

## Platinum(II) Complexes of N,N'-Dicyclopentylethylenediamine

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Received 19 January 1987; revised and accepted 20 March 1987

Eight platinum(II) complexes of formula  $[Pt(DCPEDA)X_2]$ , where DCPEDA = N,N'-dicyclopentylethylenediamine and  $X^- = Cl^-, Br^-, I^-, \frac{1}{2} C_2O_4^{2-}$  (oxalate),  $\frac{1}{2} C_3H_2O_4^{2-}$  (malonate),  $\frac{1}{2} C_6H_4O_6^{2-}$  (4-carboxyphthalate),  $\frac{1}{2} S_2O_3^{2-}$ , and  $\frac{1}{2} SO_4^{2-}$ , have been prepared and characterized. The molar conductance and ultraviolet-visible spectral studies suggest them to be non-electrolytes and to have square-planar geometry. The infrared (IR) and  $^1H$  nuclear magnetic resonance (NMR) spectral studies of the above complexes have been carried out to ascertain the mode of binding of the ligands to platinum.

*cis*-Diamminedichloroplatinum(II) (cisplatin) is an effective anticancer agent in the treatment of several human cancers<sup>1,2</sup>. Its clinical effectiveness is limited, however, by dose limiting toxicities such as nephrotoxicity, nausea, and vomiting. These limitations have stimulated a widespread search for other platinum complexes with better antitumor activity but decreased toxicities<sup>3-5</sup>. Among the platinum(II) complexes, several complexes with symmetrically C-substituted ethylenediamine derivatives such as 1,2-diaminocyclohexane and 1-amino-2-aminomethylcyclohexane have shown better antitumor activity with reduced toxicity and the lack of cross-resistance with cisplatin. There is no earlier report on platinum(II) complexes with N-alicyclic substituted ethylenediamine. Here we report the synthesis and characterization of several new platinum(II) complexes containing N,N'-dicyclopentylethylenediamine (DCPEDA) and two monoanionic or a dianionic ligand(s).

### Materials and Methods

Cyclopentylamine (Riedel-De Haen, Germany) was purified by distillation; other chemicals used were similar to those described earlier<sup>6</sup>.

### Synthetic procedures

N,N'-Dicyclopentylethylenediamine (DCPEDA) was prepared by refluxing together one mol of 1,2-dichloroethane, five mol of cyclopentylamine, and three mol of distilled water for 12 hr. Excess of cyclopentylamine was removed by distillation under reduced pressure. The solid obtained, was dissolved in water (50-100 ml). An excess amount of sodium hydroxide was added to the above solution in small portions with vigorous shaking when diamine separated from aqueous layer. It was extracted with petroleum ether. The product was recrystallized twice from petroleum ether (yield 90%).

### Preparation of complexes: $[Pt(DCPEDA)I_2].H_2O$

$K_2PtCl_4$  (415 mg) was dissolved in 20 ml of distilled water and KI (4 g) was added. N,N'-Dicyclopentylethylenediamine (214 mg) in methanol was added to the above solution when the precipitate of diiodo complex was obtained. This product was filtered, washed several times with water, ethanol, and diethyl ether, and dried *in vacuo* over anhydrous calcium chloride (yield 95%).

### $[Pt(DCPEDA)Cl_2].H_2O$

The diiodo complex (663 mg) was suspended in distilled water. A solution of  $AgNO_3$  (323 mg) in distilled water was added to the above suspension. This mixture was stirred for 24 hr in the dark and the precipitate for AgI was removed by filtration. Sodium chloride (20 mmol) in distilled water was added to the above filtrate. The yellow solid obtained was filtered, washed with water, ethanol and diethyl ether, and dried *in vacuo* over anhydrous  $CaCl_2$  (yield 60%).

### $[Pt(DCPEDA)SO_4]$

The diiodo complex (1 mmol) was suspended in 20 ml of distilled water and a solution of  $Ag_2SO_4$  (0.95 mmol) in distilled water was added. The suspension was stirred for 24 hr in dark. The precipitate of AgI was removed by filtration. The clear solution was concentrated to dryness on a water bath when the white solid was obtained. The solid was dried *in vacuo* over anhydrous  $CaCl_2$  (yield 60%).

$[Pt(DCPEDA)Br_2].H_2O$  (yield 65%),  $[Pt(DCPEDA)(C_2H_4)].2H_2O$  (yield 55%),  $[Pt(DCPEDA)(C_3H_2O_4)].H_2O$  (yield 60%),  $[Pt(DCPEDA)(C_6H_4O_6)].2H_2O$  (yield 60%), and  $[Pt(DCPEDA)(S_2O_3)]$  (yield 55%) were prepared by the synthetic procedure used for  $[Pt(DCPEDA)Cl_2].H_2O$  except that KBr (20 mmol),  $Na_2C_2O_4$  (1 mmol),

Table 1—Colour and Analytical Data of Pt(II) Complexes

Compound (Colour)	Found (Calc.) (%)		
	C	H	N
DEPEDA.H <sub>2</sub> O (White)	67.19 (67.24)	11.23 (11.28)	13.00 (13.06)
[Pt(DCPEDA)Cl <sub>2</sub> ].H <sub>2</sub> O (Yellow)	30.07 (30.00)	5.00 (5.03)	5.81 (5.83)
[Pt(DCPEDA)Br <sub>2</sub> ].H <sub>2</sub> O (Yellow)	25.05 (25.31)	4.36 (4.24)	5.08 (4.92)
[Pt(DCPEDA)I <sub>2</sub> ].H <sub>2</sub> O (Greenish Yellow)	21.75 (21.73)	3.65 (3.64)	4.07 (4.22)
[Pt(DCPEDA)(C <sub>2</sub> O <sub>4</sub> )].2H <sub>2</sub> O (White)	32.17 (32.63)	4.64 (4.69)	5.05 (5.43)
[Pt(DCPEDA)(C <sub>3</sub> H <sub>2</sub> O <sub>4</sub> )].H <sub>2</sub> O (White)	35.05 (35.22)	5.08 (5.12)	5.43 (5.47)
[Pt(DCPEDA)(C <sub>9</sub> H <sub>4</sub> O <sub>6</sub> )].2H <sub>2</sub> O (Yellow)	39.41 (39.69)	4.44 (4.75)	4.28 (4.40)
[Pt(DCPEDA)(S <sub>2</sub> O <sub>3</sub> )] (Yellow)	28.54 (28.62)	4.80 (4.80)	5.52 (5.56)
[Pt(DCPEDA)(SO <sub>4</sub> )] (White)	29.45 (29.56)	4.93 (4.96)	5.72 (5.74)

Na<sub>2</sub>C<sub>3</sub>H<sub>2</sub>O<sub>4</sub> (1 mmol), Na<sub>2</sub>C<sub>9</sub>H<sub>4</sub>O<sub>6</sub> (1 mmol), or Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (1 mmol) was used per mmol of [Pt(DCPEDA)I<sub>2</sub>] in place of NaCl.

Chemical analyses of the above compounds were performed at the Microanalytical Laboratory, I.I.T., Bombay.

Physical measurements were carried out as described elsewhere<sup>6</sup>. In the <sup>1</sup>H NMR spectra the relative peak areas corresponded to the ratio of the number of protons in each environment.

## Results and Discussion

Eight platinum(II) complexes of N,N'-dicyclopentylethylenediamine having the general formula [Pt(DCPEDA)X<sub>2</sub>] {where X<sup>-</sup> = Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>,  $\frac{1}{2}$  C<sub>2</sub>O<sub>4</sub><sup>2-</sup> (oxalate),  $\frac{1}{2}$  C<sub>3</sub>H<sub>2</sub>O<sub>4</sub><sup>2-</sup> (malonate),  $\frac{1}{2}$  C<sub>9</sub>H<sub>4</sub>O<sub>6</sub><sup>2-</sup> (4-carboxyphthalate),  $\frac{1}{2}$  S<sub>2</sub>O<sub>3</sub><sup>2-</sup>, and  $\frac{1}{2}$  SO<sub>4</sub><sup>2-</sup>} have been synthesized. The chemical analyses and colours of the above complexes are given in Table 1. The molar conductance values of the complexes in dimethylformamide (DMF) (1.9 to 8.7 cm<sup>2</sup> ohm<sup>-1</sup> mol<sup>-1</sup>) suggest them to be nonelectrolytes<sup>7</sup>. The molar conductance of the solution of freshly prepared sulphate complex in conductivity water was 1.9 cm<sup>2</sup> ohm<sup>-1</sup> mol<sup>-1</sup>. This changed to 260.0 cm<sup>2</sup> ohm<sup>-1</sup> mol<sup>-1</sup> after keeping it for 24 hr at 28°C. This suggests that the sulphate complex dissolves in conductivity water to give [Pt(DCPEDA)(H<sub>2</sub>O)<sub>2</sub>]<sup>2+</sup> and SO<sub>4</sub><sup>2-</sup> ions<sup>8</sup>.

The electronic absorption spectra of the platinum(II) complexes in DMF/H<sub>2</sub>O show three or four

 Table 2—Electronic Absorption Maxima ( $\lambda_{\max}$ ) and Extinction Coefficients ( $\epsilon_{\max}$ ) of Pt(II) Complexes in DMF

Complex $\lambda_{\max}$ ( $\epsilon_{\max}$ )	Complex $\lambda_{\max}$ ( $\epsilon_{\max}$ )
[Pt(DCPEDA)Cl <sub>2</sub> ].H <sub>2</sub> O 34.12 (0.01) 31.74 (0.21) 25.64 (0.005)	[Pt(DCPEDA)(C <sub>9</sub> H <sub>4</sub> O <sub>6</sub> )].H <sub>2</sub> O 35.97 (0.4) 34.24 (0.39) 32.46 (0.09) 28.57 (0.01)
[Pt(DCPEDA)Br <sub>2</sub> ].H <sub>2</sub> O 36.36 (0.06) 29.85 (0.02) 24.39 (0.006)	[Pt(DCPEDA)(S <sub>2</sub> O <sub>3</sub> )] 36.63 (0.34) 28.57 (0.027)
[Pt(DCPEDA)I <sub>2</sub> ].H <sub>2</sub> O 37.31 (0.17) 31.64 (0.11) 27.70 (0.10)	[Pt(DCPEDA)(SO <sub>4</sub> )] 46.29 (0.25) 39.68 (0.04) 31.25 (0.01) 28.57 (0.006)
[Pt(DCPEDA)(C <sub>2</sub> O <sub>4</sub> )].2H <sub>2</sub> O 36.63 (0.13) 30.67 (0.01) 27.77 (0.003)	
[Pt(DCPEDA)(C <sub>3</sub> H <sub>2</sub> O <sub>4</sub> )].H <sub>2</sub> O 36.90 (0.03) 31.25 (0.02) 24.39 (0.003)	

$\epsilon_{\max}$  is in litre mol<sup>-1</sup> cm<sup>-1</sup> × 10<sup>-4</sup>; 10<sup>-3</sup> M solution in water.

bands as given in Table 2. The band at ~ 46 kK is assigned to an internal diamine transition. The band between 34 and 40 kK may be assigned to singlet-singlet transition ( $d_{z^2} \rightarrow d_{x^2-y^2}$ )<sup>9</sup>. The band at 34.24 kK in 4-carboxyphthalate complex is due to a  $\pi \rightarrow \pi^*$  transition of 4-carboxyphthalate moiety. The band between 29 and 33.4 kK is assigned to singlet-singlet transition ( $d_{xz}, d_{yz} \rightarrow d_{z^2}$ ). The band between 24 and 29 kK is due to the  $d-d$  transition of lowest energy ( $d_{xy} \rightarrow d_{x^2-y^2}$ ).

The <sup>1</sup>H NMR spectra of DCPEDA and its platinum(II) complexes recorded in (CD<sub>3</sub>)<sub>2</sub>SO using tetramethylsilane as an internal reference are given in Table 3. The <sup>195</sup>Pt proton coupling constants (<sup>3</sup>J<sub>Pt-H</sub>) have also been observed in some complexes and they are also given in Table 3. Wherever <sup>3</sup>J<sub>Pt-H</sub> is located, it suggests that the nitrogen atoms of DCPEDA are coordinated to platinum<sup>10</sup>. The coordination of platinum to DCPEDA invariably produces downfield shifts of cyclopentyl protons (H-2,2', H-3,3', H-4,4', and H-5,5').

The <sup>1</sup>H NMR spectrum of free ligand, DCPEDA, shows a multiplet corresponding to sixteen protons of cyclopentyl moiety at  $\delta$  1.47 ppm. The two

Table 3—<sup>1</sup>H NMR Spectral Data on Pt(II) Complexes in (CD<sub>3</sub>)<sub>2</sub>SO

Compound	Cyclopentyl protons							
	<sup>†</sup> H-2,2', -3,3', -4,4', -5,5'	H-1,1'	<sup>3</sup> J <sub>Pt-H-1,1'</sub>	H-a	<sup>3</sup> J <sub>Pt-H-a</sub>	H-a' or H-3	H-5	H-6
DCPEDA	1.47	2.96	—	2.54	—	—	—	—
[Pt(DCPEDA)Cl <sub>2</sub> ].H <sub>2</sub> O	1.56	2.96	—	2.60	18	—	—	—
[Pt(DCPEDA)Br <sub>2</sub> ].H <sub>2</sub> O	1.64	2.96	20	2.54	—	—	—	—
[Pt(DCPEDA)I <sub>2</sub> ].H <sub>2</sub> O	1.66	3.00	24	2.54	20	—	—	—
[Pt(DCPEDA)(C <sub>2</sub> O <sub>4</sub> )].2H <sub>2</sub> O	1.60	3.22	—	2.54	—	—	—	—
[Pt(DCPEDA)(C <sub>3</sub> H <sub>2</sub> O <sub>4</sub> )].H <sub>2</sub> O	1.60	—	—	2.54	18	3.24	—	—
[Pt(DCPEDA)(C <sub>9</sub> H <sub>4</sub> O <sub>6</sub> )].2H <sub>2</sub> O	1.62	2.88	18	2.54	—	8.77	8.22	7.92
[Pt(DCPEDA)(S <sub>2</sub> O <sub>3</sub> )]	1.61	2.95	—	2.54	—	—	—	—
[Pt(DCPEDA)(SO <sub>4</sub> )]	1.65	2.96	—	2.54	—	—	—	—

<sup>†</sup>Chemical shifts are given in  $\delta$ , ppm.

H-1,1' methine protons are deshielded by the NH group and, therefore, they appear downfield at  $\delta$  2.96 ppm. The four H-a ethylene protons absorb as singlet at  $\delta$  2.54 ppm. The <sup>1</sup>H NMR spectra of [Pt(DCPEDA)Cl<sub>2</sub>].H<sub>2</sub>O, [Pt(DCPEDA)Br<sub>2</sub>].H<sub>2</sub>O, [Pt(DCPEDA)I<sub>2</sub>].H<sub>2</sub>O, and [Pt(DCPEDA)(C<sub>2</sub>O<sub>4</sub>)].2H<sub>2</sub>O show downfield shift of cyclopentyl protons (H-2,2', H-3,3', H-4,4' and H-5,5'). This suggests the bonding of DCPEDA to platinum through both nitrogen atoms. The  $\nu(\text{COO})$  band at 1650 cm<sup>-1</sup> in the IR spectrum of the oxalate complex supports the bonding of -COO<sup>-</sup> groups of the oxalate to platinum through two oxygen atoms one from each of the two -COO<sup>-</sup> groups in the solid state<sup>11</sup>. In the chloro and bromo complexes, an additional species [Pt(DCPEDA){(CD<sub>3</sub>)<sub>2</sub>SO}X] (where X<sup>-</sup> = Cl<sup>-</sup> and Br<sup>-</sup>) may also be present.

The <sup>1</sup>H NMR spectrum of the malonate complex, [Pt(DCPEDA)(C<sub>3</sub>H<sub>2</sub>O<sub>4</sub>)], shows two H-a' protons of the malonate moiety as a singlet at  $\delta$  3.24 ppm. The downfield shift of these protons as compared to the position of the corresponding protons of the malonic acid suggests the bonding of the malonate to platinum through oxygen atoms. The  $\nu(\text{COO})$  band observed at 1650 cm<sup>-1</sup> in the malonate complex in the solid state confirms the bonding of the carboxylate group of malonate to platinum through two oxygen atoms one from each of the two -COO<sup>-</sup> groups<sup>11</sup>. In the 4-carboxyphthalate complex, there are large downfield shifts of H-3 and H-6 protons as compared to the positions of the corresponding protons in the free 4-carboxyphthalate acid. The H-3, H-5 and H-6 protons of free acid appear at  $\delta$  8.29, 8.13, and 7.77 ppm, respectively. The above observation suggests the bonding of two *ortho*-COO<sup>-</sup> groups to platinum through the oxygen atoms, one from each of two -COO<sup>-</sup> groups.

The  $\nu(\text{COO})$  band in this complex is observed at 1635 cm<sup>-1</sup> and this indicates the bonding of carboxylate groups to platinum. This complex also shows another very strong band at 1720 cm<sup>-1</sup>, which is assigned to the uncoordinated -COOH group of 4-carboxyphthalate moiety<sup>11</sup>.

The <sup>1</sup>H NMR spectrum of [Pt(DCPEDA)(S<sub>2</sub>O<sub>3</sub>)] shows downfield shift of cyclopentyl protons (H-2,2', H-3,3', H-4,4', and H-5,5') suggesting the bonding of DCPEDA to platinum through two nitrogen atoms. The presence of two IR bands at 1190 and 1140 cm<sup>-1</sup> in this complex indicates the coordination of thiosulphate group to platinum through oxygen and sulphur atoms<sup>12</sup>. In the <sup>1</sup>H NMR spectrum of [Pt(DCPEDA)(SO<sub>4</sub>)] the downfield shifts of cyclopentyl protons (H-2,2', H-3,3', H-4,4', and H-5,5') suggest the bonding of DCPEDA through both nitrogen atoms. The presence of two strong bands at 1120 and 1020 cm<sup>-1</sup> in the IR spectrum of sulphate complex suggests the bidentate bonding of sulphate group to platinum through two oxygen atoms<sup>13</sup>. The Pt-O stretching band observed at 470 cm<sup>-1</sup> further confirms the bonding of sulphate ion to platinum through oxygen atoms<sup>11</sup>. The sulphate complex in (CD<sub>3</sub>)<sub>2</sub>SO may be present as [Pt(DCPEDA){(CD<sub>3</sub>)<sub>2</sub>SO}<sub>2</sub>]SO<sub>4</sub>.

The platinum(II) complexes of N,N'-dicyclopentylethylenediamine and N,N'-dihexylethylenediamine (DCHEDA)<sup>6</sup> exist in isomeric *dl* and *meso* forms as was found earlier in planar N,N'-dimethylethylenediamine platinum(II) complexes<sup>14</sup>. Interconversion of *dl* and *meso* forms due to geometrical isomerism in the chelate ring can occur by inversion at a nitrogen atom, but loss of an N-H proton must precede inversion<sup>14,15</sup>. The Pt-N bond in these platinum(II) complexes is expected to be weaker than that in N,N'-dimethylethylenediamine-

platinum(II) complexes because the nitrogen atoms are substituted by bulky cyclopentyl or cyclohexyl groups. The  $^3J_{\text{Pt-H}}$  coupling constants in  $[\text{Pt}(\text{DCPEDA})\text{X}_2]$  and  $[\text{Pt}(\text{DCHEDEA})\text{X}_2]$  are 20 and 26 Hz, respectively, and these small  $^3J_{\text{Pt-H}}$  values further support the above mechanism of rapid interconversion of *dl* and *meso* forms in these complexes.

#### Acknowledgement

We are grateful to the CSIR, New Delhi, for financial assistance.

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