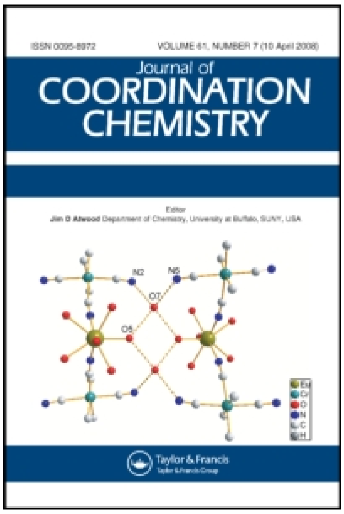

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METAL ION COORDINATION BY THE ANTIBIOTIC CYCLOSERINE. COMPLEXES OF PALLADIUM (II), PLATINUM (II) AND COPPER (II)

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METAL ION COORDINATION BY THE ANTIBIOTIC CYCLOSERINE. COMPLEXES OF PALLADIUM (II), PLATINUM (II) AND COPPER (II).

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We describe the interaction of cycloserine (Ccs), 4-amino-3-isoxazolidone, with the metal ions palladium(II), platinum(II) and copper(II). A series of complexes of general formula $M(Ccs)_nX_2$ (M = Pd and Pt, X = Cl, n = 2; M = Pd and Pt, X = Br and I, n = 3; M = Cu, X = Cl and Br, n = 2) have been prepared and characterized by chemical analysis, infrared and electronic spectra, conductivity data, magnetic susceptibility measurements and isotope exchange (deuteration) experiments. The position and multiplicity of the metal-halide stretching frequencies are discussed and used as a guide to the stereochemistry. The most convincing structural evidence for the complexes is a square-planar stereochemistry for the 1:2 derivatives with terminal ligands and terminal halides, while for the 1:3 complexes we could suggest an octahedral dimeric structure with terminal ligands and both bridging and terminal halides. The assignments for the metal-ligand and metal-halides stretching modes have been made. We have never observed a metal induced ring opening under the present experimental conditions.

INTRODUCTION

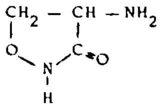
The antibiotics are known to interact with metal ions and this interaction is clearly of a complex nature. The belief that the antibiotic action of the tetracyclines is related to the ability of these compounds to form complexes with metal ions has stimulated a great deal of investigations on the complexing properties of the tetracyclines as ligands.[1–8] Complexes in the metal:ligand molar ratios 1:1 and 1:2 have been obtained depending on the pH value; the former type occurs at lower pH values, while the latter tends to occur at pH values higher than six.[1]

It has been observed that copper(II) promotes the hydrolysis of the β-lactam ring in penicillins, whereas in presence of magnesium(II), cobalt(II) and manganese(II) the hydrolysis occurs at the same rate as for the penicillin alone.[9–12] As for the influence of the side chain upon the rate of hydrolysis in presence of metal ions has been observed that a nitrogen substituent in 6 position increased markedly the rate of hydrolysis in presence of copper(II).[13] This fact seems to suggest that the nitrogen substituent is involved in a transitory complex before to ring opening.

The cycloserine has wide application in the pharmaceutical industry and is a drug commonly used in clinical therapeutics being a broad-spectrum antibiotic, inhibitory for Mycobacterium tubercolosis, Escherichia coli, Staphylococcus aureus and other microorganisms belonging to the psittacosis-lymphogranuloma group. However relatively little is known on the behaviour of this molecule as ligand towards metal ions.

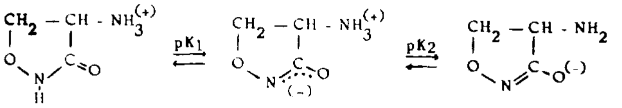
The most important factor in stimulating our interest in the study of the coordination properties of cycloserine as ligand towards palladium(II) and platinum(II) has been the fact that the complexes of group VIII metals have been reported to have considerable antibacterial power; in addition platinum complexes induce lysis in lysogenic bacteria.[14–17] We hope that the study of the stereochemistries and the chemical reactivity of its coordination compounds will help to determine what relationship exists between chemical structure and biological activity of this drug. Furthermore it is well known that the metal complexes of ligands which have biological activity are more active than the free ligands;[18,19] the use of the drug as metal complex instead of the free molecule could represent a better route of administration associated with a small risk of toxic reactions and could be a good sustained-release pharmaceutical preparation.

We report in this study the preparation and characterization of palladium(II), platinum(II) and copper(II) halide complexes with 4-amino-3-isox-



azolidone commercially known as cycloserine and hereafter abbreviated *Ccs*.

Potentiometric titrations ($pK_1 = 4.4$ and $pK_2 = 7.4$) indicate that cycloserine exists in aqueous solution as a dipolar ion[20-22] according to the proposed equilibrium:



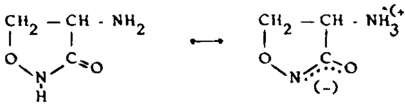
It is interesting to examine the competitiveness in the coordinating ability of the different donor atoms of this ligand having exocyclic nitrogen and oxygen atoms and the nitrogen and the oxygen heteroatoms of the ring acting as donor centres.

RESULTS AND DISCUSSION

The complexes obtained are listed in Table I, together with their analytical data and other physical properties. They have been characterized through elemental analyses, conductivity measurements, electronic spectroscopy and infrared spectra in the range 4000–35 cm^{-1}, Tables II and III. The compounds are powder-like or microcrystalline, diamagnetic the palladium(II) and platinum(II) complexes and paramagnetic with a $\mu_{eff.}$ value corresponding to one unpaired electron the copper(II) derivatives, soluble in N,N′-dimethylformamide (DMF) and acetonitrile. The molar conductances suggest that these complexes are non-conducting in DMF, Λ_M lying below 30 ohm^{-1} cm^{2}mole^{-1}, indicating the covalent nature of the compounds and the absence of ionic species in solution.

Infrared Spectral Studies

The infrared spectrum of the free ligand in the range 4000–600 cm^{-1} could be interpreted on the basis of previously reported data[20,21,23] regarding the cycloserine, its silver salt $C_3H_5N_2O_2Ag$ and the parent ring 3-isoxazolidinone. The infrared absorption spectrum, in the solid state, of the cycloserine is characteristic of a zwitter-ion involved in the equilibrium:



The medium or medium-strong bands present at 3310 cm^{-1}, at 3180 cm^{-1}, at 3090 cm^{-1} and at 3040 cm^{-1} can be attributed to the prevailing contribution of the NH, NH_2 and NH_3^+ groups vibrational modes. The band at 3090 cm^{-1} is almost certainly due to the asymmetric NH_3^+ stretching mode, while the corresponding symmetric frequency is probably amongst the broad bands found between 2800 and 2190 cm^{-1}.[24] The bands at 1585 cm^{-1}, 1338 cm^{-1}, 1140 cm^{-1}, 1112 cm^{-1}, 1010 cm^{-1}, 977 cm^{-1} and 832 cm^{-1} are related to the above reported groups[21] and the first can be attributed to the NH_3^+ asymmetric deformation frequency.[24] To the symmetric deforming mode of the NH_3^+ group is assigned the band at 1338 cm^{-1}, while the rocking frequency is associated to the 832 cm^{-1} absorption; furthermore in the region 800–600 cm^{-1} the spectrum shows broad absorptions which are presumed to correspond to the external deformation mode of the NH_2 group.

TABLE I
Analytical data and other physical properties

Compounds	Colour	Found % C	H	N	Required % C	H	N	μ B.M.	Dec. point °C
$Pd(Ccs)_2Cl_2\cdot 2H_2O$	yellow	17.7	3.7	13.5	17.3	3.9	13.4	dia.	>350
$Pd(Ccs)_3Br_2\cdot H_2O$	yellow	18.6	3.5	14.3	18.3	3.4	14.2	dia.	>350
$Pd(Ccs)_3I_2$	pale brown	15.9	2.7	12.4	16.2	2.7	12.6	dia.	>350
$Pt(Ccs)_2Cl_2$	pale yellow	15.5	2.6	12.0	15.3	2.6	11.9	dia.	250–255
$Pt(Ccs)_3Br_2\cdot 3H_2O$	orange-yellow	14.8	2.9	11.5	15.1	3.4	11.7	dia.	310–315
$Pt(Ccs)_3I_2$	orange	14.3	2.5	11.3	14.3	2.4	11.1	dia.	>350
$Cu(Ccs)_2Cl_2\cdot 2H_2O$	green	18.9	3.7	14.9	19.2	4.3	14.9	2.1	155–160
$Cu(Ccs)_2Br_2\cdot 2H_2O$	green	15.2	3.4	12.0	15.5	3.5	12.1	2.0	186–191

TABLE II

Most important infrared bands (4000–800 cm^{-1})

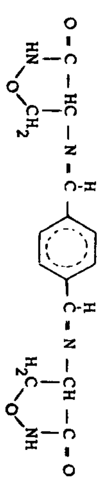
Compounds	$\nu(NH_2)$	$\nu(NH)$	$\nu_{as}(NH_3^+)$	$\nu_{sym}(NH_3^+)$	$\delta(NH_2)$	$\nu(C{=}O)$	$\delta_{as}(NH_3^+)$	$\delta_{sym}(NH_3^+)$	$\rho(NH_3^+)$	Other bands
Cycloserine	3310ms, 3040m	3180ms	3090m	2800–2190(broad)	–	1660vs	1585m	1338ms	832m	1140ms, 1112m, 1010m, 977m
Terizidone	–	3130m	–	–	–	1640vs	–	–	–	–
$Pd(Ccs)_2Cl_2 \cdot 2H_2O$	3420s, 3110vs	3210vs	–	–	1685sh	1595vs	–	–	–	1100m, 1080m, 1035m, 970vs
$Pd(Ccs)_3Br_2 \cdot H_2O$	3405s, 3100vs	3207vs	–	–	1665sh	1600vs	–	–	–	1100ms, 1075m, 1038m, 968vs
$Pd(Ccs)_3I_2$	3410s, 3115vs	3210vs	–	–	1670sh	1600vs	–	–	–	1105m, 1078m, 1036m, 970s
$Pt(Ccs)_2Cl_2$	3410s, 3080vs	3190vs	–	–	1660sh	1600vs	–	–	–	1100m, 1065m, 1040m, 970s
$Pt(Ccs)_3Br_2 \cdot 3H_2O$	3400s, 3100s	3210vs	–	–	1660sh	1598vs	–	–	–	1098ms, 1080m, 1035m, 967s
$Pt(Ccs)_3I_2$	3420s, 3070s	3200s	–	–	1660sh	1610vs	–	–	–	1105m, 1075m, 1045w, 975ms
$Cu(Ccs)_2Cl_2 \cdot 2H_2O$	3400s, 3140s	3220s	–	–	1650sh	1580vs	–	–	–	1105ms, –, 1020m, 950m
$Cu(Ccs)_2Br_2 \cdot 2H_2O$	3400s, 3130s	3230s	–	–	1655sh	1580vs	–	–	–	1095ms, –, 1042m, 950m

The very strong band present at 1660 cm^{-1} is to be due to the ν(C=O) vibrational mode.

On going from the free ligand spectrum to those of the complexes, Table II, we observe a spectral pattern completely, but significatively, different. The vibrational modes attributed to the stretchings of the amino and imino groups of the ligand are shifted towards higher wavenumbers. It is worthy of note the disappearance of the medium band at 3090 cm^{-1} and of the broad bands in the region 2800–2190 cm^{-1} due to the asymmetric and symmetric stretching modes of the NH_3^+ group; furthermore the asymmetric and symmetric deformation frequency and the rocking mode of the same group are not present in the spectra of the complexes, Table II.

The shoulder in the spectra of the complexes at some 1670 cm^{-1} can be attributed to the $\delta(NH_2)$ according to the general agreement that the NH_2 internal deformation mode occurs in this region.[24] In the free ligand spectrum this deformation was not observed being masked by the very strong ν(C=O) vibrational mode. Broad absorptions are still present, as in the free ligand spectrum, in the range 800–600 cm^{-1} and are due to the external deformation mode of the NH_2 group.

All the assignments of the free ligand bands have been made by comparing the spectrum of the cycloserine with that of the parent molecule Terizidone, N_4,N_4'-tereftal-bis-(cycloserine) or 1,4-bis-(3-oxy-4-isoxazolidinyliminomethyl)-benzene in which the



amino group is not present and as consequence the above reported equilibria are avoided. The comparative results, reported in Table II, allow us to an unequivocal assignment of the ν(C=O) and ν(NH) bands; in addition this molecule shows a strong band at 1705 cm^{-1} due to the ν(C=N) stretching mode.

The very strong bands present, in the spectra of the complexes, in the range 1610–1580 cm^{-1} can be attributed to the ν(C=O) vibrational mode; this band is shifted to lower energies on passing from the free ligand spectrum to those of the complexes by about 50–80 cm^{-1}.

These facts suggest that the donor site of the ligand is the oxygen atom of the carbonyl group; in fact the carbonyl stretching wavenumber is lowered at least by *ca.* 20 cm^{-1} whenever the oxygen atom is bonded to a metal.[25]

In addition these results have been confirmed by

TABLE III
Most important far-infrared bands (400–35 cm^{-1})

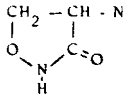
Compounds	ν(M–X)	ν(M–L)	Bending modes	Other bands
Cycloserine	–	–	–	396s, 334s, 299sh, 216ms
Pd(Ccs)$_2$Cl$_2$·2H$_2$O	327ms	256m	160vw, 134mw	390ms, 302sh, 214m
Pd(Ccs)$_3$Br$_2$·H$_2$O	245m$_t$, 174m$_b$	254m	96mw	390ms, 300sh, 222m
Pd(Ccs)$_3$I$_2$	176m$_t$, 146m$_b$	258m	92w, 86w	390m, 298sh, 214m
Pt(Ccs)$_2$Cl$_2$	315ms	255m	154mw, 123mw	402m, 303sh, 225m
Pt(Ccs)$_3$Br$_2$·3H$_2$O	239m$_t$, 171m$_b$	252m	118mw, 92mw	390m, 299sh, 210mw
Pt(Ccs)$_3$I$_2$	174m$_t$, 132ms$_b$	249m	90mw	392m, 301sh, 214m
Cu(Ccs)$_2$Cl$_2$·2H$_2$O	307ms	288m	–	388m, 301sh, 211m
Cu(Ccs)$_2$Br$_2$·2H$_2$O	228m	290m	–	386m, 300sh, 216m

t = terminal; b = bridging

isotope data on the free ligand and on the complexes. In the free deuterated ligand the vibrational modes attributed largely to the ND$_2$, ND and ND$_3^+$ are present as medium-strong bands at 2470 and 2305 cm^{-1}, at 2425 cm^{-1} and at 2330 cm^{-1} respectively. The $\delta_{\text{asym.}}$(ND$_3^+$) is located at 1100 cm^{-1}, while to the symmetric δ(ND$_3^+$) is assigned the band at 1050 cm^{-1}; the rocking ρ(ND$_3^+$) lies at 641 cm^{-1}. The stretching mode attributable to ν(C=O) is still present, as a very strong band, at 1660 cm^{-1}.

Passing to the deuterated complexes spectra we observe a spectral pattern significatively similar to that obtained for the non-deuterated derivatives as regards the behaviour of the bands related to the amino, imino and keto groups. The vibrational modes attributed to the stretchings of the ND$_2$ and ND groups of the ligand are shifted towards higher energies in the ranges 2590–2550 cm^{-1} and 2350–2340 cm^{-1} for the amino group and between 2440–2430 cm^{-1} for the imino group. The ν(C=O) mode lies, as a very strong band, in the range 1615–1580 cm^{-1}. It is worthy of note the disappearance in all the complexes of the bands due to the ND$_3^+$ group as already observed for the NH$_3^+$ group in the non-deuterated derivatives spectra.

According to the above reported results we could propose a coordination of the ligand through the oxygen atom of the carbonyl group with the ligand stabilized by the coordination in the form



In the far-infrared region, Table III, new halogen independent bands are present in the 258–249 cm^{-1} region for the palladium(II) and platinum(II) complexes and at some 290 cm^{-1} for the copper(II) ones; these stretching modes, absent in the spectra of the starting materials used in this study, can be assigned to metal-ligand vibrations involving the oxygen exocyclic atom of the ligand.[26–29] No bands are present in the range where ν(M–N) involving amino or imino groups usually lies for these metals.[27,30–32] The above conclusions are in accord with most of the observations on the previously reported complexes with similar ligands.

As for the metal-halide modes in the palladium and platinum chloroderivatives we observe a band at 327 cm^{-1} and 315 cm^{-1}, due to ν(Pd–Cl) and ν(Pt–Cl) respectively, whose position and multiplicity are indicative of *trans* square-planar D$_{2h}$ symmetry with terminal halides; as it is clear from Table III, these complexes show one ν(M–X) vibration (b$_{3u}$) and one ν(M–L) vibration (b$_{2u}$).

In the spectra of the palladium and platinum bromo- and iodo-derivatives with a 1:3 metal:ligand molar ratio the ν(M–X) absorption bands are present both for terminal and bridged halide atoms,[27] then we can propose a dimeric structure with bridging halogens for these complexes.

The medium-weak or weak absorption bands at 160 cm^{-1} and 134 cm^{-1}, at 96 cm^{-1} ,at 92 cm^{-1} and 86 cm^{-1} in the palladium chloro-, bromo- and iodo-derivatives respectively, and at 154 cm^{-1} and 123 cm^{-1}, at 118 cm^{-1} and 92 cm^{-1}, at 90 cm^{-1} in the corresponding derivatives of platinum, that can not be attributed to internal vibrations of the ligand being considerably shifted towards lower energies as the mass of the halogen increases, may be ascribed to bending modes, Table III.

In the copper derivatives, Table III, the bands at 307 cm^{-1} and 228 cm^{-1} in the chloro- and bromo-complex respectively are typical of ν(Cu–Cl) and ν(Cu–Br) for terminal halide atoms.[27,33]

The infrared results as regards ν(OH) and δ(HOH) for all the water containing complexes, clearly confirm the presence of water of crystallization; since vibrational modes such as wagging, twisting and rocking activated by coordination to the metal have not been found in the expected ranges,[34] it appears that coordinated water is not present.

Electronic Spectra

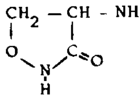
The solid state electronic spectra of the palladium and platinum chloroderivatives are indicative of a square-planar geometry. The bands at 21050 cm^{-1} and at 25100 cm^{-1} in the palladium and platinum derivative respectively may be assigned to the $^1A_{1g} \rightarrow {}^1B_{1g}$ d-d transition; by the standard treatment[29] we have obtained a Δ_1 value of 23150 and 27200 cm^{-1} for the two above complexes.

The electronic spectra of the remaining palladium and platinum complexes are significatively and markedly different: we note the disappearance of the d-d band found in the chloro-compounds. This should mean, according to the infrared results, a different arrangement of the ligands around the central atom in a different stereochemistry.

As for the copper(II) complexes, the solid state electronic spectra are similar to those reported for square-planar Cu(II) species. The band at 13650 cm^{-1} and 13750 cm^{-1} accompanied by a shoulder at 14900 cm^{-1} and 15050 cm^{-1} in the chloro- and bromo-derivative respectively are assigned to crystal-field transitions of copper(II) and are consistent with such a structure.[35]

CONCLUSIONS

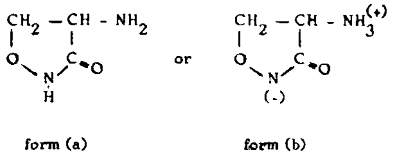
The complexes of cycloserine resulted always O-bonded with the ligand acting as monodentate only, in spite of the presence of four potential donor atoms in the ligand molecule. The coordination seems to stabilize the form



with the amino and carbonylic groups instead of the zwitter-ion form in which is present the NH_3^+ group.

The presence of a very strong ν(C=O) mode in the complexes, shifted towards lower energies in comparison to the free ligand spectrum, is indicative of a metal-ligand interaction through the oxygen of the C=O group.

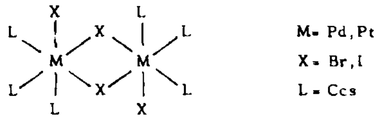
If the coordination stabilizes a keto-form, we have the possibilities represented by the following formalism:



The form (b) must be ruled out being clearly absent in the complexes the typical vibrational modes of the NH_3^+ group as confirmed too by deuteration experiments.

We can propose *trans* square-planar D_{2h} stereochemistries for the palladium and platinum chloroderivatives and for the copper complexes, with terminal halides and terminally bonded ligands. The square-planar environment of the copper complexes is confirmed by the far-infrared spectra and we can propose a *trans* geometry; in fact just one ν(Cu–X) and one ν(Cu–O) is present in the spectra of the complexes, while if the complexes were in a C_{2v} symmetry, *cis* planar or tetrahedral geometry, we should find two ν(Cu–X) and two ν(Cu–O), $a_1 + b_1$ and $a_1 + b_1$ if *cis* square-planar, or $a_1 + b_1$ and $a_1 + b_2$ if tetrahedral.

According to the infrared and electronic spectra, octahedral dimeric structures could be suggested for the 1:3 derivatives of palladium and platinum, with terminally bonded ligands and terminal and bridging halide atoms:



We can exclude a metal induced ring opening of the ligand, in fact in the infrared spectra of the complexes we have never observed the typical bands of the serine nor of the β-aminoxy-alanine methyl ester. The first product can be obtained upon acid hydrolysis of the ligand, accompanied by the formation of NH_2OH never present in our preparations, and the latter is produced upon treatment with methanolic hydrogen chloride.

Furthermore we can exclude the presence in the complexes of the dimer of the cycloserine, 2,5-bis-(aminoxymethyl)-3,6-diketopiperazine; in fact the cycloserine can be recovered, by chemical decomposition of the complexes, as white crystals with m.p. 154–155°C.

Repeated syntheses and elemental analyses gave reproducible results for the complexes reported in Table I, so we can exclude the formation of coordination compounds with ligands different from cycloserine, *i.e.* with its ring opening products. Furthermore these results allow us to exclude the possibility of a mixture of two (or more) types of complexes, because in every case the analyses should show different carbon, hydrogen and nitrogen content than any calculated, and reported in Table I, for the various ratios between metal and ligand.

EXPERIMENTAL

The cycloserine ligand, supplied by Fluka in high purity grade, was used without further purification.

Preparation of the Complexes

All the palladium(II) and platinum(II) complexes were obtained by reaction in aqueous solution, at room temperature or at *ca.* 40°C, between K_2MX_4 (M = Pd, Pt; X = Cl, Br, I) and the ligand in the molar ratios from 1:1 to 1:4. The copper derivatives were prepared by treating at room temperature an aqueous solution of the cycloserine with an aqueous solution of CuX_2 (X = Cl, Br) in the stoichiometrical ratios 1:1–1:4.

When the compounds did not separate out during the reactions, the precipitation of the complexes was induced by adding ethanol and diethyl ether. The compounds have been purified by means of repeated washing with water, ethanol and diethyl ether, then dried overnight over P_4O_{10}.

The yields for all the complexes are in the range 90–95 per cent.

Infrared Measurements

The i.r. spectra have been recorded in the range 4000–35 cm^{-1} with a Perkin-Elmer 180 spectrophotometer of the Instruments Centre of Modena University. The spectra in the range 4000–400 cm^{-1} were measured for KBr discs or nujol mulls. Far-i.r. spectra were measured for nujol mulls supported between polyethylene sheets. Atmospheric water was removed from the spectrophotometer housing by flushing with dry nitrogen.

Electronic Spectra

The electronic spectra have been recorded with a Shimadzu MPS-50L spectrophotometer in the solid state in the range 4000–27000 cm^{-1}.

Magnetic Susceptibility Measurements

These were carried out by Gouy's method at room temperature. Molecular susceptibilities were corrected for diamagnetism of the component atoms by use of the Pascal's constants.

Conductivity Measurements

These measurements were carried out with a WTW LBR conductivity bridge at 25°C for 10^{-3} M solutions in N,N'-dimethylformamide.

Analyses

Carbon, hydrogen and nitrogen have been determined with a Perkin-Elmer 240 elemental analyzer.

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