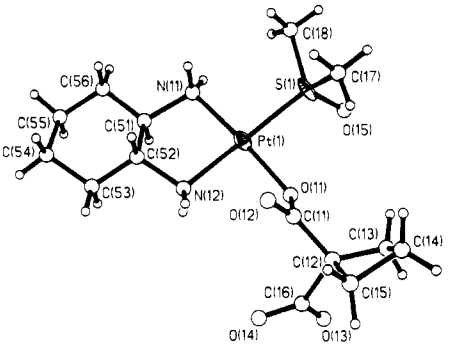


Figure 1. View of molecule 1 of Pt(CHDA*)(Me_2SO)(CBDC). The numbering schemes of the other three molecules of the unit cell use the 2, 3, and 4 prefix numbers for all atoms but the carbon atoms of the cyclohexyl rings. Ring atoms use 5, 6, 7, and 8 prefix numbers for molecules 1–4.

The ^1H and ^{13}C NMR product analyses indicated that **6a** was formed in quantitative yield from **3a**. The kinetics of the conversion of **6a** into **4a** in D_2O was investigated, and these results are summarized in Table II. Good first-order behavior was observed within 5% standard deviation of the rate constant up to at least 73% of the reaction. After over 10 half-lives (25 h at 80 °C), the reaction mixture contained 6% of **6a** and 94% of **4a**; in other words, the conversion of **6a** into **4a** almost reached completion after 10 half-lives and $k_1 = 14.7k_{-1}$.

$$\mathbf{6a} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{4a} + DMSO$$

The structures of the antitumor (malonato)platinum(II) complexes **4a–g** are all supported by their NMR and IR data and by their elemental analyses (Table I). The spectroscopic data on complexes **4a,d,g** are identical with those of authentic samples prepared by the conventional method.[18] The structures of **4a,g**[21] were determined by single-crystal X-ray analyses.

It has long been known from preparative inorganic chemistry[22] that one of two dimethyl sulfoxides in *cis*-$[PtCl_2(Me_2SO)_2]$ can be readily displaced by amines whereas a single dimethyl sulfoxide can only be replaced with difficulty. This observation has been explained in terms of stereoelectronic repulsion between the two cis sulfoxide ligands. It has also been reported that the trans effect of dimethyl sulfoxide in platinum(II) complexes is greater than that of chloride,[22,23] which in turn is greater than those of amines and carboxylates.

We have observed that the first two steps of ligand-substitution reactions of **3** were consistent with those of *cis*-$[PtCl_2(Me_2SO)_2]$.[24] The first amino function readily displaced one of the dimethyl sulfoxides in **3**, and the second amino function then displaced one of the carboxylato functions opposite to the remaining dimethyl sulfoxide. The remaining dimethyl sulfoxide was unprecedently lost by an intramolecular displacement in the third step by the free carboxylate at an elevated temperature.[25]

Two methods for the preparation of (malonato)platinum(II) complexes have been reported in the literature.[13] They are (1) reaction of *cis*-(diamine)dichloroplatinum(II) with the silver salt

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(25) In contradiction to what was reported in ref 23, heating $[Pt^+(CHDA^*)(DMSO)Cl]Cl^-$ under reduced pressure does not release dimethyl sulfoxide and give the corresponding uncharged $[Pt(CHDA^*)Cl_2]$.

Table I. New Platinum(II) Complexes Synthesized

complex[a,b]	formula	yield, %	mp, °C	IR (KBr): ν, cm^{-1}	NMR (int TMS): δ, ppm (J, Hz)			
					solv	ligand	^1H	^{13}C
cis-[Pt(Me_2SO)$_2$(CBDC)] (**3a**)	$C_{10}H_{18}O_6S_2Pt$	90	201 dec	1675, 1650, 1335, 1150, 1115, 1030	D_2O	Me_2SO	3.58 (12 H, s)	43.18 (CH_3)
						CBDC	2.80 (4 H, t, J = 7.8), 1.92 (2 H, m, J = 7.8)	180.19 (C=O), 56.60 (C), 31.60 (CH_2), 16.13 (CH_2)
cis-[Pt(Me_2SO)$_2$(CPDC)] (**3b**)	$C_9H_{16}O_6S_2Pt$	89	200 dec	1644, 1627, 1609, 1374, 1226, 1145, 1031, 560	D_2O	Me_2SO	3.74 (12 H, s)	40.34 (CH_3)
						CPDC	1.85 (4 H, s)	176.9 (C=O), 28.08 (C), 21.46 (CH_2)
cis-[Pt(Me_2SO)$_2$(mal)] (**3c**)	$C_7H_{14}O_6S_2Pt$	85	300 dec	1660, 1621, 1407, 1388, 746	D_2O	Me_2SO	3.55 (12 H, br)	43.01 (CH_3)
						mal	2.73 (2 H, s)	177.2 (C=O), 39.8 (CH_2)
cis-[Pt(CHDA*)(CBDC)]·H_2O (**4a**)	$C_{12}H_{20}N_2O_4Pt\cdot H_2O$	80	280 dec	1640, 1370, 1250, 1180, 1120, 1070, 1030, 910, 780	D_2O	CHDA*	2.37 (2 H, m), 2.05 (2 H, d, J = 13.4), 1.59 (2 H, d, J = 9.4), 1.4–1.1 (4 H, m)	
						CBDC	2.87 (4 H, t, J = 7.9), 1.90 (2 H, m, J = 7.9)	
cis-[Pt(CHDA)(CPDC)]·H_2O (**4b**)	$C_{11}H_{18}N_2O_4Pt\cdot H_2O$	70	250 dec	1635, 1615, 1380, 1230, 1180, 1070, 1030, 925	DMSO	CHDA	5.88 (2 H, d, NH, J = 8.3), 5.24 (2 H, t, NH, J = 8.3), 2.06 (2 H, br s), 1.81 (2 H, d, J = 12.3), 1.44 (2 H, d, J = 8.3), 1.20 (2 H, m), 0.99 (2 H, t)	62.00 (CH), 31.56 (CH_2), 24.08 (CH_2)
						CPDC	1.16 (4 H, s)	176.03 (C=O), 29.69 (C), 19.50 (CH_2)
cis-[Pt(CHDA)(mal)] (**4c**)	$C_9H_{16}N_2O_4Pt$	72	275 dec	1660, 1621, 1407, 1388, 962, 746	DMSO	CHDA	5.94 (2 H, d, NH, J = 9.0), 5.28 (2 H, t, NH, J = 9.0), 2.05 (2 H, br s), 1.80 (2 H, d, J = 12.6), 1.44 (2 H, d, J = 9.0), 1.19 (2 H, m), 0.98 (2 H, t, J = 9.0)	
						mal	1.22 (2 H, s)	
cis-[Pt(DMPDA)(CBDC)] (**4d**)	$C_{11}H_{20}N_2O_4Pt$	71	275 dec	1652, 1613, 1467, 1382, 1122, 910, 560	DMSO	DMPDA	5.24 (4 H, br s, NH_2), 2.00 (4 H, t, J = 4.9), 0.79 (6 H, s)	52.6 (CH_2N), 34.74 (C), 23.56 (CH_3)
						CBDC	2.68 (4 H, t, J = 7.7), 1.64 (2 H, m, J = 7.7)	177.50 (C=O), 55.6 (C), 30.42 (CH_2), 14.99 (CH_2)
cis-[Pt(DMPDA)(CPDC)] (**4e**)	$C_{10}H_{18}N_2O_4Pt$	83	252 dec	1646, 1619, 1607, 1579, 1393, 1224, 927, 555	DMSO	DMPDA	5.35 (4 H, br s, NH_2), 2.04 (4 H, t, J = 4.8), 0.79 (6 H, s)	52.63 (CH_2N), 34.63 (C), 23.55 (CH_3)
						CPDC	1.17 (4 H, s)	175.89 (C=O), 29.39 (C), 19.95 (CH_2)
cis-[Pt(CHA)$_2$(CPDC)] (**4f**)	$C_{17}H_{30}N_2O_4Pt$	71	213 dec	1631, 1594, 1580, 1397, 1056, 937, 773, 560	DMSO	CHA	4.92 (4 H, d, NH, J = 5.9), 2.27 (2 H, d, J = 11.4), 1.70 (4 H, d, J = 12.6), 1.30–1.0 (6 H, m)	53.28 (CHN), 33.21 (CH_2), 25.21 (CH_2), 24.51 (CH_2)
						CPDC	1.15 (4 H, s)	175.93 (C=O), 29.82 (C), 19.23 (CH_2)
cis-[Pt(THPDMA)(CBDC)] (**4g**)	$C_{13}H_{22}N_2O_5Pt$	47	290 dec	1640, 1610, 1370, 1240, 1100, 1025, 900	DMSO	THPDMA	5.29 (4 H, br s, NH_2), 3.48 (4 H, br t), 2.19 (4 H, br s), 1.35 (4 H, br t)	62.15 (CH_2O), 49.89 (CH_2N), 34.86 (C), 30.93 (CH_2)
						CBDC	2.69 (4 H, t, J = 7.6), 1.64 (2 H, m, J = 7.6)	177.68 (C=O), 55.73 (C), 30.51 (CH_2), 15.10 (CH_2)
cis-[Pt^+(CHDA*)(Me_2SO)-($CBDC^-$)]-H_2O (**6a**)	$C_{14}H_{26}N_2O_5SPt\cdot H_2O$	90	220 dec	1630, 1570, 1380, 1330, 1130	D_2O	CHDA*	2.35 (2 H, m), 2.11 (2 H, d, J = 10.4), 1.66 (2 H, m), 1.40 (2 H, m), 1.22 (2 H, m)	61.78 and 60.65 (CHN), 32.00 and 31.65 (CH_2), 23.62 and 23.54 (CH_2)
						Me_2SO	3.38 (3 H, s), 3.37 (3 H, s)	42.41 (CH_3)
						$CBDC^-$	2.63 (2 H, m), 2.35 (2 H, m), 1.85 (2 H, m)	182.68 and 180.65 (C=O), 56.49 (C), 29.93 (CH_2), 15.20 (CH_2)
cis-[Pt($PrNH_2$)(Me_2SO)-(CBDC)] (**7a**)	$C_{14}H_{25}NO_5SPt$	78	212 dec	1667, 1621, 1366, 1139, 1112, 1033, 450	D_2O	$PrNH_2$	2.64 (2 H, t, J = 7.6), 1.87 (2 H, m), 0.90 (3 H, t, J = 7.4)	46.47 (CH_2N), 21.75 (CH_2), 8.59 (CH_3)
						Me_2SO	3.45 (6 H, s)	41.11 (CH_3)
						CBDC	2.75 (4 H, m), 1.67 (2 H, m, J = 7.5)	178.87 and 178.79 (C=O), 54.35 (C), 29.27 (CH_2), 13.66 (CH_2)

cis-[Pt(CHA)(Me_2SO)(CBDC)] (**7b**)	$C_{11}H_{21}NO_5SPt$	79	210 dec	1669, 1638, 1350, 1140, 1120, 450	D_2O	CHA	2.75 (1 H, m), 2.20 (2 H, br s), 1.72 (2 H, br s), 1.58 (1 H, d, J = 12.7), 1.28 (4 H, m), 1.09 (1 H, m)	54.27 (CHN), 31.72 (CH_2), 23.07 (CH_2), 22.74 (CH_2)
						Me_2SO	3.44 (6 H, s)	41.10 (CH_3)
						CBDC	2.75 (4 H, m), 1.86 (2 H, m)	178.87 and 178.79 (C=O), 54.32 (C), 29.26 (CH_2), 13.64 (CH_2)
cis-[Pt(CHA)($PrNH_2$)(CBDC)] (**8a**)	$C_{15}H_{28}N_2O_4Pt$	71	250 dec	1646, 1615, 1374, 1118, 908, 470	DMSO	CHA	5.00 (2 H, d, NH_2, J = 5.9), 2.65 (1 H, m), 2.26 (2 H, d, J = 10.4), 1.69 (2 H, d, J = 12.4), 1.30–1.0 (6 H, m)	54.05 (CHN), 33.25 (CH_2), 25.22 (CH_2), 24.46 (CH_2)
						$PrNH_2$	4.93 (2 H, br t, NH_2), 2.40 (2 H, m), 1.56 (2 H, m), 0.87 (3 H, t, J = 7.3)	47.44 (CH_2N), 23.25 (CH_2), 11.13 (CH_3)
						CBDC	2.65 (4 H, m), 1.65 (2 H, m)	177.45 and 177.40 (C=O), 55.47 (C), 30.23 (CH_2), 14.93 (CH_2)
cis-[Pt($PhCH_2NH_2$)($PrNH_2$)-(CBDC)] (**8b**)	$C_{16}H_{24}N_2O_4Pt$	72	218 dec	1644, 1615, 1457, 1376, 1118, 910, 751, 699	DMSO	$PhCH_2NH_2$	7.50–7.20 (5 H, m), 5.49 (2 H, br t, NH_2), 3.67 (2 H, t, J = 6.4)	137.90 (C), 128.47 (CH), 128.30 (CH), 127.50 (CH), 94.00 (CH_2N)
						$PrNH_2$	4.92 (2 H, br t, NH_2), 2.26 (2 H, m, J = 7.4), 1.52 (2 H, m, J = 7.4), 0.85 (3 H, t, J = 7.4)	47.48 (CH_2N), 23.15 (CH_2), 11.03 (CH_3)
						CBDC	2.65 (4 H, m), 1.64 (2 H, m, J = 7.9)	177.35 and 177.27 (C=O), 55.42 (C), 30.18 (CH_2), 14.90 (CH_2)

[a] CBDC = 1,1-cyclobutanedicarboxylate; 1,1-cyclopropanedicarboxylate; CHDA* = *trans*-(-)-1,2-cyclohexanediamine; CHDA = *trans*-(+)-1,2-cyclohexanediamine; DMPDA = 2,2-dimethyl-1,3-propanediamine; CHA = cyclohexanamine; THPDMA = tetrahydro-4*H*-pyran-4,4-dimethanamine. mal = malonate. [b] The microanalyses were all within 0.4% of the calculated values (supplementary material).

Table II. Rate of the Reaction of **6a** to **4a** in D_2O

temp, °C	time, min	% of **6a**[a]	10^4k, s^{-1} [b]
80 ± 1	0	100	0.978 ± 0.048
80 ± 1	70	67.7 (65.5)	
80 ± 1	100	56.5 (53.7)	
80 ± 1	150	46.1 (42.6)	
80 ± 1	240	31.2 (26.9)	
80 ± 1	1500	6.0	
100 ± 1	40	21	6.5

[a] Values in parentheses are for amounts of **6a** after corrections are made for the remaining **6a** at the equilibrium. [b] The rate of the disappearance of **6a**.

Table III. Crystal Data for 4[Pt(CHDA*)(Me_2SO)(CBDC)]·$13H_2O$ and Pt(CHDA*)(CBDC)·H_2O

	4[Pt(CHDA*)(Me_2SO)-(CBDC)]·$13H_2O$	Pt(CHDA*)-(CBDC)·H_2O
formula	$Pt_4S_4O_{33}N_8C_{56}H_{130}$	$PtO_5N_2C_{12}H_{22}$
mol wt	2352.31	469.39
space group	$P1$	$C2$
a, Å	10.998 (3)	24.889 (16)
b, Å	13.946 (5)	5.382 (2)
c, Å	15.163 (5)	11.426 (4)
α, deg	65.39 (2)	90.00
β, deg	88.21 (2)	106.97 (2)
γ, deg	79.64 (2)	90.00
V, Å^3	2078 (1)	1464 (1)
Z	1	4
T, K	173 (2)°	
λ, Å	0.71073 (Mo Kα)	
ρ_{meas}, g/cm^3		1.98 (2)
ρ_{calc}, g/cm^3	1.88	2.13
μ, cm^{-1}	69.5	96.9
transm coeff	0.94–0.76	0.89–0.36
R, R_w (F^2)	0.064, 0.065	0.033, 0.042

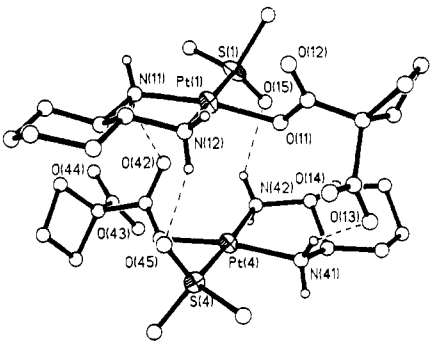


Figure 2. View showing the pairing between molecules 1 and 4 of Pt(CHDA*)(Me_2SO)(CBDC). Hydrogen-bonding interactions between molecules are shown as broken lines.

of a carboxylic acid and (2) reaction of *cis*-(diamine)dichloroplatinum(II) with silver nitrate followed by reaction of the resulting dinitratoplatinum(II) complex with the sodium salt of a carboxylic acid. The former is used for the synthesis of water-soluble platinum complexes whereas the latter is used for those with low water solubility. As is evident from Table I, our new method, which is applicable to the synthesis of both water-soluble and water-insoluble (malonato)platinum(II) complexes, is more general and efficient than the literature procedures and offers many practical advantages.

Crystallographic Structure Determination of 6a. Structural features of one of the planar Pt(CHDA*)(Me_2SO)(CBDC) complex molecules are shown in Figure 1. Selected bond distances and angles for all four molecules are given in Table VI. The CBDC ligands are coordinated to the planar, four-coordinate Pt atoms through the oxygen of one carboxylate group. The four independent complex molecules in the unit cell are paired as hydrogen-bonded dimers. Views of the pairing interactions between molecules containing platinum atoms Pt(1) and Pt(4) and paired molecules containing Pt(2) and Pt(3) are shown in Figures

Table IV. Atomic Positional Parameters ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 4[Pt(CHDA*)(Me_2SO)(CBDC)]·13H_2O

	x	y	z	U(eq)[a]		x	y	z	U(eq)[a]
Pt(1)	0	0	0	25 (1)	C(15)	−3682 (42)	3464 (33)	−1433 (30)	75 (12)
Pt(2)	−3232 (1)	1165 (1)	−5487 (1)	19 (1)	C(16)	−2283 (35)	3054 (26)	160 (26)	52 (9)
Pt(3)	−5005 (1)	−103 (1)	−3141 (1)	19 (1)	C(17)	18 (33)	891 (23)	−2346 (25)	41 (8)
Pt(4)	1790 (1)	1251 (1)	1340 (1)	23 (1)	C(18)	2084 (33)	−567 (23)	−1441 (25)	34 (8)
S(1)	1079 (8)	503 (6)	−1333 (6)	28 (3)	C(21)	−1472 (29)	−810 (19)	−4592 (21)	21 (6)
S(2)	−4375 (8)	803 (6)	−6451 (6)	25 (3)	C(22)	−1118 (26)	−2038 (17)	−3960 (19)	14 (5)
S(3)	−3953 (7)	387 (6)	−2231 (6)	22 (3)	C(23)	143 (31)	−2610 (21)	−4220 (24)	32 (7)
S(4)	803 (8)	591 (5)	2687 (6)	25 (3)	C(24)	−498 (34)	−3483 (25)	−4201 (27)	44 (8)
O(11)	−747 (21)	1535 (16)	−410 (16)	43 (5)	C(25)	−1850 (31)	−2723 (21)	−4351 (23)	35 (7)
O(12)	−2522 (23)	1233 (17)	−668 (17)	54 (6)	C(26)	−1241 (28)	−2204 (19)	−2929 (21)	25 (6)
O(13)	−1675 (24)	3665 (18)	241 (18)	62 (6)	C(27)	−3383 (32)	204 (23)	−7075 (24)	38 (8)
O(14)	−2842 (31)	2483 (24)	820 (23)	88 (9)	C(28)	−5158 (34)	1947 (23)	−7422 (25)	42 (8)
O(15)	1689 (21)	1418 (15)	−1534 (16)	33 (5)	C(31)	−6781 (32)	1871 (22)	−4012 (24)	29 (7)
O(21)	−2667 (20)	−441 (14)	−4742 (15)	23 (5)	C(32)	−7084 (32)	3032 (21)	−4615 (23)	29 (7)
O(22)	−677 (21)	−270 (14)	−4936 (16)	31 (5)	C(33)	−8346 (39)	3579 (26)	−4412 (30)	50 (9)
O(23)	−499 (24)	−1851 (17)	−2588 (18)	50 (6)	C(34)	−7706 (43)	4474 (31)	−4456 (35)	70 (12)
O(24)	−2057 (22)	−2723 (16)	−2454 (16)	44 (5)	C(35)	−6462 (29)	3803 (20)	−4423 (22)	28 (7)
O(25)	−5162 (20)	44 (15)	−5973 (15)	35 (5)	C(36)	−7085 (32)	3255 (22)	−5737 (24)	34 (7)
O(31)	−5563 (18)	1502 (13)	−4023 (14)	16 (4)	C(37)	−4999 (32)	843 (23)	−1514 (24)	40 (8)
O(32)	−7468 (22)	1290 (15)	−3612 (17)	36 (5)	C(38)	−2886 (30)	−707 (20)	−1397 (22)	32 (7)
O(33)	−6361 (23)	3757 (16)	−6284 (17)	45 (5)	C(41)	3483 (33)	−679 (24)	1381 (25)	47 (8)
O(34)	−7754 (31)	2757 (22)	−5999 (24)	73 (8)	C(42)	4479 (30)	−1683 (22)	1934 (23)	35 (7)
O(35)	−3261 (21)	1261 (15)	−2786 (15)	33 (5)	C(43)	4108 (36)	−2678 (26)	2150 (25)	54 (9)
O(41)	2987 (21)	−194 (16)	1894 (15)	41 (5)	C(44)	3997 (48)	−2761 (34)	3221 (35)	80 (13)
O(42)	3179 (21)	−493 (16)	546 (16)	46 (5)	C(45)	4796 (31)	−1909 (23)	2972 (22)	42 (7)
O(43)	6131 (34)	−601 (17)	1184 (17)	55 (6)	C(46)	5657 (31)	−1391 (23)	1250 (23)	44 (8)
O(44)	6102 (22)	−2022 (17)	885 (16)	52 (6)	C(47)	1856 (32)	68 (23)	3702 (25)	39 (8)
O(87)	−4737 (42)	4939 (36)	−9423 (34)	173 (26)	C(48)	−356 (38)	1609 (26)	2867 (28)	45 (9)
O(45)	86 (24)	−253 (16)	2730 (18)	45 (6)	C(51)	500 (28)	−2099 (20)	1672 (21)	35 (7)
O(88)	−7444 (25)	−3225 (20)	1 (23)	81 (14)	C(52)	−893 (28)	−1645 (20)	1656 (21)	36 (7)
O(89)	−2479 (24)	−4097 (18)	−598 (18)	67 (11)	C(53)	−1319 (28)	−2092 (20)	2652 (19)	30 (6)
O(90)	−4897 (19)	1578 (18)	592 (16)	52 (10)	C(54)	−1045 (32)	−3316 (24)	3142 (25)	47 (8)
O(91)	−9350 (19)	1461 (17)	−4855 (19)	48 (11)	C(55)	355 (30)	−3739 (22)	3077 (23)	40 (7)
O(92)	−8643 (20)	−767 (15)	−3506 (16)	39 (9)	C(56)	749 (34)	−3281 (23)	2085 (23)	48 (8)
O(93)	1293 (24)	3755 (17)	2175 (17)	50 (10)	C(61)	−3464 (23)	3262 (17)	−5469 (17)	20 (5)
O(94)	50 (20)	−2513 (19)	−678 (18)	49 (10)	C(62)	−2132 (23)	2737 (17)	−5067 (17)	18 (5)
O(95)	−5232 (25)	−2428 (21)	−380 (20)	56 (12)	C(63)	−1757 (28)	3121 (20)	−4399 (21)	27 (7)
O(96)	−2787 (30)	3591 (22)	−7979 (21)	69 (14)	C(64)	−1883 (31)	4367 (23)	−4860 (23)	39 (8)
O(97)	−1899 (24)	−3303 (18)	601 (17)	60 (11)	C(65)	−3215 (31)	4902 (24)	−5253 (23)	43 (8)
O(98)	3253 (21)	4841 (20)	1710 (18)	66 (12)	C(66)	−3597 (30)	4469 (20)	−6001 (21)	35 (7)
O(99)	−1159 (21)	4709 (19)	−7787 (22)	69 (13)	C(71)	−5318 (25)	−2295 (18)	−2727 (18)	23 (6)
N(11)	874 (24)	−1553 (17)	599 (17)	24 (6)	C(72)	−5387 (27)	−1705 (20)	−3856 (20)	30 (6)
N(12)	−1107 (23)	−425 (17)	1179 (17)	30 (6)	C(73)	−6199 (35)	−2149 (24)	−4373 (26)	46 (9)
N(21)	−3828 (22)	2806 (16)	−6101 (16)	19 (5)	C(74)	−5681 (29)	−3364 (20)	−3923 (20)	31 (6)
N(22)	−2097 (23)	1547 (16)	−4636 (18)	23 (5)	C(75)	−5710 (29)	−3888 (22)	−2851 (21)	38 (7)
N(31)	−4557 (24)	−1727 (17)	−2323 (17)	28 (6)	C(76)	−4924 (35)	−3452 (24)	−2375 (26)	51 (9)
N(32)	−5920 (22)	−513 (15)	−4038 (18)	22 (5)	C(81)	1522 (26)	3499 (19)	67 (20)	29 (6)
N(41)	887 (26)	2826 (18)	864 (19)	31 (6)	C(82)	1874 (29)	2957 (21)	−602 (21)	33 (6)
N(42)	2618 (21)	1804 (15)	37 (15)	22 (5)	C(83)	2522 (30)	3622 (21)	−1473 (21)	35 (7)
C(11)	−1923 (29)	1847 (22)	−655 (21)	34 (7)	C(84)	1789 (29)	4688 (21)	−2018 (21)	34 (7)
C(12)	−2351 (35)	3000 (26)	−921 (27)	49 (9)	C(85)	1534 (30)	5246 (22)	−1337 (22)	40 (7)
C(13)	−1807 (29)	3774 (22)	−1721 (22)	34 (7)	C(86)	814 (29)	4633 (21)	−449 (21)	37 (7)
C(14)	−2989 (40)	3916 (32)	−2335 (31)	72 (11)					

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

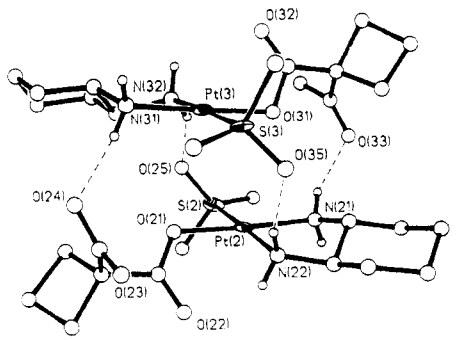


Figure 3. View showing the pairing between molecules 2 and 3 of Pt(CHDA*)(Me_2SO)(CBDC). Hydrogen-bonding interactions between molecules are shown as broken lines.

2 and 3. Four intermolecular hydrogen bonds link the paired molecules, but structural differences between molecules result in differences in hydrogen bonding within the two pairs. Hydrogen bonds between molecules 2 and 3 are between the protons of amine nitrogens and oxygen atoms of the adjacent molecule. The oxygen atoms involved are associated with either the free carboxylate group or the DMSO ligand (Figure 3). Contacts between O and N atoms are all less than 3.0 Å. Without the chirality of the diamine ligand being taken into account, the dimeric pair has approximate inversion symmetry. Paired molecules 1 and 4, shown in Figure 1, differ in structure, primarily by the rotation of the dicarboxylic ligand of molecule 4 about the Pt(4)–O(41) bond. The uncoordinated oxygen atom of this carboxylate group, O(42), is directed interior to the molecular pair. Uncoordinated oxygens of other coordinated carboxylate groups, O(12) in molecule 1 and oxygens O(22) and O(32) in Figure 3, are directed externally to the pair. Hydrogen bonds between DMSO oxygen atoms and adjacent amine protons of molecules 1 and 4 are relatively strong as is the O(13)–N(41) hydrogen bond. However, free carboxylate oxygens O(43) and O(44) interact only with water solvate mol-

Table V. Atomic Positional Parameters ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^4$) for Pt(CHDA*)(CBDC)·H_2O

	x	y	z	U(eq)[a]
Pt(1)	63 (1)	1500	7545 (1)	243 (2)
N(1)	629 (4)	263 (22)	6714 (10)	240 (37)
N(2)	633 (5)	197 (22)	9081 (11)	292 (40)
O(1)	-475 (3)	2618 (19)	8436 (8)	267 (28)
O(2)	-482 (4)	2668 (19)	5967 (9)	282 (29)
O(3)	-1334 (4)	2897 (21)	8605 (9)	357 (34)
O(4)	-1336 (4)	2904 (21)	4731 (9)	367 (34)
C(1)	-1241 (5)	1220 (33)	6732 (14)	305 (51)
C(2)	-1882 (6)	694 (30)	6308 (15)	382 (52)
C(3)	-1785 (7)	-1995 (35)	6461 (20)	593 (74)
C(4)	-1164 (6)	-1698 (24)	6813 (14)	313 (48)
C(5)	-1021 (5)	2355 (23)	8007 (12)	241 (40)
C(6)	-1023 (5)	2380 (23)	5744 (11)	229 (37)
C(7)	1149 (5)	-474 (23)	7582 (12)	227 (40)
C(8)	1014 (5)	-1541 (27)	8725 (12)	269 (43)
C(9)	1549 (5)	-2113 (27)	9728 (12)	313 (45)
C(10)	1910 (6)	-3970 (23)	9289 (14)	344 (55)
C(11)	2030 (5)	-3055 (39)	8102 (12)	370 (52)
C(12)	1499 (6)	-2369 (31)	7112 (13)	364 (46)
O(20)	0	-3626 (128)	10000	291 (64)
O(21)	0	-3695 (112)	5000	266 (79)

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

ecules and the intermolecular hydrogen bond between O(42) and the proton of N(11) is weak with a N–O separation of 3.14 Å. The Pt–Pt separations between paired molecules are 3.928 (4) Å for Pt(1)–Pt(4) and 3.900 (4) Å for Pt(2)–Pt(3). An additional intramolecular hydrogen bond exists between the free oxygen of the coordinated carboxylate group and the proton of the adjacent amine nitrogen in each of the molecules.

Bond lengths to the platinum atoms of the four independent complex molecules are within the range of values reported for other complex molecules containing diamine, carboxylate, and DMSO ligands. The average value for the Pt–S length is 2.216 (9) Å, the Pt–O length is 2.02 (2) Å, and the two Pt–N lengths average 2.04 (2) and 2.06 (3) Å, with the longest to the nitrogen *trans* to the DMSO sulfur atom.

Problems with crystal stability are related to the hydrate structure of the crystals obtained from aqueous solution. Thirteen water molecules were located in the unit cell, all are extensively involved in hydrogen-bonding interactions. The refined thermal parameters of the water oxygens, atoms O(87)–O(99) in Table IV, indicate that, with one exception, the position and occupancy of the water solvate molecules are well-defined. Eleven of the water molecules are hydrogen bonded to atoms of the complex molecules; two (O(87),O(99)) are hydrogen bonded to other water molecules. One of these, water oxygen O(87), has an anomalously high thermal parameter, possibly reflecting fractional occupancy. This molecule is the least strongly held through hydrogen bonds and is likely the water molecule that is displaced thermally, leading to deterioration in the crystal structure. Disposition of water molecules about the two hydrogen-bonded dimeric units is unsymmetrical, and they each have different solid-state environments.

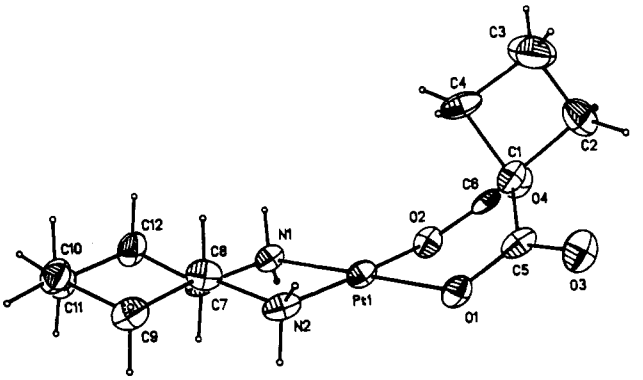


Figure 4. View showing the Pt(CHDA*)(CBDC) molecule.

Crystallographic Structure Determination of 4a. Displacement of the DMSO ligand results in chelation by the CBDC ligand. Both the CHDA* and CBDC ligands have appeared repeatedly as components in platinum complexes that have shown promise as anticancer drugs. We reported earlier the structural features of two platinum CBDC complexes which had diamine ligands that formed six-membered chelate rings with the metal ions.[21] A view of the *cis*-[Pt(CHDA*)(CBDC)] molecule is shown in Figure 4; bond distances and angles are contained in Table VII. With the five-membered cyclohexanediamine chelate ring, structural features of the CBDC ligand remain essentially the same as found in previous structures on molecules containing CBDC ligands chelated to Pt(II).[21] Pt–O bond lengths averaging a value of 2.006 (10) Å compare well with a value of 2.004 (6) Å for *cis*-[Pt(THPDMA)(CBDC)] (**4g**). Both sets of values are slightly shorter than the average value of 2.027 (5) Å found for [C($C_2H_2OH)_2(CH_2NH_2)_2$]Pt(CBDC). In both structures the O–Pt–O angles within the chelate ring were close to 90°; the same feature exists in the present structure where the O(1)–Pt–O(2) angle is 89.2 (4)°. Bond distances and angles within the CBDC ligand show two specific features of interest. First, bonding within the carboxylate groups is partially localized with C–O lengths to oxygens bonded to the metal that are slightly longer [1.32 (1) Å] than uncoordinated C–O lengths. Angles about C(1) show the contracted C(2)–C(1)–C(4) value of 86 (1)° interior to the cyclobutane ring and the expanded value of 116 (1)° for C(5)–C(1)–C(6) to the carboxylate carbon atoms. This latter value is only slightly larger than the value of 113 (2)° reported for the chelated malonate ligand of Pt(CHDA*)(mal).[19]

Structural features of the cyclohexanediamine ligand include an average Pt–N bond length of 2.03 (1) Å, which agrees well with the Pt–N lengths of the other two Pt(diamine)(CBDC) structures, and a N(1)–Pt–N(2) bond angle of 83.5 (5)°. This bite angle for the five-membered chelate ring of the cyclohexanediamine ligand is contracted relative to the values reported for the two diamine structures, which exceeded 90°, where the diamine ligands were essentially substituted 1,3-propanediamine moieties. It agrees well with values of 83.8° reported for CHDA* ligands of Pt(CHDA*)(ox) and Pt(CHDA*)(mal), however.[19]

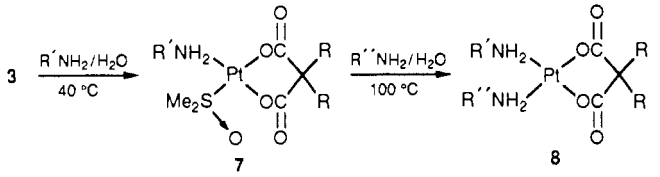
Table VI. Selected Bond Distances and Angles for 4[Pt(CHDA*)(Me_2SO)(CBDC)]·$13H_2O$

molecule 1		molecule 2		molecule 3		molecule 4	
			Distances (Å)				
Pt(1)–S(1)	2.230 (8)	Pt(2)–S(2)	2.220 (10)	Pt(3)–S(3)	2.207 (10)	Pt(4)–S(4)	2.207 (8)
Pt(1)–N(11)	2.02 (2)	Pt(2)–N(21)	2.05 (2)	Pt(3)–N(31)	2.02 (2)	Pt(4)–N(41)	2.06 (2)
Pt(1)–N(12)	2.07 (2)	Pt(2)–N(22)	2.10 (3)	Pt(3)–N(32)	2.03 (2)	Pt(4)–N(42)	2.05 (2)
Pt(1)–O(11)	1.98 (2)	Pt(2)–O(21)	2.02 (2)	Pt(3)–O(31)	2.05 (2)	Pt(4)–O(41)	2.05 (2)
			Angles (deg)				
S(1)–Pt(1)–N(11)	96.1 (7)	S(2)–Pt(2)–N(21)	96.6 (8)	S(3)–Pt(3)–N(31)	96.6 (8)	S(4)–Pt(4)–N(41)	97.0 (8)
S(1)–Pt(1)–O(11)	87.9 (7)	S(2)–Pt(2)–O(21)	87.9 (7)	S(3)–Pt(3)–O(31)	88.0 (7)	S(4)–Pt(4)–O(41)	85.9 (6)
N(11)–Pt(1)–N(12)	86.2 (9)	N(21)–Pt(2)–N(22)	82.3 (9)	N(31)–Pt(3)–N(32)	84.9 (10)	N(41)–Pt(4)–N(42)	84.3 (9)
O(11)–Pt(1)–N(12)	90.3 (9)	O(21)–Pt(2)–N(22)	93.4 (9)	O(31)–Pt(3)–N(32)	90.5 (8)	O(41)–Pt(4)–N(42)	93.8 (8)
S(1)–Pt(1)–N(12)	176.2 (7)	S(2)–Pt(2)–N(22)	177.1 (7)	S(3)–Pt(3)–N(32)	177.0 (7)	S(2)–Pt(4)–N(42)	175.1 (8)
N(11)–Pt(1)–O(12)	171.1 (11)	N(22)–Pt(2)–O(21)	173.7 (10)	N(31)–Pt(3)–O(31)	175.3 (11)	N(42)–Pt(4)–O(41)	167.7 (11)

Table VII. Bond Distances and Angles for Pt(CHDA*)(CBDC)

	Distances (Å)		
Pt(1)-N(1)	2.028 (12)	Pt(1)-N(2)	2.032 (11)
Pt(1)-O(1)	1.997 (10)	Pt(1)-O(2)	2.015 (9)
N(1)-C(7)	1.436 (14)	N(2)-C(8)	1.470 (19)
O(1)-C(5)	1.312 (15)	O(2)-C(6)	1.305 (15)
O(3)-C(5)	1.213 (19)	O(4)-C(6)	1.225 (14)
C(1)-C(2)	1.550 (18)	C(1)-C(4)	1.582 (22)
C(1)-C(5)	1.526 (20)	C(1)-C(6)	1.522 (22)
C(2)-C(3)	1.469 (25)	C(3)-C(4)	1.490 (22)
C(7)-C(8)	1.551 (20)	C(7)-C(12)	1.536 (21)
C(8)-C(9)	1.514 (16)	C(9)-C(10)	1.524 (21)
C(10)-C(11)	1.552 (23)	C(11)-C(12)	1.513 (17)
	Angles (deg)		
N(1)-Pt(1)-N(2)	83.5 (5)	N(1)-Pt(1)-O(1)	177.2 (4)
N(2)-Pt(1)-O(1)	93.8 (4)	N(1)-Pt(1)-O(2)	93.5 (4)
N(2)-Pt(1)-O(2)	176.8 (5)	O(1)-Pt(1)-O(2)	89.2 (4)
Pt(1)-N(1)-C(7)	112.1 (9)	Pt(1)-N(2)-C(8)	108.9 (8)
Pt(1)-O(1)-C(5)	123.6 (8)	Pt(1)-O(2)-C(6)	121.6 (9)
C(2)-C(1)-C(4)	86.3 (11)	C(2)-C(1)-C(5)	115.0 (13)
C(4)-C(1)-C(5)	109.8 (11)	C(2)-C(1)-C(6)	113.6 (11)
C(4)-C(1)-C(6)	112.7 (13)	C(5)-C(1)-C(6)	115.9 (12)
C(1)-C(2)-C(3)	91.5 (12)	C(2)-C(3)-C(4)	92.7 (12)
C(1)-C(4)-C(3)	89.5 (11)	O(1)-C(5)-O(3)	121.9 (12)
O(1)-C(5)-C(1)	116.4 (12)	O(3)-C(5)-C(1)	121.6 (11)
O(2)-C(6)-O(4)	119.5 (13)	O(2)-C(6)-C(1)	118.5 (10)
O(4)-C(6)-C(1)	121.9 (11)	N(1)-C(7)-C(8)	108.1 (11)
N(1)-C(7)-C(12)	115.5 (11)	C(8)-C(7)-C(12)	109.5 (11)
N(2)-C(8)-C(7)	108.2 (11)	N(2)-C(8)-C(9)	114.5 (11)
C(7)-C(8)-C(9)	110.7 (11)	C(8)-C(9)-C(10)	111.0 (11)
C(9)-C(10)-C(11)	111.2 (12)	C(10)-C(11)-C(12)	112.5 (12)
C(7)-C(12)-C(11)	111.2 (12)		

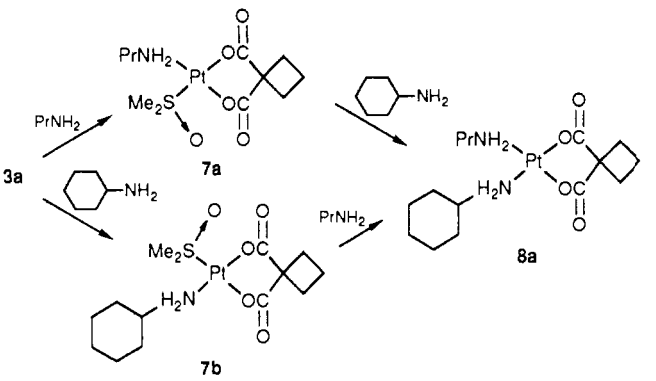
Scheme II



Hydrate water molecules contribute to the water solubility of the Pt(CBDC) complexes.[21] Water molecules of crystallization were found to be located on crystallographic 2-fold axes of the unit cell, bridging adjacent complex molecules. Water oxygen O(20) is 2.73 Å from O(1), and water O(21) is 2.70 Å from O(2).

III. Synthesis of Antitumor Dissymmetrical (Malonato)platinum(II) Complexes. Reaction of **3** with an equimolar amount of an amine (RNH_2) in water at 40 °C gave the monosulfoxide complex **7**, which further reacted with an equimolar amount of another amine ($R'NH_2$) in water at 100 °C to give the antitumor dissymmetrical platinum(II) complex **8** in excellent yield (Scheme II). Thus, reaction of **3a** with *n*-propylamine in water at 40 °C gave the monosulfoxide complex **7a** in 78% yield. The monosulfoxide complex **7a** then reacted with cyclohexylamine in water at 100 °C to give the dissymmetrical (malonato)platinum(II) complex **8a** in 71% yield. Alternatively, **3a** reacted with cyclohexylamine and then with *n*-propylamine to give the dissymmetrical complex **8a** in 60% overall yield (Scheme III). The structures of the dissymetrical complexes **8a,b** are all consistent with their NMR and IR data and their elemental analyses (Table I).

Scheme III



Three methods are available for the preparation of dissymmetrical dihaloplatinum(II) complexes from monobasic amines: (1) reaction of $K[PtCl_3(NH_3)]$ with various amines,[14] (2) photodimerization of $(C_2H_4)PtCl_2(R'NH_2)$ followed by decomposition of the dimer with another amine ($R''NH_2$),[15] and (3) reaction of *cis*-$[Pt(R'NH_2)_2I_2]$ with perchloric acid followed by decomposition of the resulting dimer, $[Pt(R'NH_2)I_2]_2$, with another amine ($R''NH_2$).[26] These methods suffer from either a low yield or a lengthy procedure for the preparation of dissymmetrical (malonato)platinum(II) complexes. In contrast, our new method is a convenient and effective way of making dissymmetrical (malonato)platinum(II) complexes that, in the case of an appropriate amine ligand, either may be linkable to monoclonal antibodies[14] or may possess a selective binding affinity to hormono-dependent tumor cells.[15,27]

Conclusion

(Malonato)bis[sulfinylbis[methane]-*S*]platinum(II) complexes **3** have been developed as versatile synthons for a new general synthesis of antitumor symmetrical and dissymmetrical (malonato)platinum(II) complexes **4**. This new synthesis is characterized by minimal byproduct formation except dimethyl sulfoxide in the final step and stepwise selective ligand-substitution reactions. It is applicable to the synthesis of both water-soluble and water-insoluble antitumor (malonato)platinum(II) complexes in high purity and yield. [1,1-Cyclobutanedicarboxylato(2−)-*O*,*O*′][tetrahydro-4*H*-pyran-4,4-dimethanamine-*N*,*N*′]platinum(II) (**4g**) prepared by this new synthesis is currently under clinical evaluation.[18]

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Supplementary Material Available: Tables of analytical data, parameters and procedures used in the structure determinations, complete bond lengths and bond angles, hydrogen atom positions, and anisotropic thermal parameters for **4a** and **6a** (14 pages); tables of observed and calculated structure factors for compounds **4a** and **6a** (26 pages). Ordering information is given on any current masthead page.

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