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# An Investion of Interaction of Transition Metal Complexes Having Oligopeptide Fragment as Ligands through Hydrogen Bonding

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We successfully prepared nickel(II) dithiocarbamates of several oligopeptide ester moieties, such as GlyGlyOMe and analogues, and investigated on the mode of their intermolecular association *via.* hydrogen bonding. Vibrational spectra and NMR observation indicated that all of them are associated through hydrogen bonding at amide within the ligands. Then we prepared cyclic nickel(II) dithiocarbamate complexes of amino acids bridged with ethylene glycol (EG), diethylene glycol (DEG), or triethylene glycol (TEG).

Key words: Hydrogen bonding, transition metal complexes, oligopeptides, supramolecules

## 1. INTRODUCTION

Hydrogen bonding is one of an important driving force in the formation of supramolecules in organisms. For example, proteins and peptides in the organs generate higher-order structure by hydrogen bonding. In addition, it is known that such peptide chains realize more topospecific structure by bridging with metal ions [1-5]. Besides, hydrogen bonding is also a key for sensing biomaterials, such as steroids, sugars and amino acids, *etc.* [6].

Therefore, it is expected that a synergetic effect of hydrogen bonding and bridging with metal ions should offer new supramolecules, which may be employed in a sensor actuator for such biomaterials. Recently, we have found and reported on the molecular recognition abilities of complexes of transition metals with oligopeptides *via.* a carboxylate linkage at *C*-terminal of the peptides for ammonium ions through an intermolecular hydrogen bonding [6]. However, these carboxylate complexes are generally labile against the ligand exchange, especially in polar media. Thus we attempted to prepare more stable metal complexes of oligopeptides in order to prepare actuators for biosensors of high performance.

Consequently, we tried to prepare some nickel(II) dithiocarbamate complexes having oligopeptide units leading to novel supramolecules. Further we investigated their mode and sites of intermolecular interactions *via.* hydrogen bonding in detail to reveal their potential abilities as actuators. Next, we also attempted to prepare new nickel(II) complexes with bidentate ligands containing two amino acid fragments connected with glycol moieties such as ethylene glycol (EG), diethylene glycol (DEG) and triethylene glycol (TEG) at their *C*-terminals, which may lead to offer a cyclic structure for the metal dithiocarbamates with differential association characteristics.

## 2. EXPERIMENTAL

### 2.1 Characterization

IR spectra were obtained with a Shimadzu FT-IR DR8500 using KBr pellets. $^{1}H$ and $^{13}C$ NMR spectra were recorded with a Varian Mercury-300 FT NMR at 29.0 ± 0.1 °C, in $CDCl_3$ or DMSO-$d_6$ solutions (concentration *ca.* 0.2 mol $dm^{-3}$). MALDI-TOF MS were measured with a PE Biosystems Voyager-DE PRO using α-CHCA as a matrix.

### 2.2 Preparation of Ni(II) dithiocarbamate complexes with dipeptide fragment

Preparation of Ni(II) dithiocarbamate complexes was carried out as previously reported [7,8]. Nickel(II) acetate tetrahydrate (1.0 mmol), dipeptide methyl ester hydrochlorides or ethyl esters (2.0 mmol) and sodium hydrogen carbonate (4.0 mmol) or sodium carbonate (2.0 mmol) were suspended in acetonitrile or methanol under nitrogen. Then carbon disulfide (2.0 mmol) was added to the suspension with stirring at 0 °C, and the mixture was further stirred at room temperature for 24-48 h. In some cases, the target complexes precipitated as green powders during the reaction and they can be isolated by filtration after the reaction. Otherwise volatiles were evaporated to dryness, and then the residues were dissolved into a small quantity of acetone. Green precipitates were obtained after mixing them with large quantities of water.

The nickel complexes obtained in this study were analyzed with EA, IR, $^{1}H$ and $^{13}C$ NMR and TOF MS, and the formation of these complexes was confirmed with those analytical data. Unfortunately, we cannot obtain any single crystals available to X-ray crystallography. Reaction conditons (periods), %yields and melting points of the complexes prepared are summarized in Table I. Additionally, some selected spectral data are also displayed in Table II.

2.3 Preparation of EG-bridged amino acids

General synthetic procedure is as following: Boc-amino acids (2.0 mmol) and ethylene glycol (EG, 1.0 mmol) were dissolved in dichloromethane (5 ml). Then DMAP (*N,N*-dimethylaminopyridine) (0.1 mmol) was added to the solution and the mixture was stirred at room temperature for 15 min. Afterwards, DIC (diisopropylcarbodiimido) (2.0 mmol) was added to the solution and the mixture was stirred for another 30 min with cooling in ice water. The solution was further stirred at room temperature for 24-48 h. After the reaction, volatiles were removed in vacuum and oily residue was obtained. The EG-bridged Boc-amino acids were obtained by column chromatography (silica gel) as colorless oil. Treating this oily product with HCl/dioxane gave EG-bridged amino acids. Similarly analogues from diethylene glycol (DEG), and triethylene glycol (TEG) were prepared in moderated to good yields. All the glycol-bridged amino acids indicated satisfactory elemental analyses

2.4 Preparation of Ni(II) dithiocarbamate complexes with bridged amino acid fragments

Nickel(II) acetate tetrahydrate (1.0 mmol) and the EG-bridged amino acid (AA-EG-AA, 1.0 mmol) were suspended in acetonitrile under nitrogen. While stirring, triethylamine (2.0 mmol) and carbon disulfide (2.0 mmol) were added to the suspension at 0 °C. Further the suspension was stirred at room temperature for 24 h. The target complexes were obtained as green powders. These complexes obtained showed satisfactory elemental analyses and their formulae are consistent with their spectroscopic data; *e.g.*, IR, and $^{1}H$ and $^{13}C$ NMR.

Table I Preparation of the Ni(II) dithiocarbamate complexes having oligopeptide fragments

$$Ni(OAc)_2 + 2\,CS_2 + [H_3N\text{-}AA\text{-}OR]^+Cl^- \xrightarrow[rt]{\text{solvent}} Ni\left[\text{dtc-AA-OR}\right]_2$$

dtc = dithiocarbamate

| AA-OR | t / h | % yield | mp / °C |
|---|---|---|---|
| GlyGly-OMe | 24 | 79 | 196.0-197.0 |
| GlyAla-OMe | 48 | 43 | 153.0-153.5 |
| GlyVal-OMe | 48 | 74 | 195.0-196.0 |
| GlyLeu-OMe | 48 | 89 | 193.0-194.0 |
| GlyIle-OMe | 48 | 73 | 189.0-190.0 |
| GlyPhe-OMe | 24 | 70 | 215.0-216.0 |
| AlaGly-OMe | 48 | 45 | 179.0-181.0 |
| LeuGly-OMe | 48 | 68 | 108.0-110.0 |
| GlyGlyGly-OMe | 48 | 57 | 198.5-199.5 |
| GlyGly-OEt | 24 | 55 | 197.0-198.0 |
| GlyAla-OEt | 48 | 81 | 178.0-179.0 |
| GlyVal-OEt | 48 | 75 | 160.0-161.0 |
| GlyLeu-OEt | 48 | 62 | 100.0-102.0 |
| GlyPhe-OEt | 48 | 66 | 170.5-171.0 |
| GlyGlyGly-OEt | 48 | 64 | 196.0-197.5 |
| GlyGlyGlyGly-OEt | 48 | 69 | 204.5-206.0 |

Table II Selected IR and $^{1}H$-NMR spectral data of the complexes containing of dipeptide moieties

| AA-OR | ν(N-H) / $cm^{-1}$ | δ($S_2CN$-*H*) | δ(CON-*H*) |
|---|---|---|---|
| GlyGly-OMe | 3339<br>3220 | 10.65 | 8.54 |
| GlyAla-OMe | 3256 | 10.68 | 8.58 |
| GlyVal-OMe | 3340<br>3184 | 10.66 | 8.43 |
| GlyLeu-OMe | 3275 | 10.68 | 8.53 |
| GlyIle-OMe | 3341 | 10.68 | 8.53 |
| GlyPhe-OMe | 3335<br>3207 | 10.63 | 8.61 |
| AlaGly-OMe | 3319<br>3204 | 10.75 | 8.65 |
| LeuGly-OMe | 3238 | 10.75 | 8.65 |
| GlyGly-OEt | 3328<br>3229 | 10.63 | 8.53 |
| GlyAla-OEt | 3348<br>3217 | 10.52 | 8.40 |
| GlyVal-OEt | 3273 | 10.66 | 8.49 |
| GlyLeu-OEt | 3310 | 10.66 | 8.49 |
| GlyPhe-OEt | 3300 | 10.65 | 8.61 |

## 3.RESULTS AND DISCUSSIONS

3.1 Preparations and characterization of Ni(II) dithiocarbamate complexes with oligopeptide fragments

Although, to prepare dithiocarbamate complexes, an aqueous solution of a strong base such as KOH is generally employed, mild bases such as $NaHCO_3$ or $Na_2CO_3$ in heterogeneous media was adopted in this study to avoid hydrolysis of an ester linkage at *C*-terminals of the oligopeptides during the reaction. Thus, overall 16 complexes were successfully prepared. Their yields and melting points are summarized in Table I. However, their single crystals suitable for X-ray crystallography could not be obtained.

In mass spectra (TOF-MS), these complexes showed the corresponding parent peaks with expectable isotope splitting. Thus they are monomeric and mononuclear complexes in vapor phase. An isobidentate nature of $CS_2$-M linkage can be read from the down field shifts of $\delta CS_2$ signals [9]. Such an isobidenticity of $CS_2$-M should lead to the planar four-coordinate geometry of nickel(II) dithiocarbamate complexes prepared in this study. Consequently, all nine atoms around the central nickel, $(NCS_2)_2Ni$ arrange onto a plane. Besides signals assignable to the amide proton appeared at around δ 8.5, in contrast, general amide protons without hydrogen bonding resonate at ca. δ 6.5. Such a large down field shift is perhaps brought by the formation of hydrogen bonding at amide.

While, vibrational absorption of amide N-H shifted to lower wavenumber region than 3400 $cm^{-1}$. It has been reported that the wavenumber of νN-H of amide moves to lower region than 3400 $cm^{-1}$ by forming hydrogen bonding [10]. Consequently, these results represented in Table II

indicate that all complexes prepared really form hydrogen bonding at amide N-H.

These nickel(II) complexes possess at least one amide within a ligand. Thus we tried to investigate the alteration of donating position with an increase of the numbers of the amino acid residues within the ligands and thoroughly investigated using NMR spectra. Fig. 1 shows the assignments of $^1$H-NMR signals of Ni(II) dithiocarbamates of oligo-glycine moieties such as diglycine(GlyGly), triglycine(GlyGlyGly) and tetraglycine(GlyGlyGlyGly). H-H COSY also confirms these assignments.

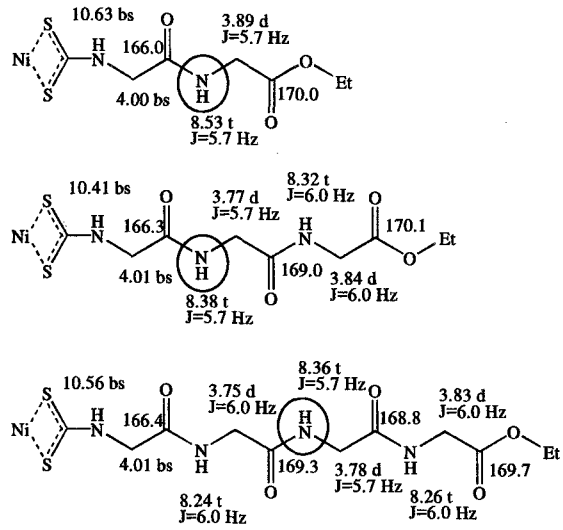


Fig.1 NMR assignments of Ni(II)dtc complexes having GlyGly, GlyGlyGly and GlyGlyGlyGly moieties. Circles indicate the preferencial sites of hydrogen bonding.

In GlyGlyGly derivative, the proton assignable to the γ–position from *N*-terminal, in other words the amide proton of the central glycine appeared at the lowest field between two amide protons. We concluded that hydrogen bonding should locate here. This can be supported by the identical coupling constant to that of the position of hydrogen bonding in the GlyGly derivative. While, more complicated aspect is arising in the GlyGlyGlyGly derivative, because it possesses three amide protons, but we can determine that hydrogen bonding locates at ζ-amide from *N*-terminal by the similar consideration to the GlyGlyGly analogue. In contrast, it has been reported that the position of hydrogen bonding of zinc(II) Z-tetraglycinate complex, $Zn(GlyGlyGlyGly\text{-}Z)_2$, is the nearest amide to the central zinc atom [6]. Such a difference should be derived from the difference of coordination geometry; four coordinated planar and tetrahedral, respectively. Thus it can be said that the position of hydrogen bonding should be tunable by the length of the peptide chain in the ligands.

3.2 Preparation of Ni dithiocarbamate complexes with bridged amino acid fragments

Next we attempted to connect two peptide chains of nickel(II) complexes having oligopeptide moieties, aiming at realizing molecular recognition by the complexes. Therefore, amino acids were bridged by ethylene glycol (EG), diethylene glycol (DEG) or triethylene glycol (TEG). Then, the preparation of nickel(II) dithiocarbamate complexes of these bridged amino acids were attempted similarly to the Ni(II) dithiocarbamates of oligopeptides.

We could isolate fifteen dithiocarmabate complexes of Gly, Ala, Val, Leu, and Ile bridged with EG, DEG and TEG in moderate yields. These complexes showed sharp mps, and the EA, IR and NMR investigations supported that these complexes possess formulae of Ni(dtcAA-G-AAdtc). Among them, we could not detect any monomeric, $M^+$ $[Ni(dtcAA\text{-}G\text{-}AAdtc)]^+$ or dimeric, $2M^+$ $[Ni_2(dtcAA\text{-}G\text{-}AAdtc)_2]^+$ peaks in TOF-MS of EG and TEG bridged derivatives; *e.g.*, G=EG or TEG. Thus these complexes should form a linear polymeric structure or larger cyclic structures than trimer; $[Ni(dtcAA\text{-}G\text{-}AAdtc)]_n$. Their spectral investigation with IR and NMR showed that these complexes have hydrogen bonding nature in the carbamoyl protons similarly to amide protons in the complexes of oligopeptides mentioned above. But we could not obtain further information about their structures.

In contrast to the EG and TEG bridged derivatives, we could detect $2M^+$ peaks with the corresponding isotope splitting patterns for DEG derivatives of Val, Leu and Ile in TOF MS as shown in Fig. 2; namely, $[Ni_2(dtc\text{-}Val\text{-}DEG\text{-}Val\text{-}dtc)_2]^+$ m/z 1024.02, $[Ni_2(dtc\text{-}Leu\text{-}DEG\text{-}Leu\text{-}dtc)_2]^+$ m/z 1080.08, and $[Ni_2(dtc\text{-}Ile\text{-}DEG\text{-}Ile\text{-}dtc)_2]^+$ m/z 1080.08. Additionally, we also detect several fragmentation peaks from these dimers. The presence of the fragments between $[2M^+]$ and $[M^+]$ suggests reasonably that these complexes obtained exist as cyclic dinuclear structures; namely two nickel atoms were combined with two bidentate ligands as illustrated in Fig. 3.

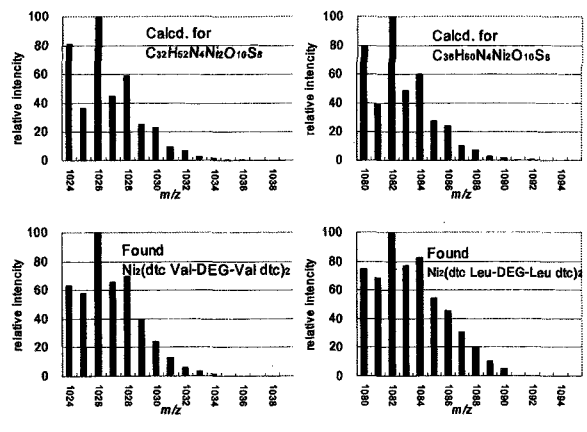


Fig.2 Molecular ion peaks ($2M^+$) of the complexes [Ni(dtc Val-DEG-Val dtc)] (left) and [Ni(dtc Leu-DEG-Leu dtc)] (right) are presented. The calculated isotope splitting patterns are also cited in the bottom.

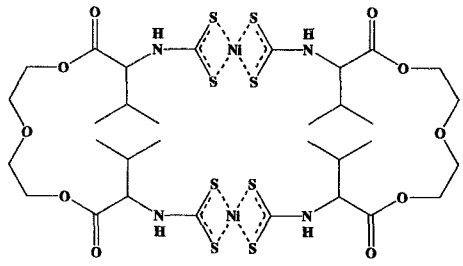

Fig.3 Structure of the cyclic dinuclear complex appeared in this study, $Ni_2$(dtcVal-DEG-Val dtc)$_2$.

Then we prepared nickel(II) dithiocarbamate complexes of two different amino acid moieties bridged with DEG such as $Ni_2$(dtcVal-DEG-Leu dtc)$_2$ in order to discard the fear of the dimer formation during the ionization in the chamber of TOF MS. We could isolate this complex under similar conditions and could detect the dimer peak of $[Ni_2$(dtc Val-DEG-Leu dtc)$_2]^+$ in TOF MS. Further, selective transesterification of this complex was done in methanol in the presence of the base. The mixture of the Ni(II) dithiocarbamate complexes was also analyzed with TOF MS, and we could detect three molecular ion peaks, such as $[Ni(dtcValOMe)(dtcLeuOMe)]^+$, $[Ni(dtcValOMe)_2]^+$, and $[Ni(dtcLeuOMe)_2]^+$ as shown in Fig.4. If this complex is presented as monomeric Ni(dtcVal-DEG-Leudtc), the transesterification should offer unsymmetrical [Ni(dtcValOMe)(dtcLeuOMe)] only. The presence of two symmetrical dithiocarbamate complexes supports the formation of the cyclic dimers as illustrated in Fig. 5.

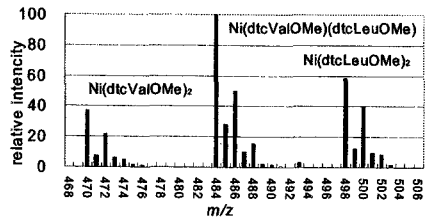


Fig. 4 Three molecular ion peaks detected for the mixture after transesterification of Ni(II) complex of dtcVal-DEG-Leu dtc with methanol.

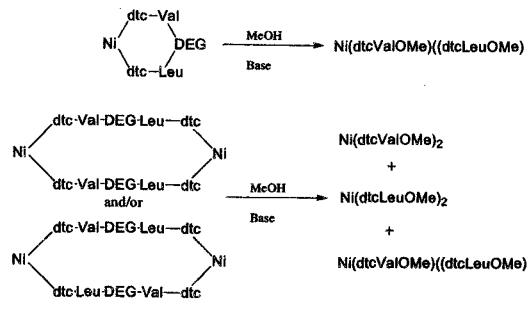


Fig. 5 Transesterification of the DEG bridged dithiocarbamate complex.

Selected spectral data for these cyclic dinuclear complexes and two dithiocarbamates of amino acid esters are summarized in Table III. From Tables II and III, the presence of intermolecular association through hydrogen bonding can be read as in the complexes of oligopeptide esters and amino acid esters [8] and these complexes, especially DEG-bridged analogues possess potential abilities for molecular recognition.

Table III Selected spectral data of Ni(II)dtc complexes having Val-DEG-Val, Leu-DEG-Leu, Ile-DEG-Ile, and Val-DEG-Leu.

| ligands | ν(N-H)/ $cm^{-1}$ | δ($S_2$CN-*H*) | δ(COO) |
|---|---|---|---|
| dtcVal-DEG-Val dtc | 3265 | 10.91 | 169.0 |
| dtcLeu-DEG-Leudtc | 3227 | 10.92 | 169.8 |
| dtcIle-DEG-Iledtc | 3275 | 10.95 | 169.1 |
| dtcVal-DEG-Leudtc | 3260 | 10.92 | 169.9<br>169.0 |
| dtcVal-OMe | 3258 | 10.95 | 169.5 |
| dtcLeu-OMe | 3258 | 10.90 | 170.2 |

## 4. CONCLUSION

Nickel(II) dithiocarbamate complexes with the oligopeptide chain, and bridging amino acids by EG, DEG or TEG were successfully prepared. These complexes form an intermolecular association through hydrogen bonding at amide within the ligands. Further, ligands consisting of DEG bridging amino acids such as two Val, two Leu, two Ile, and Val and Leu give cyclic dinuclear dithiocarbamate complexes.

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