Nickel(II) Complexes of Schiff Bases Derived from Salicylaldehyde and Glycyl-aspartate or -glutamate. Application to a Selective Hydrolysis Reaction of Dimethyl Glycylaspartate and Glycylglutamate

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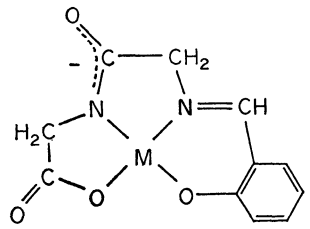
Nickel(II) complexes of Schiff bases derived from salicylaldehyde and glycylaspartate or glycylglutamate were prepared and their structures were determined on the basis of electronic absorption and ^{1}H NMR spectra. The relationship between structure of the chelates and stability of fused-ring systems was discussed in some detail, and was applied to a selective hydrolysis reaction of dimethyl glycylaspartate and glycylglutamate. Nickel(II) complexes of Schiff bases derived from salicylaldehyde and β-methyl glycylaspartate or γ-methyl glycylglutamate were obtained by a reaction between dimethyl glycylaspartate or glycylglutamate and bis(salicylaldehydato)-nickel(II) in methanol containing sodium or potassium hydroxide.

In a previous paper,[1] we reported as the result of a comparative study on copper(II) and nickel(II) complexes (**1**, **2**) of Schiff bases derived from salicylaldehyde and glycylglycine or glycyl-β-alanine that the fused-ring system of **1** (6-5-5) is more stable than that of **2** (6-5-6).[2] In connection with such delicate difference in the stability of fused-ring systems, we have extended the study to the preparation and structural determination of nickel(II) complexes of Schiff bases composed of salicylaldehyde and glycyl-aspartate and -glutamate. As an application of the result concerning the structure-stability relationship, we have also attempted selective hydrolysis reactions of dimethyl glycylaspartate and glycylglutamate.



M = Cu(II), Ni(II)

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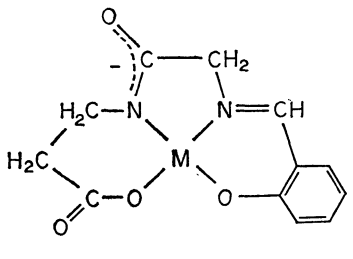

M = Cu(II), Ni(II)

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Experimental

Dibenzyl L-*Aspartate Hydrochloride* was prepared by the method of Miller *et al.*[3]

*Glycyl-*L-*aspartic Acid* was obtained by catalytic reduction of dibenzyl *N*-benzyloxycarbonylglycyl-L-aspartate, which had been prepared from *N*-benzyloxycarbonylglycine and dibenzyl L-aspartate hydrochloride according to the direction of Miller *et al.*[3]

Dibenzyl L- *and* DL-*Glutamate Benzenesulfonates* were prepared by a similar procedure to that for benzyl glycinate benzenesulfonate.[4] The L-compound was identified by comparing the melting point with that in literature.[5] Melting point and analytical data of dibenzyl DL-glutamate benzenesulfonate, which was recrystallized from ethanol are as follows: mp 118—119 °C. Found: C, 61.40; H, 5.63; N, 3.07%. Calcd for $C_{25}H_{27}O_7NS$: C, 61.83; H, 5.62; N, 2.89%.

Dibenzyl L- *and* DL-*Glutamate Hydrochlorides* were obtained from the corresponding benzenesulfonate described above.[6]

Dibenzyl N-*Benzyloxycarbonylglycyl-*L- *and* -DL-*glutamates* were prepared by the same method as that for the corresponding dibenzyl *N*-benzyloxycarbonylglycyl-L-aspartate, using dibenzyl L- and DL-glutamate hydrochlorides instead of dibenzyl L-aspartate hydrochloride.[3] These compounds were obtained as oily products, which were used for the subsequent reaction without further purification.

*Glycyl-*L- *and* -DL-*glutamic Acids.* These were obtained by the catalytic reduction of the corresponding dibenzyl *N*-benzyloxycarbonylglycyl-L- and -DL-glutamates by using palladium black as a catalyst. In all cases, methanol was used as solvent with a small amount of acetic acid. These peptides were recrystallized from water–ethanol. H·Gly·DL-Glu·OH: mp 184—187 °C (dec). Found: C, 40.78; H, 5.81; N, 13.71%. Calcd for $C_7H_{12}O_5N_2$: C, 41.17; H, 5.94; N, 13.72%.

Glycyl-L-glutamic Acid was identified from the melting point.[5]

Dimethyl DL-*Aspartate and* DL-*Glutamate Hydrochlorides* were prepared according to the ordinary method.[7]

Dimethyl N-*Benzyloxycarbonylglycyl-*DL-*aspartate.* This was prepared in a similar procedure as that reported by Winitz *et al.*[8] To a solution of 13.7 g of *N*-benzyloxycarbonylglycine, 13.0 g of dimethyl DL-aspartate hydrochloride and 9.2 cm^3 of triethylamine in 135 cm^3 of chloroform was added 14.1 g of dicyclohexylcarbodiimide. The reaction mixture was stirred at room temperature overnight. After removal of precipitated

N,N'-dicyclohexylurea, the filtrate was washed with water, 1 mol/dm³ HCl, saturated aqueous solution of $NaHCO_3$, and water. After the chloroform fraction had been dried over anhydrous magnesium sulfate, the filtrate was evaporated to dryness. The oily products obtained were recrystallized from ethyl acetate and petroleum benzine. Mp 93—95 °C. Found: C, 54.53; H, 5.75; N, 7.97%. Calcd for $C_{16}H_{20}O_7N_2$: C, 54.53; H, 5.75; N, 7.95%.

Dimethyl N-*Benzyloxycarbonylglycyl*-DL-*glutamate.* This was prepared from *N*-benzyloxycarbonylglycine and dimethyl DL-glutamate hydrochloride in the same way as described for dimethyl *N*-benzyloxycarbonylglycyl-DL-aspartate. Mp 64—65 °C. Found: C, 56.01; H, 6.18; N, 7.59%. Calcd for $C_{17}H_{22}O_7N_2$: C, 55.72; H, 6.06; N, 7.65%.

Hydrochlorides of Dimethyl Glycyl-DL-*aspartate and Glycyl*-DL-*glutamate.* These were obtained by catalytic reduction of dimethyl *N*-benzyloxycarbonylglycyl-DL-aspartate and -DL-*glu*tamate using palladium black catalyst. Methanol containing a small volume of concentrated hydrochloric acid was used as solvent. These compounds were obtained as oily products, which were recrystallized from methanol–ether. Gly·DL-Asp(OMe)$_2$·HCl: mp 146—148 °C. Found: C, 37.35; H, 5.88; N, 10.83%. Calcd for $C_8H_{15}O_5N_2Cl$: C, 37.72; H, 5.95; N, 11.00%. Gly·DL-Glu(OMe)$_2$·HCl: mp 139—141 °C. Found: C, 40.00; H, 6.38; N, 10.43%. Calcd for $C_9H_{17}O_5N_2Cl$: C, 40.22; H, 6.39; N, 10.43%.

Benzyl γ-Aminobutyrate p-*Toluenesulfonate* was prepared by the same method as that for the corresponding benzyl β-alaninate *p*-toluenesulfonate.[9] Recrystallization was carried out by using ethanol–ether. Mp 107—107.5 °C. Found: C, 59.29; H, 6.39; N, 3.91%. Calcd for $C_{18}H_{23}O_5NS$: C, 59.15; H, 6.36; N, 3.83%.

Benzyl N-*Benzyloxycarbonylglycyl-γ-aminobutyrate.* This was prepared in a similar method as that reported by Winitz *et al.*[8] To a solution of 14.6 g of *N*-benzyloxycarbonylglycine, 24.6 g of benzyl γ-aminobutyrate *p*-toluenesulfonate and 9.8 cm³ of triethylamine in 160 cm³ of chloroform was added 14.5 g of dicyclohexylcarbodiimide. The reaction mixture was stirred at 25 °C overnight. After removal of precipitated *N,N'*-dicyclohexylurea, the filtrate was washed with water, 1 mol/dm³ HCl, saturated aqueous solution of $NaHCO_3$, and water. After the chloroform fraction had been dried over anhydrous magnesium sulfate, the filtrate was evaporated to dryness. The crystalline materials obtained were recrystallized from ethyl acetate and petroleum benzine. Mp 83—84 °C. Found: C, 65.49; H, 6.39; N, 7.24%. Calcd for $C_{21}H_{24}O_5N_2$: C, 65.60; H, 6.30; N, 7.29%.

Glycyl-γ-aminobutyric Acid. This was obtained by catalytic reduction of benzyl *N*-benzyloxycarbonylglycyl-γ-aminobutyrate using palladium black catalyst. Methanol containing a small volume of glacial acetic acid was used as solvent. Recrystallization was carried out by using water and ethanol. Mp 198—202 °C (dec). Found: C, 44.50; H, 7.48; N, 17.09%. Calcd for $C_{13}H_{18}O_3N$: C, 44.98; H, 7.57; N, 17.49%.

Bis(salicylaldehydato)nickel(II) and Barium N-*Salicylideneglycyl-β-alaninatonickelate(II)*, **2** were prepared according to the direction described previously.[1]

Potassium N-*Salicylideneglycyl-γ-aminobutyratonickelate(II)*, **6.** Into 30 cm³ of a water: ethanol mixture (2: 1 by volume) were dissolved 0.8 g of glycyl-γ-aminobutyric acid and 1.5 g of bis(salicylaldehydato)nickel(II). The resulting mixture was adjusted to pH 9—10 with concentrated KOH solution and stirred at 40 °C for 3 h. After it had been filtered, the solution was evaporated to dryness *in vacuo* to give a yellowish green powder. The powder was recrystallized from hot ethanol. Found: C, 41.21; H, 4.59; N, 7.03%. Calcd for K[Ni($C_{13}H_{13}O_4N_2$)]·H_2O: C, 41.40; H, 4.02; N, 7.43%.

Dipotassium N-*Salicylideneglycyl*-L-*aspartatonickelate(II)*, **3a.** A mixture of 0.50 g of glycyl-L-aspartic acid and 0.79 g of bis(salicylaldehydato)nickel(II) was dissolved in 15 cm³ of water–ethanol (2: 1 by volume). The reaction mixture was adjusted to pH 9—10 by concentrated KOH solution and stirred at room temperature for 1 h. After it had been filtered, ethanol was added to the filtrate to give orange crystals, which were recrystallized from water–ethanol. Found: C, 35.36; H, 2.48; N, 6.33%. Calcd for K_2[Ni($C_{13}H_{10}O_6N_2$)]·H_2O: C, 35.07; H, 2.72; N, 6.29%.

Dipotassium N-*Salicylideneglycyl*-L- *and* -DL-*glutamatonickelates-(II)*, **4a** were prepared in the same way as for chelate **3a**. K_2[Ni(Sal=Gly·L-Glu)]·2.5H_2O: Found: C, 34.69; H, 4.04; N, 5.77%. Calcd for K_2[Ni($C_{14}H_{12}O_6N_2$)]·2.5H_2O: C, 34.58; H, 3.53; N, 5.76%. K_2[Ni(Sal=Gly·DL-Glu)]·3.5H_2O: Found: C, 33.33; H, 3.64; N, 5.67%. Calcd for K_2[Ni($C_{14}H_{12}O_6N_2$)]·3.5H_2O: C, 33.34; H, 3.81; N, 5.56%.

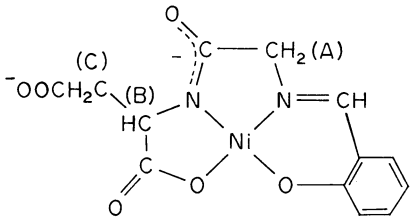
The Reaction between Dimethyl Glycyl-DL-*aspartate and Bis(salicylaldehydato)nickel(II) in Methanol.* To a mixture of 0.75 g (0.0025 mol) of bis(salicylaldehydato)nickel(II) and 0.64 g (0.0025 mol) of dimethyl glycyl-DL-aspartate hydrochloride in 10 cm³ of methanol was added a concentrated KOH methanol solution, until the color of the solution became completely orange. The reaction mixture was then stirred at room temperature for 2 h, being allowed to stand for a few more hours in a refrigerator; hereupon orange crystals were obtained in 70% yield. The products were filtered and recrystallized from methanol. Found: C, 41.35; H, 3.39; N, 6.88%. Calcd for K[Ni($C_{14}H_{13}O_6N_2$)], **7**: C, 41.71; H, 3.26; N, 6.95%.

The Reaction between Dimethyl Glycyl-DL-*glutamate and Bis(salicylaldehydato)nickel(II) in Methanol.* A mixture of 0.67 g (0.0025 mol) of dimethyl glycyl-DL-glutamate hydrochloride and 0.75 g (0.0025 mol) of bis(salicylaldehydato)nickel(II) was dissolved in 15 cm³ of methanol. To the solution was added 0.27 g of sodium hydroxide and 0.42 g of barium perchlorate. The mixture was stirred at room temperature for 2 h to give an orange crystalline material, yield 75%. This was filtered and washed several times by methanol. Found: C, 40.18; H, 3.79; N, 6.07%. Calcd for Ba/2[Ni($C_{15}H_{15}O_6N_2$)], **9**: C, 40.33; H, 3.39; N, 6.27%.

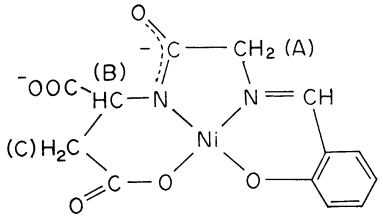
Measurements. Melting points were determined on a micro melting point apparatus and uncorrected. The PMR spectra were recorded by using a JEOL MH-100 spectrometer with sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard and deuterium oxide was used as a solvent. The pD-adjustment was carried out by the addition of concentrated NaOD–heavy water solution. A Yanagimoto pH-66A pH meter equipped with a MGR-11A combined electrode was used after standardization with a Wako standard buffer solution (pH 6.86 and 9.18 at 25 °C). The visible and ultaviolet absorption spectra were obtained with a 323 Hitachi Recording Spectrophotometer. The IR spectra were recorded with a Hitachi EPI-2 Infrared Spectrophotometer. The measurements were carried out at room temperature using the pressed KBr disk technique in the wave number range 700—4000 cm^{-1} with a rock-salt prism.

Results and Discussion

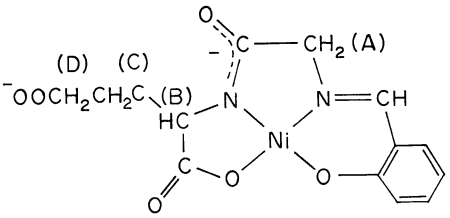
Nickel(II) Complexes of Schiff Bases Derived from Salicylaldehyde and Glycylaspartate or Glycylglutamate. These nickel(II) complexes were prepared by reactions of each dipeptide with bis(salicylaldehydato)nickel(II) in the pH range 9—10. Since the complexes do not exhibit any absorption peak in the visible and near infrared region, they are expected to have such square-planar



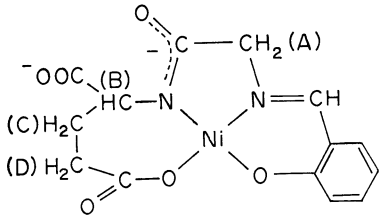
3a



3b



4a



4b

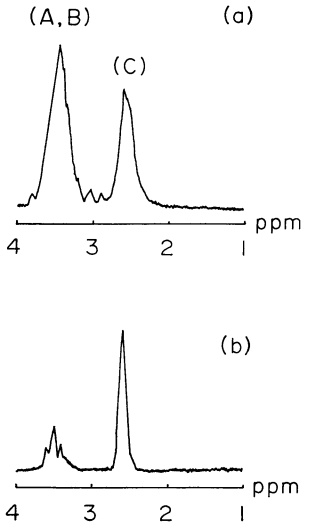
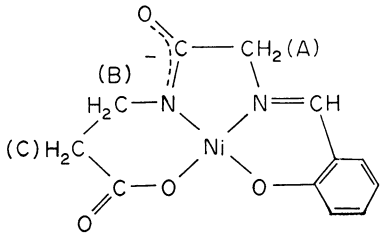


Fig. 1. PMR spectra of $[Ni(Sal{=}Gly\cdot L\text{-}Asp)]^{2-}$: (a) pD 7.8, room temp, after 2 h; (b) pD 13.1, 40 °C, after 8 days.

structures as **3-** and **4-a** or **-b**. In the structural formulas, the symbol (A) indicates the methylene group of glycinate residue, while (B), (C), and (D) indicate the methylene or methine groups of α-, β- and γ-position in the C-terminal amino acid residues. In order to confirm the structure of glycyl-L-aspartate-Schiff base complex, the PMR spectra were measured in D_2O under various conditions (Fig. 1). Inspection of the PMR spectrum represented in Fig. 1(a) reveals that signals for the methylene or methine protons of (A), (B), and (C) are not separated in three but two peaks, of which the ratio of absorption intensity at 3.56 and 2.60 ppm is 3:2. It was clealy observed that the peak at 3.56 ppm turned out triplet together with decrease in intensity after 8 days at pD 13.1, 40 °C, while the peak at 2.60 ppm remained unchanged (Fig. 1(b)). From the fact, the nickel(II) complex of Schiff base composed of salicylaldehyde and glycyl-L-aspartate may be reasonably accepted as the structure **3a** rather than as **3b**, since the deuteration of (A) methylene and (B) methine groups in **3a**, can be understood by taking into account the results obtained through the deuteration in *N*-salicylideneglycylglycinato- and -glycyl-L-α-alaninatonickelates(II).[10] In other words, (A) methylene protons of glycyl-L-aspartate residue in **3a** are entirely replaced by deuterons, whereas the (B) methine proton is not so entirely replaced as (A) under the same conditions. On the other hand, if *N*-salicylideneglycyl-L-aspartatonickelate(II) had the structural formula **3b**, only the



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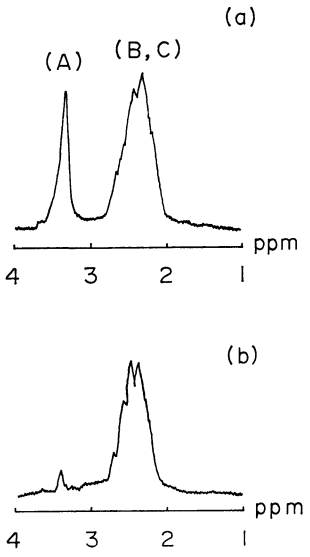
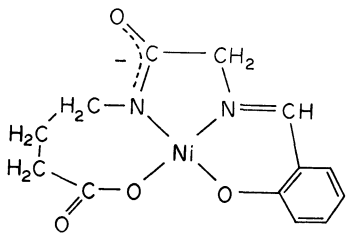


Fig. 2. PMR spectra of $[Ni(Sal{=}Gly\cdot\beta\text{-}Ala)]^{-}$: (a) pD 9.3, room temp, after 1 h; (b) pD 13.2, 40 °C, after 8 days.

deuteration of (A) methylene protons would take place. This is because of the fact that the deuteration of (A) methylene protons in *N*-salicylideneglycyl-β-alaninatonickelate(II), **5** occurs easily, whereas that of (B) and (C) methylene protons does not at all (Figs. 2(a) and (b)). Preferential formation of **3a** instead of **3b** suggests that the stability of fused-ring system decreases in the order 6-5-5>6-5-6, showing good agreement with the previous conclusion established for copper(II) and nickel(II) complexes, **1** and **2**.[1)]



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The *N*-salicylideneglycyl-L- or -DL-glutamatonickelate(II) is orange, while *N*-salicylideneglycylglycinato- and *N*-salicylideneglycyl-γ-aminobutyratonickelates(II) (**1** and **6**), are orange and brownish green, respectively. The d-d transition band of the complex, **6** was observed at 950 nm. On the basis of these facts, potassium *N*-salicylideneglycyl-γ-aminobutyratonickelate(II) is not supposed to be the square-planar type. This may be attributed to a rather weak ligand field of the *N*-salicylideneglycyl-γ-aminobutyrate, whose fused-ring structure involves a 7-membered ring. On the other hand, the square-planar structure of *N*-salicylideneglycylglycinato- and -glycylglutamato-nickelates(II) have been inferred from the absence of absorption peak in the visible and near infrared region. Thus, the nickel(II) complex of Schiff base

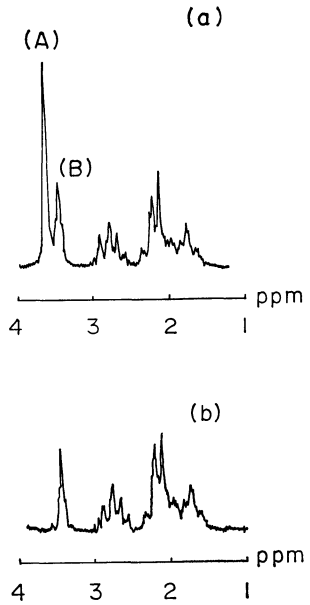
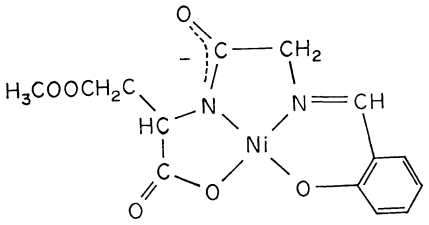


Fig. 3. PMR spectra of $[Ni(Sal{=}Gly\cdot L\text{-}Glu)]^{2-}$: (a) pD 9.6, room temp, after 1 h; (b) pD 13.8, 40 °C, after 9 days.

derived from salicylaldehyde and glycyl-L- or -DL-glutamate can be represented as the structure **4a**. The PMR spectrum shown in Fig. 3(a) also indicates that *N*-salicylideneglycyl-L-glutamatonickelate(II) is diamagnetic, and probably is planar. On the basis of the result of deuteration in *N*-salicylideneglycyl-L-aspartatonickelate(II), **3a**, it is expected that (A) methylene and (B) methine protons in **4a** are deuterated in D_2O solution. In fact, the peak at 3.64 ppm arising from the (A) methylene protons disappears on allowing the solution to stand at 40 °C, pD 13.8 for 9 days, as is clear from Figs. 3(a) and (b). On the other hand, the peak due to the (B) methine proton remains unchanged under the same conditions; the corresponding (B) methine proton of *N*-salicylideneglycyl-L-aspartatonickelate(II), **3a** was fairly deuterated under similar conditions. This may be correlated to the extent of the upfield shift of (B) methine peak in **3a** and **4a**. The (B) methine peak in **3a** and **4a** appeared at 3.58 and 3.47 ppm, respectively. We described previously that the methylene protons, of which the signal is observed at the lowest field in PMR spectra of a series of tripeptide-nickel(II) chelates, were most easily deuterated in D_2O solution.[11)] Therefore, the difficulty of deuteration of (B) methine in **4a** is thus understandable.

Selective Hydrolysis of Dimethyl Glycyl-DL-aspartate or Glycyl-DL-glutamate by Bis(salicylaldehydato)nickel(II) in Methanol. The reaction between dimethyl glycyl-DL-aspartate hydrochloride and bis(salicylaldehydato)-nickel(II) in methanol containing potassium hydroxide gave an orange nickel(II) complex. Inspection of the IR spectrum of the complex reveals the band characteristic of ester group at around 1720 cm^{-1}. The electronic spectrum in methanol–dimethyl sulfoxide solution resembles those observed for *N*-salicylideneglycyl-L-aspartato- and -glycyl-L-glutamato-nickelats(II) which are estimated to have the square planar structure. Thus, the structure of the nickel(II) complex obtained is considered as shown in formula **7** or **8**. The result of elemental analysis also supports the above presumption. Further, we are more in line with the structure **7**, since the 6-5-5-fused ring structure is supposed to be more



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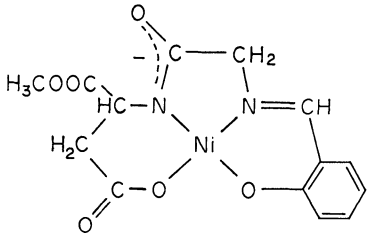

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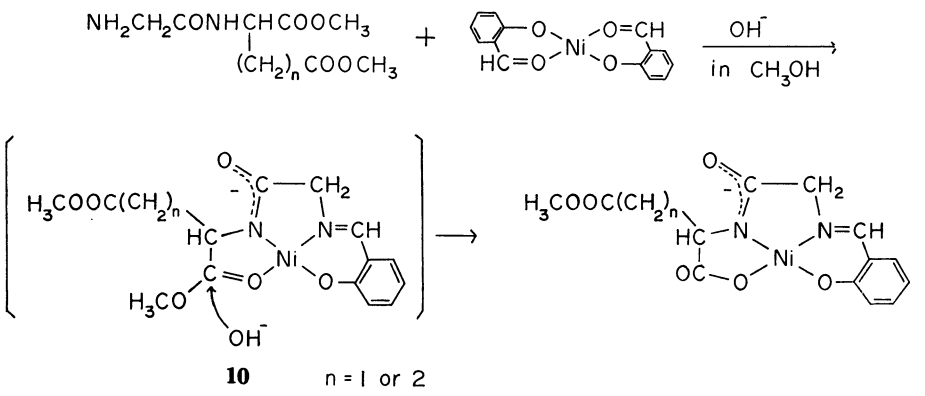
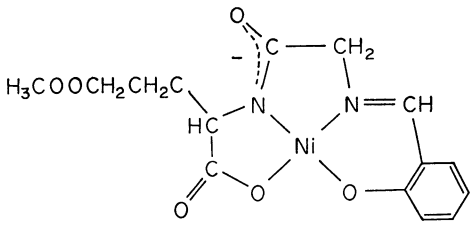


10 n = 1 or 2

Scheme 1.



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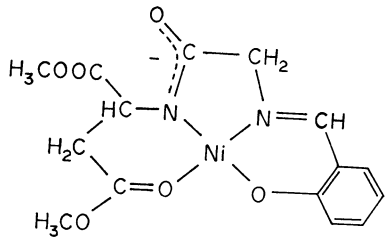
stable than the 6-5-6-fused ring structure. Accordingly, it can be concluded that the hydrolysis of ester groups occurred preferably at the α-position in the dimethyl glycyl-DL-aspartate. Likewise, the α-ester group in dimethyl glycyl-DL-glutamate is also selectively hydrolyzed under similar conditions. Since the isolation of potassium salt of γ-methyl *N*-salicylideneglycyl-DL-glutamatonickelate(II), **9** was a little more difficult, we obtained the same chelate as the barium salt. The selective hydrolysis of peptide ester of this kind can well be explained by a mechanism involving the intermediate **10** as illustrated in Scheme 1. In **10**, the carbon atom of the α-ester group would be readily attacked by hydroxide ion. Of course, there is a possibility for the ester group coming into coordination at the β- or γ-position as indicated in **11** or **12**. However, the coordination of the β- or γ-ester group is supposed to be much more difficult than that of the α-ester group. This is because of the foregoing argument that the 6-5-5-fused chelate ring is more stable than the 6-5-6 or 6-5-7 ring in the nickel(II) chelates of Schiff bases derived from salicylaldehyde and glycyl-aspartate or -glutamate.



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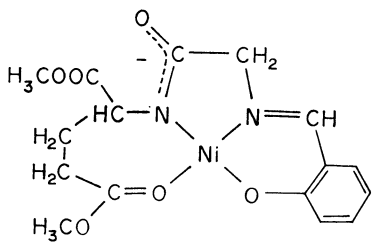

12

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