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CO-ORDINATION SITES IN BIOMOLECULES: Zn(II) COMPLEXES WITH SOME N-PROTECTED AMINO ACIDS AND DIPEPTIDES

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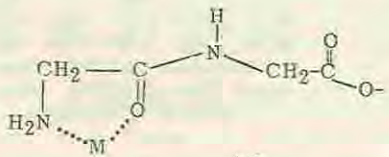
ABSTRACT. Zn(II) complexes with N-benzoyl derivatives of L-leucine, L-leucylglycine and N-formyl derivatives of DL-valine, L-phenylalanine, DL-valylglycine and L-phenylalanylglycine have been prepared. The possible stereochemistry of these compounds has been deduced with the help of analytical data, infrared spectra, thermogravimetric analysis and differential thermal analysis.

INTRODUCTION

Model studies of the interaction of Zn(II) with amino acids and peptides have become significant in order to better understand the role of the metal ion in biological systems [1]. N-protected amino acids and peptides are also of great biological importance [2]. Recently, the interaction of Cu(II) ion with N-protected amino acids has been reported [3]. In this paper we report the results of our studies dealing with the complexation behaviour of some N-benzoyl and N-formyl amino acids and dipeptides with Zn(II) ion. Our results indicate that the co-ordination sites of N-protected amino acids and dipeptides are different from those of free amino acids and peptides. The co-ordination behaviour of N-protected amino acids and peptides is governed by the nature of the protecting group. In amino acids, co-ordination occurs through the amino group and carboxylate oxygen. N-substitution should, in principle, result in the decrease of the affinity of the amino group for metal ion. In fact our investigation reveals that it is not involved at all in co-ordination. In free peptides co-ordination also occurs through the peptide group oxygen [4]. Infrared spectroscopic studies on N-protected dipeptide complexes clearly indicate that peptide group oxygen is also not involved in co-ordination. The most plausible explanation for this behaviour is that peptides form a stable five-membered ring by involving both the nitrogen of the α-amino and the oxygen of the amide groups in coordination with the metal ion as shown in structure (A).



(A)

Unlike free amino acids and their peptides, there are no marked differences in the co-ordination sites of N-protected amino acids and their peptides. This is because the amido side chain is not involved in co-ordination to the metal ion.

These complexes possess 1:2 stoichiometry irrespective of the metal/ligand ratio used. For N-benzoyl dipeptides and N-benzoyl amino acids, co-ordination occurs through the carboxylate group in bidentate manner. In the case of N-formyl dipeptides and N-formyl amino acids, in addition to carboxylate oxygen two water molecules are also involved in co-ordination.

EXPERIMENTAL

Preparation of the complexes. N-benzoyl and N-formyl amino acids and peptides were prepared by the method reported in the literature [5, 6].

$Zn(OH)_2$ was prepared as gelatinous precipitate by adding NH_4OH to the $ZnCl_2$ solution in HCl. For the preparation of Zn(II) complexes, a solution of ligand N-benzoyl, N-formyl, amino acids or dipeptides in methanol : water mixture (1:1,10 ml) was added to a suspension of freshly prepared $Zn(OH)_2$ in methanol: water mixture (1:1,10 ml). The reaction mixture was heated on a water bath. The reaction took 6-7 hrs. The excess of $Zn(OH)_2$ was filtered and the filtrate was evaporated under vacuum. The residues left were washed with acetone and recrystallized from methanol.

Physical measurements and analysis. The infrared spectra (KBr pellets) were recorded with specord 71-IR(DDR). DTA was recorded on a DTA-02-Universal (DDR) apparatus and TGA studies were carried out on a manual F.C.I. instrument.

Zinc was determined by complexometric titration with EDTA. Carbon, hydrogen and nitrogen were analysed at Australian Microanalytical service, Melbourne.

RESULTS AND DISCUSSION

The complexes, their yields and analytical data are reported in Table 1, the infrared spectra are given in Table 2, m.p., TGA and DTA are reported in Table 3.

Table 1. Yields and analytical data (Zn(II) of complexes.

S/NO	*COMPLEX	% Yield	Found% Zn	C	H	N	Expected% Zn	C	H	N
1	$[Zn(BZ\text{-}LeuO)_2)]$	80	12.10	58.22.	5.89	5.10	12.19	58.53	6.00	5.25
2	$[Zn(BZ\text{-}Leu\ GlyO)_2]$	60	10.40	55.40.	5.88	8.60	10.04	55.64	5.87	8.65
3	$[Zn(For\text{-}ValO)_2 2H_2O]$	63	16.45	36.95.	6.26	7.16	16.70	37.01	6.18	7.19
4	$[Zn(For\text{-}Val\ GlyO)_2 2H_2O]$	67	12.80	38.10.	6.09	11.10	12.92	38.17	5.96	11.13
5	$[Zn(For\text{-}PheO)_2 2H_2O]$	70	13.20	49.84.	5.08	5.70	13.40	49.48	4.94	5.77
6	$[Zn(For\text{-}PheGlyO)_2 2H_2O]$	65	10.70	47.96.	4.98	9.20	10.85	48.08	5.0	9.34

BZ = N-benzoyl; For = N-formyl; Gly = Glycine; Leu = L-Leucine; Val = DL-Valine; Phe = L-Phenylalanine
* Abbreviations for the Amino Acid and peptide ligands are in accord with the I.U.P.A.C.

Infrared spectra. The IR absorption bands of N-protected amino acids and peptides at 1720-1745 cm^{-1}, 1320-1370 cm^{-1} (ν COOH & ν COO sym. [7] and 1615-1645 cm^{-1} (ν CO) indicate the co-ordination behaviour of amino acids and peptides. The absorption bands at 1530-1555 cm^{-1} and 1380-1410 cm^{-1} have been assigned to ν COO asym. and ν COO sym. respectively. The positions of the bands and the difference between the asymmetric and symmetric stretching frequencies i.e. 145-150 cm^{-1} indicate the bidentate

co-ordination of carboxylate group [8-9]. In all these complexes positions of NH and carbonyl stretching frequencies remain unchanged as compared with those of the free ligands (Table 2), indicating the lack of co-ordination at the benzoyl-amino group, formyl-amino group and the peptide group. In the Zn(II) complexes with N-formyl dipeptides and N-formyl amino acids two absorption bands at 790 and 2280 cm^{-1} are observed which are the characteristic bands of co-ordinated water [10].

Table 2. Infrared spectra data of complexes.

S/NO	COMPLEX/LIGAND	Infrared spectra (cm^{-1})					
		νCO	νNH	νCOO_{asym}	νCOO_{sym}	νCOO	$\nu COOH$
1.	Bz Leu	1645	3320	1540	1320	220	1720
2.	$[Zn(Bz\text{-}LeuO)_2]$	1645	3320	1530	1380	150	-
3.	Bz Leu Gly	1645	3180	1560	1360	200	1730
4.	$[Zn(Bz\text{-}LeuGlyO)_2]$	1645	3180	1545	1400	145	-
5.	For Val	1625	3160	1570	1370	200	1730
6.	$[Zn(For\text{-}ValO)_2 2H_2O]$	1630	3160	1555	1410	145	-
7.	For Val Gly	1640	3300	1570	1370	200	1730
8.	$[Zn(For\text{-}Val\ GlyO)_2 2H_2O]$	1640	3300	1545	1395	150	-
9.	For Phen	1615	3330	1550	1340	210	1730
10.	$[Zn(For\text{-}PheO)_2 2H_2O]$	1620	3330	1535	1390	145	-
11.	For Phen Gly	1645	3330	1550	1330	220	1745
12.	$[Zn(For\text{-}PheGlyO)_2 2H_2O]$	1650	3330	1540	1395	145	-

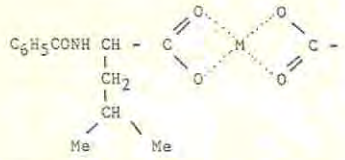
Table 3. DTA and TGA data of complexes.

S/NO	COMPLEX	m.p./decom. tem.(t°C)	DTA Peak Temperature (t°C)	(%) Loss Observed in TGA at tem. (t°C)	% Loss Calculated due to
1.	$[Zn(Bz\text{-}LeuO)_2]$	222-224	-	-	-
2.	$[Zn(Bz\text{-}Leu\ GlyO)_2]$	215-218	-	-	-
3.	$[Zn(For\text{-}ValO)_2 2H_2O]$	188-190	150, 180, 470 (endo) 560 (exo)	(4.70) 150 (4.70) 180	(4.62)$1H_2O$ (4.62)$1H_2O$
4.	$[Zn(For\text{-}Val\ GlyO)_2 2H_2O]$	185-188	180, 240, 580 (endo) 450 (exo)	(7.25) 180	(7.15)$2H_2O$
5.	$[Zn(For\text{-}PheO)_2 2H_2O]$	192-194	160, 180, 290, 630 (endo) 560 (exo)	(3.60) 160 (3.74) 180	(3.71)$1H_2O$ (3.71)$1H_2O$
6.	$[Zn(For\text{-}Phe\ GlyO)_2 2H_2O]$	194-196	150, 190, 280, 570 (endo) 440 (exo)	(3.10) 150 (3.15) 170	(3.0)$1H_2O$ (3.0)$1H_2O$

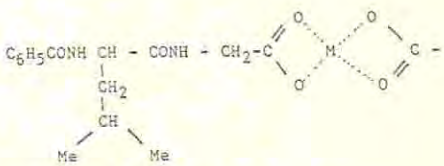
Thermogravimetric and differential thermal analysis. In the Zn(II) complexes with N-formyl-DL-valine and N-formyl-L-phenylalanine, the weight loss in TGA between 120° to 180°C corresponds to two water molecules. In the Zn(II) complex with N-formyl-DL-valine, two endothermic peaks at 150°C and 180° are recorded, whereas in the complex of N-formyl-L-phenylalanine two peaks at 160°C and 180°C are observed in the DTA curves indicating that two water molecules present in those complexes are co-ordinated to the metal ion.

In the DTA of Zn(II) complex with N-formyl-DL-valylglycine a strong endothermic peak is recorded at 180°C and corresponding loss in weight observed in TGA, due to two water molecules; whereas for Zn(II) complex of N-formyl-L-phenylalanyglycine, two endothermic peaks at 150°C to 190°C are recorded on DTA curves. These peaks are assigned to the loss of co-ordinated water molecules. Further heating of these complexes results in their decomposition and ultimately the formation of metal oxides with the loss of the ligands. Some endothermic and exothermic peaks are observed during this process of decomposition on DTA curves but since the loss in weight in TGA above 190°C is continuous and no stable species detected corresponding to these peaks; it is difficult to make assignment of any of these peaks.

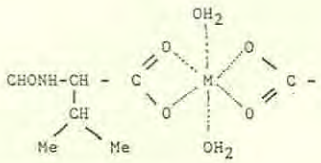
On the basis of the above studies distorted tetrahedral structures are proposed for Zn(II) complexes with N-benzoyl-DL-valine and N-benzoyl-DL-valylglycine (B-C). Similar co-ordination of Zn(II) ion has been reported with enzymes and other biomolecules [11-12]. An octahedral co-ordination of Zn(II) ion is suggested for formyl amino acid and formyl dipeptide complexes (D-G). Such octahedral co-ordination has been reported in the X-ray structure of Zn(II) complexes with GlyGlyGly and Glutamic acid [13, 14].



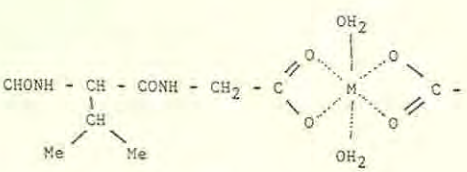
B: $Zn(Bz\text{-}LeuO)_2$



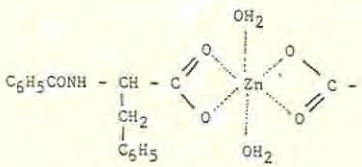
C: $Zn(Bz\text{-}LeuGlyo)_2$



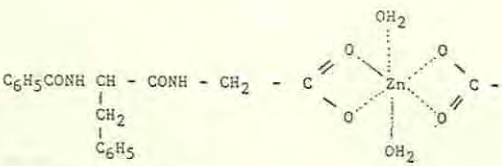
D: $Zn(For\text{-}ValO)_2 2H_2O$



E: $Zn(For\text{-}ValGlyo)_2 2H_2O$



F: $Zn(For\text{-}PheO)_2 2H_2O$



G: $Zn(For\text{-}PheGlyO)_2 2H_2O$

Scheme 1. Proposed structures of Zn(II) complexes.

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