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Study of Lead(II) Chelates of Penicillins

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LEAD salts have been shown to induce renal adenomas and renal adenocarcinomas in rodents following administration by dietary and parenteral routes[1-3]. In addition, carcinomas of the testis and adenomas of the adrenal, thiroid, pituitary, postate and lungs following chronic dietary administration of lead acetate to rats have been reported[4]. The carcinogenicity of tetraethyl lead has been tested following subcutaneous infection into neonatal Swiss mice[5]. Recent study in metal carcinogenesis in experimental animals has shown prohibition of tumours in the control rats receiving penicillin solutions[6]. Since cancer formation and its inhibition both are supposed to involve chelation[7], the value of formation and thermodynamic constants of metal complexes of these drugs will give important information in the understanding of their biological activity.

Hence, in the present note we report the thermodynamic parameters and characterisation of the isolated complexes of Pb^{II} with penicillins, V and G (PV and PG).

Experimental

All the chemicals used were of high purity, while the experimental details remain the same as in our previous communications[8].

Stoichiometry of the various species formed was determined using conductometric titrations and the stability constants were computed by Bjerrum-Calvin *p*H titration technique as adopted by Irving and Rossotti[9].

Thermodynamic parameters—the values of the changes in free energy (ΔG), enthalpy (ΔH) and entropy (ΔS) accompanying the metal ligand complex forming reactions have been calculated at various temperatures using the relations

$$\Delta G = -RT \log k$$

$$\Delta H = \frac{4.57 \text{ (d log k)}}{\text{d (1/T)}}$$

$$\Delta S = \frac{\Delta H - \Delta G}{T}$$

Equimolar solution of the metal and the ligand (penicillin G or V) in 1 : 2 ratio in 80% acetone-water (v/v) solution was refluxed for 4 h. The solution was then concentrated to one-fifth the original volume on a water bath. The complex was separated by vacuum filtration, washed with ether and dried under vacuum.

The composition of the complexes was ascertained by elemental analyses and the presence of the lattice water was estimated from the difference in the weight obtained on heating them to 110°. The results are recorded in Table 1. Ir spectra (KBr) were recorded on Perkin-Elmer Model 237 spectrophotometer.

TABLE 1—ANALYTICAL DATA OF Pb^{II} CHELATES

PG = $C_{16}H_{17}O_4N_2S$
PV = $C_{16}H_{17}O_5N_2S$

Compd.	Analysis % : Found/(Calcd.)					
	C	H	N	S	M	H_2O
PG chelate	32.10 (31.70)	3.81 (3.74)	6.33 (6.41)	7.41 (7.33)	23.11 (22.89)	3.40 (3.52)
PV chelate	31.30 (30.62)	3.70 (3.60)	6.23 (6.19)	7.12 (7.07)	22.15 (22.89)	3.47 (3.40)

Results and Discussion

The conductometric titrations show formation of ML and ML_2 complexes between Pb^{II} and penicillin G and V, while *p*H titrations indicate removal of one proton during complexation of each molecule. The *p*H titrations did not indicate formation of 1 : 3 complex in these systems. All attempts to trace possibility of complexation of more than two molecules of the ligand gave negative results. This may be due to the steric hindrance caused by the bulky molecules of PG and PV. Thus, the complex formation may be as follows :

$$M^{2+} + HL = ML^{+} + H^{+} \quad (1)$$

$$ML^{+} + HL = ML_2 + H^{+} \quad (2)$$

where HL = penicillin G or V.

An analysis of the formation curves (Fig. 1) indicates that addition of PV follows the mechanism of simultaneous addition and the two species co-exist in solution. The addition of PG on the other hand follows the mechanism of independent addition.

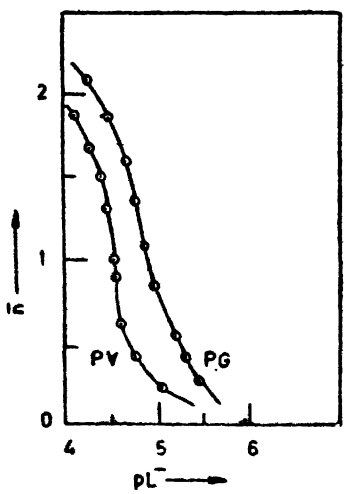

Fig. 1. Formation curves at 30°.

The values of formation constants and free energy change (Table 2) show that the penicillin G complex is more stable than that with penicillin V. This is in accordance with the base strengths of the two ligands (log k_1^H values for penicillin G and penicillin V, at 30° and 0.1 *M* ionic strength, being 4.77 and 3.98, respectively)[8].

The perusal of the values of the thermodynamic parameters (Table 2) clearly indicates that the reactions of these penicillins with Pb^{II} are enthalpy characterised reactions, since the values of entropy change are negative. The high values of negative enthalpy change indicate considerable degree of covalence in metal to ligand bond[11] which presumably involve metal to nitrogen bonding. Further, the value of ΔG for each stage is less negative than those of ΔH and each substitution therefore has negative ΔS (Table 1). The negative value of ΔS was predicted also to be due to the effect of solvent[12].

The analytical data indicate the general formula for the complexes to be $ML_2.2H_2O$. The ratio of the successive formation constants, k_1/k_2, are positive and show no abrupt or unusual changes, indicating the normal stoichiometry for the complexes studied. Further, with the use of very dilute solution ($1\times10^{-4}M$) of the metal possibility of the formation of polynuclear complexes may be ruled out.

The ir spectra of the complexes show that while most of the bands remain unchanged on complexation, there is a considerable shift in the frequencies of the carbonyl group and a slight deviation in that of the tertiary nitrogen of the β-lactam thiazolidine ring. Whereas the band due to tertiary nitrogen of the β-lactam thiazolidine at 1770 cm^{-1} varies

TABLE 2—STABILITY CONSTANTS AND THERMODYNAMIC PARAMETERS OF Pb^{II} CHELATES

μ=0.1 *M* ($NaClO_4$)

	Temp.	Ligand	Pb^{II} Chelate			Method*
		log β_1	log k_1	log k_2	log β_2	
Penicillin G**	20°	4.89	5.45	4.85	10.30	a
			5.44	4.95	10.40	b
	30°	4.77	5.34	4.70	10.04	a
			5.20	4.70	9.90	b
	40°	4.37	4.96	4.45	9.41	a
			4.95	4.39	9.34	b
Penicillin V**	20°	4.17	4.88	4.55	9.43	a
			5.02	4.55	9.56	b
	30°	3.98	4.60	4.32	8.92	a
			4.68	4.28	8.96	b
	40°	3.49	4.32	4.03	8.35	a
			4.37	3.90	8.27	b
			$-\Delta G_1$	$-\Delta G_2$	$-\Delta G_2$ (overall)	Temp.
			kcal mol^{-1}			°C
Penicillin V			6.81	6.14	12.92	20
			6.54	5.99	12.53	30
			6.24	5.70	12.53	40
Penicillin G			6.35	6.61	13.96	20
			6.84	6.57	13.41	30
			6.50	6.87	12.87	40
			$-\Delta H_1$	$-\Delta H_2$	$-\Delta H_2$ (overall)	
			kcal mol^{-1}			
Penicillin V			18.05	18.00	25.65	30
Penicillin G			13.71	13.25	21.94	30
			$-\Delta S_1$	$-\Delta S_2$	ΔS_2 (overall)	
			cal $k^{-1}mol^{-1}$			
Penicillin V			37.97	39.64	43.30	30
Penicillin G			25.96	22.06	26.32	30

* a=Half ñ method ; b=Least square method.
**Ref. 8.

slightly, the band due to antisymmetric stretching of $-C\begin{matrix}O\\O\end{matrix}\}^{\ominus}$ in potassium salts of penicillin G or V shifts from ~1600 to ~1700 cm^{-1}. This clearly indicates that the penicillin molecules are attached to the metal by chelation (forming a five membered ring) through the carboxyl group (replacing the hydrogen) and the tertiary nitrogen of the β-lactam with donation of the lone pair of electrons on it (Fig. 2).

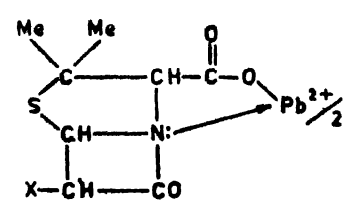

Fig. 2. Complex.

With the attachment of two molecules of the ligand (PG or PV) only four coordination sites are filled, the remaining two coordination positions in the octahedral geometry of the complexes being occupied with two water molecules. This finds confirmation[13,14] in the presence of bands near

3200, 1600 and 800 cm^{-1}. Low values of *p*Ka for these drugs ensure that they are almost entirely in the form of the complex forming species (the anion) at the physiological *p*H 7.3. Formation of only ML and ML_2 complexes indicates that the coordination number six for the metal ion is not attained. This may favour the attachment of the drug-chelate with the tissue, thus binding these drugs with the nucleic acid and affecting the structure and functions of nucleic acids, resulting in beneficial effects.

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Chromatographic Behaviour of Copper(II), Cadmium(II), Bismuth(III), Cobalt(II) and Nickel(II) Ions in Solvents Containing Dimethyl Sulphoxide

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THE present investigation is aimed at a study of the effect of dimethylsulphoxide (DMSO) when admixed with solvents of varying polarity on the paper chromatographic migrations of cations, namely Cu^{2+}, Cd^{2+}, Bi^{3+}, Co^{2+} and Ni^{2+}.

Experimental

Solutions of Cu^{II}, Cd^{II}, Bi^{III}, Co^{II} and Ni^{II} ions were prepared from their salts and the mixed solutions were prepared by mixing their individual solutions in suitable proportions.

Pure isopropanol, n-butanol, methylethylketone, chloroform, ethyl acetate, DMSO, and 50% nitric acid were used as eluents. The binary mixtures consisted of different proportions of DMSO in various solvents and adding a definite percentage of 50% nitric acid to minimise the diffusion and increase the sharpness of the band (Table 1).

Rutter's technique[1] of circular paper chromatography was adopted using 12.5 cm circles of Whatman No. 1 chromatographic paper and the elution carried out until the solvent front reached the premarked boundary. 0.05 to 0.1 ml of the solution was spotted containing 10 to 20 μg of the cations. For the comparison of Rr values of the ions Kawerau's modification of Rutter's technique was adopted. The spots were dried at 50-60° in air oven and the ions detected by spraying yellow ammonium sulphide[2].

Results and Discussion

In isopropanol, n-butanol, methylethylketone, the cations show only a diffusive migration. Rr values of the ions increases with increase in polarity. In other nonpolar solvents like ester, chloroform the ions do not migrate at all. However, in DMSO all the ions migrated almost to the solvent front. Due to its highly polar and donor nature, DMSO is capable of desorbing the adsorbed ions and subsequently solubilizes the ions due to its complex forming tendency with ions.

As in the case of pure solvents, the rate of migration of the ions increases with an increase in dielectric constant of the binary system. Thus, with higher concentration of DMSO, the Rr value is at its maximum and migration occurs almost to the solvent front, whereas with low proportion of DMSO the migration of ions was restricted. High donor capacity of DMSO is supported by non-linear graphs obtained from plot of Rr values of the ions with dielectric constant.

Quantitative separation of binary and ternary ions is possible with solvent systems such as DMSO : isopropanol : HNO_3 (50%) (20 : 70 : 10) ; DMSO : n-butanol : HNO_3 (50%) (10 : 84 : 6), (20 : 74 : 6) ; and DMSO : methylethylketone : HNO_3 (50%) (30 : 60 : 10) (Table 2).

From the above it can be inferred that DMSO plays a dual role in the chromatographic migration of ions on paper in solubilizing the ions, as well as enhancing the rate of migration because of its high polar nature and donor capacity.