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Platinum(II) Complexes with 2,4-Diaminobutyric Acid, Ornithine, Lysine and 4,5-Diaminovaleric Acid

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Abstract

L-2,4-Diaminobutyric acid (Dab) reacts with K_2PtCl_4 yielding $PtCl_2$(N,O-Dab), which rearranges to $PtCl_2$(N,N-Dab). Reaction with L-ornithine and L-lysine yields the corresponding $PtCl_2$(N,O-Orn) and $PtCl_2$(N,O-Lys), respectively, whereas reaction with 4,5-diaminovaleric acid (Dav) yields $PtCl_2$(N,N-Dav).

Introduction

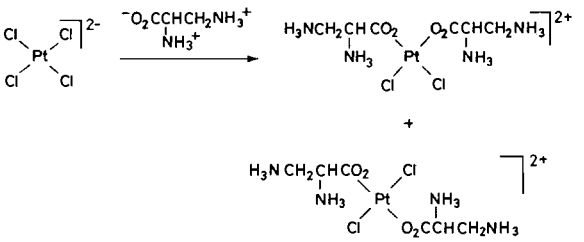
Many platinum(II) complexes with amino acids have been investigated [1], among which the chelates of basic amino acids have received little attention. Complexes of arginine, histidine and 2,3-diaminopropionic acid have been reported: arginine has been shown to bind to Pt(II) through the α amine group only [2], whereas histidine binds both through the amine and the nitrogen of the imidazole ring [3]. Diaminopropionic acid (Dap) forms N,N-bidentate complexes in 2:1 and 1:1 ratios [4, 5]. Lysine ethyl ester has also been bound (although indirectly) to Pt(II), through an N,N-bis(diphenylphosphine) bridge [16].

Recently we have shown that under mild reaction conditions Dap also forms oxygen monodentate compounds and a N,O-bidentate chelate [7]. In this regard, the formation of metastable oxygen bound monodentate complexes of glycine and Pt(II) was demonstrated by Appleton and Hall using ^{195}Pt NMR [8]. These facts prompted us to study reactions of K_2PtCl_4 with other basic amino acids under mild reaction conditions.

Results and Discussion

Dap and K_2PtCl_4 are known to yield several types of compounds [4, 5, 7]. However, Pt(II) complexes with the common basic amino acids do not appear in the literature. With this in mind, the following questions arise:

1. Does the vicinal diamine in Dap, with the positively charged amine in the β position, stabilize the oxygen-monodentate complexes, thus permitting they isolation [7] (see Scheme 1)? Would such a stabilization decrease if one of the amine groups were displaced from the other?



Scheme 1

2. Does the position of the positively charged amine in the chain also affect the stability of a $PtCl_2$(N,O-A) complex (where A is any basic amino acid)?

3. Does the distance of the amine in the chain have an influence on the rearrangement of an N,O-bidentate complex into an N,N-bidentate complex?

4. What kind of complex may be obtained if the carboxyl group is separated from the vicinal diamine system?

To answer these questions we studied the reaction of K_2PtCl_4 with L-diaminobutyric acid (Dab), L-ornithine (Orn), L-lysine (Lys) and 4,5-diaminovaleric acid (Dav). The amino acids were introduced into reactions as monohydrochlorides, in which the negatively-charged zwitterionic carboxy group is the most nucleophilic. In contrast from previous results with Dap [7], when the other amino acids were mixed with K_2PtCl_4 in 1:1 or 2:1 molar ratios, none yielded crystalline products bound to Pt(II)

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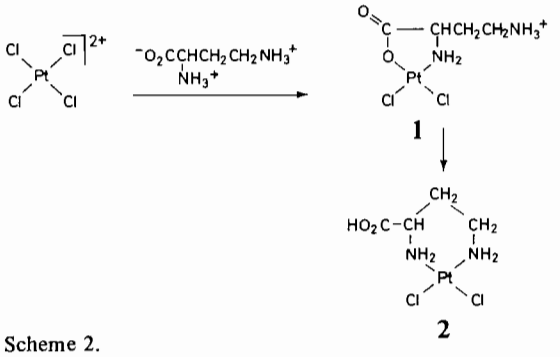
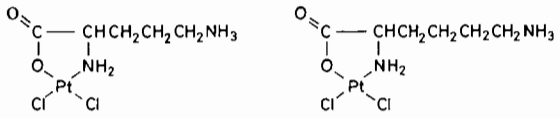
via oxygen only. Upon prolonged standing at room temperature, all basic α-amino acids yielded cyclic N,O-bidentate chelates. Their formation could be accelerated by heating (Schemes 2, 3).



Scheme 2.



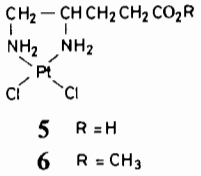
Scheme 3.

The formation of N,O-chelates requires proton abstraction and, as the reaction proceeds, the pH decreases from the initial value of 5.6 to 1.5. The lowering of the pH has a self-inhibiting effect and the yields never exceed 30–40%. From the concentrated mother liquids the unreacted K_2PtCl_4 may be isolated.

Upon prolonged heating $PtCl_2$(N,O-Dab) (**1**) tends to rearrange to the six-membered $PtCl_2$(N,N-Dab) (**2**). Alternatively **1** is transformed to **2** when heated in diluted solution at pH 6.5 for 1 h.

Ornithine and K_2PtCl_4, even after a prolonged period of reaction, yield only the $PtCl_2$(N,O-Orn) (**3**) (Fig. 3). Compound **3** could not be rearranged from the five-membered N,O-chelate to the seven-membered N,N-chelate when heated at pH 6 or 7. Volshtein *et al.* have studied kinetics of cyclization of *trans* $K_2(PtCl_2A_2)$ salts (where A is an amino acid bound to Pt(II) by an amine group only). They obtained many five-membered N,O-inert chelates from α-amino acids, but only two N,O-six-membered chelates from β-alanine and β-phenylalanine [9–11]. They also succceded in demonstrating the slow formation of the seven-membered N,O-compound derived from γ-aminobutyric acid [12].

A molecule such as Dav, the isomeric γ-ornithine previously prepared by us [13] (Scheme 4), may theoretically react according to two possible pathways, leading to the formation of N,O-seven-membered or N,N-five-membered compounds. In these studies,



Scheme 4.

however, only the N,N-five-membered chelate **5** was obtained.

L-Lysine yields the corresponding $PtCl_2$(N,O-Lys) (**4**) when heated for 2 h with K_2PtCl_4 at 85 °C. Upon prolonged reaction times or at higher bath temperatures the complex tends to decompose. The tendency to decompose only occurs in solutions where Pt(II) is apparently reduced by water to Pt(0). As a solid **4** is stable, similar to its shorter homologues, whereas its deuterated analogue is more stable to heating in solution.

There are some general features worth noting in the ultraviolet and infrared spectra for each class of compounds. N,O-Chelates in their electronic spectra exhibit a maximum between 322–328 nm and two distinct shoulders at 288–292 and 390–400 nm (Table I). The absorptions of the N,N-chelates shift to shorter wavelengths (274, 300 and 360 nm) and are in agreement with the observation that upon successive binding of amines, the transition moves progressively to higher energies [14]. The intensities of the six-membered $PtCl_2$(N,N-Dab) (**2**) are much weaker than those of the five-membered analogues.

In their infrared spectra, the N,O-chelates have the carboxyl antisymmetric stretching frequencies of the bound carboxylate in the 1617–1645 cm^{-1} region (Talbe II). They have two bending NH absorption bands: the bound amine group in the 1560–1604 cm^{-1} region and the free NH_3^+ group in the 1498–1519 cm^{-1} region. Deuteration leads to the disappearance of the NH-bending bands and to the shift of the carbonyl absorption to longer wavelengths. The N,N-bidentate compounds (**2** and **5**) exhibit a C=O stretching vibration of a de-ionized CO_2H group at 1719 and 1700 cm^{-1} respectively and only one NH_2 bending band, which disappears upon deuteration (Fig. 1).

In summary, diaminobutyric acid, ornithine and lysine do not form crystalline oxygen-only monodentate complexes, as had been detected with Dap. They all yield N,O-bidentate chelates. The position of the amine group is crucial for their ability to rearrange into N,N-bidentate complexes, as well as for their stability. When the amine group is in the β or γ position, five-membered $PtCl_2$(N,N-Dap) or six-membered $PtCl_2$(N,N-Dab) are obtained upon heating. In the case of ornithine, where the amine group is in the δ-position, the $PtCl_2$(N,O-Orn) com-

TABLE I. The Ultraviolet Absorptions of the Platinum(II) Basic Amino Acid Complexes.

Complex	d–d transitions (10^{-3} cm^{-1})			ϵ		
$PtCl_2$(N,O-Dap)[a]	34.7 sh	30.6 max	25.0 sh	67	94	16
$PtCl_2$(N,O-Dab)	35.0 sh	31.0 max	25.3 sh	124	160	23
$PtCl_2$(N,O-Orn)	34.2 sh	30.5 max	25.6 sh	114	178	25
$PtCl_2$(N,O-Lys)	34.5 sh	30.6 max	25.6 sh	125	200	29
$PtCl_2$(N,N-Dap)[a]		33.5 br max			165	
$PtCl_2$(N,N-Dab)	36.5 max	33.3 sh	27.7 sh	10	7	
$PtCl_2$(N,N-Dav)	36.2 sh	33.3 max	27.7 sh	96	150	24
$PtCl_2$(N,N-Dav Me-ester)	36.2 sh	33.3 max	27.0 sh	130	198	32

[a]See ref. 7.

TABLE II. The Infrared Frequencies of the Platinum(II) Basic Amino Acid Complex.

Complex	Infrared frequencies (cm^{-1})				
	(NH)	(ND)	(C=O)[a]	(NH)[b] bound	(NH)[b] unbound
$PtCl_2$(N,O-Dap)[c]	3180m, 3090m		1630s	1575s	1510m
		2385m, 2320m, 2280m, 2200w	(1620s)		
$PtCl_2$(N,O-Dab)	3206m, 3091s, 3054s		1617s	1560s	1498s
		2394w, 2320m, 2271m, 2180w	(1593s)		
$PtCl_2$(N,O-Orn)	3392w, 3242w, 3184w, 3044w		1645s	1576w	1519m
		2420w, 2393w, 2285w, 2195w	(1635s)		
$PtCl_2$(N,O-Lys)	3248m, 3191m, 3126m		1643s	1603m	1507m
		2427m, 2357m, 2308m	(1637s)		
$PtCl_2$(N,N-Dap)[c]	3255s, 3200s, 3130m, 3105m		1750	1550s	
		2440m, 2420m, 2360w, 2310w	(1750s)		
$PtCl_2$(N,N-Dab)	3252m, 3237m, 3187m, 3127m		1718s	1589m	
		2423w, 2413m, 2313s	(1717s)		
$PtCl_2$(N,N-Dav)	3273s, 3220w, 3200w, 3180w		1700s	1557s	
		2450m, 2397w, 2375w	(1700s)		
$PtCl_2$(N,N-Dav Me-ester)	3270s, 3190m		1730s	1568s	

[a]The carbonyl absorption of deuterated complexes are given in parentheses. [b]The assignments are confirmed by comparison with the spectra of deuterated compounds. [c]See ref. 7.

plex is stable upon heating. When the amine is moved further away, as in lysine, the compound becomes sensitive to reductive decomposition in water upon heating.

Experimental

Physical Measurements

Electronic spectra

Electronic spectra were measured on a Cary 219 spectrophotometer in freshly prepared water solutions.

Infrared spectra

Full range (4400–400 cm^{-1}) spectra were obtained on a Nicolet MX-1 spectrophotometer in KBr disks.

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 analyzed by Mrs. Sara Rogozinsky of the Biophysics Department at the Weizmann Institute (see Table III).

*Synthesis of $PtCl_2$(N,O-Dab) (**1**), $PtCl_2$(N,O-Orn) (**3**) and $PtCl_2$(N,O-Lys) (**4**)*

In a typical reaction procedure for preparation of compounds **1**, **3** and **4**, a solution of 0.5 mmol K_2PtCl_4 in 1 ml water was added to a solution of amino acid monohydrochloride (0.5 mol in 1.5 ml H_2O). Alternatively the acid as dihydrochloride was neutralized to pH 5.8 prior to the addition of K_2PtCl_4. For compounds **1** and **3** the reaction was allowed to proceed for 2 h at 100 °C and for the lysine analogue **4** at 85 °C for 2 h. The solution

TABLE III. Analytical Results, Colour Change and Decomposition Points.

Compound	Formula	Analysis, found (calculated) %				Colour change[a] °C	Decomposition[b] °C
		C	H	N	Cl		
$PtCl_2$(N,O-Dap)	$C_4H_{10}Cl_2N_2O_2Pt$	12.58 (12.50)	2.82 (2.62)	7.29 (7.29)	17.91 (18.46)	200	230
$PtCl_2$(N,O-Orn)	$C_5H_{12}Cl_2N_2O_2Pt$	15.32 (15.08)	3.33 (3.03)	6.68 (7.03)	17.71 (17.80)	190	210
$PtCl_2$(N,O-Lys)	$C_6H_{14}Cl_2N_2O_2Pt$	17.24 (17.48)	3.18 (3.42)	6.57 (6.79)		190	210
$PtCl_2$(N,N-Dab)	$C_4H_{10}Cl_2N_2O_2Pt$	12.50 (12.50)	2.90 (2.62)	7.02 (7.29)	17.95 (18.46)		240
$PtCl_2$(N,N-Dav)	$C_5H_{12}Cl_2N_2O_2Pt$	14.90 (15.08)	3.22 (3.03)	7.23 (7.03)	18.18 (18.80)		250
$PtCl_2$(N,N-Dav-methyl ester	$C_6H_{14}Cl_2N_2O_2Pt$	17.58 (17.48)	3.45 (3.42)		17.23 (17.47)		240

[a]Compound becomes brighter. [b]Compound darkens.

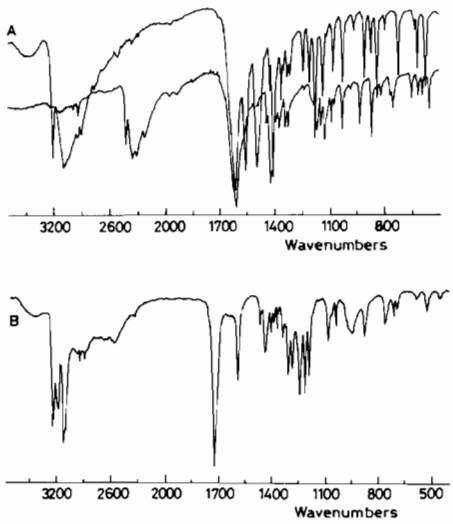


Fig. 1. Infrared spectra of A, $PtCl_2$(N,O-Dab) and its deuterated analogue; B, $PtCl_2$(N,N-Dab).

was filtered when hot and left to stand for 24–48 h. The products were recrystallized from water and dried *in vacuo*. The yields were in the range of 20–40%.

Synthesis of $PtCl_2$(N,N-Dab) (2) and $PtCl_2$(N,N-Dav) (5)

The complexes **2** and **5** were prepared by heating 0.5 mmol of amino acid and 0.5 mmol K_2PtCl_4 at 100 °C for 24 h. The products were filtered and recrystallized from water. The yields were in the range of 20–40%. $PtCl_2$(N,N-Dab) was also prepared by rearrangement of **1**: 30 mg of **1** were dissolved in 3.5 ml water, brought to pH 6.5 heated for 1 h, acidified to pH 2, lyophilized, and the residue was triturated with 0.5 ml cold water. A yield of 27 mg (90%) of **2** was obtained.

The ester **6** was prepared from equimolar amounts of 4,5-diaminovaleric acid methyl ester and K_2PtCl_4 by heating for 24 h. The pH was kept between 5.0 and 5.5 with dilute $NaHCO_3$. The yield was 60%.

The deuterated samples were prepared in D_2O (Merck) from previously deuterated amino acids.

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