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Intermolecular Interaction of Transition Metal Complexes Consiting of Amino Acid Moieties

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Zinc dicarboxylate complexes having Z-glycine and Z-oligopeptides as functional units in the ligands were prepared. Molecular aggregation of these complexes was investigated using several spectral techniques. The interaction of these complexes with ammonium salt etc. was also investigated using ^{1}H and ^{13}C NMR spectra.

Key words: Amino acid, Hydrogen bonding, Self-aggregation, Molecular recognition

1. INTRODUCTION

Recently, it has been clarified that metal complexes can be associated together and can make specific molecular aggregates. Among them several porous skeleton structures have been reported [1-5]. These porous skeleton structures contain micropores in nano meter size, and they can be applied to store, enclose and transmit specific small molecules in the pores. Meanwhile it is well known that hydrogen bonding plays an important role for several biological materials such as proteins and nucleic acids to maintain their higher order structure and to evaluate their functions. On the other hand amino acids themselves as building blocks of proteins are multifunctional molecules and can play as functional ligands as amino and/or carboxylato [6]. Consequently we attempted to prepare a specific aggregate of transition metal complexes having Z-glycine and Z-oligopeptides as ligands through intermolecular hydrogen bonding.

2. EXPERIMENTAL

2.1 Preparation of Zn(II) complexes with Z-oligopeptide

General synthetic method is as following; zinc oxide (1.0 mmol) was suspended in CH_3CN under N_2. Z-Amino acid or Z-oligopeptide (2.0 mmol) was added to the suspension with stirred at 80 ℃. After the reaction, precipitates were filtered off and the complexes were obtained as coloroless solids.

2.2 Characterization

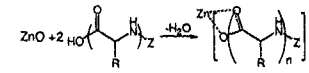
IR spectra were measured with a SHIMADZU FT-IR DR8500 using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded with a Varian UNITY 300 FT NMR apparatus (300MHz) at 29.0 ± 0.1 ℃. Concentrations of the complexes and the additives weere fixed as 0.42 mol dm^{-3} using DMSO-d_6 as a solvent.

3. RESULTS AND DISCUSSIONS

3.1 Preparations and identification of zinc complexes

The reactions of zinc oxide with Z-glycine or Z-oligopeptides in acetonitrile successfully gave zinc(II) dicarboxylate type complexes, which was confirmed with their elemental analysis (CHN) data; the range of the deviations from the calculated values based on $Zn[OC(O)R]_2$, where R is Z-$NHCH_2$ or Z-oligopeptides, were within ± 0.04%. Yields and mps of the complexes prepared in this study are summarized in Table I. Unfortunately, we can not obtain good single crystals of them for X-ray crystallography.

Table I Preparations of the Zn(II) dicarboxylate complexes



complexes	time / h	%-yields	mp / °C
$[Z\text{-}GlyO]_2Zn$	24	84	>300
$[Z\text{-}GlyGlyO]_2Zn$	24	95	240.0-241.0
$[Z\text{-}GlyGlyGlyO]_2Zn$	48	71	247.0-248.0
$[Z\text{-}GlyGlyGlyGlyO]_2Zn$	72	73	225.5-226.5
$[Z\text{-}GlyAlaO]_2Zn$	24	81	218.0-219.0
$[Z\text{-}GlyValO]_2Zn$	24	38	205.0-206.0
$[Z\text{-}GlyLeuO]_2Zn$	24	63	189.0-190.0
$[Z\text{-}AlaGlyO]_2Zn$	24	68	212.0-213.0
$[Z\text{-}ValGlyO]_2Zn$	24	75	221.0-222.0
$[Z\text{-}LeuGlyO]_2Zn$	24	72	190.5-191.5

Reactions were carried out at 80 ° C in acetonitrile. All elemental analysis data were well coinsided to calculated values.

Table II Selected vibrational modes of the ligands and complexes [a)]

ligands	wavenumbers / cm^{-1}		
	ligands	complexes	
	ν(COOH)	ν_{as}(COOZn)	ν_{s}(COOZn)
Z-GlyO	1730	1570	1400
Z-GlyGlyO	1736	1564	1395
Z-GlyGlyGlyO	1703	1553	1400
Z-GlyGlyGlyGlyO	1703	1551	1390
Z-GlyAlaO	1708	1552	1392
Z-GlyValO	1700	1538	1398
Z-GlyLeuO	1695	1530	1406
Z-AlaGlyO	1702	1535	1399
Z-ValGlyO	1704	1543	1399
Z-LeuGlyO	1710	1535	1407

a) Measurements were done using solid samples.

Selected vibrational absorption bands of the free ligands and the complexes are also summarized in Table II. Z-Glycine and other Z-oligopeptides showed characteristic ν(CO_2H) band at around 1695-1730 cm^{-1}. This range of the absorption maxima should indicate that these carboxylic acids exist as dimers [7]. The condensation of these acids with zinc oxide resulted in the disappearance of the above ν(CO_2H) band and in the appearance of two carboxylate bands; 1530-1570 cm^{-1} [$\nu_{as}(CO_2)$] and 1400 cm^{-1}[$\nu_{s}(CO_2)$] [7,8]. Elemental analysis data showed that two acids are bonded to a central zinc atom. Additionally, the presence of two absorption bands assignable to bidentate carboxylate suggested that the linkages between zinc and carboxylate are anisobidentate.

Consequently we concluded reasonablly that these zinc complexes with Z-glycine or Z-oligopeptides should be four-coordinated dicarboxylates and have T_d symmetry similar to zinc diacetate molecule. Further we could detect slightly higher wavenumber shifts of ν(N-H) of carbamoyl and/or amide that may be derived from the formation of some kinds of aggregates through an intermolecular hydrogen bonding. Significant coalescence of these ν(N-H) bands was, however, observed and we could not assign these bands to the identical N-H sites.

Next, we attempted to identify NMR signals to the corresponding protons and carbons of the complexes. Selected results of identifications are illustrated in Fig. I, focusing Z-glycine and Z-oligoglycines and their zinc complexes. These assignments appeared in Fig.I for the acids were coincided to the literature data [9]. Then the assignments for the complexes should proceed based on those of the acids and the coupling constants in ^{1}H NMR spectra between methylene protons and N-H. From Fig. I, the signals of $^{13}CO_2$-Zn in the complexes appeared at lower fields than those of $^{13}CO_2H$ in the acids, which again supported the presence of bidentate carboxylate linkage [9]. Signals relating to Z group and neighboring carbamoyl N-H did not move with bonding to zinc atoms. In contrast, both δ(CH_2) and δ(N-*H*) of the nearest glycine unit from zinc were shifted to higher fields in ca. 0.1 and 0.3-0.5, respectively. Such higher field shifts may be influenced by an induction effect from COOZn moiety in part and may indicate that the complexation with zinc should decrease the strength of intermolecular hydrogen bondings among the ligands. Significant line broadening was observed for signals of three amide units from *C*-terminal especially in Z-GlyGlyGlyGlyOH and its complex, which suggested the formation of aggregates of this Z-protected tetrapeptide unit through hydrogen bonding.

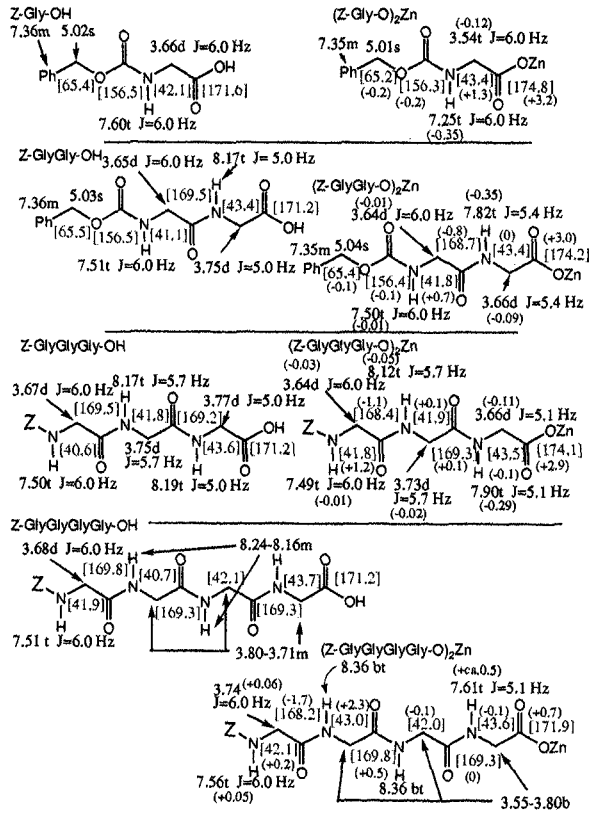


Figure I NMR assignments of ligands and Zn complexes. Chemical shifts δ of ^{1}H and [^{13}C] are displayed around the molecular formulae and the differences of the chemical shifts between the ligands and complexes are also represented in parentheses.

3.2 Specific interaction of (Z-GlyGlyGlyGlyO)$_2$Zn with methylammonium salts

We attempted to investigate on an interaction of the complexes with some active hydrogen compounds using NMR spectra in order to evaluate molecule recognition ability of these complexes. The active hydrogen compounds employed are as following; alkylamides such as butyramide, isobutyraminde, benzylamide, *N*-methylpropionamide, or *N*-ethylacetamide, urea and methylammonium [$(CH_3)_nNH_{4-n}$] salts. Conditions of measurement were as following; complexes (0.25 mmol) and the active hydrogen compounds (additives, 0.25 mmol) were dissolved together in 0.6 cm^3 of DMSO-d_6 (concentration 0.42 mol dm^{-3} for each components). Among these active hydrogen compounds employed, trimethylammonium hydrochloride specifically lowered the signals of δ(N-*H*) in the nearest glycine unit of (Z-GlyGlyGlyGlyO)$_2$Zn as shown in Fig. II. and III.

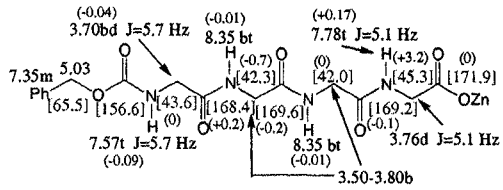


Figure II Chemical shift data of (Z-GlyGlyGlyGlyO)$_2$Zn in the mixture system with trimethylammonium hydrochloride. Chemical shifts δ of ^{1}H and [^{13}C] are displayed around the molecular formulae and the shifts from the free complex are represented in parentheses.

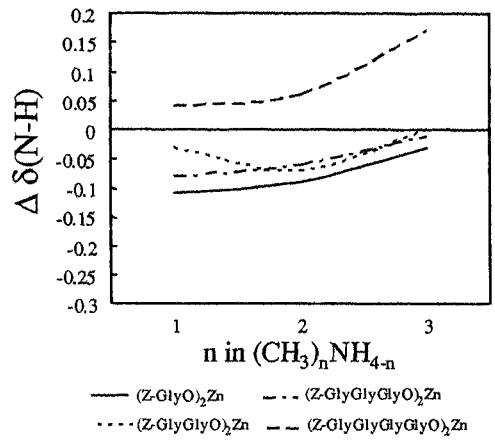


Figure III Chemical shift changes of δ(N-*H*) in the mixture of (Z-GlyO)$_2$Zn, (Z-GlyGlyO)$_2$Zn, (Z-GlyGlyGlyO)$_2$Zn or (Z-GlyGlyGlyGlyO)$_2$Zn with $(CH_3)_nNH_{4-n}$, n=1,2 and 3. Δδ(N-H) means the difference of the chemical shifts of N-H of the nearest glycine unit from zinc in free ligands and the complexes. Lower field shifts are represented by positive values and higher field shifts negative values. In the following figures, the term Δδ(N-H) indicate the same meanings.

Such a significant chemical shift change could not be observed in any other mixture systems consisting of (Z-GlyO)$_2$Zn, (Z-GlyGlyO)$_2$Zn, (Z-GlyGlyGlyO)$_2$Zn or (Z-GlyGlyGlyGlyO)$_2$Zn with $(CH_3)_nNH_{4-n}$, where n = 1,2 and 3, and other active hydrogen compounds. Thus, (Z-GlyGlyGlyGlyO)$_2$Zn may recognize trimethylammonium among several active hydrogen compounds employed, which should be detected by NMR. Although the scheme for such molecular recognition is not clear in this stage, it can be said that (Z-GlyGlyGlyGlyO)$_2$Zn should detect the presence of trimethylammonium by the change of the mode of molecular aggregates. The balkiest ammonium $(CH_3)_3NH$ perhaps has largiest effect to change such molecular aggregates.

3.3 Molecular recognition behavior of zinc complexes having dipeptide chains.

Investigations for similar molecular recognition behavior of Zn(II) dicarboxylate complexes having dipeptide chains as ligands towards $(CH_3)_nNH_{4-n}$, where n=1,2 and 3, were carried out and the results obtained are shown in Figure IV and V. These complexes of dipeptides are four-coordinated complexes, which was also confirmed by elemental analyses and ^{13}C NMR spectra as described above. At first the effect of substituents at outer amino acid units was investigated using (Z-AlaGlyO)$_2$Zn, (Z-ValGlyO)$_2$Zn and (Z-LeuGlyO)$_2$Zn together with (Z-GlyGlyO)$_2$Zn.. Figure IV represents the relations of Δ δ(N-H) of the nearest glycine unit to zinc atoms with the class of methylammonium salts.

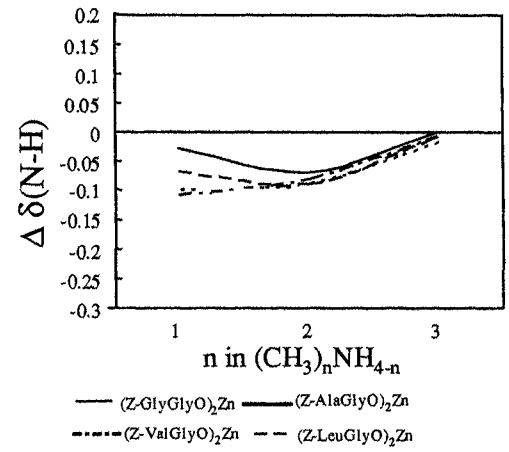


Fig. IV Chemical shift changes of δ(N-*H*) in the mixture of (Z-GlyGlyO)$_2$Zn, (Z-AlaGlyO)$_2$Zn, (Z-ValGlyO)$_2$Zn and (Z-LeuGlyO)$_2$Zn with $(CH_3)_nNH_{4-n}$, n=1,2 and 3.

No specific change of the chemical shifts was detected in the mixture systems of these complexes of dipeptide chains with methylammonium salts. The presence of alkyl substituents at the outer amino acid units perhaps prevents the formation of self-aggregation and the interaction with ammonium ions.

Next the effect of substituents at inner amino acid units was also investigated using $(Z\text{-GlyAlaO})_2Zn$, $(Z\text{-GlyValO})_2Zn$ and $(Z\text{-GlyLeuO})_2Zn$. Figure V shows the relations of $\Delta\delta$(N-H) of the nearest amino acid units to the zinc atoms with the class of methylammonium salts.

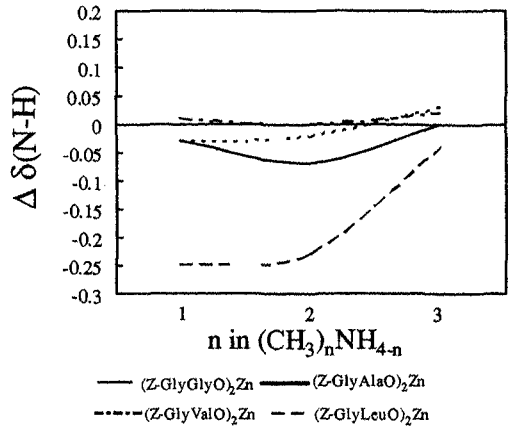


Fig. IV Chemical shift changes of δ(N-*H*) in the mixture of $(Z\text{-GlyGlyO})_2Zn$, $(Z\text{-GlyAlaO})_2Zn$, $(Z\text{-GlyValO})_2Zn$ and $(Z\text{-GlyLeuO})_2Zn$ with $(CH_3)_nNH_{4-n}$, where n=1,2 and 3.

In these cases it was expected that an intermolecular association was strongly prevented by the inner alkyl substituents. Further a weak interaction with ammonium ions were also expected. However, leucine derivatives showed specific behavior. Thus, δ(N-*H*) of leucine should move to higher field in the mixture with methylammonium and dimethylammonium chlorides. This phenomenon should be explained as following; because of low degree of association of $(Z\text{-GlyLeuO})_2Zn$, methylamonium and dimethylammonium ions, the smaller ammonium ions among $(CH_3)_nNH_{4-n}$, where n=1,2 and 3, can readily replace any intermolecular hydrogen bonding between $(Z\text{-GlyLeuO})_2Zn$ molecules at the outer glycine unit. Hence, $(Z\text{-GlyLeuO})_2Zn$ can recognize methylamonium and dimethylammonium ions.

4. CONCLUSION

Zinc oxide can react with Z-glycine and Z-oligopeptides such as Z-GlyGlyOH, Z-GlyGlyGlyOH, Z-GlyGlyGlyGlyOH, Z-GlyAla,OH, Z-GlyValOH, Z-GlyLeuOH, Z-AlaGlyOH, Z-ValGlyOH, and Z-LeuGlyOH to give zinc dicarboxylate complexes. Molecular recognition behavior was detected for $(Z\text{-GlyGlyGlyGlyO})_2Zn$ and $(Z\text{-GlyLeuO})_2Zn$ towards trimethylammonium hydrochloride and methylammonium or dimetylammonium chlorides, respectively, by the change of their molecular aggregation..

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