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Coordination properties of the bioligands creatinine and creatine in various reaction media

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Contents

Abstract

Data on the ability of the important bioligands creatinine and creatine to form various types of complexes with different metal ions are summarized. The crucial role of the nature of the reaction medium in complex formation with these ligands is emphasized. The conditions for obtaining paramagnetic oligomeric platinum complexes of the "platinum blue" type (resulting from multistep redox and coordination processes) are presented.

Keywords: Creatinine; Creatine; Metal complexes; structure; "Platinum blue" complexes; Mechanism of "platinum blue" formation

List of Abbreviations

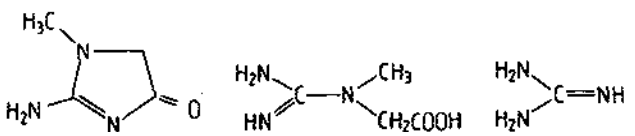
An	acetonitrile
$AsPh_4$	tetraphenylarsinium
cr	creatine

SSDI 0010-8545(94)01122-2

creat	creatinine
DMF	dimethylformamide
DMSO	dimethylsulphoxide
DTA	differential thermal analysis
EPR	electron paramagnetic resonance
ESCA	electron spectroscopy for chemical analysis
$EtNH_2$	ethylamine
HFS	hyperfine structure
HMPA	hexamethylphosphortriamide
NMR	nuclear magnetic resonance
py	pyridine
SHFS	superhyperfine structure
TGA	thermogravimetric analysis
TPB	tetraphenylborate

1. Introduction

Creatinine (2-amino-1-methyl-imidasolidinone) (**1**) can be considered as a cyclic derivative of creatine (**2**) or as a condensation product of guanidine (**3**) and glycolic acid.



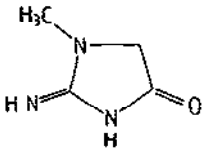
1 **2** **3**

The importance of creatinine in clinical chemistry is well recognized: its level in serum and urine is indicative of the renal function (Creatinine Clearance Test). At the same time it is the final metabolic product of creatine. The latter participates in energy flow in muscle tissues and is present in blood, muscles and the brain [1]. On the other hand, the cardiovascular activity of aromatic derivatives of guanidine has also been proven [2].

Muralidharan et al. [1] suggested that the metabolism of creatinine might be connected with its complexation to different metal ions. Owing to the presence of several bonding sites in molecules of both creatinine and creatine, their ability to coordinate via different donor groups depending on the reaction conditions and their ability to form oligomeric platinum species of the "platinum blue" type [3], studies of their coordination properties are of significant interest. In the present paper data on the synthesis and structure of creatinine and creatine complexes obtained under various reaction conditions are summarized.

2. Ligand properties

Several tautomeric forms have been proposed for creatinine (**1**, **4**–**6**) in which the C=N bond is assumed to be either endocyclic (**4**, **5**) or exocyclic (**1**, **6**) to the five-membered ring [4].



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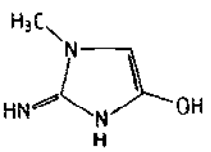

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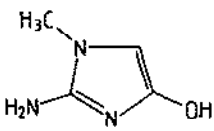
On the basis of ^{1}H NMR and chemical transformation data, the endocyclic C=N bond tautomers are preferred over those with exocyclic C=N bonds [5], the structure **1** being most probable.



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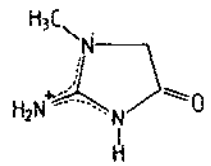


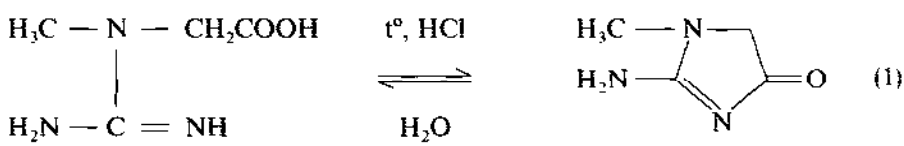
7

In water solution creatinine shows acidic properties ($pK_a = 4.89$ at 20 °C) [4]. In acidic medium it is protonated, resulting in the formation of **7** [6].

^{13}C NMR data obtained later are in agreement with this supposition [7].

The IR spectrum of creatinine was studied in detail using the ^{15}N isotope shift method [8] and by normal coordinate analysis in the generalized valence field approximation [9]. The results show extensive π electron delocalization in the molecule. The stretching modes of both C=N and C−N bonds are mixed with other vibration modes in the ring and therefore cannot be considered characteristic. This is more or less true for all other vibrations in the ring.

Creatine is readily transformed into creatinine in acidic medium according to



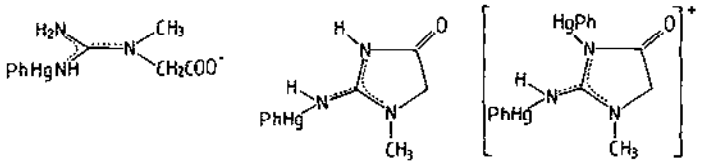
(1)

and for this reason only a few metal complexes of creatine are known.

3. Complexes with main group and first-row transition metal ions

Canty et al. [6] first obtained phenylmercury(II) organometallic compounds with both creatine and creatinine. By varying the nature of the reaction medium, com-

plexes with different contents and structures were obtained. In water medium a complex with a PhHg:L ratio of 1:1 was formed. In basic medium a zwitterionic complex **8** with creatine was synthesized. The reaction of creatinine hydronitrate in strongly acidic solution (pH 1.4) also yielded a 1:1 complex **9**.



8 **9** **10**

In acidic water–ethanolic solution, however, both creatinine and creatine react with $PhHg[(OH)NO_3]_{1/2}$ to form a 1:2 creatinine:PhHg complex (**10**)[1], the latter existing in two different crystalline forms. The complexes PhHg(creat) and $(PhHg)_2$(creat) can be interconverted.

X-Ray diffraction [6] indicates that the structure of $[(PhHg)_2(Hcreat)]^+(NO_3)$ (Fig. 1) shows coordination of PhHg to both exo- and endocyclic N atoms and planarity of the creatinine molecule.

^{1}H NMR and IR (including ^{2}D shift) data for the various complexes were obtained and structures proposed [6].

Udupa and coworkers [1,10–12] studied the coordination properties of creatinine towards various M(II) ions (Zn(II), Cd(II), Hg(II), Co(II), Cu(II) and Ag(I)).

Neutral zinc, cadmium and mercury complexes of creatinine of the type $M(creat)_2X_2$ (X≡Cl, Br or I) were obtained in methanolic or water–methanolic solutions [1]. IR data show an increase in the NH (cyclic) stretching frequency in these complexes (3350 cm^{-1}) compared with the free ligand (3300 cm^{-1}), indicating coordination via secondary nitrogen. The shift in the resonances of both the cyclic NH proton in the ^{1}H NMR spectrum and the carbonyl and imine carbon atoms in

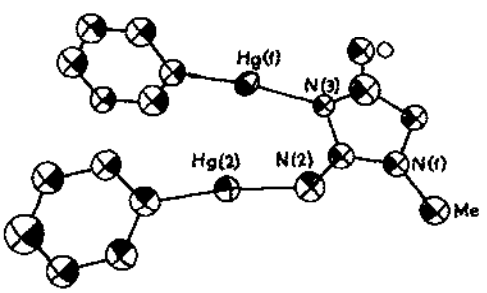


Fig. 1. Molecular structure of the cation $[(PhHg)_2(Hcreat)]^+$ in $[(PhHg)_2(Hcreat)](NO_3)_2$ (hydrogen atoms are omitted). (Reproduced with permission from Ref. [6].)

[1] Due to cyclization of creatine resulting in creatine formation in acidic solution.

the ^{13}C NMR spectrum in comparison with the free ligand also suggested coordination via the cyclic N atom.

In acidic medium ($HClO_4$) bis(creatinine)silver(I) perchlorate dihydrate ($[Ag(C_4H_7N_3O)_2]ClO_4 \cdot 2H_2O$) was obtained and its structure solved by X-ray diffraction [10]. The $[Ag(creat)_2]^+$ ion is linear, the coordination being realized through the cyclic nitrogen atoms (Ag–N distance of 2.100(3) Å) (Fig. 2). The ligand molecules are planar, participating in their amino form 1. Intermolecular H bonding involving the C=O and $-NH_2$ groups of the ligand, water molecules and ClO_4^- exists.

Several different Cu(II)–creat complexes were obtained by the reaction of Cu(II) salts with creatinine under various conditions. Udupa and Krebs synthesized creatininium tetrachlorocuprate(II) from $CuCl_2$ and creatinine (1:2 molar ratio) in alcoholic–water medium containing a few drops of 2 M HCl [11]. The molecular and crystal structures of the complex salt were solved using X-ray diffraction (Figs. 3 and 4). The $CuCl_4^{2-}$ is bound to a pair of creatininium cations via hydrogen bonds of the type N–H···Cl in which both imino and amino nitrogen atoms are involved. The $CuCl_4^{2-}$ unit is square planar.

Another type of Cu(II)–creat complex was obtained in neutral water medium (pH about 6, M:L=1:5), namely $[Cu(creat)_2]TPB$ [13]. IR data showed that both C=O and cyclic =NH groups are involved in the complexation: the corresponding

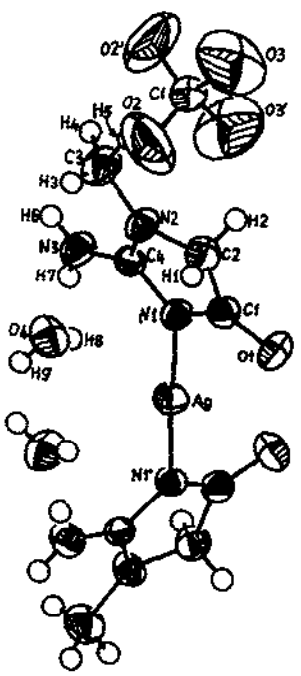


Fig. 2. Molecular structure of bis(creatinine)silver(I) perchlorate dihydrate. (Reproduced with permission from Ref. [10].)

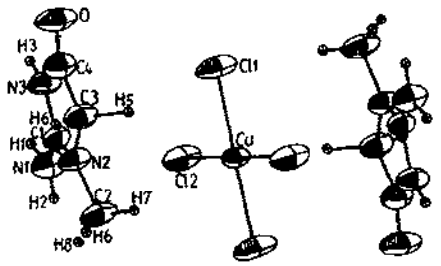


Fig. 3. Structure of $CuCl_4^{2-}$ ion with neighbouring creatininium cations. (Reproduced with permission from Ref. [11].)

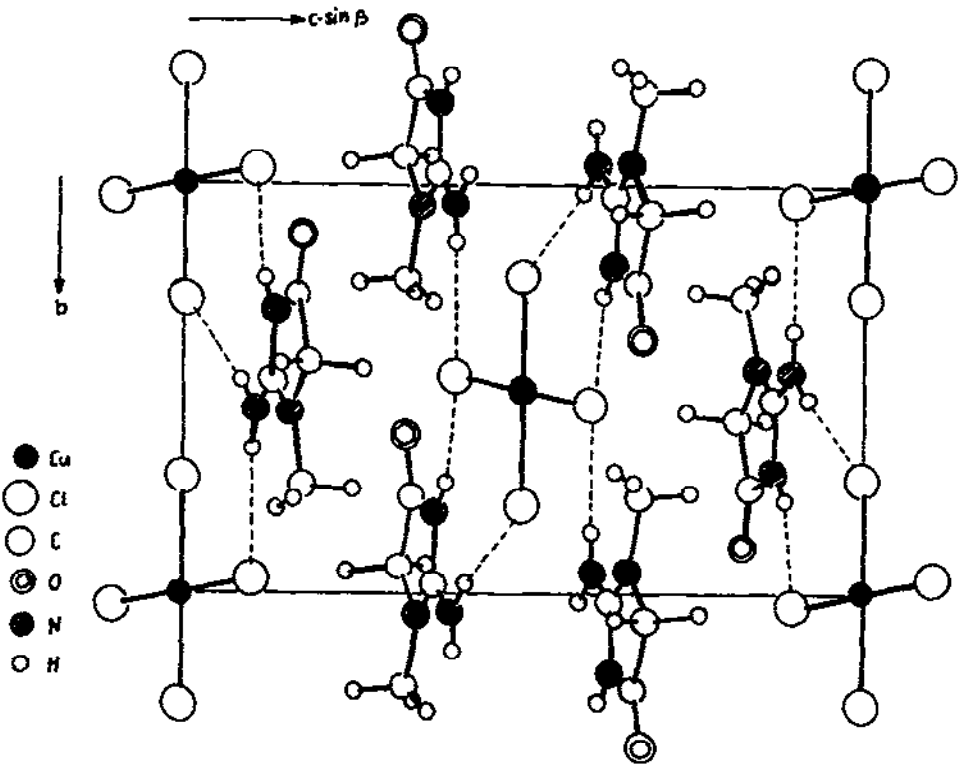


Fig. 4. Projection of the unit cell of creatininium tetrachlorocuprate(II) showing the intermolecular hydrogen bond system. (Reproduced with permission from Ref. [11].)

vibration bands are shifted in the spectrum of the $Cu(creat)_2$ complex and on this basis a four-membered chelate formation was assumed. The EPR data (anisotropic EPR spectrum with $g_{\parallel} > g_{\perp}$) are typical for rhombic symmetry, i.e. a structure close to square planar.

EPR investigation of solutions of $Cu(creat)_2^{2+}$ in a series of organic solvents (py, HMPA, DMSO) showed a 1 : 1 adduct with solvent molecules generating an increase

in g values ($g_{\parallel}$ and $g_{\perp}$) and a decrease in A (hyperfine splitting constant due to $^{63,65}Cu$ ($I=\frac{3}{2}$)).

New types of monomeric and dimeric Cu(II) complexes with creatinine were synthesized in organic media using $Cu(NO_3)_2$ as the starting Cu(II) salt [14]. In methanol a monomeric complex species containing four creatinine and two solvent molecules is formed (as proven by EPR and magnetochemical ($\mu=2.0$ BM) evidence), while in acetonitrile two dimeric species are formed:

$$\text{Cu(II)} + \text{creat} \xrightarrow{\text{CH}_3\text{OH}} \text{Cu(creat)}_4(\text{OCH}_3)_2 \qquad \text{Cu(II)} + \text{creat} \xrightarrow[\text{An}]{} \text{Cu}_2(\text{creat})_6 \rightarrow \text{Cu}_2(\text{creat})_4 \tag{2}$$

The monomeric species contains four creatinine molecules (coordinated via the endocyclic N atom as shown by IR evidence) and two deprotonated solvent molecules (CH_3O^-) in the inner coordination sphere. The coordination of the latter was proven by means of the kinetic isotopic effect (use of CD_3OD instead of CH_3OH as solvent).

The μ_{eff} value and the polycrystalline EPR parameters ($g_{\parallel}=2.400$, $g_{\perp}=2.064$, $A^{\parallel}=162$ Oe) are temperature independent, suggesting an octahedral structure. The anisotropic g values ($g_{\parallel} \gg g_{\perp} > 2$) correspond to an elongated octahedral structure with a $d_{x^2-y^2}$ ground state.

EPR evidence for creatinine coordination via the N atom is also available. In frozen DMF solution a poorly resolved nine-component SHFS due to four ^{15}N ($I=1$) atoms ($A_N \approx 13$ Oe) was also observed. On the basis of these data it can be assumed that the four creatinine molecules are placed in the xy plane while the two CH_3O^- groups are coordinated along the z axis.

The formation of the dimeric Cu(II) complex species was proven using both magnotochemical ($\mu_{eff}=1.5$ and 1.6 BM) and EPR (appearance of a half-field transition signal with $g=2.94$ typical for dimeric Cu(II) species) measurements. IR data are also available showing a bridging coordination of the ligand creatinine (lowering of the $\nu_{C=O}$ band in the dimeric complexes [14].

Another Cu(II)–creat complex, namely $Cu(creat)_2Cl_2$, was obtained by the reaction of $CuCl_2$ and creatinine in methanol [15]. IR data indicate a tetrahedral or cis square planar geometry due to a well-defined doublet at 305 and 288 cm^{-1} ascribed to Cu—Cl vibrations. Other IR evidence is consistent with the coordination of both creatinine molecules via the endocyclic N atom.

When $CuSO_4$ was reacted with creatinine in ethylamine–water solution a ternary diamagnetic Cu(I)–creatinine–$EtNH_2$ complex was obtained ($Cu(creatH_{-1})$-$(EtNH_2)\cdot H_2O$) [15]. The white colour of the complex together with the analytical data and the presence of methylguanidine (a known oxidation product of creatinine) in the reaction mixture indicates the reduction of Cu(II) to Cu(I).

Both tetrahedral and octahedral Co(II)–creat complexes of the types $Co(creat)_2X_2$ ($X \equiv Cl$, Br, SCN) and $Co(creat)_2X_2\cdot 2H_2O$ ($X \equiv HCOO^-$, $HOCH_2COO^-$, $N{=}CCH_2COO^-$) have also been prepared [12]. Elemental analysis and electronic

spectral data (absorption maxima at about 17400 and 5800 cm^{-1}) and magnetochemical measurements ($\mu \approx 4.4$ BM) suggest a tetrahedral geometry for the halide and thiocyanate complexes, while for the carboxylate complexes ($\mu \approx 5.0$ BM, absorption maxima at 20000 and 8330 cm^{-1}) an octahedral geometry is assumed.

IR data show evidence for halide coordination through the endocyclic N atom, while the thiocyanate group is coordinated via the N atom and the COO^--containing ligands are monodentate. The fifth and sixth coordination sites are occupied by two water molecules (their presence was proven by TGA). Polarographic measurements showed that the complexes undergo reversible two-electron reduction.

No complexation of Ni(II) with creatinine proceeds in water [16]. However, several different complexes were established in organic media [16–18].

Using $Ni(NO_3)_2 \cdot 6H_2O$ as starting material [16] in methanol and acetonitrile, three octahedral Ni(II) complexes are formed differing in colour and containing different numbers of water molecules in their inner coordination spheres: $[Ni(creat)_3(H_2O)_3](NO_3)_2 \cdot H_2O$ (blue), $[Ni(creat)_4(H_2O)_2](NO_3)_2 \cdot 2H_2O$ (green) and $[Ni(creat)_6](NO_3)_2 \cdot 4H_2O$ (yellow).

The complexes are unstable in water. IR and ESCA data (binding energies E_b for Ni 2p and N 1s are typical for Ni(II) complexes with N coordination ligands [19]) show coordination via the endocyclic N atom. An octahedral structure was assumed on the basis of magnetochemical and EPR measurements. All the complexes are paramagnetic ($\mu_{eff} = 3.2$–3.3 BM at 300 K), thus ruling out a square planar structure. They are also EPR active, exhibiting a rather peculiar temperature-dependent paramagnetism. These data are indicative of an octahedral structure [16]. The presence of water molecules in either the inner or the outer sphere was proven by thermogravimetric methods.

The complexation of creatinine with anhydrous $NiCl_2$ in dry acetonitrile resulted in the formation of a dimeric Ni(II) species $[Ni_2(creat)_8]Cl_4$ [18]. The complex is paramagnetic with $\mu_{eff} = 2.28$ BM. This value is lower than expected for monomeric octahedral Ni(II) complexes (2.8–3.4 BM), possibly owing to an antiferromagnetically coupled dimeric or polymeric structure. Since the complex is readily soluble in organic solvents, a dimeric structure is more probable. IR data indicate two creatinine molecules serving as bridging ligands via the amide groups, since significant shifts are observed in both the C=O and C=N frequencies.

Studies of the formation constants of creatinine and creatine performed in the physiological pH range (7.2–7.3) showed no complex formation with Ca^{2+} or Sr^{2+} [20].

4. Complexes with platinum group metal ions

Almost simultaneously Martin-Gil and Martin-Gil [21] and Bontchev et al. [3] began systematic investigations on the complexation of creatinine with Pt(II) and Pd(II). These first studies showed the crucial role of the reaction conditions in determining the nature of the reaction products.

4.1. Synthesis of monomeric diamagnetic complexes (synthesis with excess ligand)

$[Pt(creat)_4]^{2+}$ species were obtained when $PtCl_4^{2-}$ was reacted with excess creatinine (L:M > 4) (pH 3) [3,22,23] and precipitated with TPB or ClO_4^-. In the latter case [22,23] the molecular and crystal structures were solved by X-ray diffraction [22] (Fig. 5). The Pt atom is square planar coordinated by the endocyclic N atom of the four ligand molecules. The latter is almost planar and tilted towards the PtN_4 plane by 82.1(8)°–93.5(9)°. The Pt—N bond lengths range from 2.00(2) to 2.00(3) Å. The structure consists of $[Pt(creat)_4]^{2+}$ cations with approximately D_2 symmetry and rotationally disordered perchlorate anions (Fig. 6). The ClO_4^- ions in the structure are surrounded by four creatinine ligands, the latter being parallel in pairs (Fig. 7). A set of intermolecular hydrogen bonds is observed between the amino hydrogen atoms and the C=O and ClO_4^- groups.

Under the same conditions the $PdCl_4^{2-}$–creatinine interaction resulted in the formation of analogous $Pd(creat)_4A_2$ ($A \equiv ClO_4^-$, TPB) as characterized by IR spectroscopy [22].

When $Pt(NO_2)_4^{2-}$ was reacted with creatinine (L:M > 4) in acidic medium, *cis*-bis(creatinine-*N*)dinitroplatinum(II) was obtained [24]. The molecular structure again shows square planar PtN_4 coordination of a pair of cis-disposed NO_2^- ligands and another pair of creatinine molecules (via the endocyclic N atom) (Fig. 8), the corresponding Pt—N $Pt-N_{(NO_2)av} = 2.023(7)$ Å and $Pt-N_{(endo)av} = 1.991(8)$ Å respectively. The creatinine molecules are planar and tilted to the equatorial plane by approximately 80° [24].

The structure consists of the neutral $Pt(creat)_2(NO_2)_2$ disposed in general positions and joined by a series of H bonds (Fig. 9).

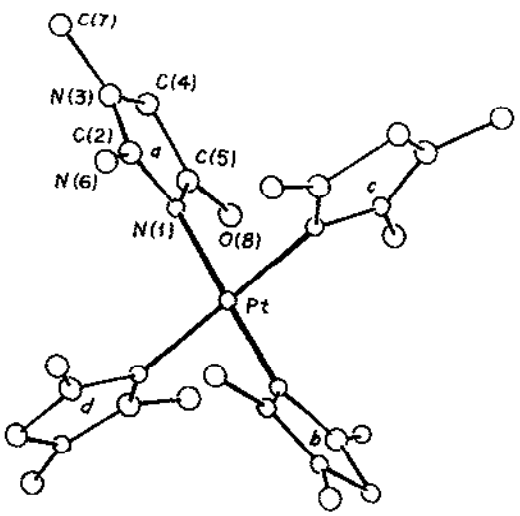


Fig. 5. ORTEP drawing of the $Pt(creat)_4^{2+}$ cation with atom and ring labelling schemes (hydrogen atoms are omitted). (Reproduced with permission from Ref. [22].)

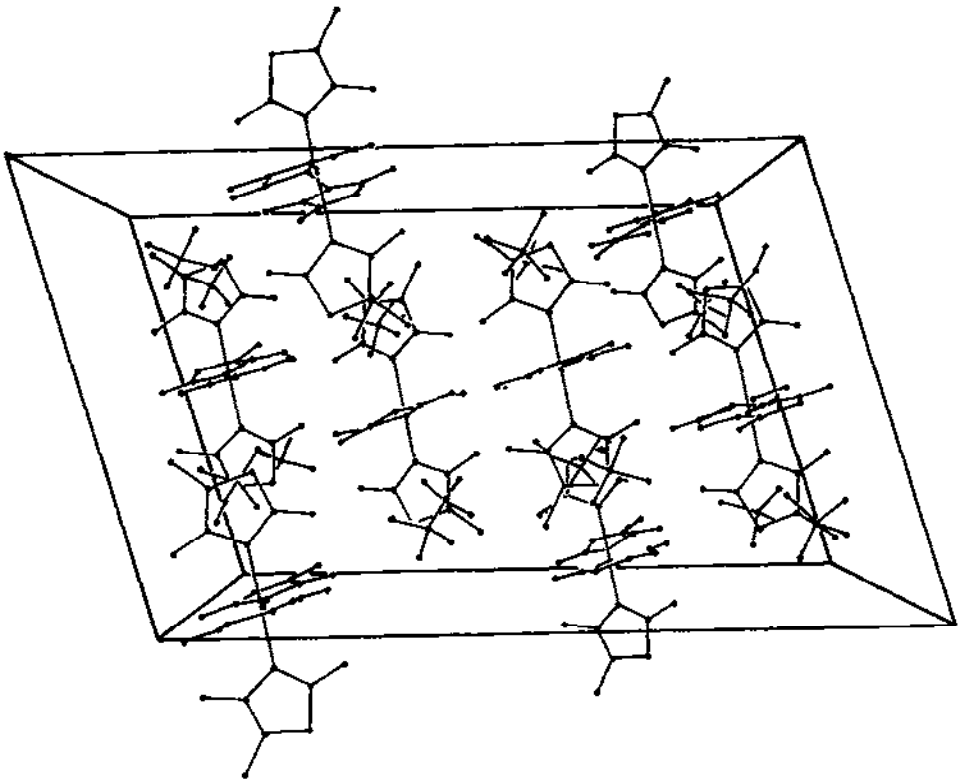


Fig. 6. Unit cell structure of $Pt(creat)_4(ClO_4)_2$ viewed along the *b* axis. (Reproduced with permission from Ref. [22].)

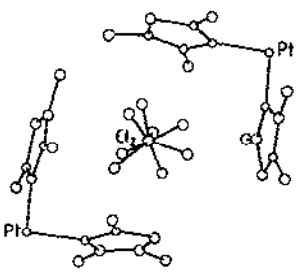


Fig. 7. Mutual disposition of $Pt(creat)_4^{2+}$ and ClO_4^- in $[Pt(creat)_4](ClO_4)_2$.

Reaction of PtI_4^{2-} with creatinine (M : L = 1 : 2) yielded *cis*-$Pt(creat)_2I_2$, while *trans*-$M(creat)_2Cl_2$ (M ≡ Pt, Pd) complexes were obtained with $PtCl_4^{2-}$) [21]. The structures of *trans*-$Pd(creat)_2Cl_2 \cdot 2H_2O$ and *cis*-$Pt(creat)_2I_2 \cdot 3H_2O$ were solved by X-ray diffraction [25] (Figs. 10–12). In both cases square planar coordination was proven, the Pt−N distances being 2.069(4) and 2.069(4) Å respectively. The creatinine mole-

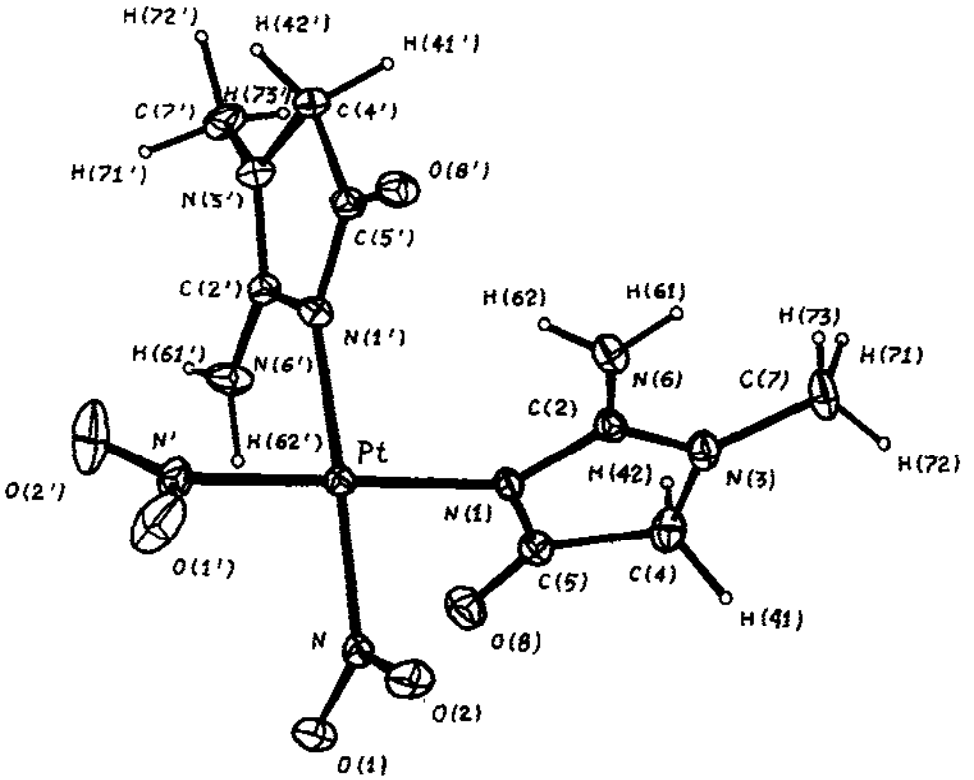


Fig. 8. Molecular structure of $Pt(creat)_4(NO_2)_2$ with the atom numbering scheme. (Reproduced with permission from Ref. [24].)

cules are planar. In *cis*-$Pt(creat)_2I_2 \cdot 3H_2O$ the creatinine molecules are not coplanar (interplanar angle of 98.7(2)°).

In both complex species extensive hydrogen bond systems were established, their schemes being shown in Figs. 10 and 12.

The thermal characteristics of both complexes were also studied [25] and TGA and DTA data show similar stabilities.

Crystallographic data on *trans*-$Pd(creat)_2Cl_2 \cdot 2H_2O$ [26] show the existence of two allotropic forms: monoclinic (M) yellow crystals and triclinic (T) green crystals.

Single crystals of both allotropic forms were obtained by reaction of K_2PtCl_4 and creatinine in an M : L ratio of 2 : 1 in a minimum amount of water. The crystal data are presented in Figs. 13–15.

Structure M consists of chains of coordinated creatinine molecules realized through hydrogen bonding with water molecules. Only van der Waals interaction was found to operate between the chains.

The main difference between the two allotropic forms is connected with intermolecular H bond formation: while in the triclinic structure the two creatinine molecules are parallel, in the monoclinic structure they are not parallel, since a glide plane is present [26].

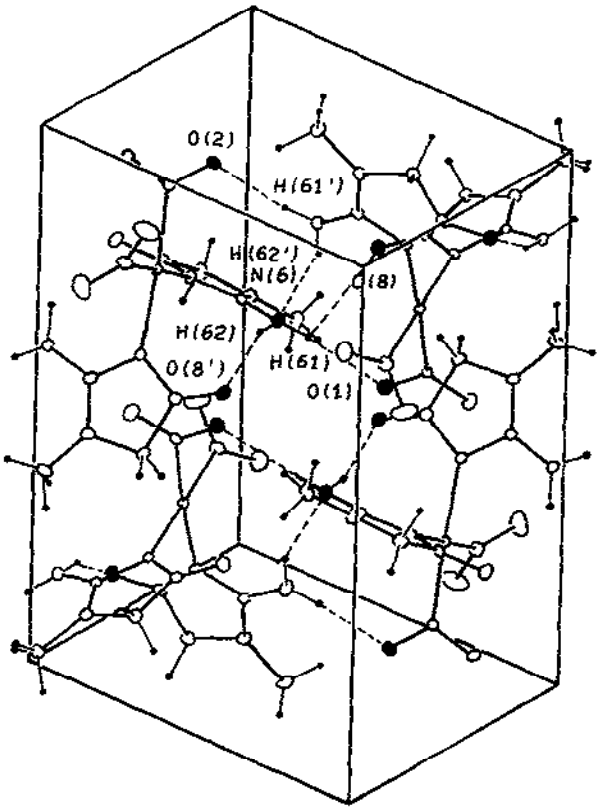


Fig. 9. $Pt(creat)_4(NO_2)_2$ unit cell packing with the hydrogen bond system. Free circles are hydrogen bond acceptors. (Reproduced with permission from Ref. [24].)

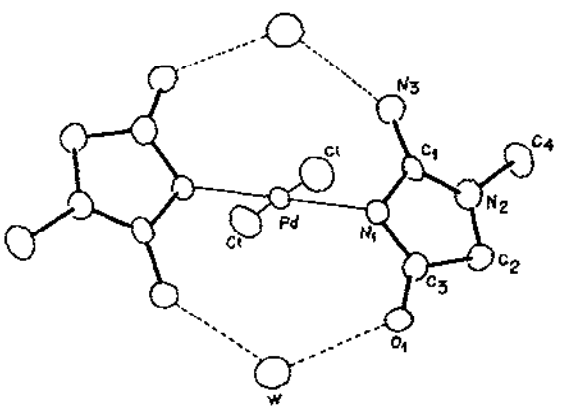


Fig. 10. Molecular structure of *trans*-$Pd(creat)_4Cl_2 \cdot 2H_2O$ ($w \equiv H_2O$; hydrogen atoms are omitted). (Reproduced with permission from Ref. [25].)

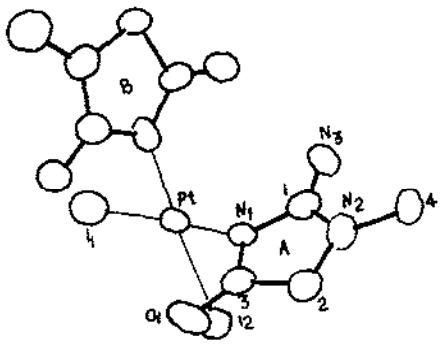


Fig. 11. Molecular structure of *cis*-Pt(creat)$_4$I$_2$·3H$_2$O (hydrogen atoms and water molecules are omitted). (Reproduced with permission from Ref. [25].)

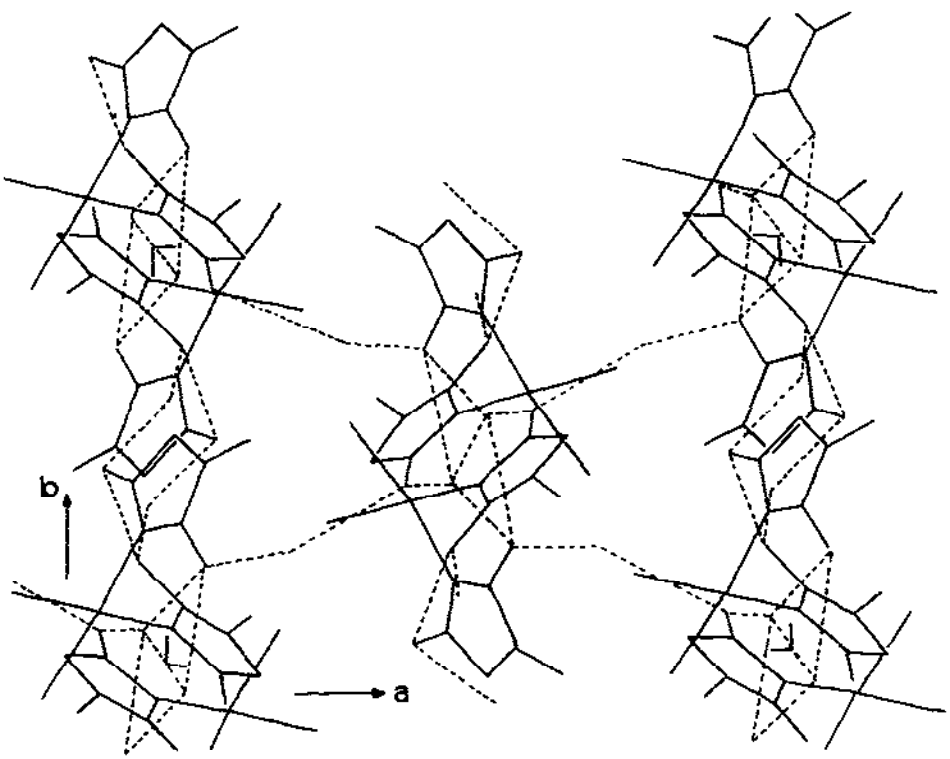


Fig. 12. Perspective view showing the packing of *cis*-Pt(creat)$_4$I$_2$·3H$_2$O molecules and the H bond system realized. (Reproduced with permission from Ref. [25].)

TGA and DTA studies on the monoclinic (M) crystals show that the range of stability of the trans Pt(II)–creatinine complex is wider than that of the corresponding trans Pd(II)–creatinine complex [26].

Pt(II)– and Pd(II)–creatinine complexes were obtained using $PtCl_6^{2-}$ and

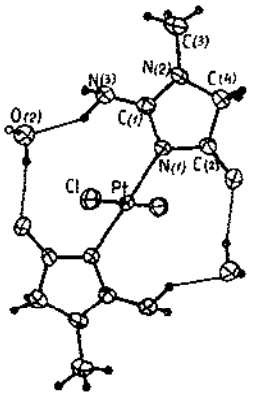


Fig. 13. ORTEP view of *trans*-dichlorobis(creatinine)platinum(II) dihydrate (allotropic form M) with the H bond system. (Reproduced with permission from Ref. [26].)

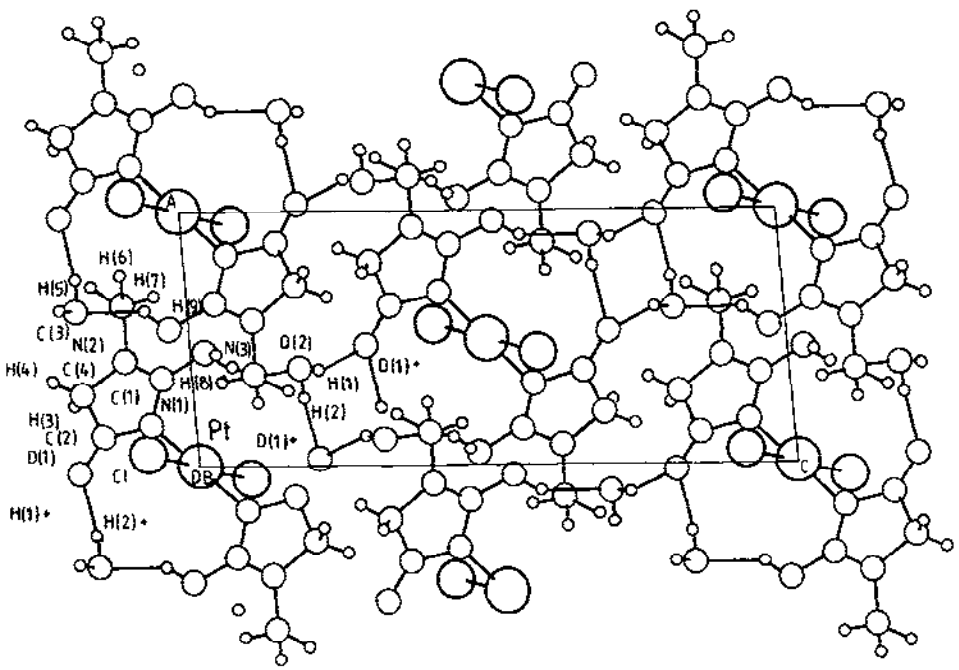


Fig. 14. PLUTO view of the molecular packing in *trans*-dichlorobis(creatinine)platinum(II) dihydrate (allotropic form M) projected on to the (010) plane, showing the H bond scheme. (Reproduced with permission from Ref. [26].)

$PdCl_6^{2-}$ [27]. According to IR, ^1H NMR and ESCA data, with an excess of ligand (M : L = 1 : 8), $Pt(creat)_4^{2+}$ and $Pd(creat)_4^{2+}$ are formed respectively. EPR of the reaction mixture of $PtCl_6^{2-}$–creat in strong acidic medium (pH 0.8) showed the formation

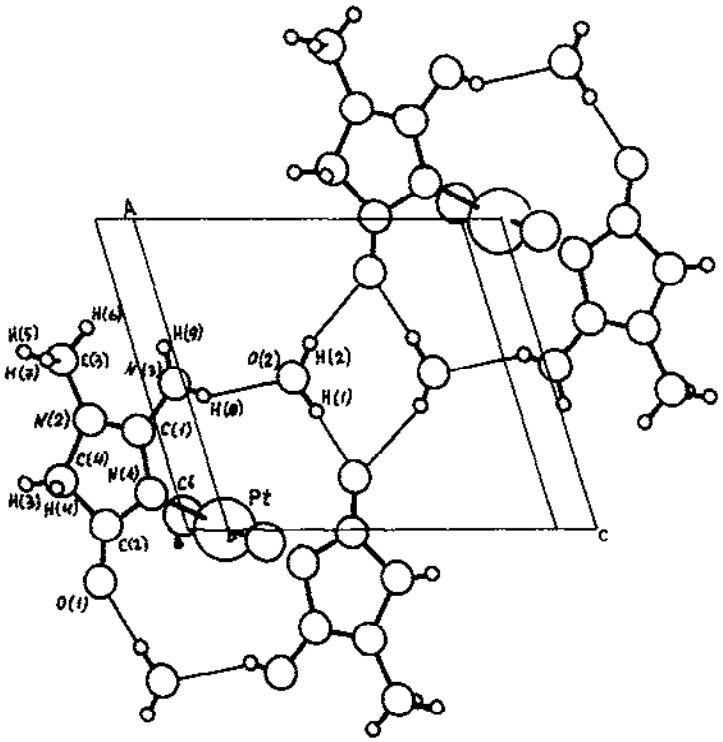


Fig. 15. PLUTO projection of *trans*-dichlorobis(creatinine)platinum(II) dihydrate (allotropic form T) on to the (010) plane, showing the H bond scheme. (Reproduced with permission from Ref. [26].)

of intermediate EPR-active species (anisotropic EPR signal with $g = 2.106$), most likely transient Pt(III) species.

The photoinduced formation and decay of intermediate $[Pt^{III}Cl_5\text{-creat}]^{2-}$ in the course of $PtCl_6^{2-}$ reduction in methanol were also studied [28]. Using pulsed laser photolysis (excimer laser, XeCl, 308 nm), the formation of this transient species was shown spectrophotometrically (appearance of broad absorption bands at 470 and 530 nm). Some kinetic and thermodynamic data of the photoinduced reaction were also determined. Under stationary irradiation (Hg lamp, 500 W) the end product of $PtCl_6^{2-}$ reduction is the known complex $Pt(creat)_4^{2+}$.

Recently the complexation of creatinine with $RhCl_6^{3-}$ was studied [29]. The replacement of Cl^- by creatinine and H_2O in the inner coordination sphere of Rh(III) proceeded rather slowly (reflux at 60 °C for 24 h), resulting in the formation of octahedral $[Rh(creat)_3(H_2O)_3]^{3+}$.

4.2. *Synthesis of paramagnetic and oligomeric complexes*

Creatinine, being a cyclic amide, is capable of forming oligomeric paramagnetic species of "platinum blue" type [3,21,23]. Complex species were obtained either by

hydrolysis of *trans*-Pt(creat)$_2$Cl$_2$ [21,30] or by reacting $PtCl_4^{2-}$ (or *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$) with creatinine in 1:1 M:L ratio [3,23,30–33].

The $PtCl_4^{2-}$–creatinine reaction yielded three "platinum blue" species: positively charged, neutral and negatively charged [33]. The neutral species precipitated spontaneously from the reaction mixture, while the other two were isolated by addition of TPB or $AsPh_4^+$ respectively.

Spectrophotometric, IR, EPR and ESCA data were obtained [3,23,33]. EPR and ESCA data for several paramagnetic and diamagnetic platinum complexes of creatinine are summarized in Table 1 [33].

Both the EPR and ESCA data are typical for "platinum blue" species [19,35]. The EPR spectra are anisotropic two-component spectra with $g_\parallel < g_\perp$. The binding energy values for Pt $4f_{7/2}$ of the oligomeric species are higher than those of monomeric complexes but lower than those of Pt(IV) complexes, thus indicating an oxidation state higher than +2 for the platinum ions.

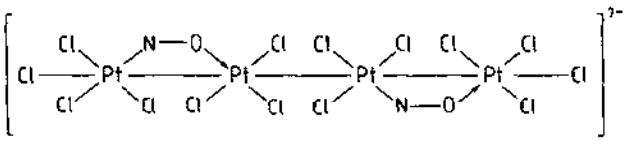
The negatively charged "platinum blue" complex was isolated as a stoichiometric paramagnetic complex salt with the tetraphenylarsinium ion ($AsPh_4^+$), namely [Pt$_4$(creat)$_2$Cl$_{14}$](AsPH$_4$)$_7$·6H$_2$O, and its EPR spectrum studied in detail [32,36]. The latter shows an anisotropic two-component signal with $g_\perp = 2.432$ and $g_\parallel = 1.962$. A multicomponent HFS due to ^{195}Pt ($I = \frac{1}{2}$, natural abundance 33.8%) is observed. A simulation procedure was developed on the basis of a non-equivalent polynuclear model [36] and using the experimentally determined A and g values. The best fit is observed for a tetrameric platinum chain [32]. On the basis of elemental analysis, IR, EPR, TGA and DTA data obtained, structure **11** was proposed [32].

Another paramagnetic complex was obtained from the $PtCl_4^{2-}$–creatinine (M:L = 1:1) reaction mixture after precipitation of the oligomeric "platinum blue" complex [Pt$_4$(creat)$_2$Cl$_{14}$](AsPh$_4$)$_7$·6H$_2$O [34]. Several hours after the removal of the latter, green single crystals of [Pt(creat)Cl$_3$](AsPh$_4^+$) were obtained in the filtrate (pH about 3). The molecular and crystal structures of the complex were solved by means of X-ray diffraction [34] (Figs. 16–18).

Table 1
EPR and ESCA data for some platinum complexes with creatinine

Compound[a]	EPR data		ESCA data, $E_b \pm 0.15$ (eV)			
	$g_\parallel$	$g_\perp$	Pt $4f_{7/2}$	N 1s	O 1s	Cl 2p
Creatinine	Diamagnetic		—	401.7	533.4	—
Pt(creat)$_4$(TBP)$_2$	Diamagnetic		74.1	400.7	[b]	—
[PtCl$_3$(creat)](AsPh$_4$)	$g_{iso} = 2.35$		73.1	400.0	[b]	198.6
[Pt$_2$(creat)$_6$](TBP)$_2$·4H$_2$O	Diamagnetic		75.7	402.5	534.0	—
Pt-Bl (neutral)	1.96	2.40	76.6	403.4	535.5	201.8
[Pt$_4$(creat)$_2$Cl$_{14}$](AsPh$_4$)$_7$·6H$_2$O (Pt-Bl)	1.96	2.43	75.7	402.2	[b]	200.8
[Pt-Bl]$_x$(TPB)$_y$	1.96	2.40	[b]	[b]	[b]	[b]

[a] Pt-Bl stands for "platinum blue"; [b] not measured.



11

In the complex the creatinine molecule is again coordinated via the endocyclic N atom (Fig. 16). Another interesting feature of the molecular structure is the formation of short Pt···H intermolecular bonds (2.73(2) Å). Thus the coordination number of this Pt(II) complex is five and its geometry is close to square pyramidal. These features are rather rare for Pt(II) complexes.

The complex salt crystallizes to form a columnar honeycomb motif of tetraphenylarsinium cations, the six-membered channels being occupied by $[Pt(creat)Cl_3]^-$ (Fig. 17). The shortest Pt—Pt distance was found to be 7.622(1) Å.

Remarkably the complex is paramagnetic and EPR active [34] (Figs. 19 and 20). Despite the fact that the formal oxidation state of the Pt ions is +2, the complex displays a complicated temperature- and orientation-dependent EPR signal (Figs. 19 and 20). The magnetic moment is also temperature dependent, varying from 0.9 to 1.3 BM in the temperature range 150–250 K and then reducing to about 1 BM at 300 K. A similar change in the temperature dependence of the g value of the main EPR signal is also observed (Fig. 20).

The origin of this paramagnetism is not clear, but evidently it is due to a charge transfer along the Pt—Pt chain.

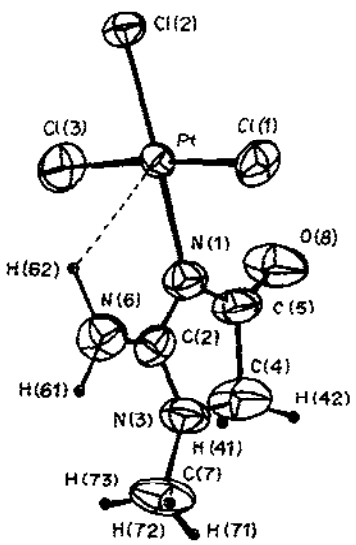


Fig. 16. Conformation and atom numbering scheme in the $[Pt(creat)Cl_3]^-$ anion. The short Pt—H distance is marked by a broken line. (Reproduced with permission from Ref. [34].)

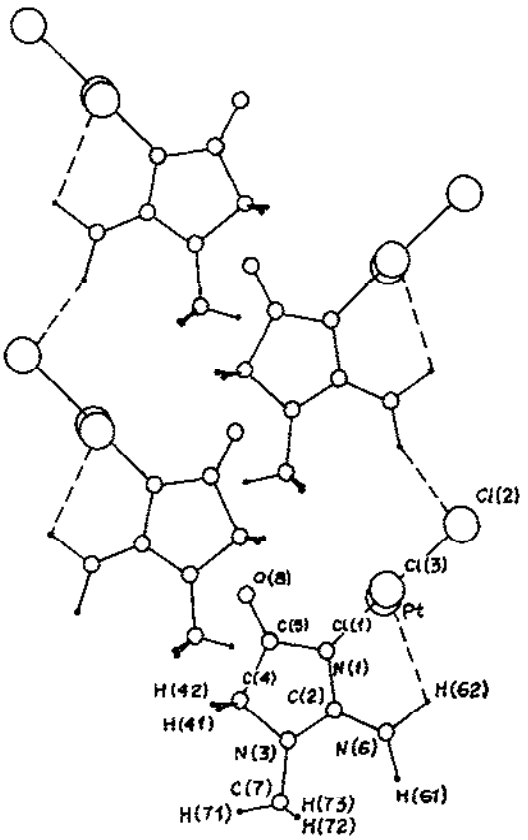


Fig. 17. Chain sequence of $[Pt(creat)Cl_3]^-$ projected on the *bc* plane with the hydrogen bond system. (Reproduced with permission from Ref. [36].)

In connection with investigations on the mechanism of "platinum blue" formation, a dimeric diamagnetic $[Pt_2(creat)_6](TPB)_2 \cdot 4H_2O$ complex was synthesized under anaerobic conditions (argon flow) [32] in which two of the creatinine molecules serve as bridging ligands.

Using ^{195}Pt and ^{13}C NMR spectroscopy, the reaction products formed by the reaction of $[Pt(NH_3)_2(H_2O)_2]^{2+}$ with creatinine at 1:1 metal-to-ligand ratio in neutral medium (pH about 6–7) were identified and their structures studied [31]. Two Pt(II) dimers, being in fact isomers with the formula $[Pt(NH_3)_2(creat)_2]$ (Fig. 21), were formed together with *cis*-$Pt(NH_3)_2(creat)_2$ after acidification to pH 4. It was assumed that the head-to-head isomer is the precursor of the "platinum blue" species, obtained after addition of nitric acid to pH 1, while the oxidation state of the platinum ions in the other isomer remained unchanged (+2) [31].

In a recent paper Coronado et al. [30] report in detail the preparation, EPR and magnetochemical properties and thermal stability of two oligomeric species obtained by the hydrolysis of *trans*-$Pt(creat)_2Cl_2$ in a minimum amount of water at 40 °C and

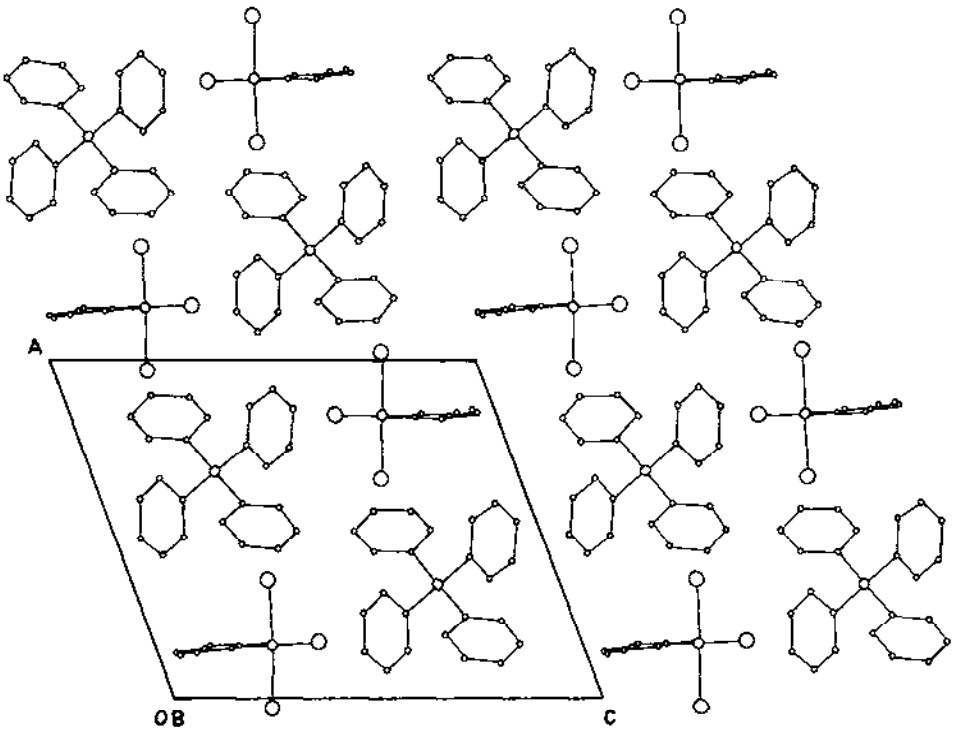


Fig. 18. $[AsPh_4]^+$ columns projected on the *ac* plane exibiting a honeycomb motif. The $[Pt(creat)Cl_3]$ anions are accommodated in the six-membered channels. (Reproduced with permission from Ref. [34].)

in darkness. The first product was green in colour and exhibited an anisotropic EPR spectrum with ill-resolved HFS. Its stoichiometry varied from batch to batch, while the second product (violet in colour) could be obtained as a pure species with the formula $[Pt(creat)(H_2O)Cl]_4Cl$.

This complex is rather stable in solution and shows an axial EPR spectrum ($g_{\parallel}=1.96$ and $g_{\perp}=2.43$) and extensive HFS typical of "platinum blue" species. On the other hand it exhibits an unusually high magnetic moment varying from 4.5 BM per unit at ambient temperature to 1 BM per unit at 5 K [30].

A monomeric paramagnetic palladium complex with creatinine was obtained by reacting $PdCl_4^{2-}$ and creatinine in large ligand excess ($L:M \geqslant 10$)[2] and maintaining constant the acidity of the reaction mixture at pH about 6 [38].

The reaction of $PdCl_4^{2-}$ with creatinine at $M:L=1:2$ and pH 2.5–3 resulted in the formation of a neutral dimeric Pd(II,II) complex of creatinine [32]. It includes four deprotonated ligands, all acting as bridges [32].

While studying the conditions for the formation of transient Pt(III) species and their stabilization as "platinum blue" [39], the ability of creatine to form a tetrameric "platinum blue" species was also proven [40]. This complex gives rise to an aniso-

[2] Under these conditions a paramagnetic palladium–acetamide species has been obtained [37].

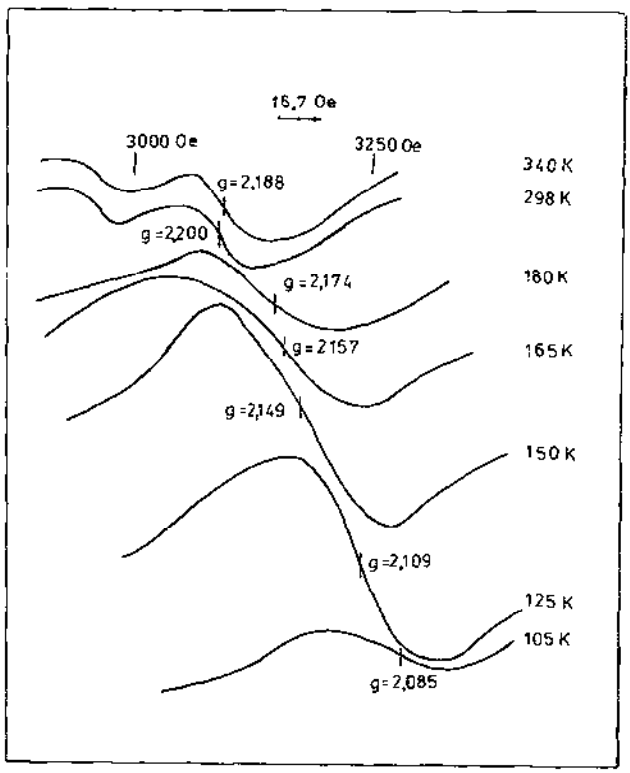


Fig. 19. Temperature dependence of the EPR signal of [Pt(creat)Cl_3] ($AsPh_4$).

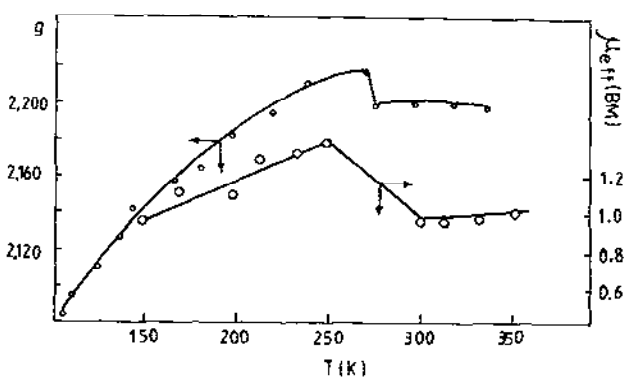


Fig. 20. Temperature dependence of the magnetic moment (μ_{eff}) and g value of [Pt(creat)Cl_3] ($AsPh_4$).

tropic multicomponent EPR signal ($g_{\parallel} = 1.959 \pm 0.002$ and $g_{\perp} = 2.428 \pm 0.002$). The latter was simulated using the same procedure as in the case of the "platinum blue" creatinine species and the results again indicated the formation of a tetrameric species. Two alternative structures **12** and **13** were proposed ($Pt_4(cr)_4Cl_5$).

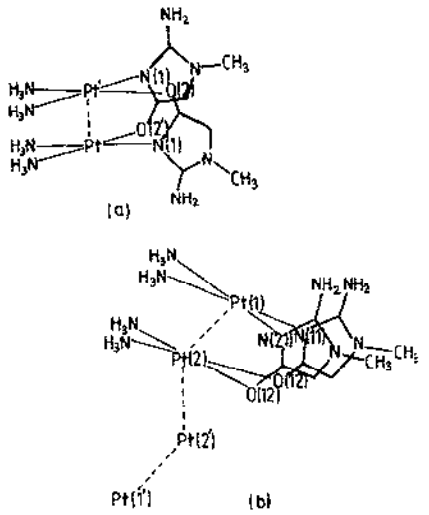
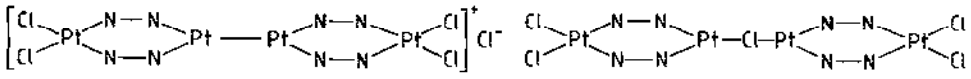


Fig. 21. Proposed structure of the creatinine-bridged complexes $[Pt_2(NH_3)_4(creat)_2]^{2+}$: (a) head-to-tail platinum(II) dimer; (b) head-to-head platinum(II) dimer. (Reproduced with permission from Ref. [31].)



12 **13**

IR data showed coordination of the bridging ligand via the guanidine part of the molecule, namely $HN{=}C{-}NH_2$, since no changes in the $\nu_{C=O}$ and ν_{OH} regions of the IR spectrum of the complex are observed. In contrast, bands observed in the ν_{NH} region of the complex are significantly influenced. Thus the ability of this type of ligand to form "platinum blue" complexes similarly to amides and α-diacetyl groups has been demonstrated for the first time [40].

4.3. Mechanism of "platinum blue" formation; role of the reaction medium

The "platinum blues" are oligomeric paramagnetic complexes containing platinum ions in both +2 and +3 oxidation states [35]. Some experimental data concerning the mechanism of their formation have been reported [17,23,33,41].

Using EPR, transient Pt(III) species (most probably monomeric) were detected in the course of $PtCl_4^{2-}$–creatinine reaction in water medium [41]. (These transient species give rise to a singlet EPR signal with $g \approx 3.3$).

Depending on the reaction conditions, the transient Pt(III) species are either reduced to Pt(II) (forming $Pt(creat)_4^{2+}$) in acidic medium (pH 3 or less) and excess

of the ligand or stabilized as "platinum blue" (appearance of a multicomponent EPR signal) at an M:L ratio of 1:1 in neutral medium.

The kinetics of the latter reaction in water medium at 1:1 M:L ratio were also studied spectrophotometrically and potentiometrically [17,23,33]. These data showed that "platinum blue" formation is connected with the appearance of a series of new bands in the electronic spectrum (560, 680, 750, 1200 and 1500 nm) [23]. At the same time the acidity of the reaction mixture increases (Fig. 22). (Analogous kinetic data were obtained for the $PtCl_4^{2-}$–creatine reaction at an M:L ratio of 1:1 [39–41].)

Thus transient Pt(III) species can be stabilized only as oligomeric complexes of the "platinum blue" type [39,41]. These are formed under conditions of ligand deficiency (M:L = 1:1) when creatinine (or creatine) acts as a bridging ligand [32,33,40].

Kinetic data obtained for the formation of "platinum blue" complexes with creatinine showed a significant decrease in reaction rate when D_2O was used instead of H_2O, indicating the participation of H_2O in the rate-limiting step [23]. On the other hand, when using non-aqueous solvents (absolute CH_3OH and C_2H_5OH, dimethylformamide, dimethylsulphoxide, hexamethylphosphorotriamide, methylacetamide, etc.), no "platinum blue" formation occurred, the only exception being acetonitrile [17,23]. Thus the H_2O molecule participates in "platinum blue" formation.

The participation of O_2 in the redox process was also checked [32]. Under anaerobic conditions and 1:1 M:L ratio the $PtCl_4^{2-}$–creatinine reaction formed the diamagnetic dimeric Pt(II,II) complex of Section 4.2. However, the kinetic data obtained for the $PtCl_4^{2-}$–creatinine reaction in an O_2 flow (Fig. 23) showed that "platinum blue" formation is significantly accelerated.

A mass spectrometric study of the $PtCl_4^{2-}$–creatinine reaction showed N_2

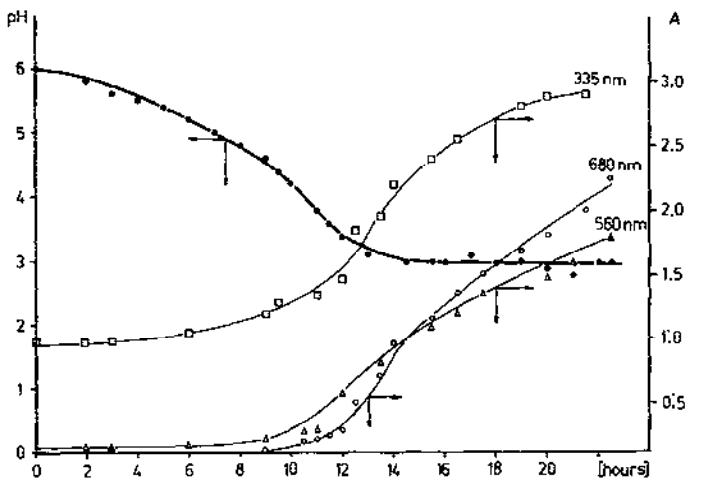


Fig. 22. Time dependences of pH and absorbance of the $PtCl_4^{2-}$–creatinine system (M:L = 1:1). (Reproduced with permission from Ref. [23].)

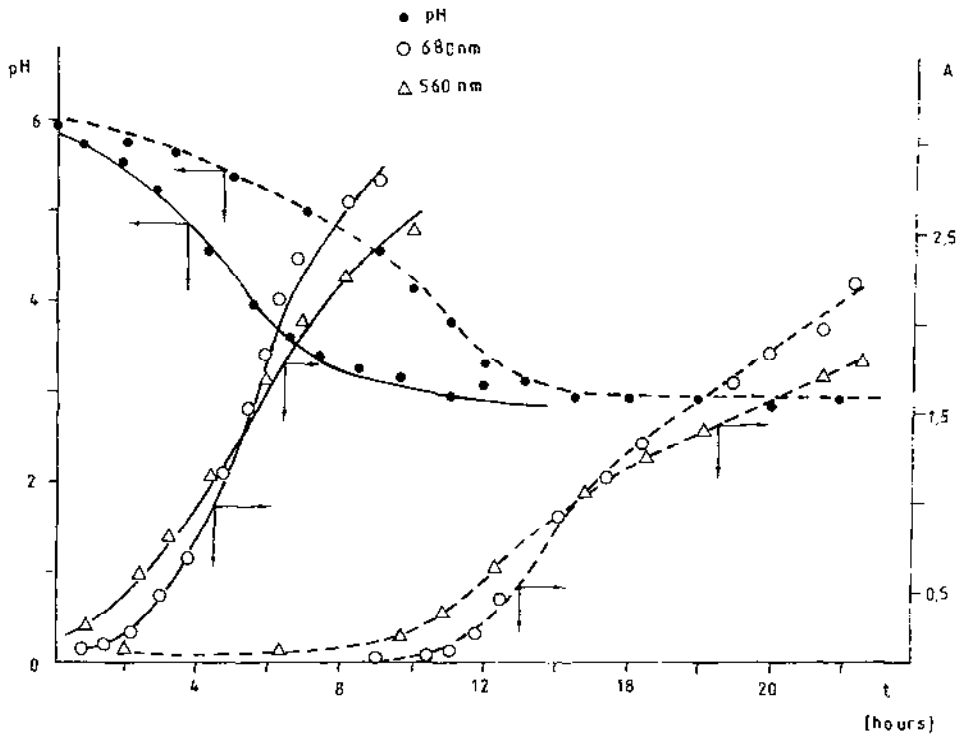


Fig. 23. Time dependences of pH and absorbance of the $PtCl_4^{2-}$–creatinine system (M : L = 1 : 1) in O_2 flow (—) and in air (---).

evolution in the course of the process [42]. This might be explained by partial decomposition of the ligand as a result of the auto-oxidation process. Recently, in studies of reactions of $PtCl_4^{2-}$ and $[Pt(NH_3)_2(H_2O)_2]^{2+}$ with numerous bases in water medium [33,39], autoredox processes were found to proceed in all cases and transient paramagnetic Pt(III) species were formed, which might be stabilized as "platinum blues" in the presence of an appropriate bidentate ligand capable of acting as a bridge.

A general method for obtaining these "platinum blue" species [33,39] is to react $PtCl_4^{2-}$ with an appropriate bridging ligand in water medium and the presence of OH^- (neutral or basic medium) and O_2 at ligand deficiency (M : L = 1 : 1):

$$PtCl_4^{2-} + XY \xrightarrow[H_2O,\,O_2]{OH^-} \text{"platinum blue"} \qquad (3)$$

Both creatinine and creatine are excellent bridging ligands for this purpose.

Figure 24 summarizes all the experimental data available for the $PtCl_4^{2-}$–creatinine reaction under various conditions [33].

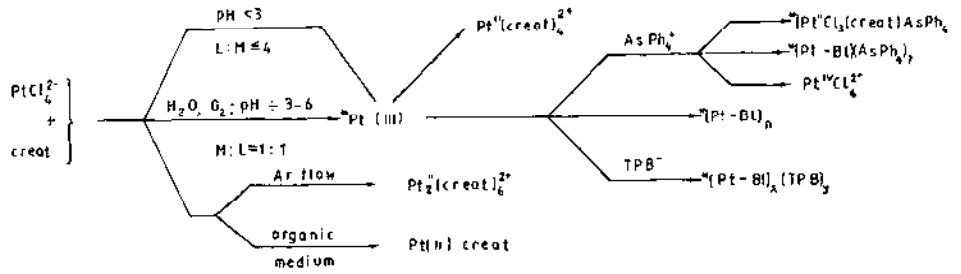


Fig. 24. Reaction scheme for $PtCl_4^{2-}$ reactions with creatinine under various conditions.

5. Biological significance

Both creatine and creatinine are important bioligands. Creatine is a "physiological component" of blood, the brain and muscles and is connected with energy flow [20]. Creatinine is an important end product of nitrogen metabolism in vertebrates and its level in urine and serum is recognized as an indicator of certain deseases (Creatinine Clearance Test) [5,20]. Udupa and co-workers [10–12] pointed out the importance of their complexation ability with metal ions for understanding their metabolism and thus inspired investigations on the coordination ability of these ligands towards metal ions. Rather surprisingly, however, no biochemical investigation on the complexation of creatine and creatinine in living systems has yet been performed. Nevertheless, some general conclusions can be drawn on the basis of the results discussed above.

(1) The formation of cationic complexes of creatinine with heavy metal ions such as Cu(II), Co(II), Pt(II), Pd(II) and Hg(II) in water medium suggests a significant influence of creatinine on the metabolisms of these metal ions and their excretion. (In this respect Ni(II) is a notable exception.) Determination of the corresponding formation constants would provide valuable information.

(2) Systematic screening of the various creatinine and creatine Pt(II) and Pd(II) complexes for potential antitumour activity is worthwhile, since their fast excretion might be expected. Special attention should be paid to "platinum blue" species with creatinine and creatine. A detailed study of "platinum blue" conduction in cells would also be of interest.

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