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Spectroscopic and Biological Characterization of the Palladium(II) and Platinum(II) Complexes with Benzoxazole and 2-Methylbenzoxazole

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Complexes of the type ML_2X_2 (where M = Pd(II), Pt(II); L = benzoxazole (BO), 2-methylbenzoxazole (MeBO); X = Cl, Br, I, NO_3, SCN) have been prepared and characterized by spectroscopic methods and conductivity measurements. The two ligands act as monodentate; the benzoxazole behaves as N-bonded, the 2-methylbenzoxazole as O-bonded. The compounds are non electrolytes and generally trans-*square planar with exception of* cis-*square planar $Pt(BO)_2X_2$ (X = Cl, Br), $Pt(MeBO)_2Cl_2$ and $Pd(MeBO)_2X_2$ (X = Cl, Br, NO_3).*

The biological activity of some compounds was also investigated.

Introduction

In previous papers we have reported palladium(II) and platinum(II) complexes with heterocyclic ligands of biological and pharmacological interest, such as isoxazole and 3,5-dimethylisoxazole [1], 2,5-diphenyloxazole and 2,5-dimethylbenzoxazole [2] where these ligands act generally as monodentate N-bonded and sometimes as bidentate N,O-bonded.

This paper presents our results with benzoxazole (BO) and 2-methylbenzoxazole (MeBO). These ligands are of importance in medicine and in biological systems.

The aims of this work are: *i*) to study the coordination behaviour of these ligands with two potential donor atoms, nitrogen and oxygen, and to gain information on the stereochemistry of the complexes; ii) to test the inhibitory activity on the Ca, Mg dependent ATP-ase.

Results and Discussion

The complexes obtained, together with the analytical data and the other physical properties, are reported in Table I. The most important I.R. data are listed in Table II while the electronic reflectance spectra and the Δ_1 values are shown in Table III. In Table IV are shown the inhibitory activities of some complexes with respect to Ca, Mg dependent ATP-ase.

The complexes are powder-like or microcrystalline, diamagnetic, generally soluble in dimethylformamide(DMF) and dimethylsulfoxide(DMSO); little soluble or insoluble in other organic solvents. The molar conductivity values suggest that these complexes are not conductors in DMF.

In the far I.R. region (Table II) the spectra of the ML_2X_2 complexes show generally a M–X band in the expected range for terminal halides in *trans*-square planar stereochemistry [3]. Only the spectra of the $Pt(BO)_2X_2$ (X = Cl, Br), $Pt(MeBO)_2Cl_2$ and $Pd(MeBO)_2X_2$ (X = Cl, Br, NO_3) derivatives are indicative of *cis*-square planar in C_{2v} stereochemistry involving terminal halides [4].

The reflectance electronic spectra are indicative of a square planar geometry [5]. The bands in the 26300–21750 cm^{-1} range could be assigned to the ν_1 transition. $^1A_{1g} \rightarrow {}^1B_{1g}$. In the U.V. region there are strong absorptions in the 37000–30000 cm^{-1} range that may be due to a charge transfer band

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TABLE I. Analytical and Physical Data.

Compound	Dec. Point °C	Found (Calcd) %			Λ_M[a] (DMF) ($cm^2\ \Omega^{-1}\ mol^{-1}$)
		C	H	N	
$Pd(BO)_2Cl_2$	245–261	40.9(40.4)	2.7(2.4)	6.6 (6.7)	16
$Pd(BO)_2Br_2$	257–269	33.4(33.3)	2.1(2.0)	5.5 (5.5)	22
$Pd(BO)_2I_2$	150–170	28.3(28.0)	1.7(1.7)	4.7 (4.7)	0
$Pd(BO)_2(NO_3)_2$	160–180	36.2(35.8)	2.3(2.2)	11.3(11.9)	36
$Pd(BO)_2(SCN)_2$	141	41.5(41.6)	2.2(2.2)	12.2(12.2)	0
$Pt(BO)_2Cl_2$	230–250	33.5(33.5)	2.0(2.0)	5.6 (5.5)	0
$Pt(BO)_2Br_2$	>300	28.4(28.3)	1.8(1.7)	4.7 (4.7)	0
$Pt(BO)_2I_2$	180–220	24.2(24.4)	1.5(1.5)	3.9 (4.1)	0
$Pd(MeBO)_2Cl_2$	208–230	43.6(43.3)	3.4(3.2)	6.4 (6.3)	0
$Pd(MeBO)_2Br_2$	>300	35.6(36.0)	2.9(2.6)	5.3 (5.3)	0
$Pd(MeBO)_2I_2$	140–170	30.6(30.6)	2.2(2.2)	4.4 (4.4)	0
$Pd(MeBO)_2(NO_3)_2$	240–260	38.1(38.6)	2.9(2.8)	11.1(11.2)	35
$Pd(MeBO)_2(SCN)_2$	203	44.5(44.2)	2.8(2.8)	11.4(11.4)	0
$Pt(MeBO)_2Cl_2$	>300	36.1(36.1)	2.6(2.6)	5.4 (5.3)	0
$Pt(MeBO)_2Br_2$	264–270	30.9(31.0)	2.6(2.3)	4.6 (4.5)	0
$Pt(MeBO)_2I_2$	195–219	26.8(26.9)	2.0(2.0)	3.9 (3.9)	0
$Pt(MeBO)_2(SCN)_2$	210–217	37.0(37.4)	2.4(2.4)	9.8 (9.7)	0

[a]The reference values, under the same conditions, are: 65–90 for 1:1 electrolytes.

TABLE II. The Most Important Bands in the Far Infrared Spectra (400–100 cm^{-1}).

Compound	ν(M–X)	ν(M–L)
$Pd(BO)_2Cl_2$	324vs	250s
$Pd(BO)_2Br_2$	279w,br	249m
$Pd(BO)_2I_2$	168m	249s
$Pd(BO)_2(NO_3)_2$	383s,br	235m
$Pd(BO)_2(SCN)_2$	297vs,br	237s
$Pt(BO)_2Cl_2$	341vs, 333vs	237m, 228m
$Pt(BO)_2Br_2$	249s, 243s	235m, 222m
$Pt(BO)_2I_2$	175m	207s
$Pd(MeBO)_2Cl_2$	336vs,br	317vs,br; 306vs
$Pd(MeBO)_2Br_2$	270vs,br	315vs,br; 308s
$Pd(MeBO)_2I_2$	168m	320s
$Pd(MeBO)_2(NO_3)_2$	389vs,br	340vs, 331vs
$Pd(MeBO)_2(SCN)_2$	293vs	312m
$Pt(MeBO)_2Cl_2$	338vs,br; 331vs,br	311m, 306m
$Pt(MeBO)_2Br_2$	242sh, 237s	310m, 303s
$Pt(MeBO)_2I_2$	170mw	299vs
$Pt(MeBO)_2(SCN)_2$	292m	304m

TABLE III. Electronic Reflectance Spectra (d–d bands and Δ_1 Values cm^{-1}).

Compound	$\nu_1 = {}^1A_{1g} \rightarrow {}^1B_{1g}$	Δ_1
$Pd(BO)_2Cl_2$	25000	27100
$Pd(BO)_2Br_2$	23600	25700
$Pd(BO)_2I_2$	21750	23850
$Pd(BO)_2(NO_3)_2$	23800	25900
$Pd(BO)_2(SCN)_2$	24100	26200
$Pt(BO)_2Cl_2$	24250	26350
$Pt(BO)_2Br_2$	23500	25600
$Pt(BO)_2I_2$	22200	24300
$Pd(MeBO)_2Cl_2$	25000	27100
$Pd(MeBO)_2Br_2$	23500	25600
$Pd(MeBO)_2I_2$	23550	25650
$Pd(MeBO)_2(NO_3)_2$	23800	25900
$Pd(MeBO)_2(SCN)_2$	24300	26400
$Pt(MeBO)_2Cl_2$	26300	28400
$Pt(MeBO)_2Br_2$	24300	26400
$Pt(MeBO)_2I_2$	22750	24850
$Pt(MeBO)_2(SCN)_2$	25200	27300

TABLE IV. Inhibitory Activity of Some Pd(II), Pt(II) Complexes.

Compound	Inhibitory activity (±2)%		Solvent
	10^{-4} *M*	10^{-3} *M*	
$Pd(MeBO)_2Cl_2$	20	–	C_2H_5OH
$Pd(MeBO)_2Br_2$	16	–	$CHCl_3$
$Pd(BO)_2Br_2$	16	–	$CHCl_3$
$Pt(MeBO)_2Cl_2$	0	12	H_2O (hot)
$Pt(MeBO)_2Br_2$	0	7	H_2O (hot)

L → M. By assuming a value of $F_2 = 10F_4 = 600$ cm^{-1} for the Slater Condon interelectronic repulsion parameters [6], it is possible to derive from the first spin-allowed transition d–d the value $\Delta_1 = \nu_1 + 3.5\ F_2$. These values lie in the 28400–24850 cm^{-1} range.

BO Complexes

In the far I.R. region the spectra of the $Pt(BO)_2X_2$ (X = Cl, Br) complexes show two Pt–X bands whose position and multiplicity are indicative of *cis*-square planar compounds in C_{2v} stereochemistry [4].

Other complexes present a ν(M–X) vibration that is diagnostic of terminal halides for *trans*-square planar compounds in D_{2h} stereochemistry [3].

The $Pd(BO)_2(NO_3)_2$ shows in the near I.R. spectrum bands characteristic of unidentate nitro groups [7] (ν_1 = 1315s, ν_2 = 1040m, ν_4 = 1478s, ν_5 = 718m. $\nu_2 + \nu_3$ = 1780wbr cm^{-1}). The strong band at 383 cm^{-1} can be assigned to a palladium–oxygen stretching mode involving the oxygen atom of the nitrate group [8].

In the $Pd(BO)_2(SCN)_2$ complex the ν(CS) = 710 cm^{-1} is typical of S-bonded thiocyanate; this fact is supported by the ν(CN) = 2120 cm^{-1} and the δ(NCS) = 422 cm^{-1} [9]. The band at 297 cm^{-1} can be assigned to the palladium–sulphur stretching mode involving the sulphur atom of the SCN group [10].

The BO ligand acts always as monodentate N-bonded. The medium or strong band present in the palladium and platinum compounds in the 250–207 cm^{-1} range may be attributed to ν(M–N) vibrations in accordance with the literature data [11]. The $Pt(BO)_2X_2$ (X = Cl, Br) show two M–N bands (237, 238 and 235, 222 cm^{-1}); this fact together with the two metal–halogen stretching frequencies confirms a *cis*-square planar stereochemistry for these compounds.

MeBO Complexes

The 2-methylbenzoxazole behaves in a different way with respect to the benzoxazole. In all complexes the bands in the 340–299 cm^{-1} range arising from metal–oxygen vibrations indicate that the ligand is oxygen bonded in palladium and platinum complexes [8, 12]. The far I.R. spectrum of $Pt(MeBO)_2Cl_2$ shows two bands that are assigned to ν(Pt–Cl) terminal metal–halogen stretching in C_{2v} *cis*-square planar stereochemistry [4].

The near I.R. spectrum of the $Pd(MeBO)_2(NO_3)_2$ is indicative of unidentate nitrate groups (ν_1 = 1340m, ν_2 = 1050ms, ν_4 = 1510vs, ν_5 = 710m, $\nu_2 + \nu_3$ = 1780w cm^{-1}) [7]. In the far I.R. region the stretching vibration at 389 cm^{-1} has been assigned to $\nu(Pd–ONO_2)$ [8], and there are also present strong bands at 340 and 331 cm^{-1} of vibrational stretching due to ν(Pd–O) of the ligand. From this fact we assume that the $Pd(MeBO)_2(NO_3)_2$ has a *cis*-square planar C_{2v} stereochemistry.

In the $Pd(MeBO)_2Cl_2$ and $Pd(MeBO)_2Br_2$ far I.R. spectra are present two Pd–O bands and also a broad ν(Pd–X) stretching, probably not well resolved; we have therefore assumed that these complexes are also *cis*-square planar.

All other compounds present a strong band in the range expected for the M–X terminal stretching vibration for D_{2h} *trans*-square planar complexes [3].

The $Pd(MeBO)_2(SCN)_2$ derivative shows the ν(CS) band at 745 cm^{-1}, diagnostic of the S-bonded thiocyanate group; this fact is supported by the ν(CN) and δ(NCS) frequencies respectively at 2120 and 432 cm^{-1} [13]. Furthermore the band in the far I.R. region at 293 cm^{-1} can be assigned to the palladium–sulphur stretching mode of the thiocyanate anion [10]. The $Pt(MeBO)_2(SCN)_2$ present bands at 2120 ν(CN) and at 418 δ(NCS) [13]. This fact together with the band at 292 cm^{-1} [10] assigned to Pt–S stretching indicates that the thiocyanate groups are S-bonded.

Inhibitory Activity

In a previous paper we studied the inhibitory activity of the $M(L)_2X_2$ complexes (M = Pd(II), Pt(II); X = Cl, Br; L = isox and its methyl and/or phenyl derivatives) on the membrane bonded ATP-ase. The results show that the Pd(II) complexes have a greater effect than the Pt(II) derivatives, except to the $Pt(4\text{-ADI})_2Cl_2$ (4-ADI is 4-amino-3,5-dimethyl-isoxazole) where this activity drops probably due to the presence of hydrogen bonds. The chloride compounds have higher activity with respect to the bromide derivatives because of the higher lability of the chloride in comparison with the bromide ions [14].

We have extended this research to the monomeric $Pd(ox)(L)_n$ (n = 2 for L = N-PropIm, NEtIm and N-MeIm where ox = oxalate and Im = imidazole) and to the dimeric $Pd(ox)(L)$ (L = isox, 3,5-diMeisox, 2MeBO and 2,5-diMeBO, where isox = isoxazole and

BO = benzoxazole). In this case for the $Pd(ox)(L)_2$ derivatives the inhibitory activity decreases in the order N-PropIm, N-EtIm, N-MeIm for the major length of the ligand chain, which increases the solubility of the enzyme in the lipidic part.

For the Pd(ox)(L) compounds this effect increases with the steric hindrance of the heterocyclic ligand and is generally higher than in the $Pd(ox)(L)_2$ derivatives due to the presence of the bridging ligand with weak bonds which are easily replaced by water molecules and by the sulphur ion of the thiol group of the enzyme [15].

The inhibitory activity with respect to the Ca-Mg dependent ATP-ase of the $M(L)_2X_2$ complexes (M = Pd(II), Pt(II), L = BO and MeBO) soluble in water or in C_2H_5OH or in $CHCl_3$, shows that this effect for the Pd(II) complexes is greater than for the Pt(II) derivatives.

The chloride compounds have as usual a greater effect with respect to the bromides due to the greater lability of the first in comparison with the second ion. The introduction of a methyl group in the 2 position of the BO ring seems not to modify the inhibitory effect of the Pd(II) complexes.

With regard to the inhibitory mechanism, it seems, as shown in the preceding papers, that the irreversible interaction of the complexes on the ferment occurs with the sulphur anion of the thiol groups of the enzyme which replaces the ligands in the square planar complexes. It is probable also that there is an interaction with the $-NH_2$ of the tryptophan, the other active centre of the ATP-ase.

Conclusions

The benzoxazole ligand with two potential donor atoms, oxygen and nitrogen, acts as monodentate N-bonded according to previously reported data [13].

The introduction of a methyl group in the 2 position in the benzoxazole does not modify the inhibitory activity of the complexes, but modifies the coordination mode of this ligand. In fact the 2-methylbenzoxazole binds in our compounds through the oxygen atom because the oxygen is more electronegative and basic than the nitrogen due to the inductive effect of the methyl group in the 2 position [2].

Experimental

The BO (EGA-Chemie purum) and the MeBO (Fluka 98%) ligands were used without further purification.

Starting Materials

$Pd(NO_3)_2$, $PdCl_2$, $PtCl_2$ and K_2PtCl_4 are commercially available. MX_2 (M = Pd. Pd; X = Br, I) and $Pt(SCN)_2$ were prepared according to the literature methods.

Preparation of the Complexes

The BO and MeBO compounds were obtained by refluxing for about 6 hr the metal salts and the ligands in excess as solvent or in methanolic solution with the ligand in the required stoichiometric ratio. The complexes were purified by means of repeated washings with petroleum ether and dried over P_4O_{10}.

Analyses

Carbon, hydrogen and nitrogen were determined using a Perkin-Elmer 240 elemental analyser.

Infrared Measurements

The I.R. spectra were recorded in the 4000–100 cm^{-1} range with a Perkin Elmer 180 spectrophotometer. The spectra in the 4000–400 cm^{-1} range were measured for KBr discs in nujol mulls. The far I.R. spectra were measured between polyethylene sheets; atmospheric water was removed from the spectrophotometer housing by flushing with nitrogen.

Electronic Spectra

The electronic spectra in the solid state were recorded with a Shimadzu MPS-5 OL spectrophotometer in the range 40000–15000 cm^{-1}.

Conductivity Measurements

These measurements were carried out using a WTW LBR conductivity bridge at 25 °C for 10^{-3} *M* solution in DMF.

Biological Activity

The extraction method of the sarcoplasmatic reticulum (SR) containing Ca, Mg dependent ATP-ase, the ferment activity and the SH groups determination by amperometric titrations were previously published [14]. The complex insoluble in water is dissolved in a becker in chloroform or in ethylic alcohol. When the solvent evaporates completely we add an aqueous solution of ATP-ase that reacts with the film of the complex in the internal wall of the becker.

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