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Palladium(II) Complexes Containing Pyrazole-derived Ligands of Biological Interest. Four, Five and Six coordinate Palladium(II) Complexes with 5(3)-Methylpyrazole-3(5)-carboxamide and 5(3)-Methylpyrazole-3(5)-carbohydrazide

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Abstract

Neutral bis-complexes of palladium(II) with 5(3)-methylpyrazole-3(5)-carboxamide (mpa) and 5(3)-methylpyrazole-3(5)carbohydrazide (mph) of the type $PdX_2 \cdot 2L$ (where L = mpa, mph; X = Cl, Br, I, SCN, NO_3, ClO_4) have been synthesised and spectroscopically characterised. Available physico-chemical data indicate the mpa complexes of Pd(II) to be *trans*-square planar species with the primary ligand molecule showing monodentate behavior through the pyrazolyl ring nitrogen only. The Pd(II)–thiocyanate complex of mpa is proposed to have a pseudo-square pyramidal geometry attained through bridging anionic component. The complexes $PdX_2 \cdot 2mph$ (X = Cl, NO_3) appear to be six-coordinate species at least in the solid state; the corresponding thiocyanato variety has in all probability a five coordinate structure. The species, $Pd(ClO_4)_2 \cdot 2mph$ is a usual four coordinate one with non-coordinating perchlorate group. The monochelates, $PdX_2 \cdot mph$ (X = Br, I), are *cis*-square planar varieties. The ligand molecule, mph, in all cases is believed to function as (N,N) bidentate ligand in its 'imidol' form except in the thiocyanate complex where unusually it exhibits both the monodentate and bidentate functions in the same species.

Introduction

The encouraging anti-tumour activity of *cis*-dichlorodiammineplatinum(II) [1], commonly known as '*cis*-Platin' has initiated a search for similar related compounds which could mimic the interaction of metal ions with DNA. In line with the first suggestion of Furst [2], group VIIIB metals, in general, have been included in recent years in the design of model metallic species to have potentiality as anticancer drugs [3]. As reported by Williams *et al.* [4], the introduction of Pd(II) in search of anti-cancer materials is based on the fact that Pd(II) complexes are more reactive than those of Pt(II) and rapid ligand exchange can occur. The present communication, in continuation of our earlier report [5], describes the synthesis and spectroscopic identification of a host of new Pd(II) species with biologically potent pyrazole derived ligands, *viz.*, 5(3)-methylpyrazole-3(5)-carboxamide (mpa) and 5(3)-methylpyrazole-3(5)-carbohydrazide (mph), which might have potential antitumour activity.

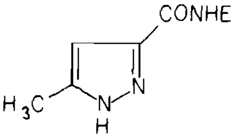

Fig. 1. Structural formulation of the ligands. mpa E = H; mph E = NH_2.

Experimental

The ligands, mpa and mph, were prepared in the pure state and characterised as described earlier [6, 7].

Preparation of the Complexes

(i) $PdCl_2 \cdot 2L$ (L = mpa, mph)

An aqueous solution of palladium(II) chloride (2.5 mmol, 0.45 g in 20 ml of 1.5 N HCl) was added with constant stirring to a hot ethanolic solution of the respective ligand (5.0 mmol, 0.63 g mpa, 0.70 g mph in 30 ml 95% alcohol) at water-bath temperature. The resulting mixture (pH ~ 3) was heated at water-bath temperature for about 10 min during which time the desired compounds precipitated out. These were filtered off, washed well with water and alcohol and finally dried over anhydrous calcium chloride.

(ii) $PdX_2 \cdot 2L$ (X = Br, SCN, NO_3, ClO_4)

Aqueous solution (15 ml) of the potassium/sodium salt of the appropriate anion, e.g., KBr, KSCN, $NaNO_3$, $NaClO_4$ (in slignt excess of 5.0 mmol)

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TABLE I. Some Important Physico-chemical Properties of the Compounds[a]

Complex[b]	Λ_m in 10^{-3} M DMF solution (mho cm^2/mol)	Reflectance spectral data (kK) (ϵ in cases DMF medium)	Characteristic IR data (cm^{-1})			
			ν_{Pd-L}	ν_{Pd-X}	Anion frequencies	
$PdCl_2 \cdot 2mpa$ (yellow)	14.6	24.15br; 28.90; 33.33sh 37.17 (5150)	315(ms)[e]	360(s)		
$PdBr_2 \cdot 2mpa$ (deep yellow)	18.3	23.81br; 28.17 37.59 (5070)	310(ms)	280(ms)		
$PdI_2 \cdot 2mpa$ (deep brown)	22.9	21.50; 24.39ssh; 28.17ssh 37.31(3520)	300(ms)	220(ms)		
$Pd(SCN)_2 \cdot 2mpa$ (orange)	59.1[c]	22.90br; 28.01sh; 33.90wsh 37.45 (5130)	310(w); 300(ms);	335(ms); 315(w); 275(ssh);	2160(vs), 2115(ms) 780(ssh), 760(ms) 435(wb), 420(ms)	ν_{CN} ν_{CS} δ_{NCS}
$Pd(NO_3)_2 \cdot 2mpa$ light yellow	22.0	24.69br; 28.57ssh	300(w)	265(w) Pd–O–NO_2	1770(ssh) ($\nu_2 + \nu_5$) 1210(s) (ν_4) 1060(s) (ν_2) 820(s) (ν_6)	in C_{2V} symmetry
$Pd(ClO_4)_2 \cdot 2mpa$ light yellow	41.7	24.10br; 28.57; 33.90wsh 37.18(5680)	305(w)	290(ssh) Pd–O–	1120(ms) 1100(ssh) (ν_3) 1050(s) 960(w) (ν_1)	in C_{3V} symmetry
$PdCl_2 \cdot 2mph$ (yellow)	21.8	24.69; 26.31sh; 27.77ssh 36.63sh(2707); 37.18(3608)	450(s)[f]	360(s)		
$Pd(SCN)_2 \cdot 2mph$ (reddish brown)	85.2 92.6[d]	20.84; 25.31; 26.81sh 33.31(2015)	450(ms) 290(w)	325(w) 280(ssh)	2125(vs); 2090(s) 775(ms); 720(ms) 480(ssh), 420(w)	ν_{CN} ν_{CS} δ_{NCS}
$Pd(NO_3)_2 \cdot 2mph$ (pale yellow)	36.4	24.69; 27.03sh 36.50sh(15630); 37.18(18500)	445(ms) 305(ssh)	265(w) Pd–O–NO_2	1265(ssh) (ν_1) 1035(ms) (ν_2) 825(ms) (ν_6)	in C_{2V} symmetry
$Pd(ClO_4)_2 \cdot 2mph$ (cream)	37.7	26.31br 36.50(4411); 37.31(2863)	440(wb) 300(ssh)		1095(s) (ν_3) 620(ms)((ν_4)	in T_d symmetry
$PdBr_2 \cdot mph$ (deep yellow)	22.2	25.97br; 28.98wsh 33.31(2010)	445(wb) 440(sh) 310(ssh) 300(w)	280(ssh) 270(ws)		
$PdI_2 \cdot mph$ (brown)	25.9	37.31(2736)	450(wb) 440(ssh) 300(w) 290(w)	230(ms) 215(ms)		

[a] mpa = one molecule of 5(3)-methylpyrazole-3(5)-carboxamide; mph = one molecule of 5(3)-methylpyrazole-3(5) carbohydrazide. [b] C, H. N and metal analyses conform well to the formulations and data are with the senior author. [c] Λ_m in DMF after heating over waterbath for 10 min. [d] Λ_m in methanol. [e] Metal ring nitrogen frequency. [f] Metal nitrogen frequency due to hydrazinic tail.

was instantaneously added to a mixture containing aqueous solution of Pd(II) chloride and alcoholic solution of the ligand. The resulting solution was then heated at water bath temperature with constant stirring for about 15 min and then cooled to room temperature (25–30 °C) when the desired compounds with different shades of color came down as microcrystalline species. The compounds were collected as before. A mono-species $PdBr_2 \cdot mph$ (Table I) was obtained unexpectedly from the above general reaction. The thiocyanato derivative of mph initially produced, on heating for a longer time (~1 h) went into solution which on cooling yielded the desired reddish brown crystals of composition, $Pd(SCN)_2 \cdot 2mph$ (Table I).

(iii) $PdI_2 \cdot mpa$ and $PdI_2 \cdot mph$

The dichloro bis-compound of Pd(II) with mpa was heated with KI solution over waterbath for about 30 min while brown diiodobis-compound resulted. Similar treatment with bis-mph compound afforded the mono-variety of the type $PdI_2 \cdot mph$.

The palladium contents in the complexes were determined as palladium dimethyl glyoximate in the usual way. The carbon, hydrogen and nitrogen analyses were done microanalytically. Other physicochemical measurements were carried out as reported earlier [5].

Results and Discussion

The analytical data found unequivocally support the empirical compositions of the reported Pd(II) complexes. All the compounds, except $Pd(SCN)_2 \cdot 2mph$, are highly insoluble in water, low molecular weight alcohols and in other organic solvents like acetone, benzene, chloroform, nitromethane, acetonitrile etc.; these are, however, appreciably soluble in donor solvents like DMF and DMSO. The conductance values of the complexes in DMF (Table I) generally fall in the range 15–40 mho cm^2 which is much lower than that expected for the uni-univalent electrolyte. The $Pd(SCN)_2 \cdot 2pma$ is difficultly soluble in DMF; the DMF solution on heating on waterbath for about half an hour afforded a deep red solution which gave a comparatively higher Λ_m value (60 mho cm^2). It is pertinent to note that the Λ_m value of this species increases with the increased dilution reaching a maximum value of 120 mho cm^2 at 0.3×10^{-3} M concentration. The corresponding thiocyanato complex of mph is fairly soluble in both methanol and DMF and Λ_m values in both these solvents point out to the (1:1) electrolytic nature of the species.

The amide ligand, mpa, is characterised by its characteristic IR bands at 1670(s), 1420(ms), 660(s) and 560(wb) cm^{-1} which are assigned as $\nu_{as}(OCN)$, $\nu_s(OCN)$ in plane $>C=O$ deformation and out of plane $>C=O$ deformation vibrations respectively of the amide component of the ligand. In the spectra of the Pd(II) complexes these bands are found virtually stationary which points out for the non-involvement of the amide grouping in complexation. The pyrazole ring deformation vibrations on the other hand, experience positive shifts in the complexes suggesting the participation of the pyrazolyl nitrogen; this has been further substantiated by far IR data (discussed later). This observation is in fine agreement with those of the earlier workers with heterocyclic acid amide complexes of palladium(II) and platinum(II) [8–10]. The observed positive shift in some cases at 1420 cm^{-1} may be due to overlap contribution of pyrazole ring bending vibrations as these are expected to go up on coordination through its heteronitrogen [8, 9, 11]. The new bands in the range of ~300 cm^{-1} in the complexes in FIR region are assigned to $\nu_{Pd-N(ring)}$ vibrations [6, 12] and the bands at ~360 cm^{-1} (s), ~280 cm^{-1} (ms) and ~220 cm^{-1} (ms) in the chloro-, bromo- and iodo-complexes are attributable to the respective ν_{Pd-X} [13]. The characteristic anion frequencies of NO_3^- and ClO_4^- in the concerned complexes show them to be present in the unidentate (C_{2v} and C_{3v}, respectively) forms [14]. The thiocyanato complex shows bands representative of S-bonded and bridging thiocyanate species as expected for soft metal ions [15].

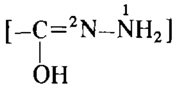
The reflectance spectra of the mpa complexes are characterised by broad bands around 21.5–24.5 kK, often attended with prominent shoulders, which can safely be assigned to respective transitions of $^1A_{1g} \rightarrow {}^1A_{2g}$, $^1B_{1g}$ and $^1E_{1g}$ type [16]. The respective ligand field parameters have been calculated [17] by resolving the observed bands through Gaussian analyses; the Δ_1 values (24 100–27 000 cm^{-1}) have always been found to be greater than the summation of the concerned Δ_2(3100–5600 cm^{-1}) and Δ_3 (2800–4100 cm^{-1}) values which tentatively suggest a square planar environment around palladium(II) ion in the complexes [18]. Following the average environment rule the Δ_1 values of the present halide complexes were found to be in almost intermediate between those of $[PdN_4]^{2+}$ and $[PdX_4]^{2-}$ species [18, 19]. This points to the nature of $d_{x^2-y^2}$ orbitals of the metal atoms in the complexes to be more anti-bonding than in $[PdX_4]^{2-}$ species and less anti-bonding than those in $[PdN_4]^{2+}$ species [16]. From the Δ_1 values the halide complexes were further found to exhibit the following spectro-chemical series Cl > Br > SCN > I. This is fairly consistent with the S-bonded thiocyanate formulation as reported by Meek *et al.* [20]. The respective values decrease in the order: SCN ⩾ Cl > Br > I, which indicates the instability order of d_{z^2} orbitals in the complexes compared to their respective d_{xz} and d_{yz} orbitals [16]. The solution spectral bands are obviously of CT type involving both $M \rightarrow L_\pi$ and $L_\pi \rightarrow M$ bonds. The greater intensity of CT bands have perhaps obscured the d–d transitions in the visible range of the spectra. The Λ_m values in DMF are much lower than the uni-univalent electrolyte values in the said solvent. This may be due to the partial solvolysis phenomenon as outlined below (Scheme 1):

$$[Pd(mpa)_2X_2] \xrightleftharpoons{DMF} [Pd(mpa)_2(DMF)X]^+ + X^-$$

Scheme 1.

The thiocyanato complex is, however, deemed to be a 5-coordinate one, at least in the solid state, emerging through bridging SCN group which breaks up during warming up with DMF to the monomeric form and thus accounts for the poor solubility even in donor solvents under ordinary condition. The appearance of IR bands at 335(ms), 315(w) and 275(ssh) cm^{-1} in the complex confirms the presence of S-bonded and bridging thiocyanato group [15] in the same.

In the palladium(II) complexes of mph new IR bands are found in the range of ~1570 cm^{-1}, ~1350 cm^{-1} and ~1060 cm^{-1} which may be assignable to ν'(OCN), ν''(OCN) and ν(C–O–) respectively [21, 22] confirm the participation of the hydrazide residue of the ligand molecule through its amide nitrogen (N^2) in its imidol form



$$[-\underset{\text{OH}}{\underset{|}{\text{C}}}={}^2\text{N}-\overset{1}{\text{N}}\text{H}_2]$$

The bands at 3μ region (appearing either at higher wave numbers than those in the uncomplexed ligand or remaining virtually stationary) along with NH$_2$-deformation vibrations indicate the non-involvement of N^1-atom in complexation. The observed positive shifts in the pyrazole ring vibrations, however, definitely illustrate the involvement of the ring system in coordination. The new bands appearing in FIR region at ~300 cm^{-1} and ~450 cm^{-1} may safely be assigned to $\nu_{\text{Pd-N(pz)}}$ [12] and $\nu_{\text{Pd-N(hydrazinic tail)}}$ [23] respectively. The appearance of the band at 360(s) cm^{-1} in the chloro compound is assigned to $\nu_{\text{Pd-Cl}}$ [13], while the bands at 280(ssh), 270(ms) cm^{-1} and 230(ms), 215(ms) cm^{-1} may be attributable to the respective $\nu_{\text{Pd-Br}}$ and $\nu_{\text{Pd-I}}$ (both A$_1$ and B$_1$ types [23] in the respective compounds. The characteristic anion frequencies of NO_3^- and ClO_4^- in the compounds indicate the unidentate (C_{2v}) and ionic (T_d) form [14] respectively. The thiocyanato species, however, yields IR frequencies characteristic of the presence of both N-bonded and S-bonded thiocyanate groups in the same compound [24]. The most noticeable observation for this complex is, perhaps, the appearance of a strong specific band at 1670 cm^{-1} (in addition to the said ν'(OCN), ν''(OCN and ν(C–O–) frequencies) which may be detectable to the hydrogen bond free undisturbed >C=O frequency (amide-I) of one of the participating ligand molecules. This is substantiated from the IR spectrum of the ligand molecule, mph, taken in acetonitrile medium where the amide I band appeared at 1670 cm^{-1} (in place of 1640 cm^{-1} in the hydrogen bonded solid state) indicating the total rupture of the hydrogen bonding in the said medium [6]. Thus, the thiocyanato complex in all probability belongs to a five coordinate environment where one of the interacting ligand molecules is believed to function as a monodentate one operating through the pyrazole ring nitrogen atom while the rest one behaves as the generalised (N,N) bidentate one. The reflectance spectral data further favour the above proposition exhibiting bands around *ca.* 21–28 kK, which are so far defined as the characteristics of penta-coordinate palladium(II) complexes [25]. The expected four coordinate species of the bis-perchlorate variety afforded broad reflectance spectral band at ~26 kK while the principal bands in bis-chloro and nitrato complexes appeared at much lower energy side, *ca.* 24.7 kK. This hypsochromic shift in band energy may be compatible with their possible tetragonal structures involving weak association of the anions. The Λ_m values for these seemingly six coordinate species are much less than the uni-univalent electrolyte value in DMF. This may be interpreted in the light of the dissociation of the bis-chelate species into the monochelate one and the subsequent equilibrium of bis- and the solvated mono-varieties in the medium [26].

$$[\text{Pd(mph)}_2\text{X}_2] \underset{}{\overset{\text{DMF}}{\rightleftharpoons}} \text{mph} + [\text{Pd(mph)X}_2] \overset{\text{DMF}}{\rightleftharpoons} [\text{Pd(mph)(DMF)X}]^+ + \text{X}^-$$

Scheme 2.

This is further substantiated through their respective electronic spectral bands in the said medium. The lower Λ_m value for ClO_4^- derivative is, however, reconcilable in terms of ion-pairing [26] originating from hydrogen bonding of the anions with the nonparticipating amino groups of the hydrazinic tail of the ligand molecules in the compound.

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