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Platinum(II) and Palladium(II) Complexes of Creatinine. Platinum Blues*

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Abstract

In recent years, great interest has been shown in platinum blues. This interest has been mainly focused on their potential antitumor activity and low nephrotoxicity compared with the anticancer drug cisplatin.

We now describe the synthesis of new crystalline platinum creatinine complexes and particularly their chromophore derivatives, the properties of which substantially enhance our understanding of this interesting class of compounds. Creatinine has been chosen as ligand because of its importance in clinical chemistry and its similarity to 2-pyrrolidone which is structurally characterized in platinum tans.

The intriguing colors observed in solution depend upon the anion present, and their stability with time at ambient temperatures has been a very important fact in facilitating this study by UV–Vis.

Introduction

Creatinine ($H_3C-\overline{N-C(NH)-NH-CO-CH_2}$) the level of which in serum and urine is a very sensitive index of renal function (Creatinine Clearance Test), is the final catabolic product of creatine. The latter is a physiological component in blood, brain and muscles and is important in the flow of energy in muscle tissue. Muralidharan and coworkers [1] have suggested that an understanding of the biological aspects of creatinine metabolism can be reached through the knowledge of metal–creatinine complexes. Creatinine has more than one bonding site towards metal ions and is capable of forming cationic, anionic and neutral metal complexes similar to those of adenine [2]. In this connection, only the crystal structures of creatininium tetrachlorocuprate(II) and bis(creatinine)silver(I) perchlorate have been investigated [3]. In this paper we report the preparation and crystal structure of the first complexes of Pd and Pt(II) with creatinine as neutral ligand.

In addition, the *cis*-form of diiododicreatinineplatinum is of considerable pharmacological interest as it is analogous to *cis*-dichlorodiammineplatinum (cisplatin) which is used as an antitumoral.

On the other hand, although the *trans*-isomers are inactive, hydrolysis of the *trans*-dichlorodicreatinineplatinum complex produces blue products for which also a potential antitumor activity is expected.

'Platinum blues' were first reported in 1975 but up to now only cisplatin α-pyridone [4], ethylenediamineplatinum α-pyridone [5] and cisplatin 1-methyluracil [6] blues have been fully characterized structurally. However, comparative studies hint that all the known blue compounds are multivalent, metal–metal bonded and amidate-bridged oligomers.

The standard procedure for the preparation of blue complexes arises from the reaction between the aquated products of cisplatin and uracil, thymine, uridine and other related pyrimidines. However, a second preparation procedure involves the reaction between tetrachloroplatinate(II) anion and primary amides or orotic acid. Following this latter method, we have also obtained blue solutions using creatinine as ligand.

Studies of the solutions of the platinum creatinine blues as a function of the anions, acidity and temperature suggest a possible explanation of the color changes to violet, green or yellow. Such an explanation concerns the different complexation sites of the creatinine, the study of which is a main aim of this work.

Experimental

Preparation

cis-Pt(Creat)$_2$I$_2$·3H$_2$O

The preparation was carried out in dim light, which seemed to minimize formation of dark iodoplatinum precipitates. A total of 415 mg (1 mmol) of K_2PtCl_4 was dissolved in 20 ml of water, and 4 g (about 24 mmol) of KI was added to yield a solution of 0.05 M PtI_4^{2-} and 1 M I^-. To this solution 226 mg (2 mmol) of creatinine was added. The *cis*-

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compound precipitated immediately and was filtered, washed with ethanol and dry diethyl ether, and dried under vacuum at room temperature.

trans-M(Creat)$_2$Cl$_2$·2H$_2$O (M = Pd, Pt)

The complexes were obtained by mixing in aqueous medium the free creatinine with $PdCl_2$·$2H_2O$ or K_2PtCl_4 in the respective stoichiometry 2/1.

trans-M(Creat)$_2$Cl$_2$·2HCl (M = Pd, Pt)

The HCl adducts were prepared by the method of Durig *et al.* [7]. An aqueous solution of creatinine (2 mmol) was added to an HCl solution of K_2MCl_4 M = Pd, Pt) (1 mmol) to produce crystals by slowly cooling the solution to room temperature. All the complexes undergo decomposition at a temperature range 260–280 °C. This is due to the melting of the creatinine ligand.

Platinum creatinine blues

These complexes were obtained by reaction of K_2PtCl_4 and creatinine (2:1) in the minimum amount of water or by hydrolysis of *trans*-Pt(Creat)$_2$-Cl_2·$2H_2O$. After preparation, the solutions were left in the dark for 1 h at 40 °C, gradual color changes being observed from green* to violet and simultaneous precipitation of a white slightly coloured powder. Redissolution of this solid in hot water gave new blue solutions.

The analyses of the solid compounds are not related to calculated data since the experimental results vary slightly from batch to batch. On the other hand, the nature of the complexes in solution remain questionable mainly because of the difficulty of their crystallization.

Chemical Analysis

The elemental analyses for C, H, N and X were performed according to standard microanalytical procedures.

Results and Discussion

Structures of trans-Pd(Creat)$_2$Cl$_2$·2H$_2$O and cis-Pt(Creat)$_2$I$_2$·3H$_2$O

The molecular structures of these complexes as determined by X-ray crystallography are shown in Figs. 1 and 2. The geometry at platinum and palladium is closely square-planar.

The complex *trans*-Pd(Creat)$_2$Cl$_2$·$2H_2O$ consists of monomeric units which are well separated from each other. There is an intermolecular hydrogen bonding system involving the water, the carbonyl and the exocyclic NH group of the ligands.

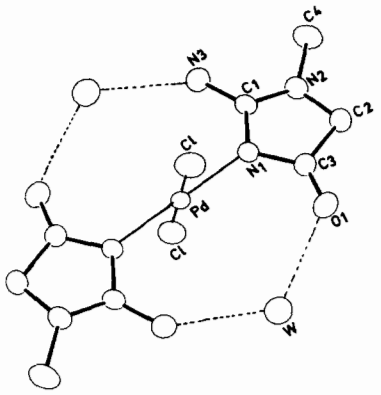


Fig. 1. *trans*-Pd(Creat)$_2$Cl$_2$·$2H_2O$

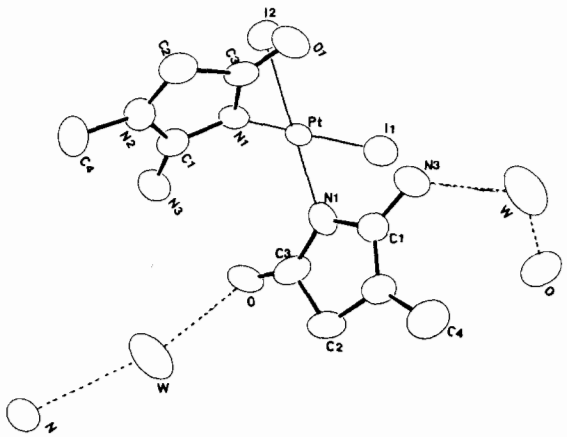


Fig. 2. *cis*-Pt(Creat)$_2$I$_2$·$3H_2O$

For *cis*-Pt(Creat)$_2$I$_2$·$3H_2O$ the hydrogen bonding also involves the same groups but the water is placed between neighboring monomeric units. In this instance, the above crystallographic data are particularly interesting since they show the occurrence of hydrogen bonding in the reported complexes in contrast to no evidence for this kind of bonding or strong intermolecular interactions in *cis*-Pt(*N*-methylimidazole)$_2$Cl$_2$ and *cis*- and *trans*-Pt(metronidazole)$_2$Cl$_2$ complexes.

The dihedral angles between the planes of the creatinine rings and the square-plane around the metal are almost the same as those found in *cis*-Pt(*N*-methylimidazole)$_2$Cl$_2$.

The structures are being refined and attempts to locate the hydrogen atoms are for the moment only partially successful.

*Green and red solutions were also obtained by reaction between the aquated products of cisplatin and creatinine.

TABLE I. Principal IR Spectral Data (cm^{-1})

	ν(CO)	ν(NH) (cyclic)	ν(M–S)	Other vibrations, M–ligand
Creatinine	1685	3270		
	ν(CO)	ν(NH)		
cis-Pt(Creat)$_2$I$_2$ •3H$_2$O	1704	3390	(213)	361, 347, 316
trans-Pt(Creat)$_2$Cl$_2$ •2H$_2$O	1702	3374	344	319, 255
trans-Pd(Creat)$_2$Cl$_2$ •2H$_2$O	1701	3388	356	298, 224, 212
	γ-lactam	ν(C=N$^+$)		
trans-Pt(Creat)$_2$Cl$_2$ •2HCl	1798, 1771, 1698	1672	329	262
trans-Pd(Creat)$_2$Cl$_2$ •2HCl	1799, 1771, 1697	1672	330	260

Structural Solvate Effects

IR Data

The effects of solvate formation on the structures of the complexes were studied by means of IR spectroscopy in the range 4000–2000 cm^{-1} (Table I)*. Only with M(Creat)$_2$Cl$_2$•2HCl do major changes occur (Fig. 3). For these complexes, the spectra show two strong bands at 1798 and 1771 cm^{-1} not identified in free creatinine and the M(Creat)$_2$Cl$_2$•2H$_2$O complexes. This feature is consistent with an alteration of the γ-lactam pattern of the creatinine when this ligand is coordinated to metal in the absence of the intermolecular hydrogen bonding present in H_2O adducts.

These changes are accompanied by a moderate shift of the M–Cl modes: 330 cm^{-1} (Pd) and 329 cm^{-1} (Pt) in the HCl adducts *vs. ca.* 356 cm^{-1} and 344 cm^{-1} in the respective aqueous adducts. In addition, the latter bands are the typical stretching vibrations of *trans*-dichloroplatinum (or palladium) species.

*IR spectra were recorded for solids in CsI and KBr pellets on a Perkin-Elmer 580 B spectrometer.

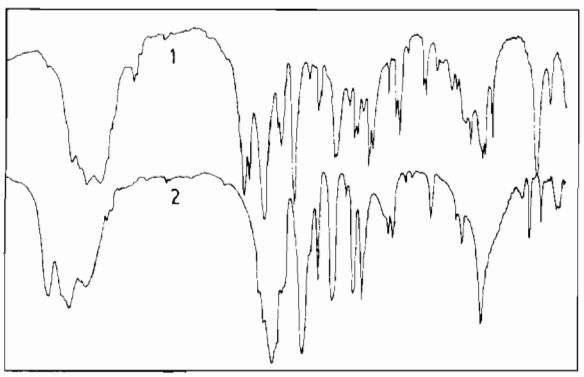


Fig. 3. IR spectra in CsI of: (1) *trans*-Pt(Creat)$_2$Cl$_2$•2HCl; (2) *trans*-Pd(Creat)$_2$Cl$_2$•2H$_2$O.

In the IR spectrum of the iodoplatinum complex with creatinine there are four bands at 361, 347, 316 and 213 cm^{-1}. The bands are due to the M–N and M–I vibrations, and must be assigned to a *cis*-configuration. This conclusion is supported by the results of the X ray structure determination.

Spectral Properties of the Creatinine Blues

UV spectra

In solutions of neutral complexes a withdrawal of electron density from the creatinine ring results in a hypsochromic shift in the longest wavelength $\pi-\pi^*$ electronic transition of creatinine: 232 nm to 228 nm. In platinum creatinine blues the 232 nm wavelength $\pi-\pi^*$ of creatinine is not appreciably modified by coordination to Pt(II). Only in the blue complexes does enhancement of the maximum suggest coordination.

Vis spectra

The visible spectrum of creatinine blue displays a broad transition centered at 586 nm. The blue solution changes to other colors as a result of the pH variations or by a number of oxidizing or reducing agents according to Scheme 1.

This suggests that the intense colors are related either to the simultaneous presence of Pt(II) and Pt(IV) ions or to a strong electronic delocalization along a number of platinum atoms, the variation of metal–metal distances being responsible for the variation in energy of the metal-to-metal charge-transfer

oxidants/acids/cold/darkness →

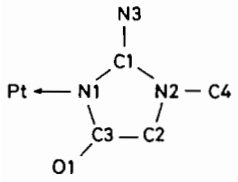
Violet	Blue	Green	Yellow
550 nm	586 nm	605 nm	

← reductants/bases/heat/light

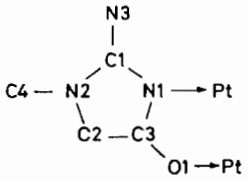
Scheme 1.

bands. Thus, green colors may indicate shorter Pt–Pt(IV) ions or to a strong electronic delocalization ones, although structural data are required before this correlation can be reliably extended [8, 9].

Nevertheless it is worth noting that for creatinine complexes there is an interconversion of the complexation sites going from the yellow to the blue complexes. While in the yellow complex only a creatinine coordination site to platinum via N(1) occurs (**I**), for the blue complex, the γ-lactam oxygen is involved in a chelating process together with the N(1) site (**II**).



I



II

Consequently, the γ-lactam O(1) complexation site should not be neglected when biological processes are studied. This site may be favoured by subtle factors leading to a stabilization of the blue species. For example, we have recently found that green solutions of platinum turn to blue within 2 min of irradiation with sunshine in a tetrafluoroboric acid medium.

Blue solutions obtained from tetrachloroplatinate as starting materials ($\lambda(PtCl_4^{2-})$ at 565, 470, 385 and 328 nm) exhibit besides the characteristic band at 586 nm a maximum at 800 nm, and others in the near UV region, with shoulders at 310 (d–π^*) and 370 nm (d–d*) [10]. On addition of hydrochloric acid a progressive shift of the last shoulder towards larger wavelengths occurs. Since similar and more marked results were obtained for *cis* and *trans* neutral complexes in solution in the presence of a larger excess of 1 N hydrochloric acid, we can conclude that this shift, or the appearance of a new well-defined band to 405 nm, is associated with HCl-solvated complexes in *trans*-configuration.

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