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Structure-antitumour activity relationship for the Pt^{2+}, Pd^{2+}, Pd^{4+}, Os^{4+} complexes and complex salts with sulphonamide derivatives

by

A. DOADRIO *, D. CRACIUNESCU **+, C. GHIRVU **

Resumen

En el presente trabajo se presenta la síntesis y el estudio preliminar I. R., de los complejos $Pd(L)_2X_2$; (X = Cl⁻, Br⁻); $Pt(L)_2B_{R_2}$; $\{PdX_4\}(LH)_2$ (X = Cl⁻, Br⁻); $\{PdX_6\}(LH)_2$ (X = Cl⁻, Br⁻) y $\{OsX_6\}(LH)_2$ (X = Cl⁻, Br⁻). En todos estos complejos y sales complejas se ha trabajado con los siguientes ligandos (L): sulfanilamida, sulfametazina, sulfamerazina, sulfadiazina, sulfapiridina, sulfaquinoxalina, sulfacetamida.

Las propiedades antitumorales de estos nuevos complejos (ensayados sobre las ratas portadoras de tumores L1210, P388 y ascíticos S-180) han sido estudiadas en relación con los resultados de los cálculos O. M. Huckel obtenidos para las moléculas de las sulfamidas (L).

Summary

The synthesis and I. R. spectra for the $Pt(L)_2X_2$ (X = Cl⁻, Br⁻), $Pd(L)_2X_2$ (X = Cl⁻, Br⁻), $\{PdX_4\}(LH)_2$ (X = Cl⁻, Br⁻), $\{PdX_6\}(LH)_2$ (X = Cl⁻, Br⁻) and $\{OsX_6\}(LH)_2$ (X = Cl⁻, Br⁻) complexes and complex salts were described at first. In those new compounds, L = sulphonamide derivatives (e. g. Sulphanilamide; Sulphamethazine; Sulphamerazine; Sulphadiazine; Sulphapyridine; Sulphaquinoxaline; Sulphacetamide).

The antitumour properties of those new componds (assayed against mices bearing the established L1210, P388 and S-180 tumours) were studied in connection with the results of the M. O. Huckel's diagrams, performed on the sulphonamides molecules.

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* Department of Inorganic & Analytical Chemistry, Faculty of Pharmacy Madrid, University, Madrid-8, Spain.

** Department of Physical Chemistry, Faculty of Chemistry & Chemical Engineering. «Institutul Politchnic Iasi», Iasi, Romania.

+ Author to whom all the correspondence should be addressed.

I. Introduction

The discovery that cis-dichlorodiamineplatinum (II), is an effective anti-tumor drug, has spurred a large research effort to obtain additional coordination complexes of the VIII group metals, which would be active against a broad spectrum of tumour systems and exhibit minimal dose-limiting size effects (1, 2). This research effort has resulted in the synthesis of many anlogues of cis-Pt $(NH)_3Cl_2$ and some $\{Pt\ Cl_6\}^{2-}$ complex salts, as well as of some Rh^{3+} complexes that show promising activity at favorable therapeutic dosages (3-8).

Low toxicities and marginal or moderate antitumour activities were assigned to the cis-Pt^{2+} complexes and to the Pt^{4+} complex salts with sulphonamide derivatives (6). Neverthless, some Pt^{4+} and Os^{4+} complex salts with thiazole derivatives provided excellent inhibition of the Ehrlich ascitic tumours (9). In addition $\{Pt\ Cl_6\}^{2}$ and $\{Os\ Cl_6\}^{2}$ complex salts with piperazine derivatives provided also promising T/C (%) values (against mices bearing L1210 and Ehrlich asatic tumours) as well as interesting radioprotective properties (7, 9). According, to Dehand, Jordanov and Craciunescu, potential antitumour complexes of the VIII group metals can be synthetized with such ligands as N, S, containing heterocycles (e. g. Benzothiazole and Sulphamide derivatives) (6, 7, 9-12).

In this paper we describe the following complexes and complex salts, formed by the VIII group metals with sulphonamide derivatives (L)*:

$Pt(L)_2X_2$ ($X = Br^-, Cl^-$); $Pd(L)_2X_2$ ($X = Cl^-, Br^-$); $(Pd\ X_4)(LH)_2$ ($X = Cl^-$, Br^-), $(Pd\ X_6)(LH)_2$ ($X = Cl^-, Br^-$) and $(Os\ X_6)(LH)_2$ ($X = Cl^-, Br^-$).

II. Experimental part

1. *Synthesis of the* $Pt(L)_2X_2$ ($X = Br^-, Cl^-$); *and* $Pd(L)_2X_2$ ($X = Cl^-, Br^-$) *complexes where* (L = *sulphonamide derivatives*)

The synthesis of those neutral complexes was performed at pH = 6-7 (in water) by the reaction between $K_2(Pt\ X_4)$; $K_2(Pd\ X_4)$ ($X = Cl^-, Br^-$) dissolved in water, with the corresponding amount of the ligands (L), dissolved in 400-500 cm^3 hot water. (Pt^{2+}: L = = 1:2; Pd^{2+}: L = 1:2).

* The following sulphonamide derivatives were employed: Sulphanilamide; Sulphamethazine; Sulphamerazine; Sulphadiazine; Sulphapyridine; Sulphaquinoxoline; Sulphacetamide (L).

Concentration of the reaction's mixture (at 80-100 °C), under vigorous stirring, allow the precipitation of the complexes as amorphous powders. $Pt(L)_2X_2$; $Pd(L)_2X_2$; complexes were filtered on a G_3 sinter glass and washed repeateadly with hot water, ethanol and ether. The brown dark coloured complexes were kept in a vacuum dessicator over $CaCl_2$. They are stables at light & air exposure, and partially solubles in DMSO, and DMF. The neutral complexes are less solubles in water and the most common solvents.

2. *Synthesis of the* $(Pd\ X_4)(LH)_2$, $(Pd\ X_6)(LH)_2$ *and* $(Os\ X_6)(LH)_2$ ($X = Cl^-, Br^-$, L = *Sulphonamide derivatives*) *complex salts.*

$(Pd\ X_4)(LH)_2$; $(Pd\ X_6)(LH)_2$; $(Os\ X_6)(LH)_2$ complex salts were obtained, respectively by the reaction of the $(NH_4)_2(Pd\ X_4)$; $(NH_4)_2(Pd\ X_6)$ $(NH_4)_2(Os\ X_6)$ ($X = Cl^-, Br^-$) dissolved in 50 % HX-water 1:1 mixture ($X = Cl^-, Br^-$) with the corresponding amount of sulphonamide derivatives disolved in a 1:1 mixture water — HX (50 %; $X = Cl^-, Br^-$).

We employed always 1:2 steochiometries (Pd^{2+}: L = 1:2; Pd^{4+}: L = 1:2; Os^{4+}: L = 1:2).

Concentration of the reaction's mixture, till reached 1/3-1/5 of it's original volume, under vigourrous stirring, allow the precipitation of the complex salts as microcrystalline powders.

The complex salts (brown dark coloured in the case of the Pd^{2+}, Pd^{4+} and red coloured in the case of the Os^{4+}) were filtered on a G_3 sinter glass and washed with 1 N HX ($X = Cl^-, Br^-$), ethanol and ether. They were kept in a vacuum dessicator over $CaCl_2$. The complex salts formed by the $(Pd\ Cl_4)^{2-}$; $(Pd\ Cl_6)^{2-}$; $(Os\ Cl_6)^{2-}$; $(Pd\ Br_4)^{2-}$; $(Pt\ Br_4)^{2-}$; $(Os\ Br_4)^{2-}$ anions are stables at air & light exposure. Neverthless, we obtained $(Os\ Cl_6)^{2-}$ and $(Os\ Br_6)^{2-}$ complex salts only with sulphacetamide. $(NH_4)_2(Os\ Cl_6)$ and $(NH_4)_2(Os\ Br_6)$ did not react (under different temperatures) with the others sulphonamides.

All those complex salts of the Pd^{2+}, Pd^{4+}, Os^{4+} are solubles in DMSO, DMF and partially solubles in hot water. They are almost insolubles in water and the most commun solvents.

Cis Pt^{2+} and cis Pd^{2+} complexes were obtained by the classical procedure (1-3).

3. *Analysis of the new complexes and complex salts.* **

Pt content was found by the calcination of the samples at 950 °C and subsequent weighting as metal.

N %, S % were found by microcombustion and Cl^-, Br^- content as AgCl, AgBr, respectively. The samples were destroyed with $HCl - HNO_3$ (3:1) mixture, and their Pd^{2+}, Pd^{4+} and Os^{4+} content analyzed gravimetrically with dimethylglioxime (Pd^{2+}, Pd^{4+}) and with thioureea (Os^{4+}).

The results of the chemical analysis stroungly support our formulations as $Pt(L)_2X_2$ ($X = Br^-$), $Pd(L)_2X_2$ ($X = Cl^-$, Br^-) $(PdX_4)(LH)_2$: $(PdX_4)(LH)_2$; $(OsX_6)(LH)_2$ ($X = Cl^-$, Br^-).

4. *I. R. Spectra*

I. R. spectra for the new compounds were registered with a Perkin Elmer 457 I. R. spectrophotometer (4.000-250 cm^{-1}) in KBr or KCl pellets.

Spectra of the solid ligands were also registered in KBr pellets.

5. *Antitumour assay*

Antitumour assay of the new complexes and complex salts were done on mices bearing the established L1210 and P388 tumours. Those assays (see Table I) were performed at the «National Cancer Institute» (U. S. A.).

Some of the complexes were assayed also against mices bearing ascitic S-180 tumours, at the «Michigan State University» (USA).

The new complexes were administered intraperitoneally (i. p.) as DMSO solutions or as saline suspensions. Alternatively, the new compounds were administered subcoutaneously, as suspensions in «arachis oil».

Criteria for the antitumour activity was T/C (%) parameter ***.

** All those chemical analysis were done at the Tel Aviv University, Tel-Aviv (Israel).

*** Ratio of the T (survival's time for the «Treated» animals) and C (survival's time for the «Control» animals). T/C > 100 indicated antitumour activity.

TABLE I

The results of the antitumor assay for the new complexes and complex salts formed by sulphonamides derivatives.

Complexe	Vehicle	Tumour	Dosis (mg/kg)	T/C (%)
cis-Pt (Sulfanilamide)$_2$Br$_2$	DMSO	L1210	400	114
	Saline	»	»	104
	«oil»	»	»	120
» » »	DMSO	P388	»	120
	»	S-180	»	121
cis-Pt (Sulphapyridine)$_2$Br$_2$	DMSO	L1210	400	112
	Saline	»	»	103
	«oil»	»	»	118
» » »	DMSO	P388	»	120
	»	S-180	»	122
cis-Pt (Sulphaquinoxaline)$_2$Br$_2$	DMSO	L1210	400	114
	»	»	200	108
	»	»	100	102
trans-Pt (Suphadiazine)$_2$Cl$_2$	Saline	P388	400	Inactive
	»	»	200	Inactive
	»	»	100	Inactive
» » »	DMSO	»	400	Inactive
cis-Pd (Sulphacetamide)$_2$Cl$_2$	Saline	P388	400	106
	»	»	200	104
	»	»	100	Inactive
» » »	DMSO	»	»	120
cis-Pd (Sulphanilamide)$_2$Br$_2$	DMSO	P388	400	116
	»	L1210	400	105
	»	»	200	Inactive
» » »	Saline	L1210	»	Inactive
cis-Pd (Sulphapyridine)$_2$Br$_2$	DMSO	P388	400	117
	»	»	200	120
	»	»	100	118

TABLE I (continuation)

Complexe	Vehicle	Tumour	Dosis (mg/kg)	T/C (%)
» » »	DMSO	L1210	400	104
cis-Pd (Sulphaquinoxaline)$_2$Br$_2$	DMSO	P388	400	115
	»	»	200	122
	»	»	100	116
» » »	»	L1210	400	104
cis-Pd (Sulphamethazine)$_2$Br$_2$	DMSO	L1210	400	106
	»	»	200	Inactive
	»	»	100	»
» » »	Saline	»	»	Inactive
cis-Pd (Sulphamerazine)$_2$Br$_2$	Saline	L1210	400	102
	»	»	200	Inactive
	»	»	»	Inactive
» » »	DMSO	P388	»	118
Trans-Pd (Sulphadiazine)$_2$Br$_2$	Saline	L1210	400	Inactive
	»	»	200	»
	»	»	100	»
» » »	DMSO	»	400	»
cis-Pd (Sulphacetamide)$_2$Br$_2$	Saline	L1210	400	104
	»	»	200	Inactive
	»	»	100	Inactive
» » »	DMSO	P388	400	112
(PdCl$_4$) H$_2$ (Sulphanilamide)$_2$	Saline	L1210	400	106
	»	»	200	104
	»	»	100	102
» » »	»	P388	200	108

TABLE I (continuation)

Complexe	Vehicle	Tumour	Dosis (mg/kg)	T/C (%)
(PdCl$_4$) H$_2$ (Sulphapyridine)$_2$	Saline	P388	400	107
	»	»	200	104
	»	»	»	102
» » »	»	L1210	400	Inactive
(PdCl$_4$) H$_2$ (Sulphaquinoxaline)$_2$	Saline	L1210	400	106
	»	»	200	104
	»	»	100	102
» » »	»	P388	200	110
(PdCl$_4$) H$_2$ (Sulphamethazine)$_2$	DMSO	L1210	400	110
	»	»	200	Inactive
	»	»	100	Inactive
» » »	»	P388	400	119
(PdCl$_4$) H$_2$ (Sulphamerazine)$_2$	Saline	P388	400	108
	DMSO	»	»	120
	«oil»	»	200	120
» » »	Saline	L1210	400	102
(PdCl$_6$) H$_2$ (Sulphaquinoxaline)$_2$	DMSO	L1210	400	106
	»	»	200	102
	»	»	100	Inactive
» » »	DMSO	P388	400	110
	»	S-180	400	111
(PdCl$_6$) H$_2$ (Sulphamethazine)$_2$	Saline	L1210	400	106
	»	L1210	200	102
	»	L1210	100	104
» » »	»	P388	400	108
	»	»	200	105

TABLE I (continuation)

Complexe	Vehicle	Tumour	Dosis (mg/kg)	T/C (%)
$(PdCl_6)\ H_2$ (Sulphamerazine)$_2$	»	L1210	400	102
	»	L1210	200	Inactive
	»	L1210	100	»
» » »	»	»		»
	DMSO	L1210	440	109
$(PdCl_6)\ H_2$ (Sulphadiazine)$_2$	DMSO	L1210	400	106
	»	»	200	Inactive
	»	»	100	Inactive
» » »	»	P388	100	115
	»	»	200	Inactive
$(PdCl_6)\ H_2$ (Sulphacetamide)$_2$	»	»	100	Inactive
	»	»	50	»
$(PdBr_6)\ H_2$ (Sulphamilamide)$_2$	DMSO	P388	400	106
	»	L1210	200	Inactive
	Saline	»	400	Inactive
» » »	»	»	200	»
	»	»	100	»
$(PdBr_6)\ H_2$ (Sulphapyridine)$_2$	DMSO	S-180	400	106
$(PdBr_6)\ H_2$ (Sulphaquinoxaline)$_2$	»	»	200	Inactive
$(PdBr_6)\ H_2$ (Sulphamethazine)$_2$	»	L1210	400	105
$(PdBr_6)\ H_2$ (Sulphamerazine)$_2$	Saline	L1210	400	Inactive
$(OsBr_6)\ H_2$ (Sulphacetamide)$_2$	«oil»	P388	400	108
	»	S-180	»	108
	»	L1210	»	Inactive

6. *M. O. Huckel's calculations for the ligand's molecules.*

M. O. Huckel's diagrams for the sulphonamide derivatives were recently calculated by us (8) thus providing informations about the most probables «donor» sites at the ligand's molecules (see Table II). We employed the parameters as indicated in other of our papers (9).

TABLE II

The results of the M. O. Huckel's calculations performed on the sulphonamides molecules.

Sulphanamide's derivatives	Q_N ($-NH_2$)	Q_O ($-SO_2$)	Q_N (—NH—) or —NHR—	Q_N (> N heterocyclic atom)
Sulphanilamide.....	1,9484	1,6816	1,9612	—
Sulphamethazine.....	1,9828	1,6798	1,9079	1,2306
Sulphamerazine.....	1 9484	1,6800	1,9106	1,1091
Sulphadiazine	1,9484	1,6800	1,9106	1,1091
Sulphapyrinine	1,9762	1,6800	1,9106	1,1091
Sulphaquinoxaline.....	1.9484	1,6798	1,9080	1,043 1,0583
Sulphacetamide.....	1,9484	1,6778	1,8701	—

III. RESULTS AND DISCUSSION

It seems that the reaction between $(NH_4)_2$ (Pt Br_4); $(NH_4)_2$ (Pd Cl_4) and $(NH_4)_2$ (Pd Br_4), in water (pH = 6-7), with the sulphonamides, produced *cis* o *trans* complexes Pt $(L)_2$ Br_2; Pd $(L)_2$ Cl_2 and Pd $(L)_2$ Br_2.

According to the study of the I. R. spectra of the neutral Pt^{2+} and Pd^{2+} complexes, we assigned the *cis* or the *trans* structures. For the *cis* Pt $(L)_2$ Cl_2 complexes, two bands were observed at the far I. R. region (310 cm^{-1} and 300 cm^{-1}) and were assigned to the ν_{asym} Pt-Cl and ν_{sym} Pt-Cl vibrations according to our precedent results and to the Blumenthal and Razumowsky's papers (6-7, 13).

For the trans-Pt $(L)_2Cl_2$ complexes a single and relative sharp band was observed at 310-280 cm^{-1} range, thus accounting for the higher simmetry of the *trans*-isomers.

Tentative structures (*cis* or trans) were assigned for the $Pt(L)_2Br_2$ and $Pd(L)_2Br_2$ complexes, since ν Pt-Br and ν Pd-Br bands were placed out of the register of our I. R. apparatus, by analogy with the structures assigned to the $Pt(L)_2Cl_2$ and $Pd(L)_2Br_2$ (6-7) complexes.

Coordination of the sulphonamides occurs, generally, through $-NH_2$ exocyclic group placed at the para position of the benzenic ring.

The $-NH^-$, O = S = O, as well as the tertiary nytrogen atoms (> N :) were not involved at the coordinate process.

In fact, the ν_{assym} (SO_2) band is displaced towards highest wave numbers (10-25 cm^{-1}) from its position in the pure ligands (1.325, 1.165-1.160 cm^{-1}).

The ν NH wave numbers of the aromatic aminogroup of the sulphonamides are displaced by 110-200 cm^{-1} comparing with the free ligands; this displacements was observed by. Shafransky and Fusu (14-15) in the spec ra of the dioximato complexes of Co^{3+} with sulphamides (p-NH_2 $C_6H_4SO_2N$ $(C_2H)_5$) and aromatic amines (p-NH_2 C_6H_4R) in which the bands with the metal can be formed only by the nytrogen atom of the free $-NH_2$ group.

ν_{SN} band were not shifted afted the coordination of the ligands (1.325-1.340 cm^{-1}).

In the case of those sulphonamide derivatives ($_2HN-C_6H_4-SO_2-NHR$), the donors atoms of the $-SO_2-NHR$ group do not take part in the establishment of the coordinative bonds, since, according to Shafransky (14-15), we observed very small magnitude of the changes in the ν (NH), ν SO_2 and ν SN bands for the sulphonamide's radical ($-SO_2-NHR$) on complex formation.

No coordination of the sulphonamides having aromatic substitute (R), (e. g. sulphamerazine, sulphamethazine, sulphapyridine, sulphaquinoxaline and sulphadiazine) thorough the tertiary nytrogen atoms (> N :) were observed, since the ν C = N bands presented no shifts towards littlest wave numbers or were shifted towards highest wave numbers after complex formation.

This behaviour of the sulphonamides towards Pt^{2+}, and Pd^{2+} ions can be accepted if we think that, according to the results of the M. O. Huckel's calculations (see table II), the highest π electronic charges were always placed on the $-NH_2$ exocyclic groups of the ligands. Minor π electronic changes were placed on the $-SO_2-$, $-NH-$, and on the tertiary nytrogen atoms belonging to the heterocyclic moieties (R) of the ligands ($_2HN-C_6H_4-SO_2-NHR$).

Thus, taking into consideration the results of the chemical analysis, of our preliminary I. R. study and of the O. M. Huckel's calculations we may conclude that those sulphonamide derivatives coordinated towards Pt^{2+} and Pd^{2+} ions, exclusively through the

$-NH_2$ exocyclic group placed at the *para* position of the benzenic ring, and presented the same monodentate behaviour as pointed out by Shafransky and Fusu (14-15).

The disscusion of the I. R. spectra of the complex salts formed by sulphonamides with the $(Pd\,X_4)^{2-}$, $(Pd\,X_6)^{2-}$ and $(Os\,X_6)^{2-}$ (X = Cl^-, Br^-) anions was less effective, since the ν $\overset{+}{N}H_3$ sym, ν $\overset{+}{N}H_3$ assym and, probably, ν $-\overset{+}{N}H_2$ vibrations were not no cleary separated. But thinking to the general behaviour of the sulphonamides, to the results of the chemical analysis and, later, to the results of the M. O. Huckel's diagrams we may adventurate that also in this case the sulphonamides coordinated through the $-NH_2$ exociclic groups, exclusively ****.

Tetrachloropalladates (IV) presented a sharp and intensive ν Pd — Cl band at the range of the 300-330 cm^{-1}; ν Pd — Cl vibrations were also placed at the same range of the far I. R. for the tetrachloropalladites (II).

ν Os — Cl vibrations (for the complex salts formed by $(Os\,Cl_6)^{2-}$ anions with sulphacetamide, were placed at 280 cm^{-1} ranges.

ν Pt — Br, ν Os — Br, and ν Pd — Br vibrations falled out of the recorder of our I. R. spectrophotometer.

The results of the antitumour assays, performed on the mices bearing the established L1210 and P388 tumours (see table I), indicated the following general features:

1) The complexes are more actives against P388 tumours, than against L1210 tumours. Trans neutral complexes were inactives.

2) The disscussion of the antitumour action against ascitic S-180 tumours was limited by the fact that only part of those new compounds were assayed against this tumour line.

There is a close relationship between the activity against P388 and ascitic S-180 tumours, at least for the few complexes that were tested against S-180 tumour system.

3) Better results were observed when the complexes were administrated as suspensions in «arachis oil», than in the case in which they were administered i. p. in DMSO or saline suspensions.

4) *cis*-$Pt(L)_2Br_2$ complexes were most active, against the three tumours lines, comparing with the *cis*-$Pd(L)_2Cl_2$ and *cis*-$Pd(L)_2Br_2$ complexes.

5) The complex salts formed by the $(Pd\,X_4)^{2-}$, and $(Pd\,X_6)^{2-}$ (X = Cl^-, Br^-) presented similar T/C (%) range values, for the same dosis. $(Os\,X_6)^{2-}$ (X = Cl^-, Br^-) complex salts were less

**** An I. R. detailed analysis of the complex salts will be continuted at those Laboratories and subsequently published.

actives comparing with the $(Pd\ X_4)^{2-}$ and $(Pd\ X_6)^{2-}$ complex salts.

6) All the complex salts which were described in this paper, presented a lower or moderate range of the T/C (%) values, comparing with the cis-Pt $(L)_2Cl_2$ complexes and with Pd $(L)_2Cl_2$ complexes but not with *cis*-Pd $(L)_2Br_2$ complexes.

7) It seems that the substitutions of the R moities with heterocyclic rings (e. g. the case of the sulphamerazine, sulphamethazine, sulphaquinoxoline, sulphapyridine and sulphadiazine) leeds to the lowest T/C values ; but this observations does not keep any regularity with the sequence in which Q_{-NH_2}, Q_{-NH^-}, $Q_{\geq N}$ values decreases or increases.

Future assay of those complexes and complex salts, against plasma tumours (especially PC6/ADJ tumours) may be of great interest according with the previous observations of Connors (16) and Craciunescu (7).

8) It seems that the complex salts of the Pd^{4+} are less active than the corresponding Pd^{2+} complex salts. This observation also applay when $X = Cl^-$ and $X = Br^-$ {$(Pd\ X_4)^{2-}$ and $(Pd\ X_6)^{2-}$ anions}. $(Pd\ Br_6)^{2-}$ containing complex salts were quite inactives.

9) Bromocomplexes were, generally less active than the corresponding chlorocomplexes (cis-Pd $(L)_2X_2$).

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