Selective Ester-exchange Reactions of Dibenzyl-aspartate and -glutamate in the Coordination Sphere of Copper(II) Ion

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Copper(II) complexes of the Schiff bases derived from salicylaldehyde and dibenzyl aspartate or glutamate have been prepared for the first time. Upon refluxing the solution of these complexes in methanol for 30 min, bis(α-methyl β-benzyl *N*-salicylideneaspartato)copper(II) and bis(α-methyl γ-benzyl *N*-salicylideneglutamato)-copper(II) were obtained. The mechanism of these selective ester-exchange reactions in the metal-coordination sphere has been discussed. Several Schiff bases were obtained and characterized.

Many reactions of amino acids, such as transamination, racemization, substitution of α-hydrogen and decarboxylation, proceed *via* formation of metal Schiff base chelates as intermediates, most of them being useful as models for pyridoxal-dependent enzymatic reactions.[1,2]

A number of studies have been carried out on the ligand reactivities of the metal complexes of Schiff bases derived from amino acid esters and carbonyl compounds. The ester-exchange reaction was reported by Pfeiffer *et al.*,[3] extended by other investigators.[4–7] However, most of the studies have been confined to the reactions of those containing simple amino acid esters. Nakao and Nakahara studied the selective ester-exchange reaction in copper(II) chelate of the Schiff base composed of salicylaldehyde and dibenzyl DL-aspartate.[8] In this paper we report on the mechanism of selective ester-exchange reactions occurring in the coordination sphere of copper(II) ion, on the basis of our recent study on the other copper(II) chelates.

Experimental

Benzyl Glycinate Benzenesulfonate was prepared by the method of Cipera and Nicholls.[9]

p-*Toluenesulfonates of Benzyl β-Alaninate and γ-Aminobutyrate* were prepared according to the reported method.[10]

Dibenzyl L- *and* DL-*Aspartate Benzenesulfonate* were obtained by a similar procedure to that for benzyl glycinate benzenesulfonate.[9] Melting points and analytical data of these compounds recrystallized from ethanol are as follows: L-Asp(OBzl)$_2$·$C_6H_5SO_3H$: mp 113—114 °C. Found: C, 60.99; H, 5.41; N, 3.01%. DL-Asp(OBzl)$_2$·$C_6H_5SO_3H$: mp 134—134.5 °C. Found: C, 60.81; H, 5.47; N, 3.05%. Calcd for $C_{24}H_{25}O_7NS$: C, 61.12; H, 5.35; N, 2.97%

Dibenzyl L- *and* DL-*Glutamate Benzenesulfonate* were prepared according to the reported method.[10]

Dibenzyl DL-*Glutamate Hydrochloride* was obtained from the corresponding benzenesulfonate described above.[11]

α-Methyl-β-benzyl L- *and* DL-*Aspartate Hydrochloride.* β-Benzyl L- and DL-Aspartate were prepared by the procedure reported by Izumiya *et al.*[12] The L-compound was identified by a comparison of melting point. Melting point and analytical data of β-benzyl DL-aspartate recrystallized from hot water containing a small volume of triethylamine are as follows: mp 211—214 °C (dec.). Found: C, 59.25; H, 5.89; N, 6.30%. Calcd for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28%.

β-Benzyl N-*Benzyloxycarbonyl-*L- *and* -DL-*aspartate*: The L-compound was obtained by the method reported by Ariyoshi *et al.*[13] from β-benzyl L-aspartate. The DL-compound was prepared by the same method, being recrystallized from ethyl acetate–petroleum ether. Mp 99—101 °C. Found: C, 63.60; H, 5.39; N, 3.95%. Calcd for $C_{19}H_{19}O_6N$: C, 63.86; H, 5.36; N, 3.92%.

*β-Benzyl-*N-*carboxy-*L- *and* -DL-*aspartate Anhydride*: The compounds were prepared from β-benzyl *N*-benzyloxycarbonyl-L- and -DL-aspartate by the method of Berger and Katchalski.[14] The L-compound was identified by comparing the melting point with that reported.[14] Melting point and analytical data of DL-compound washed with petroleum ether are as follows: mp 150—153 °C. Found: C, 57.70; H, 4.54; N, 5.66%. Calcd for $C_{12}H_{11}O_5N$: C, 57.82; H, 4.46; N, 5.62%.

α-Methyl β-benzyl L- and DL-Aspartate Hydrochloride were prepared according to the method of Ariyoshi *et al.*[13] DL-Asp(α-OMe)(β-OBzl)·HCl: mp 120—121 °C. Found: C, 52.72; H, 5.97; N, 5.13%. Calcd for $C_{12}H_{16}O_4NCl$: C, 52.66; H, 5.90; N, 5.12%.

α-Methyl-γ-benzyl L-*Glutamate Hydrochloride.* γ-Benzyl L-Glutamate,[15] γ-Benzyl *N*-Benzyloxycarbonyl-L-glutamate[16] and γ-Benzyl *N*-carboxy-L-glutamate Anhydride[16] were prepared according to the reported method.

α-Methyl γ-benzyl L-Glutamate Hydrochloride was prepared by the same method as that for the corresponding α-methyl β-benzyl L-aspartate hydrochloride,[13] using γ-benzyl-*N*-carboxy-L-glutamate anhydride instead of β-benzyl-*N*-carboxy-L-aspartate anhydride. Mp 129—131 °C. Found: C, 53.81; H, 6.25; N, 5.03%. Calcd for $C_{13}H_{18}O_4NCl$: C, 54.26; H, 6.32; N, 4.87%.

Copper(II) Complex of the Schiff Base Derived from Salicylaldehyde and Benzyl Glycinate, [*Cu(Sal=GlyOBzl)*$_2$], ***1a.*** A mixture of 6.4 g (0.02 mol) of benzyl glycinate benzenesulfonate and 3.1 g (0.01 mol) of bis (salicylaldehydato)copper (II) was dissolved in 40 cm^3 of water. The reaction mixture was then stirred at 40 °C for 2 h. After it had been cooled, a brownish green crystal was filtered, and washed several times by water, yield 60%. IR(KBr) 1735 cm^{-1} (ester C=O). Found: C, 63.44; H, 5.06; N, 4.69%. Calcd for [$Cu(C_{32}H_{28}O_6N_2)$]: C, 64.04; H, 4.71; N, 4.67%.

Copper (II) Complexes of the Schiff Bases Derived from Salicylaldehyde and Benzyl β-Alaninate and γ-Aminobutyrate, [*Cu(Sal=β-AlaOBzl)*$_2$], ***1b*** *and* [*Cu(Sal=γ-*N*-BuOBzl)*$_2$], ***1c.*** These complexes were prepared in a similar manner using benzyl β-alaninate *p*-toluenesulfonate and benzyl γ-aminobutyrate *p*-toluenesulfonate, respectively. [Cu(Sal=β-AlaOBzl)$_2$]: yield 60%. IR (KBr) 1730 cm^{-1} (ester C=O). Found: C, 64.80; H, 5.47; N, 4.29%. Calcd for [$Cu(C_{34}H_{32}O_6N_2)$]: C, 65.00; H, 5.14; N, 4.46%. [Cu(Sal=γ-*N*-BuOBzl)$_2$]: yield 43%. IR (KBr) 1725 cm^{-1} (ester C=O). Found: C, 64.58; H, 5.31; N, 4.00%. Calcd for [$Cu(C_{36}H_{36}O_6N_2)$]·1/2H_2O: C, 64.99;

H, 5.62; N, 4.21%.

The Reactions of Copper(II) Complexes ***1a***, ***1b***, *and* ***1c*** *with Methanol.* The reaction mixture of 1 g of the complex **1a**, **1b**, or **1c** and methanol (200 cm^3)–chloroform (100 cm^3) was heated under reflux for 30 min. After it had been filtered, the filtrate was cooled to give brownish green crystals. They were collected by filtration, the same additional product being obtained by removing the solvent. The products were identified as the copper(II) chelates of the Schiff bases derived from salicylaldehyde and methyl glycinate, β-alaninate, and γ-aminobutyrate, respectively, from the results of elemental analyses. [Cu(Sal=GlyOMe)$_2$]: 92% yield. IR(KBr.) 1750 cm^{-1} (ester C=O). Found: C, 53.20; H, 4.76;N, 6.14%. Calcd for [Cu($C_{20}H_{20}O_6N_2$)]: C, 53.62; H, 4.51; N, 6.25%. [Cu(Sal=β-AlaOMe)$_2$]: 66% yield. IR(KBr) 1720 cm^{-1} (ester C=O). Found: C, 55.16; H, 5.33; N, 5.95%. Calcd for [Cu($C_{22}H_{24}O_6N_2$)]: C, 55.50; H, 5.09; N, 5.88%. [Cu(Sal=γ-*N*-BuOMe)$_2$]: 60% yield. IR(KBr) 1730 cm^{-1} (ester C=O). Found: C, 55.45; H, 5.78; N, 5.57%. Calcd for [Cu($C_{24}H_{28}O_6N_2$)]·H_2O: C, 55.21; H, 5.80; N, 5.37%.

Copper(II) Complexes of Schiff Bases Derived from Salicylaldehyde and Dibenzyl L- *and* DL-*Aspartates,* [*Cu(Sal=*L- *or* DL-*Asp(OBzl)$_2$)$_2$*], ***3a***. To a mixture of 5.6 g (0.012 mol) of dibenzyl L- or DL-aspartate benzenesulfonate and 60 cm^3 of water was added 1.9 g (0.006 mol) of bis(salicylaldehydato)-copper (II). The reaction mixture was stirred at 40 °C for 3 h, and allowed to stand for a few hours at room temperature. The precipitate was collected by filtration, and washed with water and ethanol. [Cu(Sal=L-Asp(OBzl)$_2$)$_2$]: 40% yield. Mp 130.5—132 °C. IR(KBr) 1735 cm^{-1} (ester C=O). Found: C, 67.04; H, 5.11; N, 3.30%. Calcd for [Cu($C_{50}H_{44}O_{10}N_2$)]: C, 66.98; H, 4.96; N, 3.13%. [Cu(Sal=DL-Asp(OBzl)$_2$)$_2$]: 96% yield. Mp 138—140 °C. IR(KBr) 1735 cm^{-1} (ester C=O). Found: C, 67.30; H, 5.12; N, 3.17%. Calcd for [Cu($C_{50}H_{44}O_{10}N_2$)]: C, 66.98; H, 4.96; N, 3.13%.

Copper(II) Complexes of Schiff Bases Derived from Salicylaldehyde and Dibenzyl L- *and* DL-*Glutamate,* [*Cu(Sal=*L- *or* DL-*Glu(OBzl)$_2$)$_2$*], ***3b***. The complexes were prepared by a similar procedure to that for **3a** using dibenzyl L-glutamate benzenesulfonate and dibenzyl DL-glutamate hydrochloride. [Cu(Sal=L-Glu(OBzl)$_2$)$_2$]: 82% yield. Mp 105—107 °C. IR (KBr) 1740, 1710 cm^{-1} (ester C=O). Found: C, 66.70; H, 5.29; N, 3.03%. Calcd for [Cu($C_{52}H_{48}O_{10}N_2$)]·1/2H_2O: C, 66.90; H, 5.30; N, 3.00%. [Cu(Sal=DL-Glu(OBzl)$_2$)$_2$]: 86% yield. Mp 98—100 °C. IR(KBr) 1745, 1710 cm^{-1} (ester C=O). Found: C, 67.70; H, 5.34; N, 2.75%. Calcd for [Cu($C_{52}H_{48}O_{10}N_2$)]: C, 67.55; H, 5.24; N, 3.03%.

Reactions of Copper(II) Complexes ***3a*** *and* ***3b*** *with Methanol.* Complex **3a** (1 g) was refluxed in a mixture of methanol (200 cm^3)–chloroform (30—50 cm^3) for 30 min, and then filtered. The filtrate was cooled to give brownish green needles. After removing the solvent from the mother liquor, the same prcduct was also isolated. A similar treatment was carried out for **3b**. The reaction prouduct from [Cu(Sal=L-Asp(OBzl)$_2$)$_2$] and CH_3OH: 30% yield. Mp 134—135.5 °C. IR (KBr) 1740 cm^{-1} (ester C=O). Found: C, 60.83; H, 4.88; N, 3.91%. Calcd for [Cu($C_{38}H_{36}O_{10}N_2$)]: C, 61.32; H, 4.89; N, 3.76%. The reaction product from [Cu(Sal=DL-Asp(OBzl)$_2$)$_2$] and CH_3OH: 63% yield. Mp 130—131 °C. IR (KBr) 1740 cm^{-1} (ester C=O). Found: C, 61.00; H, 5.03; N, 3.98%. Calcd for [Cu($C_{38}H_{36}O_{10}N_2$)]: C, 61.32; H, 4.89; N, 3.76%. The reaction product from [Cu(Sal=L-Glu(OBzl)$_2$)$_2$] and CH_3OH: 40% yield. IR(KBr) 1730, 1710 cm^{-1} (ester C=O). Mp 114—115 °C. Found: C, 61.88; H, 5.41; N, 3.91%. Calcd for [Cu($C_{40}H_{40}O_{10}N_2$)]: C, 62.20; H, 5.23; N, 3.63%. The reaction product from [Cu(Sal=DL-Glu(OBzl)$_2$)$_2$] and CH_3OH: 52% yield. IR (KBr) 1740, 1715 cm^{-1} (ester C=O). Mp 102—104 °C. Found: C, 61.72; H, 5.56; N, 3.70%. Calcd for [Cu($C_{40}H_{40}O_{10}N_2$)]: C, 62.20; H, 5.23; N, 3.63%.

Copper(II) Complexes of the Schiff Bases Derived from Salicylaldehyde and α-Methyl β-benzyl L- *and* DL-*Aspartate,* [*Cu(Sal=*L- *or* DL-*Asp(α-OMe)(β-OBzl))$_2$*], ***4a***. A mixture of 0.81 g (0.0030 mol) of α-methyl β-benzyl L- or DL-aspartate hydrochloride and 0.45 g (0.0015 mol) of bis(salicyladehydato)copper (II) was dissolved in 10 cm^3 of water. The mixture was stirred at 30—40 °C for 3 h, and then cooled. A brownish green crystalline product was filtered and washed several times with water containing a small amount of ethanol. [Cu(Sal=L-Asp(α-OMe) (β-OBzl))$_2$]: 43% yield. Mp 132—132.5 °C. IR(KBr) 1740 cm^{-1} (ester C=O). Found: C, 61.16; H, 4.89; N, 3.82%. Calcd for [Cu($C_{38}H_{36}O_{10}N_2$)]: C, 61.32; H, 4.89; N, 3.76%. [Cu(Sal=DL-Asp(α-OMe) (β-OBzl))$_2$]: 56% yield. Mp 131—133 °C. IR(KBr) 1740 cm^{-1} (ester C=O). Found: C, 61.41; H, 4.94; N, 3.95%. Calcd for [Cu($C_{38}H_{36}O_{10}N_2$)]: C, 61.32; H, 4.89; N, 3.76%.

Copper(II) Complex of the Schiff Base Derived from Salicylaldehyde and α-Methyl γ-benzyl L-*Glutamate,* [*Cu(Sal=*L-*Glu(α-OMe) (γ-OBzl))$_2$*], ***4b*** was prepared in the same way as that for chelate **4a**. 32% yield. IR(KBr) 1740, 1710 cm^{-1} (ester C=O). Found: C, 60.61; H, 5.27; N, 3.76%. Calcd for [Cu($C_{40}H_{40}O_{10}N_2$)]·H_2O: C, 60.78; H, 5.37; N, 3.55%.

Isolation of Schiff Bases ***5a—d*** *from Various Copper (II) Chelates.* To a solution of 0.5 g of each copper(II) chelate in 20 cm^3 of chloroform was added 10% aqueous solution of disodium ethylenediaminetetracetate (20 cm^3). The mixture was stirred at room temperature for several hours (Scheme 3). After the chloroform fraction had been dried over anhydrous magnesium sulfate, the filtrate was evaporated to dryness. Characterization of the yellow crystals or oily products obtained is given in Table 1. The results of elemental analysis are as follows. SalH=DL-Asp(OBzl)$_2$: Found: C, 72.19; H, 5.26; N, 3.50%. Calcd for $C_{25}H_{23}O_5N_2$: C, 71.92; H, 5.56; N, 3.36%. SalH=L-Asp(OBzl)$_2$: Found: C, 72.06; H, 5.26; N, 3.50%. Calcd for $C_{25}H_{23}O_5N$: C, 71.92; H, 5.56; N, 3.36%. SalH=DL-Asp(α-OMe) (β-OBzl): Found: C, 66.21; H, 5.69; N, 4.09%. Calcd for $C_{19}H_{19}O_5N$: C, 66.65; H, 5.89; N, 4.09%. SalH=L-Glu(OBzl)$_2$: Found: C, 72.37; H, 5.82; N, 3.23%. Calcd for $C_{26}H_{25}O_5N$: C, 72.37; H, 5.84; N, 3.25%.

*Direct Synthesis of SalH=*DL-*Asp(OBzl)$_2$.* The Schiff base was also synthesized from salicylaldehyde and dibenzyl DL-aspartate benzenesulfonate. The dibenzyl DL-aspartate[11] prepared from 4.7 g (0.01 mol) of dibenzyl DL-aspartate benzenesulfonate was dissolved in 50 cm^3 of chloroform. To the mixture was added 1.2 g (0.01 mol) of salicylaldehyde and refluxed for 2 h. After it had been filtered, the filtrate was evaporated to dryness. The dry residue obtained as a syrup was rubbed with petroleum ether, and the resulting crystalline suspension filtered. The other Schiff bases were obtained by the same method.

*Reduction of SalH=*L-*Asp(OBzl)$_2$.* Sodium cyanohydroborate was added to a cold solution of SalH=L-Asp(OBzl)$_2$ (1 g) in methanol (200 cm^3) until the yellow color of the solution disappeared. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was washed several times with water and then extracted with chloroform. After the chloroform fraction had been dried over anhydrous magnesium sulfate, the solvent was removed from the filtrate under reduced pressure to give the ligand **11**, as a pale yellow oily product. IR(Nujor) 3300 cm^{-1} (N–H) and 1740 cm^{-1} (ester C=O). NMR($CDCl_3$) δ 2.74 (2H, d, –CH–C$\underline{H}_2$), 3.69 (1H, t, –C$\underline{H}$–CH_2), 4.61 (2H, s, –C$\underline{H}_2$–NH–), 5.03 and 5.10 (2H, s, Ar–C$\underline{H}_2$), and 7.26—6.59 ppm (14H, m, Ar-$\underline{H}$).

This substance was used for subsequent reaction without further purification.

Copper(II) Chelate **12**. To a solution of 0.8 g (0.002 mol) of **11** in 20 cm^3 of chloroform was added 0.13 g (0.001 mol) of anhydrous copper (II) chloride. The mixture was stirred at room temperature for 3 h. After it had been filtered, the filtrate was evaporated to give a greenish oily product, which was washed with petroleum ether. IR (Nujor) 3300 cm^{-1} (N–H) and 1735 cm^{-1} (ester C=O).

Reaction of Copper(II) Complex **12** *with Methanol*. A mixture of complex **12** (0.5 g) and methanol (150 cm^3) was heated under reflux for 30 min. After it had been filtered, a green-brown oily product, **13**, was obtained upon removal of methanol from the filtrate. IR(Nujor) 3300 cm^{-1} (N–H) and 1735 cm^{-1} (ester C=O).

Isolation of **14** *from Copper(II) Complex* **13**. Isolation was carried out in the same way as that for **3a**—**b** or **4a**—**b** (Scheme 3). Compound **14** was obtained as an oily product. IR (Nujor) 3300 cm^{-1} (N–H) and 1740 cm^{-1} (ester C=O). NMR ($CDCl_3$) δ 2.82 (2H, d, –CH–C$\underline{H}_2$), 3.68—3.79 (4H, m, –C$\underline{H}$–CH_2 and –COOC$\underline{H}_3$), 4.71 (2H, s, –C$\underline{H}_2$–NH–), 5.18 (2H, s, –COOC$\underline{H}_2$–Ar), and 7.42—6.82 ppm (9H, m, Ar–$\underline{H}$).

*Reaction of SalH=*L*-Asp(OBzl)*$_2$, **5a**, *with Methanol in the Presence of* $CuCl_2$. A typical reaction is as follows: To a solution of **5a** (0.8 g, 0.002 mol) in 200 cm^3 of methanol was added 0.0027 g (0.00002 mol) of anhydrous copper (II) chloride. The reaction mixture was heated under reflux for 30 min. After it had been filtered, the filtrate was evaporated to dryness. A greenish oily product obtained was treated by the same procedure as for the isolation of **14** from **13**. Evaluation of the extent of the ester-exchange reaction occurred in the system was carried out on the basis of each peak area for –COOC$\underline{H}_3$, –COOC$\underline{H}_2$–Ar and –CH=N in PMR spectrum.

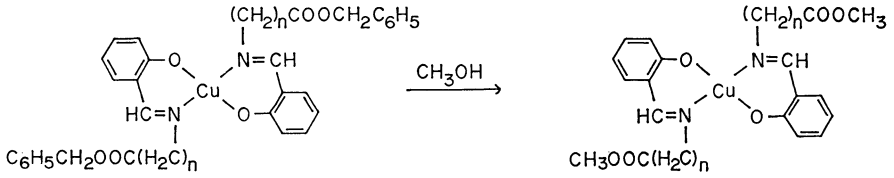
Measurements. Melting points were determined on a micro melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 215 grating infrared spectrophotometer with KBr disk and Nujor mull, UV absorption spectra with a Union Giken SM-401 high sensitivity recording spectrophotometer, and PMR spectra with a JEOL JNM-MH-100 spectrometer with TMS reference. Thin layer chromatography (TLC) was carried out on silica gel (Merck Silica Gel 60 F_{254}). Chloroform was used as a solvent in all cases.

Results and Discussion

Ester-exchange Reactions in the Copper(II) Chelates of the Schiff Bases derived from Salicylaldehyde and Benzyl Glycinate, β-Alaninate or γ-Aminobutyrate. The copper(II) chelates of benzyl *N*-salicylidene-glycinate, -β-alaninate, and -γ-aminobutyrate, **1a**—**c**, were prepared by the condensation of bis(salicylaldehydato)copper(II) with benzyl ester of each amino acid. When chelates **1a**—**c** were refluxed in methanol for 30 min, the copper(II) chelates **2a**—**c** of methyl *N*-salicylidene-glycinate, -β-alaninate, and -γ-aminobutyrate were obtained in good yields. This indicates that the benzyl ester groups at α-, β-, or γ-position in the copper(II) chelates **1a**—**c** can be replaced by a methyl ester group (Scheme 1).

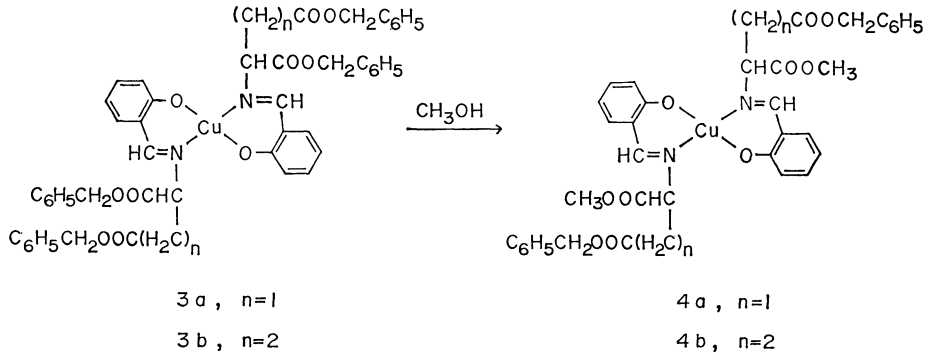
Selective Ester-exchange reactions in the Copper(II) Chelates of the Schiff Bases derived from Salicylaldehyde and Dibenzyl Aspartate or Glutamate. The copper(II) chelates of dibenzyl *N*-salicylidene-aspartate and -glutamate, **3-a** and **-b**, were prepared by warming a mixture of bis(salicylaldehydato)copper(II) and dibenzyl aspartate or glutamate. A methanol–chloroform solution of complex **3a** was refluxed for 30 min to yield a copper(II) chelate, of which half of the original benzyl groups were replaced by methyl groups. Elemental analysis of the reaction product shows that ester-exchange reaction takes place, though it is not clear in what position. We therefore, synthesized separately the copper(II) chelates of the Schiff bases derived from salicylaldehyde and α-methyl β-benzyl-DL- or -L-aspartates **4a**. The IR spectra of the authentic complexes thus obtained and the products of ester-exchange reaction agree with each other. The melting points for both the compounds showed no essential difference. From the results it can be concluded that the ester-exchange reaction in the complexes **3a** occurs selectively at the α-position in dibenzyl L- and DL-aspartate moiety (Scheme 2). No ester-exchange reaction in compound **5a**, the ligand of complex **3a**, was observed in the absence of copper(II). The α-ester group in dibenzyl L- and DL-glutamate moiety of the complexes **3b** is also preferably replaced in the same way by methyl groups.

For the sake of confirmation, the Schiff bases were isolated from the copper(II) complexes **3-** and **4-a** and **-b** (Scheme 3). The physical properties of Schiff bases **5a**—**d** are given in Table 1 and the PMR spectra of the L-isomers in Figs. 1 and 2. By comparing Figs. 1-a and -b we see that ligand **5a** of the original complex **3a** exhibits two peaks around 5 ppm (5.05 and 5.14 ppm), and ligand **5b** of the reaction product **3b** only one peak (5.08 ppm) in the same region. Since these peaks are caused by benzyl groups, the decrease in the number of peaks from 2 to 1 shows that the ester-exchange reaction takes place at only one of the two benzyl



1a, n=1 2a, n=1
1b, n=2 2b, n=2
1c, n=3 2c, n=3

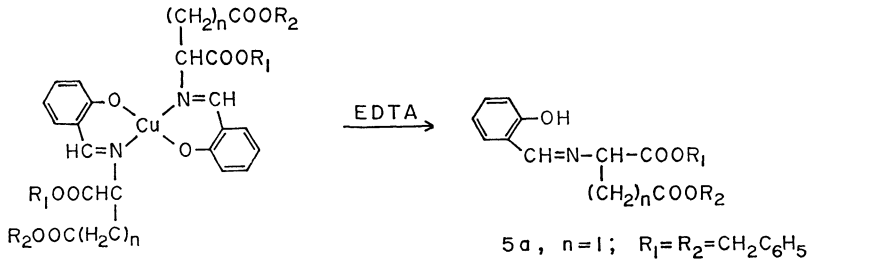
Scheme 1.



3a, n=1 4a, n=1

3b, n=2 4b, n=2

Scheme 2.



3- and 4-a and -b

5a, n=1; $R_1=R_2=CH_2C_6H_5$

5b, n=1; $R_1=CH_3$, $R_2=CH_2C_6H_5$

5c, n=2; $R_1=R_2=CH_2C_6H_5$

5d, n=2; $R_1=CH_3$, $R_2=CH_2C_6H_5$

Scheme 3.

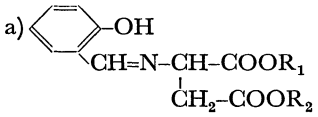
Table 1. Physical properties of Schiff bases, **5a—d**

Compound	Mp/°C	UV($CHCl_3$) λ_{max}/nm	UV($CHCl_3$) log ε	IR, ν/cm^{-1} C=O(ester)	IR, ν/cm^{-1} C=N
5a(DL–)	69—70.5	260	4.1	1730	1625
		324	3.6		
5a(L–)	69.5—70.5	260	4.1	1730	1620
		324	3.6		
5b(DL–)	46—47	260	4.2	1740	1630
		323	3.7		
5b(L–)	a)	260	4.1	1735	1630
		325	3.6		
5c(DL–)	a)	260	4.1	1740	1630
		324	3.7		
5c(L–)	46—51	260	4.1	1735	1625
		323	3.7		
5d(DL–)	a)	260	4.1	1735	1630
		323	3.7		
5d(L–)	a)	259	4.3	1730	1625
		323	3.8		

a) Oily product.

Table 2. TLC for Schiff bases[a] of L-aspartate

R_1	R_2	R_f
$C_6H_2C_6H_5$	$CH_2C_6H_5$	0.41[b]
CH_3	$CH_2C_6H_5$	0.32[c]
CH_3	$CH_2C_6H_5$	0.32[d]
CH_3	CH_3	0.23[e]

a) 

b) [Cu(Sal=L-Asp(OBzl)$_2$)$_2$] $\xrightarrow{EDTA}$ reaction product.

c) Salicylaldehyde+L-Asp(α-OMe)(β-OBzl)⟶reaction product. d) [Cu(Sal=L-Asp(OBzl)$_2$)$_2$] $\xrightarrow[\text{reflux, 30 min}]{CH_3OH}$ reaction product $\xrightarrow{EDTA}$ reaction product. e) Salicylaldehyde+L-Asp(OMe)$_2$ ⟶ reaction product.

ester groups. This is also supported by the following facts. The peak (3.69 ppm, s, 3H) due to methoxyl group is seen in the spectrum for ligand **5b** of the reaction product, the number of protons of aromatic rings decreasing from 14 to 9 with the exchange reaction. The results of TLC for the Schiff bases consisting of salicylaldehyde and some diesters of L-aspartic acid are summarized in Table 2. It was confirmed from the R_f values that the ester-exchange reaction takes place selectively at the α-position in the chelates **3a**. The same variation in PMR spectra was also observed in glutamate-Schiff base chelates (Fig. 2). The two peaks at 5.02 and 5.12 ppm arising from the methylene protons of benzyl groups in **5c** decrease to one peak (5.08 ppm) in the ligand **5d** of the reaction product. Appearance of a new peak (3.72 ppm) due to the methoxyl group and decrease of the peak for protons of aromatic rings with the ester-exchange reaction were also observed.

Reaction Mechanism. Two essentially different mechanisms have been proposed[5,7] to elucidate the ester-exchange reactions occurring in the presence of metal ion. Although both mechanisms were proposed

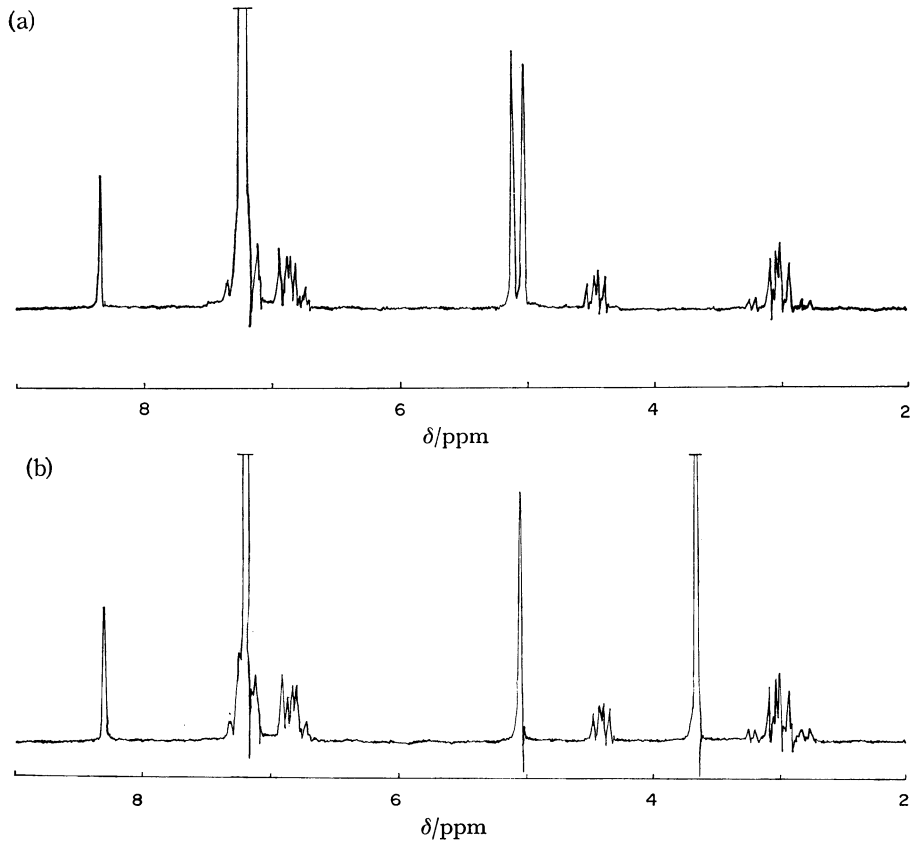


Fig. 1. PMR spectra of; a) SalH=L-Asp(OBzl)$_2$ **5a** and b) SalH=L-Asp(α-OMe) (β-OBzl) **5b.**

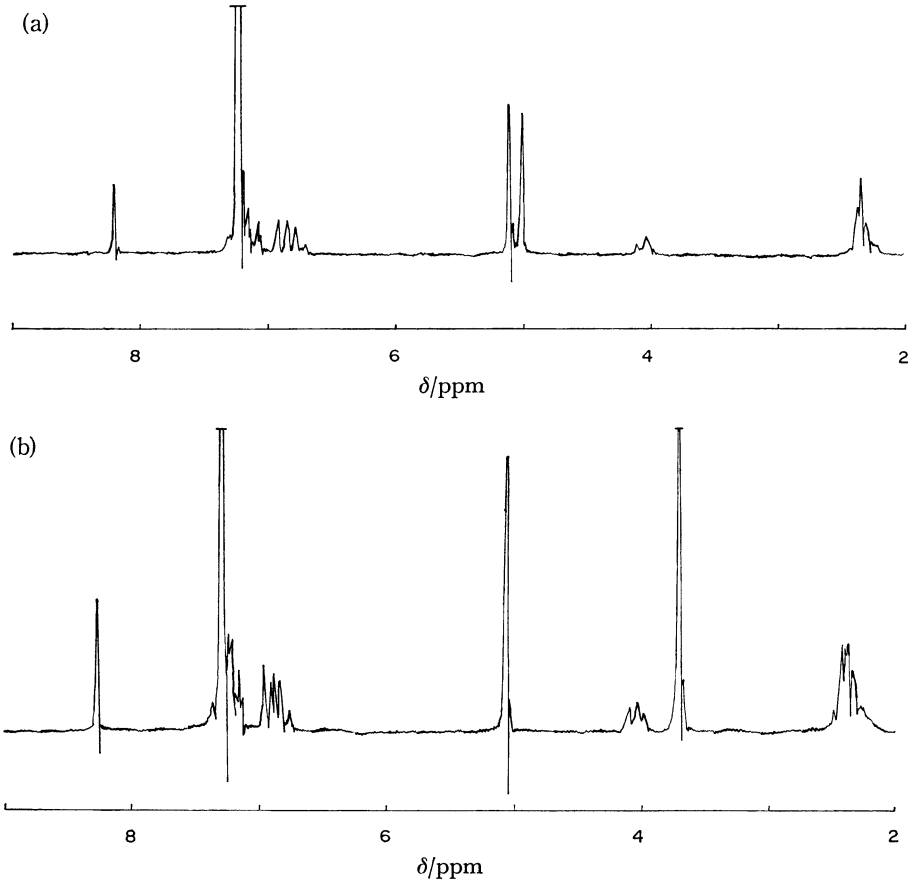
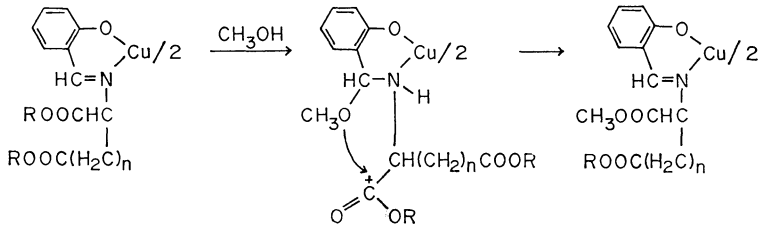


Fig. 2. PMR spectra of; a) SalH=L-Glu(OBzl)$_2$ **5c** and b) SalH=L-Glu(α-OMe) (γ-OBzl) **5d.**

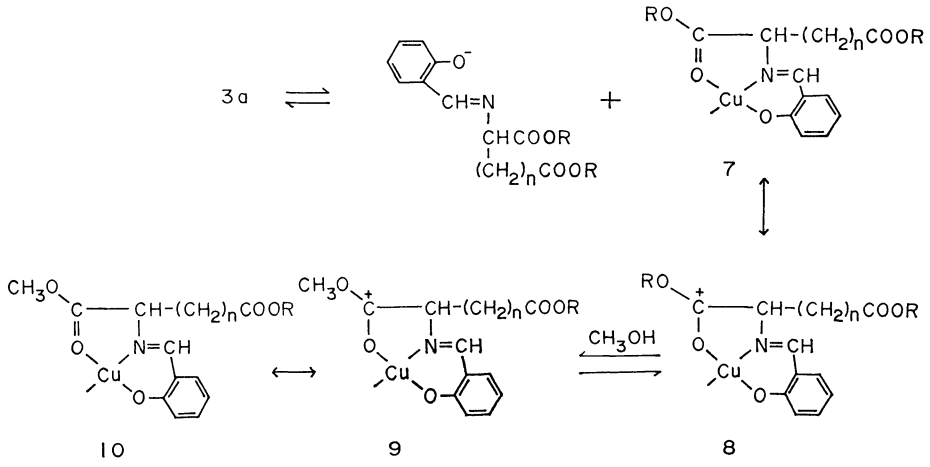


3-a and -b 6 4-a and -b

$R = CH_2C_6H_5$, n = 1 or 2

Scheme 4.

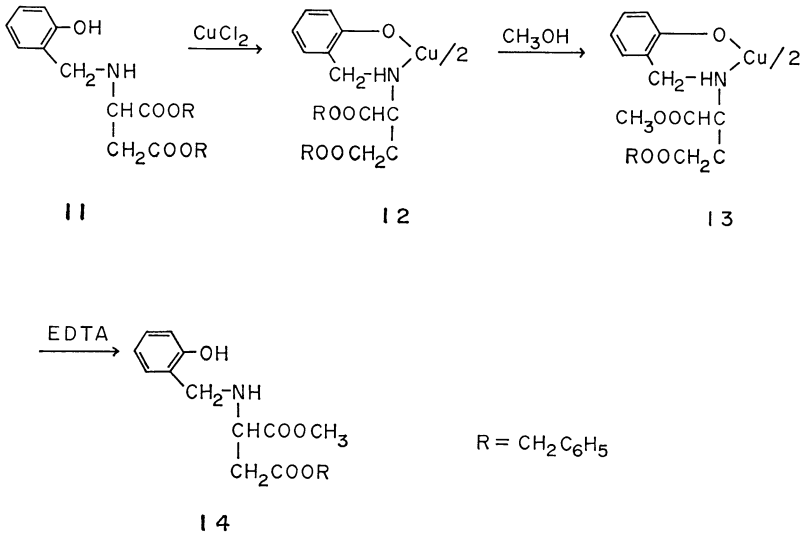
for the esters of the neutral amino acids such as glycine, α- and β-alanine, they were applied to explain the present kind of diesters of acidic amino acids. In the mechanism of Gillard and Wootton[7] (Scheme 4), the addition of methanol molecule would first take place at the azomethine double bond. In the structure of the intermediate **6**, the oxygen atom of the methoxyl group would readily attack nucleophilically the carbon atom of the α-ester group, since the methoxyl group is located very closely to the α-ester group. On the other hand, the attacking of the same methoxyl group seems to be difficult against the β- or γ-ester group because of its distant location. Furthermore, there might be a steric interruption of the α-ester group. The reason why the selective ester-exchange reaction occurs is thus reasonably explained on the basis of the mechanism of Gillard and Wootton.[7] The selective and highly catalytic activity of enzyme reactions are said to be understandable on the basis of the proximity and the orientation effects of the functional groups in enzymes and substrates. In this respect, the present mechanism bears a resemblance to the enzyme reactions. In the mechanism according to Houghton and Pointer[5] (Scheme 5), the reaction begins with a dissociation of one of the two Schiff base ligands in complex **3a**, followed by the formation of tridentate chelation of the remainder ligand. In structure **7** (or **8**) the carbon atom of α-ester group would be readily attacked by oxygen atom of methanol because of the electrophilic character of the former and the nucleophilic character of the latter. Although coordination of the ester group at the β- or γ-position is also possible, it would be much more difficult than that of the α-ester group, in view of the structure-stability relationship in the fused chelate ring system.[10,17] In the Houghton and Pointer mechanism, preferential formation of the terdentate chelate **7** (or **8**) would play an important role for the selective ester-exchange reaction. If the selective ester-exchange reactions of the present kind proceed *via* the Gillard and Wootton mechanism, the reactions would not occur in chelates **12** which lacks azomethine double bonds. As a matter of fact, the selective ester-exchange reaction in **12** was observed under the same conditions. Accordingly, the possibility of the Gillard and Wootton mechanism is slight. Further, the reactions of **5a** with methanol in the presence of catalytic concentrations of copper(II) chloride indicate that a slight amount of copper(II) ion is insufficient to cause the ester-exchange reaction, while increasing amount of copper(II) chloride promotes it (Table 3). The mechanism of Houghton and Pointer has the advantage of interpreting the result described above. Though the efficiency of the ester-exchange reaction is low in the presence of minute quantities of copper(II), it is understandable in view of the observa-



10 9 8

$R = CH_2C_6H_5$, n = 1 or 2

Scheme 5.

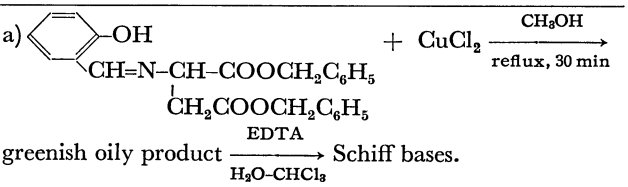


11 12 13 14

Scheme 6.

Table 3. Relation between the amounts of $CuCl_2$ used and the extent of ester-exchange reaction occurring[a)]

	Amount of $CuCl_2$ used (mol/mol % against Schiff base)		
	1/100	1/10	1/5
Extent of ester-exchange reaction occurring (%)	0	5	10

a)  greenish oily product $\xrightarrow[H_2O\text{-}CHCl_3]{EDTA}$ Schiff bases.

tion that the major complex in solution is probably **3a** rather than **7** which are the active species for ester-exchange reaction. In conclusion, we are more in line with the Houghton and Pointer mechanism, which involves the dissociation and recoordination of Schiff base ligand.

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