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SYNTHESIS AND CHARACTERIZATION OF CADMIUM COMPLEXES WITH PHOSPHORYLATED LIGANDS

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SYNTHESIS AND CHARACTERIZATION OF CADMIUM COMPLEXES WITH PHOSPHORYLATED LIGANDS

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ABSTRACT

Complexes of cadmium(II) with phosphorylated ligands were studied in the solid state. One of these ligands is phosphocreatine (HPCR), an important natural compound and the others are diisopropylphosphorylguanidine (DPG) and diisopropylphosphorylthiourea (DPT). The complexes were synthesized and characterized by elemental and thermogravimetric analyses and IR and Raman spectroscopy. The formed complexes are: $[Cd(PCr)Cl]_2$, $Cd(DPG)Cl_2$ and $[Cd(DPT)_3Cl]Cl$. In the HPCR and DPG complexes, Cd(II) is bound through the oxygen of the phosphoryl group and the nitrogen of the guanidine group and in the DPT complexes through the sulfur atom.

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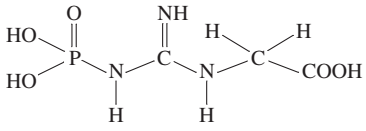
INTRODUCTION

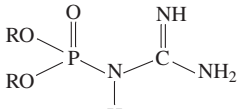
Phosphorylated compounds perform many biological functions (1). They participate in hydrolytic and enzymatic biochemical processes (2). The cleavage occurring in natural compounds releasing phosphates provides the energy required by living organisms for muscular movement, synthesis of complex biological molecules and transport of solutes against concentration gradients (3). On the other hand, hydrolytic cleavage releasing alkyl groups is important clinically since alkylating agents are used in cancer therapy. One example is cyclophosphamide, which requires enzymatic activation in the liver to perform its role (4).

The hydrolysis of phosphocreatine (HPCR, Figure 1) to creatine (CR), which is catalyzed by creatinekinase (CK) allows the transfer of high-energy phosphate groups to ADP (5,6). Muscles of vertebrates contain very high amounts of HPCR and CK.

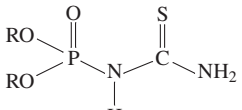
This phosphagen system (hydrolysis of HPCR) quickly regenerates ATP and buffers transient changes in the ATP-free ADP ratio. At the same time it provides inorganic phosphate for glycolysis, oxidative phosphorylation and other regulatory functions. Furthermore, in the last decade it was demonstrated that HPCR possesses important pharmaceutical properties, being employed for the treatment of acute ischemic diseases (7).



H PCR



DPG



DPT

HPCR = Phosphocreatine
DPG = Diisopropylphosphorylguanidine
DPT = Diisopropylphosphorylthiourea
R = isopropyl group

Figure 1. Structures of the ligands.

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Cadmium is known to be a toxic metal and a potent inhibitor of neuromuscular enzymes. This element can cause several undesirable effects in human beings including carcinogenesis, mutagenesis, oxidative stress and alterations in the antioxidant system resulting in toxicity to liver, kidneys, brain, lungs, heart, testes and the nervous system. It may react with groups present in the proteins such as S-H, S-S, OH, COO^-, NR_2 (8–10) and with phosphates (11). However, according to recent studies, it seems that under conditions where zinc is scarce, some marine organisms produce a cadmium-specific carbonic anhydrase (12). Thus, in spite of its toxicity cadmium may have a biological function. For these reasons, we decided to study cadmium complexes with HPCR and other similar ligands in solution and in the solid state (Figure 1).

Besides HPCR, we chose the ligands diisopropylphosphorylguanidine (DPG) and diisopropylphosphorylthiourea (DPT) to compare their binding sites. The structure of these three ligands can be seen in Figure 1.

RESULTS AND DISCUSSION

As it can be observed in Figure 1, all three ligands have one possible coordination site in common: the oxygen of the phosphonate. DPT also has a sulfur atom and in DPG the latter one is substituted by the nitrogen of the guanidine group. Besides, the phosphate and guanidine, HPCR has one carboxylate group being all potential binding sites for metals.

Synthesis

The formation of the complexes may be represented by the following general equations:

$$2CdCl_2 + 2\ HPCR \rightarrow [Cd(PCR)Cl]_2, + 2H^+ + 2Cl^-$$

$$CdCl_2 + DPG \rightarrow Cd(DPG)Cl_2$$

$$CdCl_2 + 3DPT \rightarrow [Cd(DPT)_3Cl]Cl.$$

The yields of the three complexes are all about 50%. The composition of the complexes can be seen in Table I.

Spectroscopic Data

The IR and Raman spectra of the ligands and their cadmium complexes were used to assign the various groups and compare the shifts due to complexation. Some bands of the ligands and their cadmium complexes are listed

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Table I. The Analytical Data for Cadmium Complexes

Compound	$[Cd(PCR)Cl]_2$ $(CdC_4H_9N_3O_5PCl)_2$	$Cd(DPG)Cl_2$ $CdC_7H_{18}N_3O_3PCl_2$	$[Cd(DPT)_3Cl]Cl$ $[CdC_{21}H_{51}N_6O_9P_3S_3\ Cl]Cl$
%C Found (Calc)	13.6 (13.4)	20.7 (20.7)	28.7 (27.9)
%H Found (Calc)	2.7 (2.8)	4.5 (4.4)	5.5 (5.6)
%N Found (Calc)	11.6 (11.7)	10.2 (10.3)	9.6 (9.3)
%O Found (Calc)	22.0 (22.3)	11.9 (11.8)	15.5 (15.9)
%S Found (Calc)	–	–	10.2 (10.6)
%Cd Found (Calc)	32.2 (31.2)	27.7 (27.6)	12.3 (12.4)
%Cl Found (Calc)	9.5 (9.9)	17.2 (17.5)	7.6 (7.9)
%P Found (Calc)	8.4 (8.7)	7.8 (7.7)	10.6 (10.3)
F.W.	715	406	903
D.T. (°C)	285	280	240
% Yield	49	52	48

in Table II. The spectral assignments for DPG were studied by our group earlier (13). All of these values were compared to those found in the literature (14).

When DPG is not bound to any metal, the PO group binds with the NH of the guanidine group through an intermolecular hydrogen bond (15). This hydrogen bond is broken on coordinating to cadmium. This can be seen by the shift of $\nu(PO)_{as}$ to higher frequencies. On the other hand, $\nu(PO)_s$ of the $Cd(DPG)Cl_2$ complex shifts to lower frequencies indicating coordination through this group. The C═N bands also shift to lower frequencies. In the case of HPCR and $[Cd(PCR)Cl]_2$, all of these bands are similar and the bands related to the carboxylic group also shift to higher frequencies suggesting that the ligands DPG and HPCR bind to cadmium through the oxygen of the phosphonates and the nitrogen of the guanidine group. However, additional spectroscopic evidence (e.g. NMR) will be required before the binding mode of these ligands is unambiguously demonstrated. We also found the presence of Cd-N and Cd-O bands in the far-IR region.

DPT differs from DPG because it has a C═S group in place of a C═N−H group. The absence of shifted bands in the region of C═N and of P−O and the presence of a band for C═S at 1099 cm^{-1} in DPT that disappears in the complex (16) demonstrates that sulfur is the donor atom in $[Cd(DPT)_3Cl]Cl$. The ν(Cd−S) band could not be found in the IR spectrum. Only in the Raman spectrum it was possible to attribute $\nu = 360$ cm^{-1} to ν(Cd–S). Weak Cd-S bands in far-IR are a characteristic behavior of thioureas systems (17,18).

It is also possible to see that the ν(Cd−Cl) bands of $Cd(DPG)Cl_2$ and $[Cd(DPT)_3Cl]Cl$ are at higher frequencies (217 and 223 cm^{-1}) than that of [Cd(PCR)

Table II. Some IR Spectral Assignments (cm^{-1}) for HPCR, DPG, DPT, and Their Cadmium Complexes

	DPG	$Cd(DPG)Cl_2$	HPCR	$[Cd(PCR)Cl]_2$	DPT	$[Cd(DPT)_3Cl]Cl$
ν(NH)	3436 w	3441 w	3413 w	3390 w	3350 m	3349 m
	3311 vw	3320 vw	3291 w	3320 vw	3269 w	3269 w
	3171 vw	3184 vw			3170 m	3171 m
ν(C=N)	1602 m	1557 w	1675 m	1642 w	–	–
ν(C=S)	–	–	–	–	1099 vw	–
ν(PO)	1187ν_{as} w	1205ν_{as} w	1169ν_{as} w	1194ν_{as} w	1223ν_{as} w	1222ν_{as} w
	1005ν_s m	997ν_s w	984ν_s w	945ν_s vw	1003ν_s w	998ν_s m
$\nu(COO)^-$	–	–	1619ν_{as} w	1715ν_{as} w	–	–
			1446ν_s vw	1500ν_s w		
ν(Cd–Cl)	–	304 vw	–	308 vw	–	
		300 R				
		217 R		187 vw		223 R
		210 vw				
ν(Cd–N)	–	355 vw	–	407 vw	–	–
		354 R		385 R		
ν(Cd–O)	–	246 w	–	264 vw	–	–
		244 R		275 R		
ν(Cd–S)	–	–	–	–	–	360 R

vw = very weak; w = weak; m = medium; R = Raman.

$Cl]_2$, (187 cm^{-1}) indicating a terminal chloride in $Cd(DPG)Cl_2$ and $[Cd(DPT)_3Cl]$ Cl and a bridging chloride in $[Cd(PCR)Cl]_2$, (14).

Thermogravimetric Analysis

The decomposition of the complexes, $Cd(DPG)Cl_2$, $[Cd(PCR)Cl]_2$ and [Cd $(DPT)_3Cl]Cl$, were observed by TG analysis. They showed that $Cd(DPG)Cl_2$ was stable up to 280°C. At this temperature it begins to decompose releasing the oxygen atoms and the isopropyl groups bound to them. At 440°C it loses PNH and from this temperature up to 900°C the cleavage continues, losing $N{=}C{-}NH_2$. At this temperature the remaining residue is Cd, Cl and O. The complex $[Cd(PCR)Cl]_2$ was stable up to 285°C, again indicating similar coordination sites for the cadmium complexes with DPG and HPCR. At this temperature it begins to decompose releasing the OH groups and at 710°C it loses one creatine group. Up to 900°C it loses the other creatine group bonded to a phosphorus atom. At 900°C 2Cd, 2Cl, 2O and P remain as residue. The complex $[Cd(DPT)_3Cl]Cl$ has a completely different behavior. It loses 68% of its weight at 240°C and this means that it loses

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Table III. Mass of Residue (%) After TG Analysis of the Cadmium Complexes

Compound	Temperature Range (°C)	Weight Loss (%)	Experimental (g) (Calculated)	Probable Fragment lost
$[Cd(PCR)Cl]_2$	20–285	8.93	63.87 (68)	4 OH
	285–710	17.76	126.96 (129)	creatine group
	710–900	21.64	154.72 (160)	P-creatine group
	>900	51.67	369.46 (358)	2Cd, 2Cl, 2O, P
		Residue		Residue
$Cd(HDPG)Cl_2$	20–280	27.56	111.88 (118)	2 C_3H_7O
	280–440	12.00	48.70 (46)	PNH
	440–900	18.76	76.15 (77.5)	$N{=}C{-}NH_2 + Cl$
	>900	41.69	169.26 (163.5)	Cd, Cl, O
				Residue
$[Cd(HDPT)_3Cl]Cl$	20–240	68.35	617.22 (624)	3 DPT but S
	240–540	10.53	95.05 (96)	3 S
	540–605	16.67	150.53 (147.5)	Cd, Cl
	>605	4.45	40.18	Ash, Residue

all of the three DPT molecules but the sulfur atoms, which still remain bound to cadmium. At 540°C it loses the three sulfur atoms and at 605°C it decomposes the remaining Cd and Cl and there is only a small residue left. The residual mass loss data are given in Table III.

EXPERIMENTAL

Materials

All chemicals used were analytical-grade. $CdCl_2.H_2O$ and $Ag(NO_3)$ were obtained from Merck, Darmstadt, and HPCR (as the dissodium salt) from Sigma. DPG and DPT were synthesized following a known procedure (19). The solvents used to prepare the cadmium and ligand solutions for the synthesis of the complexes were methanol, ethanol and acetone (Merck Darmstadt).

Synthesis of $[Cd(PCR)Cl]_2$

The $[Cd(PCR)Cl]_2$ complex was prepared according to the following process: A $CdCl_2.H_2O$ solution (1 mmol, 201.32 mg dissolved in 10 mL of ethanol) was added drop-wise, using a dropping funnel to a HPCR solution (1 mmol, 255.1 mg dissolved in 10 mL of methanol). The resulting mixture was stirred at room

temperature for concentration due to evaporation. After approximately 20 hours, the volume of the solution was concentrated to 5 mL. The white precipitated complex was then filtered and dried at room temperature in a desiccator over silica. The resulting solid was analytically pure.

Synthesis of $Cd(DPG)Cl_2$

The $Cd(DPG)Cl_2$ complex was prepared according to the following process: A $CdCl_2.H_2O$ solution (1 mmol, 201.32 mg dissolved in 10 mL of ethanol) was added drop-wise, using a dropping funnel, to a DPG solution (1 mmol, 223 mg dissolved in 10 mL of acetone). The resulting mixture was stirred at room temperature to partially evaporate the solvent. After approximately 20 hours, the volume of the solution was concentrated to 5 mL. The white precipitated complex was then filtered and dried at room temperature in a desiccator over silica. The resulting solid was analytically pure.

Synthesis of $[Cd(DPT)_3Cl]Cl$

The $[Cd(DPT)_3Cl]Cl$ complex was prepared according to the following process: A $CdCl_2.H_2O$ solution (1 mmol, 201.32 mg dissolved in 10 mL of ethanol) was added drop-wise, using a dropping funnel, to a DPT solution (1 mmol, 240 mg dissolved in 10 mL of 1:1 acetone:ethanol). Due to the poor solubility of DPT, its solutions were prepared with the aid of ultrasound. The resulting mixture was stirred at room temperature to partially evaporate the solvent. After approximately 20 hours, the volume of the solution was concentrated to 5 mL. The white precipitated complex was then filtered and dried at room temperature in a desiccator over silica. The resulting solid was analytically pure.

Elemental Analyses

The CHNS−O determinations were performed using a model EA 1110 elemental analyzer (CE Instruments) and cadmium was determined by atomic absorption spectrometry using a model 5 Varian Techtron spectrometer. The chloride content was determined by titration with $AgNO_3$. Phosphorus was determined by difference.

Spectroscopic Measurements

The infrared spectra were carried out using a model FT-IR 2000 Perkin Elmer spectrophotometer. Samples were prepared as KBr pellets for the range of

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4000–370 cm^{-1} and polyethylene ones for the range of 710–30 cm^{-1}. The Raman spectra were carried out on a Nicolet 950 FT-Raman.

Thermogravimetric Analysis

Thermogravimetric analyses were performed with a Perkin-Elmer TGA 7. The temperature range used was from 20 to 900°C, with a scanning rate of 10.0°C.min^{-1} in a nitrogen atmosphere.

CONCLUSIONS

The coordination site proposed for $Cd(DPG)Cl_2$ and $[Cd(PCR)Cl]_2$ are the oxygen of the phosphate and one nitrogen atom of the guanidine group (see Figure 2). In the $Cd(DPG)Cl_2$ complex the other positions are occupied by two

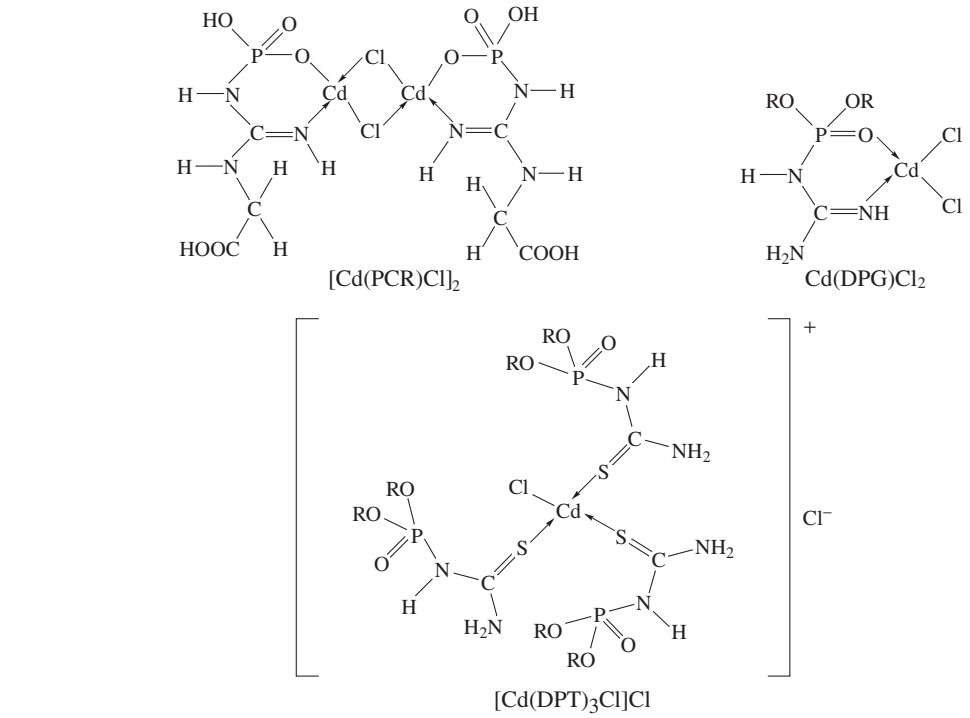

Figure 2. Suggested structures of the complexes.

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chloride ions. In the $[Cd(PCR)Cl]_2$ complex the two chlorides bridge two monomeric molecules of the complex.

In the case of the $[Cd(DPT)_3Cl]Cl$ complex the proposed structure involves monodentate behavior of the ligand. Three molecules of DPT bind to cadmium through the sulfur atom; the fourth position is occupied by a chloride ion, forming a cationic complex that is neutralized by another chloride.

The binding of Cd(II) through the phosphoramidate in HPCR and other ligands inhibits its cleavage and does not permit HPCR to perform its biological role.

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