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Palladium(II) and Platinum(II) Complexes with Pentamethylenetetrazole and their Interaction with Nucleosides

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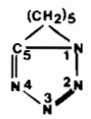
The reactions of pentamethylenetetrazole with palladium(II) and platinum(II) in aqueous solutions have been studied and the complexes cis-$M(PMT)_2X_2$ *where M is Pd or Pt and X is Cl, Br, or I, isolated and characterized by elemental analysis, IR spectra, conductivity measurements and molecular weight determinations. The complexes further react with nucleosides to yield the mixed ligand complexes* $[M(PMT)_2(Nucl)_2]Cl_2$, *where Nucl is inosine, guanosine, or cytidine. In the case of adenosine the dimeric* $\{[M(PMT)_2Ado]_2\}Cl_4$ *or polymeric* $\{[M(PMT)_2Ado]Cl_2\}_n$ *complexes have been isolated in which adenosine bridges two metal atoms through its* N_1 *and* N_7 *atoms. These mixed ligand complexes were characterized besides the above techniques and by their* ^1H *NMR spectra.*

Introduction

Pentamethylenetetrazole (PMT) (I) is a member of the cyclopolymethylene-tetrazole series, which



Structure I

present very interesting pharmacological and chemical properties. As a drug it is characterized by a strong, stimulating action on the central nervous system and, in sufficient dosage, acts as convulsant [1]. Chemically it acts as an extremely weak Brönsted base [2, 3], but is capable of forming fairly stable complexes with transition metal ions as well as with molecular Lewis acids [4]. Each of the four nitrogen atoms of the tetrazole ring, in principle, is capable of acting as a coordination site. In general, however cyclopolymethylenetetrazoles, as well as other 1,5-disubstituted tetrazoles, acts as monodentate ligands. This leads to the conclusion that either complexation at any of the four ring nitrogens deactivates the ring toward further complexation, or there is only one preferred bond site available for coordination. In fact X-ray crystallography has shown [5, 6] that coordination occurs *via* the 4th nitrogen of the tetrazole ring. In one case, namely the complex $AgNO_3 \cdot 2PMT$, it was found that pentamethylenetetrazole acts as a bidentate bridging ligand through its 3rd and 4th nitrogens [7].

Although there are several studies on the ligation properties of pentamethylenetetrazole toward the first transition and post-transition series, there are no such studies concerning the group of the platinum metals. This lack together with the fact that the new platinum complexes may exhibit antitumour properties [8–11] prompted us to examine the reactions of pentamethylenetetrazole with the platinum metals. In this paper we report on the reactions of palladium(II) and platinum(II) and on the interaction of the isolated complexes with several nucleosides in aqueous solutions.

Results and Discussion

A) The Pentamethylenetetrazole Complexes

The general procedure for the preparation of *cis*-dichloro complexes of platinum(II) and palladium(II) with nitrogenous bases *via* the corresponding *cis*-diiodides [12, 13] cannot be applied for the respective complexes of pentamethylenetetrazole. The interaction of potassium tetraiodopalladate(II) and potassium tetraiodoplatinate(II) with pentamethylenetetrazole yields the corresponding complexes *cis*-$M(PMT)_2I_2$ (Table I). However they cannot be converted to the respective aquo complexes by removing the iodide ions with silver nitrate, due to the interaction of the coordinated pentamethylenetetrazole with silver ions, and the formation of polynuclear complexes. The bromides, *cis*-$M(PMT)_2Br_2$, were prepared by an analogous method starting from the respective tetrabromo complexes, K_2MBr_4. The dichloro complexes, *cis*-$M(PMT)_2Cl_2$ were similarly prepared by direct interaction of the respective tetrachloro complexes, K_2MCl_4, with pentamethylenetetrazole in aqueous solutions. The

TABLE I. Analytical[a] and Physical Data of the Complexes.

Compound[b]	%C	%H	%N	%M	Λ_M Ω^{-1} cm^2 M^{-1}	M.W.[c]
$Pd(PMT)_2Cl_2$	31.51	4.37	24.42	23.65	7	430
	(31.73)	(4.41)	(24.68)	(23.45)	(dmf)	(453.4)
$Pd(PMT)_2Br_2$	26.67	3.70	20.82	19.30	5	560
	(26.53)	(3.68)	(20.63)	(19.60)	(dmf)	(542.4)
$Pd(PMT)_2I_2$	22.31	3.25	17.90	16.32	5	658
	(22.61)	(3.14)	(17.59)	(16.71)	(dmf)	(636.4)
$Pt(PMT)_2Cl_2$	26.67	3.59	20.35	36.17	8	529
	(26.55)	(3.69)	(20.65)	(35.95)	(dmf)	(542)
$Pt(PMT)_2Br_2$	22.59	3.27	17.89	30.50	6	650
	(22.81)	(3.17)	(17.74)	(30.88)	(dmf)	(631)
$Pt(PMT)_2I_2$	19.60	2.70	15.10	26.50	5	710
	(19.85)	(2.76)	(15.44)	(26.88)	(dmf)	(725)
$[Pd(PMT)_2(Ino)_2]Cl_2$	38.58	4.30	22.20	10.50	240	
	(38.78)	(4.44)	(22.62)	(10.75)	(water)	
$[Pd(PMT)_2(Guo)_2]Cl_2$	37.40	4.38	24.30	10.80	235	
	(37.63)	(4.51)	(24.70)	(10.43)	(water)	
$[Pd(PMT)_2(Cyd)_2]Cl_2$	38.51	4.98	21.15	11.65	180	
	(38.29)	(4.89)	(20.85)	(11.32)	(water)	
$\{[Pd(PMT)_2Ado]Cl_2\}_{2 \text{ or } n}$	36.87	4.37	25.02	14.40	400	
	(36.64)	(4.58)	(25.26)	(14.77)	(dmf:H_2O, 1:3)	
$[Pt(PMT)_2(Ino)_2]Cl_2$	35.35	3.95	20.31	17.80	200	
	(35.60)	(4.08)	(20.76)	(18.08)	(water)	
$[Pt(PMT)_2(Guo)_2]Cl_2$	34.30	4.00	22.18	17.85	195	
	(34.63)	(4.15)	(22.72)	(17.58)	(water)	
$[Pt(PMT)_2(Cyd)_2]Cl_2$	35.31	4.32	18.70	19.36	170	
	(34.99)	(4.47)	(19.05)	(18.95)	(water)	
$\{[Pt(PMT)_2Ado]Cl_2\}_{2 \text{ or } n}$	24.45	3.95	22.10	24.60	360	
	(24.10)	(4.08)	(22.49)	(24.10)	(dmf:H_2O, 1:3)	

[a]The numbers in parentheses represent the calculated values. [b]PMT = pentamethylenetetrazole, Ino = inosine, Guo = guanosine, Cyd = cytidine, Ado = adenosine. [c]M.W. = molecular weight.

reaction with Pd(II) is quite fast and precipitation is complete within 0.5 hrs. The reaction, however, with Pt(II) is much more slower and requires overnight stirring for complete precipitation.

The analytical and physical data of the complexes are listed in Table I, and fit well to the proposed formulae. The conductivities of the complexes *cis*-$M(PMT)_2X_2$ show that they all are non-electrolytes in dimethylformamide. Other solvents tested include dmf–water mixtures, acetone, and ethanol, and the complexes show the same behavior. The experimental molecular weights show that the complexes are monomeric in acetone.

The proposed *cis*-geometries of the complexes were deduced from the fact that both sets of complexes respond to the Kurnakoff's test [14]. So treatment of all the complexes with thiourea liberates the pentamethylenetetrazole and yields the known $M(thu)_4X_2$ complexes. The Kurnakoff test originally applied to platinum(II) complexes was found to be applicable and to the palladium(II) complexes [15]. The *cis*-geometry, at least for the chloro-complexes, was also deduced from the study of their far IR spectra. This region is very complex due to the abundance of bands of the ligand itself. The bands however at 335 and 327 cm^{-1} for the complex Pd-$(PMT)_2Cl_2$ and at 328 and 320 cm^{-1} for the complex $Pt(PMT)_2Cl_2$ which are absent from the spectrum of the free ligand and also from the spectra of the respective bromo- and iodo- complexes, may be assigned to the Pd–Cl and Pt–Cl stretchings respectively. The doublet character of these bands is in accordance with the proposed *cis*-geometry of the complexes [16].

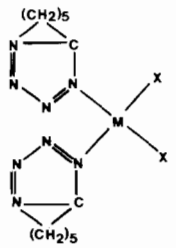
The structural information obtained from the remaining part of the IR spectra is very limited. So there are only two noticeable changes in the spectrum of the ligand, which occur upon complexation. A quartet of bands at 1100 cm^{-1} is transformed into two sets of bands and the PMT band at 1000 cm^{-1} is not observed in the spectra of the complexes. The same pattern of behavior was also found to apply in the silver nitrate complex [2] and other complexes of the first transition series ions [17].

TABLE II. ^{1}H NMR Spectra of Platinum and Palladium Nucleoside Complexes (Hz).

Compound	H_2	H_5	H_6	H_8	H_1'	J_{Pt-H_8}
Inosine	482			490	368*	
					360	
$\{Pt(PMT)_2(Ino)_2\}Cl_2$	490			520	372*	26
					366	
$\{Pd(PMT)_2(Ino)_2\}Cl_2$	488			513	373*	
					368	
Guanosine				470	372*	
					364	
$\{Pt(PMT)_2(Guo)_2\}Cl_2$				526	372*	26
					364	
$\{Pd(PMT)_2(Guo)_2\}Cl_2$				518	372*	
					366	
Cytidine		364*	468*		350*	
		355	460		344	
$\{Pt(PMT)_2(Cyd)_2\}Cl_2$		369*	468*		353*	
		361	461		348	
$\{Pd(PMT)_2(Cyd)_2\}Cl_2$		371*	470*		355*	
		363	464		348	
Adenosine	485			495	373*	
					368	
$\{Pt(PMT)_2Ado\}_2Cl_4$	530			545	372*	26
					367	
$\{Pd(PMT)_2Ado\}_2Cl_4$	523			535	372*	
					367	

*Doublet.

The monomeric character of the complexes together with the other physical data suggest that pentamethylenetetrazole acts as a monodentate ligand in these complexes, with probable ligation site the nitrogen of the 4th position, as was found in other similar cases [5, 6]. The probable structure of the complexes may therefore be represented as in (II).



Structure II

B) The Interaction of Pentamethylenetetrazole Complexes with Nucleosides

The interaction of the complexes *cis*-$M(PMT)_2Cl_2$ (where M is Pd or Pt) with nucleosides was investigated and the isolated complexes together with their analytical and other physical data are listed in Table I.

The complexes were prepared by the reactions:

$$cis\text{-}M(PMT)_2Cl_2 + 2Nucl \xrightarrow[\text{reflux}]{H_2O:\text{acetone}(2:1)} [M(PMT)_2(Nucl)_2]Cl_2$$

where Nucl is inosine (Ino), guanosine (Guo), and cytidine (Cyd), and

$$2cis\text{-}M(PMT)_2Cl_2 + 2Ado \xrightarrow[\text{reflux}]{H_2O:\text{acetone}(2:1)} [M(PMT)_2Ado]_2Cl_4$$

The conductivities (Table I) show that the complexes of inosine, guanosine and cytidine are 2:1 electrolytes in water, while those of adenosine, in the dimeric formulation, are 4:1 electrolytes in water/dmf mixtures [18] and showed no change on ageing. In their UV spectra, the nucleosides shifted only slightly on complexation. The infrared bands in the region of 1650–1750 cm^{-1} remain unchanged.

The binding sites of the nucleosides to the metals in these new mixed ligand complexes were deduced from their ^{1}H NMR spectra, in the aromatic proton region, which are summarized in Table II.

a) Inosine Complexes

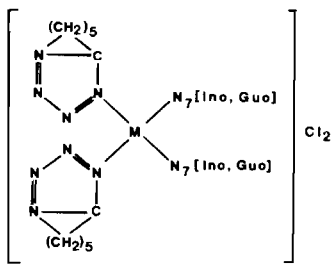
The two signals of protons (H_2, H_8) of inosine are close together (8 Hz or 0.13 ppm), while in the spec-

trum of the platinum complex and in that of the palladium complex they are separated by about 30 Hz (0.5 ppm) and 25 Hz (0.4 ppp) respectively. In the spectrum of the platinum complex the downfield peak is accompanied by two satellites, due to the coupling of H_8 to ^{195}Pt with a coupling constant of about 26 Hz and this together with the downfield shifting of the H_8 indicates that the N_7 of the purine ring is the binding site of the inosine to the platinum [19]. The downfield shift of the H_8 signal by 0.4 ppm in the spectrum of the palladium complex is comparable to that observed in the spectrum of the complex $[Pd(Ino)_4]Cl_2$ [15] and may be taken as an indication for the N_7 involvement in coordination to palladium. Charge densities are generally affected more at the carbons that are closest to the binding sites, and the protons attached to them are shifted more downfield [20] than the others and generally give larger coupling constants with the central metal atom [19, 21].

b) Guanosine Complexes

One signal was observed for guanosine at 470 Hz because there is only one aromatic proton, the H_8. This signal was shifted downfield by about 56 Hz in the spectrum of the platinum complex and was accompanied by two satellites due to the coupling of ^{195}Pt to H_8 with a coupling constant of about 26 Hz again indicating the N_7 involvement in coordination. In the palladium complex the H_8 was observed as a singlet shifted 48 Hz downfield as compared with the spectrum of free guanosine. This downfield shifting is again an indication that the N_7 of the purine ring is the ligation site of the guanosine [15, 19].

The structures therefore, of the inosine and guanosine complexes, assuming that the *cis*-geometry of the parent compounds remains unchanged due to the inner character of the Pd–N and Pt–N bonds, may be represented as in (III):



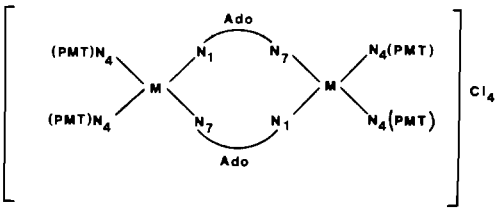
Structure III

c) Cytidine Complexes

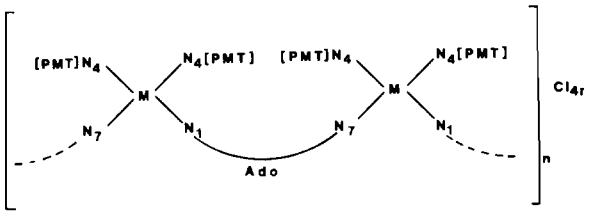
After complexation the separation of the signals of H_1' and H_5 became larger and the H_5 was shifted downfield the most. This result is the same as that found for cytidine–platinum [22] and cytidine–palladium complexes [15] and indicates that the N_3 of the pyrimidine ring is the ligation site, with structure analogous to (III).

d) Adenosine Complexes

The interaction of *cis*-$M(PMT)_2Cl_2$ with adenosine gives 1:1 (M:Ado) products eventhough a large excess of adenosine was used. The products are insoluble in water and conductivity measurements (in H_2O:dmf mixtures) indicate two ionic chlorides per metal atom. Adenosine shows two signals in the aromatic proton region at 485 and 495 Hz due to H_2 and H_8 respectively. Upon complexation both signals are displaced to higher frequencies to the same extent (530 and 545 Hz for the platinum complex and 523 and 535 Hz for the palladium complex). In addition the spectrum of the platinum compound shows coupling of ^{195}Pt to both H_2 and H_8 with coupling constants about 26 Hz. Since both signals are shifting downfield to the same extent and in the case of the platinum complex have the same coupling constants, the two protons are equally affected by the metals, and therefore adenosine must act as a bidentate ligand, linked to two metal atoms through its N_1 and N_7 [20, 22, 23] in a dimeric or polymeric bridged structure as in (IVa) or (IVb) respectively.



Structure IVa



Structure IVb

In conclusion, the behavior of *cis*-$Pt(PMT)_2Cl_2$ and the *cis*-$Pd(PMT)_2Cl_2$ towards nucleosides is comparable to that of *cis*-$Pt(NH_3)_2Cl_2$ or *cis*-$Pd(en)_2Cl_2$ and it may be that this new pentamethylenetetrazole complex of platinum exhibits potential antitumour properties like its simple ammino congener.

Experimental

Material. Pentamethylenetetrazole was a gift from the Pharmaceutical Company Chrispa S.A. All other chemicals were from Fluka A.G.

Methods. Infrared spectra were recorded on a JASCO Model DS-701G spectrophotometer in KBr pellets. Electronic spectra were obtained with a Cary Model 17D spectrophotometer. The ^1H nmr spectra were recorded on a Varian T60 high resolution spectrophotometer. The molecular weights were determined by a Hewlett-Packard Model 300 Vapor Pressure Osmometer. The microanalyses were performed in the Laboratories of the National Hellenic Research Foundation.

Preparation of the Complexes

a) cis-*Pt(PMT)$_2$I$_2$ and* cis-*Pd(PMT)$_2$I$_2$*

1 mmol K_2PtCl_4 or K_2PdCl_4 was dissolved in 20 ml of water and 4 g (about 24 mmol) of KI were added to yield a solution of 0.05 *M* MI_4^{2-} and 1 *M* I^-. To this solution 0.267 g (2 mmol) of pentamethylenetetrazole were added. The compounds precipitated immediately and were filtered, washed with water and dried at 60 °C over phosphorus pentoxide under high vacuum. Yield *ca.* 95%.

b) cis-*Pt(PMT)$_2$Br$_2$ and* cis-*Pd(PMT)$_2$Br$_2$*

These compounds were synthesized by the above outlined procedure (a), using KBr in the place of KI. Yield *ca.* 90%.

c) cis-*Pt(PMT)$_2$Cl$_2$ and* cis-*Pd(PMT)$_2$Cl$_2$*

1 mmol of K_2PtCl_4 or K_2PdCl_4 was dissolved in 15 ml of H_2O and to that was added pentamethylenetetrazole (0.276 g 2 mmol) dissolved in 10 ml of water and stirred at room temperature. The palladium complex was precipitated in a few minutes, while the platinum complex required overnight stirring. The yellow precipitates were filtered, washed with water and dried at 60 °C over phosphorus pentoxide under high vacuum. Yield *ca.* 90%.

d) *[M(PMT)$_2$(NuCl)$_2$]Cl$_2$ (M = Pt or Pd, and Nucl is inosine, guanosine, or cytidine)*

Two mmol from each of the nucleosides inosine, guanosine and cytidine were dissolved or suspended in 50 ml of water and to that was added 1 mmol from each of the complexes *cis*-$M(PMT)_2Cl_2$ (M = Pt or Pd) dissolved in 25 ml of acetone. The mixtures were refluxed for 2 hrs. After this period the acetone was evaporated, and refluxing was continued for one more hour. After cooling to room temperature the mixtures were filtered, evaporated to dryness at 60 °C under vacuum and redissolved in a small volume of D_2O. The ^1H NMR spectra showed the presence of only one product which was precipitated with excess of acetone: ether (1:2), filtered, washed with ether and dried at 50 °C under vacuum. The yields were in the range of 90 to 95%.

d) $\{[M(PMT)_2Ado]Cl_2\}_{2\text{ or }n}$ *(M = Pt or Pd)*

Adenosine (1 mmol) was dissolved in 50 ml of water and 1 mmol from each of the complexes *cis*-$M(PMT)_2Cl_2$ (M = Pt or Pd) dissolved in 25 ml acetone was added. The mixture was refluxed for 2 hrs and the precipitate formed, was filtered, washed with water, acetone and ether and dried at 60 °C under vacuum. Yield 85%.

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