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Platinum(II) Complexes with Diaminopropionic Acid as Oxygen-Bound Unidentate, Nitrogen–Oxygen and Nitrogen–Nitrogen Chelate Complexes

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Abstract

Reaction of diaminopropionic acid (Dap) monohydrochloride with K_2PtCl_4 in water gives two isomeric $PtCl_2(O\text{-}Dap{\cdot}HCl)_2$ complexes co-ordinated through oxygen only which can be isolated in solid form; both isomers are converted upon short heating to $PtCl_2(N,O\text{-}Dap)$, whereas prolonged heating yields $PtCl_2(N,N\text{-}Dap)$.

Introduction

Many complexes of platinum with amino acids have been reported [1], all of which contain the ligand bound to the metal either as a bidentate ligand through nitrogen and oxygen, or as a unidentate ligand through nitrogen alone. Among the basic amino acids, complexes of arginine and histidine have been investigated. Arginine binds to Pt(II) through the α-amine group only [2], whereas histidine binds both through the amine and the nitrogen of the imidazole ring [3].

Recently, in connection with a study of the binding of platinum salts to antibodies for targeting [4], the N,N-bidentate complex of 2,3-diaminopropionic acid (Dap) with a free carboxyl group was required for coupling to the antibodies. Such N,N-complexes, either in 2:1 or 1:1 ratio, have previously been described [5, 6] and the ethyl ester of diaminopropionic acid Pt(II) was shown to possess some antitumor-activity against leukemia L-1210 and P-388 in the mouse. Unfortunately, in repeating the described procedures of Inagaki *et al.* [6] we met with some difficulties, and it was decided to analyse each product and intermediate formed.

Results and Discussion

When the aqueous solutions of Dap·HCl and K_2PtCl_4 are mixed together at room temperature, a copper-coloured complex $PtCl_2(Dap{\cdot}HCl)_2$ (Fig. 1) is precipitated after a few minutes. Lyophilisation of the mother liquid yields the more soluble off-white isomer. Both compounds are stable as solids at room temperature. The less soluble copper-coloured complex is probably the *cis* isomer (2), since the solid tends to change, upon prolonged standing in water, to the off-white *trans* isomer (3). However, the unequivocal assignment of the *cis* and *trans* configurations cannot be based on the M–Cl absorption in the far IR spectrum, since both isomers exhibit very similar patterns in the 400–300 cm^{-1} region (345 vw, 300 and 320 m cm^{-1}).

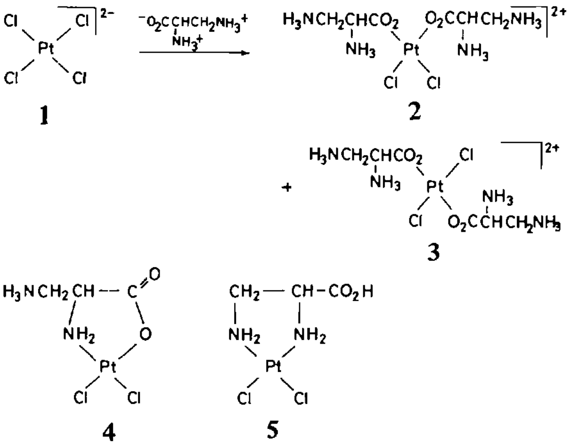

Fig. 1. Platinum(II) diaminopropionic acid complexes.

The formation of the two isomers and their IR spectra rule out the trivial possibility of exchange of potassium cations in K_2PtCl_4 by protonated Dap species. The antisymmetric carboxylate-stretching vibration and the NH bending absorption are very sensitive to coordination, varying from 1580 to 1660 cm^{-1} for the bound carboxylate and changing from broad bands of the NH_3^+ of the free ligand in the range 1500–1600 cm^{-1} to a narrow band of NH_2 in the chelate complex [7–9]. Dap·HCl itself exhibits the carboxyl absorption at 1620 cm^{-1}, and two broad NH_3^+ bending vibrations at 1550 and 1485 cm^{-1} (see Table I). Both complexes 2 and 3 have the co-ordinated antisymmetric carboxylate vibration at 1642 cm^{-1} and non co-ordinated NH_3^+ absorptions at 1580, 1498 and 1450 cm^{-1}, indicating that Dap is bound to Pt(II) only through the O-donor site of the

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TABLE I. Spectroscopic Data of Platinum(II) Diaminopropionic Acid Complexes. Absorption frequencies in cm^{-1}.

	$C{=}O^{a,b}$ stretching	$C{-}N{-}H^{c}$ bending	$d{-}d^{d}$ transition	ϵ
Dap·HCl	1620s, br (1610s, 1588s)	1550m, br, 1485m, br		
2	1642 (1615s)	1580m, br, 1498m, 1450s		
3	1642s (1615s)	1580m, br, 1498m, 1450s	30400	80
			25600	67
			21000sh	17
4	1630s (1620s)	1575s, 1507s	34800sh	67
			30500	88
			25100sh	16
5	1750s (1750s)	1574s	33600	110

[a] As KBr pellets. [b] The absorptions of deuterated complexes are given in parentheses. [c] The assignments are confirmed by comparison with the spectra of deuterated compounds. [d] In freshly prepared water solutions.

carboxylate. Coordination of amino acids through the carboxylate alone is known for 'harder' or more 'class a' metal ions than Pt(II) [10]. The presence of such a monodentate for Pt(II) as a metastable complex in solution was recently shown by Appleton and Hall [11] from ^{195}Pt NMR studies of the reaction between glycine and $Pt(NH_3)_2(H_2O)_2^{+2}$.

When **2** or **3** are heated for a few minutes in water until dissolved and then left to cool slowly, orange crystals of Pt(N,O-Dap)Cl_2 chelate (**4**) are formed. This complex has the co-ordinated carboxylate stretching frequency at 1630 cm^{-1}, the co-ordinated NH_2 bending band at 1575 cm^{-1} and the free NH_3^+ band at 1506 cm^{-1}.

The transformation of **3** to **4** is well demonstrated by the changes in the UV-visible spectra. Compound **3** has maxima at 30500, 25600 and 21000 cm^{-1}; **4** has a maximum at 30500 cm^{-1} and shoulders at 34800 and 25100 cm^{-1}. The UV spectrum of **2** could not be recorded owing to its insolubility in water and in organic solvents.

When **2**, **3** or **4**, are submitted to prolonged heating a yellow Pt(N,N-Dap)Cl_2 chelate is formed. Compound **5** is the same as that described previously by Inagaki *et al.* [6]. It exhibits a C=O stretching vibration of an un-ionized CO_2H group at 1750 cm^{-1}, and a single strong and narrow NH_2 bending vibration at 1574 cm^{-1}. The maximum of its absorption in the UV spectrum shifts to 33600 cm^{-1}, and is in agreement with the observation that upon successive binding of amines, the transition moves progressively to higher energies [12].

Formation of the N,N-ring requires deprotonation, and the decrease of pH is indeed observed when equimolar amounts of Dap·HCl and K_2PtCl_4 are heated. The pH decreases from the initial value of 3.5 to 1.5 towards the end of the reaction. The reaction is irreversible, suggesting that the Pt(N,N-Dap)-Cl_2 chelate is thermodynamically more stable than are the other complexes described.

Some additional structure assignments may be deduced from the infrared spectra of deuterated samples. All deuterated compounds exhibit the characteristic ND stretching absorptions in the 2200–2360 cm^{-1} region and are missing NH bending bands in the 1500–1580 cm^{-1} region. Also the carbonyl absorption of the charged deuterated compounds is affected by deuteration. In **2** and **3**, with the two positively charged amine groups, the carbonyl stretching frequency is shifted by 27 cm^{-1} to the longer wavelengths. In **4**, with one charged amine group there is a shift of 10 cm^{-1} whereas no change is observed in **5** with the two bound amines.

Experimental

Physical Measurements

Full range (4000–200 cm^{-1}) infrared spectra were obtained on a Perkin Elmer model 580B spectrophotometer in potassium bromide and cesium iodide disks. UV-Visible spectra were performed using a Cary 219 instrument in freshly prepared water solutions.

Microanalyses

Carbon and hydrogen analyses were performed by the Microanalytical Services of the Chemistry Department at the Hebrew University of Jerusalem, nitrogen and chlorine was analysed by Mrs. Sara Rogozinsky of the Biophysics Department at the Weizmann Institute.

TABLE II. Analytical Data of the Pt(II) Diaminopropionic Acid Complexes.

Compound	Yield	Formula	Analyses: Found (calculated) [%]			
			C	H	N	Cl
2	72	$C_6H_{18}Cl_4N_4O_4Pt$	13.30 (13.16)	3.40 (3.29)	10.40 (10.24)	25.71 (25.96)
3	15	$C_6H_{18}Cl_4N_4O_4Pt$	13.26 (13.16)	3.29 (3.29)	10.55 (10.24)	25.90 (25.96)
4	57	$C_3H_8Cl_2N_2O_2Pt$	9.76 (9.72)	2.41 (2.16)	7.93 (7.56)	 (19.18)
5	65	$C_3H_8Cl_2N_2O_2Pt$	9.78 (9.72)	2.16 (2.16)	7.65 (7.56)	19.58 (19.18)

Preparation of Compounds

Cis-dichlorobis[(d, l)-diaminopropionic acid hydrochloride]platinum(II), $\{cis\text{-}PtCl_2[O_2CCH(NH_3)CH_2NH_3Cl]_2\}$, *(2)*

A solution of Dap·HCl (281 mg, 2 mmol in 15 ml of water) was added to a solution of K_2PtCl_4 (415 mg, 1 mmol in 10 ml of water) and the mixture was stirred for 6 h. The pH changed slightly from the initial value of 3.5 to 3.0. The red precipitate which formed was filtered off, washed twice with 2 ml of water and dried *in vacuo* overnight. The compound becomes white above 200 °C and darkens at 207 °C. When left as a solid in water for several days at room temperature its colour becomes gradually brighter. For analytical data see Table II.

Trans-dichlorobis[(d, l)-diaminopropionic acid hydrochloride]platinum(II), $\{Trans\text{-}PtCl_2[O_2CCH(NH_3)CH_2NH_3Cl]_2\}$, *(3)*

The mother liquid was lyophilized and the residue was triturated with 5 ml of cold water. The off-white solid was filtered, washed twice with 1 ml of cold water and dried overnight *in vacuo*. The compound darkens at 207 °C.

Dichloro[(d, l)-diaminopropionic acid]platinum(II), $\{PtCl_2[O_2CCH(NH_2)CH_2NH_2]\}$, *(4)*

The red compound (2, 68 mg) was dissolved in 1 ml of boiling water and heated for a few minutes until the colour of the solution became orange. Upon standing for 2 or 3 days at room temperature, orange crystals are formed. The compound darkens at 230 °C.

The same compound was obtained when the off-white isomer was boiled a few minutes or Dap·HCl (35 mg, 0.25 mmol) and K_2PtCl_4 (103.5 mg, 0.25 mmol) were subjected to the same procedure.

Dichloro[(d, l)-diaminopropionic acid]platinum(II), $\{PtCl_2[NH_2CH_2CH(NH_2)CO_2H]\}$, *(5)*

Dap·HCl (70.25 mg, 0.5 mmol) was added to a solution of K_2PtCl_4 (207.5 mg, 0.5 mmol in 5 ml of water) and the mixture was boiled overnight. The pH of reaction changed during this period from the initial value of 3.5 to 1.5. After cooling the yellow precipitate was filtered off, washed with 2 ml of cold water and dried.

The deuterated samples were prepared from the previously deuterated Dap·DCl in D_2O.

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