Bull Soc Chim Fr (1997) 134, 645-651

Copper (II) complexes with ethers of tyrosine and γ-esters of glutamic acid

Mônica de Lourdes de Araujo Silva[1,2], Emanoel de Castro Antunes Felício[1]*

[1] *Departamento de Química, Instituto de Ciências Exatas, Universidade Federal de Juiz de Fora, Campus Universitário, 36036-330 Juiz de Fora - MG, Brazil*
[2] *Departamento de Química, Instituto de Ciências Exatas, Universidade Federal de Minas Gerais, Pampulha, 31270-901 Belo Horizonte - MG, Brazil*

(Received 7 January 1997; accepted 7 July 1997)

Summary — The synthesis of five long-chain (C_8 to C_{12}) alkyl ethers of *S*-(−)-tyrosine and of five long-chain (C_8 to C_{12}) alkyl esters of *S*-(+)-glutamic acid is described. Among these ligands, only *n*-octyl tyrosine and *n*-decyl tyrosine have been reported previously. Ten new Cu(II) complexes of these novel tyrosine and glutamic acid derivatives were synthesized. Spectroscopic evidence suggests that these square-planar complexes adopt a *trans*-configuration and shows that the ligands are bidentate. Bonding occurs via the oxygen atoms of the carboxylate groups and the nitrogen atoms of the amino groups.

tyrosine / glutamic acid / etherification / esterification / copper (II) complex

Résumé — Complexes de cuivre(II) comportant des éthers de tyrosine et des γ-esters d'acide glutamique. Les synthèses de cinq éthers alkyliques à longue chaîne (C_8 à C_{12}) de la *S*-(−)-tyrosine et cinq esters alkyliques à longue chaîne (C_8 à C_{12}) de l'acide *S*-(+)-glutamique sont ici décrites. Parmi ces composés, seules la *n*-octyl tyrosine et la *n*-décyl tyrosine ont déjà été reportées. Les dix ligands ont été utilisés dans la préparation de nouveaux complexes de l'ion cuivre (II). Les examens spectroscopiques suggèrent que les ligands sont bidentés et que tous les complexes sont plans carrés avec une géométrie *trans*. La coordination des ligands se fait par l'un des atomes d'oxygène du groupe carboxylate et par l'atome d'azote du groupe amino.

tyrosine / acide glutamique / éthérification / estérification / complexe de cuivre(II)

Introduction

The synthesis of alkyl ethers, α-alkyl esters and γ-alkyl esters derived from α-aminoacids has been reported by several authors [1–4]. Glutamic acid and tyrosine, with the addition of long alkyl chains via esterification and etherification respectively, lead to amphiphilic molecules. These molecules have great applicability. In the chemistry industry, they have been utilized as tensioactives, in the pharmaceutical industry as drug transporters, and in biology as fluorescence markers for biological system studies [5]. On the other hand, the copper (II) ion plays an important role in the catalysis of α-aminoacid ester hydrolysis [6]. Chronic copper (II) ion toxicity is also involved, for example, in Wilson's disease [7]. In Wilson's disease copper accumulates in the tissues, whereas in other diseases, such as leukemia and Hodgkin's disease, the level of blood copper is elevated. It has also been suggested that copper complexes may mediate physiological copper transport [8]. The coordination via carboxylate groups and α-amino groups may also function as protection for reactions in other molecular centers. In the particular case of glutamic acid γ-esters, the added carbonic chain may protect the carboxylate group in the γ position, to impede the coordination by this group. Chelation may also serve as an easy method to isolate the derived γ-esters. This is pointed out in the experimental section of this paper. Finally, it is desirable to emphasize that our scope is the preparation of new tensioactives and in the study of the amphiphilic properties of these molecules. In that context we are interested in examing and characterizing the products of the reaction of the amphiphilic molecules with various transition metal ions, beginning from copper, in order to establish which ions will inactive the tensioactive properties of these molecules by precipitation or hydrolysis.

Experimental section

All of the ligands and solvents used in this study were reagent grade and were used without further purification. Octyl iodide was prepared according to literature procedures. Elemental micro-analyses were performed by the Chemistry Institute of São Paulo University, Brazil. Melting points were obtained with a Mettler FP 90 apparatus and are uncorrected. The infrared spectra were recorded in the

* Correspondence and reprints

4000–200 cm^{-1} region using a Perkin-Elmer Model 283-B grating infrared spectrophotometer. All spectra were calibrated with polystyrene film and frequencies are accurate to better than 1 cm^{-1}. Spectra were measured as Nujol mulls supported on CsI plates. ^1H and ^{13}C NMR spectra were recorded in CF_3COOD on Bruker Avance DRX-400 and WM-200 spectrometers, using TMS as internal standard. Mass spectra were obtained with a HP 5989A spectrometer by the method of direct insertion. Ionization was achieved by electron impact at 70 eV electrons. Spectra were calibrated by addition of perfluoroalkanes.

Preparation of the ligands

• *Synthesis of alkyl ethers of tyrosine*

A solution of 2.0 g (0.01 mol) L-tyrosine in 0.17 g (4.2×10^{-3} mol) 10% aqueous sodium hydroxide was added to 44 mL of dimethyl sulfoxide and heated in a water bath at 80 °C. Equimolar quantities of the appropriate alkyl halides were added and the reaction was then heated in an oil bath to 110–120 °C. Heating and stirring were continued for 6 h[(1)] and the reaction mixture was then poured into 250 g of crushed ice. The resulting white precipitate was filtered off, washed with water, diethyl ether, and then dried. The crude product was recrystallized from 60% acetic acid.

The alkyl halides used in the reaction of etherification were: *n*-octyl iodide, *n*-nonyl and *n*-undecyl bromide, and *n*-decyl and *n*-dodecyl chlorides. We utilized the commercially available products and prepared the *n*-octyl iodide [9].

■ *[(S)-2-Amino-3-[4-(octyloxy)phenyl]propanoic acid] (n-oct tyr)*

30.8%, Mp 216.2–217.4 °C.

IR: 3 200 (ν NH_3^+), 2 960–2 880 (δ C–H aliph), 1 610 (δ_a NH_3^+), 1 600 (ν_a COO^-), 1 260 (δ_a CH_2–O–Ph), 1 380 (ν_s COO^-).

^1H NMR: 0.7 (t, 3H, CH_3, $J = 6.76$); 1.3 (m, 12H, $(CH_2)_6$); 1.9 (t, 2H, CH_2–O, $J = 6.80$); 3.4 (m, 2H, CH_2–Ph); 4.2 (t, 1H, CH, $J = 5.32$); 6.7–7.2 (dd, 4H, H–Ph, $J = 8.54$).

^{13}C NMR: 8.6 (CH_3), 18.8–30.4 (CH_2 aliph), 57.8 (CH), 102.0 (CH_2–O), 167.5 (COOH).

MS (*m/z*, %): (294, 6.7); (186, 66.2); (136, 9.9); (107, 26.5); (88, 100.0); (57, 21.5).

Anal calc for $C_{17}H_{27}NO_3$ (293.14): C 69.40, H 9.20, N 4.78; found: C 69.19, H 9.26, N 4.73.

■ *[(S)-2-Amino-3-[4-(nonyloxy)phenyl]propanoic acid] (n-non tyr)*

45.9%, Mp 215.5–216.8 °C.

IR: 3 210 (ν NH_3^+), 2 970–2 890 (δ C–H aliph), 1 600 (δ_a NH_3^+), 1 590 (ν_a COO^-), 1 260 (δ_a CH_2–O–Ph), 1 370 (ν_s COO^-).

^1H NMR: 0.9 (t, 3H, CH_3, $J = 6.78$); 1.3 (m, 14H, $(CH_2)_7$); 1,8 (t, 2H, CH_2–O, $J = 6.84$); 3.5 (m, 2H, CH_2–Ph); 4.5 (dd, 1H, CH, $J = 5.24$); 7.0–7.2 (dd, 4H, H–Ph, $J = 8.60$).

^{13}C NMR: 14.3 (CH_3), 23.8–36.2 (CH_2 aliph), 57.2 (CH), 63.6 (CH_2–O), 173.8 (COOH).

MS (*m/z*, %): (308, 10.0); (200, 78.3); (136, 7.3); (107, 81.1); (88, 100.0); (57, 36.9).

Anal calc for $C_{18}H_{29}NO_3$ (307.15): C 70.36, H 9.45, N 4.56; found: C 69.37, H 9.32, N 4.53.

(1) In the cases of decyl and dodecyl chorides, heating and stirring were continued for 12 h.

■ *[(S)-2-Amino-3-[4-(decyloxy)phenyl]propanoic acid] (n-dec tyr)*

23.7%, Mp 220–222 °C.

IR: 3 200 (ν NH_3^+), 2 980–2 880 (δ C–H aliph), 1 600 (δ_a NH_3^+), 1 590 (ν_a COO^-), 1 260 (δ_a CH_2–O–Ph), 1 380 (ν_s COO^-).

^1H NMR: 0.9 (t, 3H, CH_3, $J = 6.77$); 1.2 (m, 16H, $(CH_2)_8$); 1.8 (t, 2H, CH_2–O, $J = 6.87$); 3.6 (m, 2H, CH_2–Ph); 4.4 (t, 1H, CH, $J = 5.35$); 6.9–7.3 (dd, 4H, H–Ph, $J = 8.61$).

^{13}C NMR: 8.6 (CH_3), 18.3–30.4 (CH_2 aliph), 57.9 (CH), 103.9 (CH_2–O), 167.8 (COOH).

MS (*m/z*, %): (322, 3.4); (214, 74.6); (136, 11.9); (107, 81.4); (88, 100.0); (57, 32.2).

Anal calc for $C_{19}H_{31}NO_3$ (321.16): C 71.00, H 9.70, N 4.40; found: C 69.70, H 9.40, N 4.27.

■ *[(S)-2-Amino-3-[4-(undecyloxy)phenyl]propanoic acid] (n-und tyr)*

53%, Mp 214.9–218.1 °C.

IR: 3 190 (ν NH_3^+), 2 950–2 880 (δ C–H aliph), 1 600 (δ_a NH_3^+), 1 590 (ν_a COO^-), 1 260 (δ_a CH_2–O–Ph), 1 370 (ν_s COO^-).

^1H NMR: 0.9 (t, 3H, CH_3, $J = 6.80$); 1.3 (m, 18H, $(CH_2)_9$); 1,8 (t, 2H, CH_2–O, $J = 6.94$); 3.5 (m, 2H, CH_2–Ph); 4.4 (dd, 1H, CH, $J = 5.44$); 7.0–7.2 (dd, 4H, H–Ph, $J = 8.60$).

^{13}C NMR: 14.5 (CH_3), 24.0–34.1 (CH_2 aliph), 56.7 (CH), 64.3 (CH_2-O), 174.6 (COOH).

MS (*m/z*, %): (336, 20.0); (228, 75.7); (136, 10.0); (107, 42.9); (88, 100.0); (57, 25.7).

Anal calc for $C_{20}H_{33}NO_3$ (335.17): C 71.60, H 9.84, N 4.18; found: C 70.47, H 9.74, N 4.24.

■ *[(S)-2-Amino-3-[4-(dodecyloxy)phenyl]propanoic acid] (n-dod tyr)*

12.9%, Mp 213.5–214.2 °C.

IR: 3 190 (ν NH_3^+), 2 950–2 860 (δ C–H aliph), 1 600 (δ_a NH_3^+), 1 580 (ν_a COO^-), 1 250 (δ_a CH_2–O–Ph), 1 370 (ν_s COO^-).

^1H NMR: 0.7 (t, 3H, CH_3, $J = 6.81$); 1.1 (m, 20H, $(CH_2)_{10}$); 1.9 (t, 2H, CH_2–O, $J = 6.86$); 3.4 (m, 2H, CH_2–Ph); 4.2 (t, 1H, CH, $J = 5.25$); 6.7–7.2 (dd, 4H, H–Ph, $J = 8.59$).

^{13}C NMR: 8.5 (CH_3), 18.2–30.4 (CH_2 aliph), 57.8 (CH), 112.7 (CH_2–O), 167.5 (COOH).

MS (*m/z*, %): (350, 15.0); (242, 76.3); (136, 9.5); (107, 37.8); (88, 100.0); (57, 33.4).

Anal calc for $C_{21}H_{35}NO_3$ (349.18): C 72.28, H 10.00, N 4.00; found: C 71.24, H 10.17, N 3.50.

• *Synthesis of S-glutamic acid 5-n-alkyl ester hydrochlorides*

The γ-ester hydrochlorides were prepared by the methods described by Coleman [3] and Dantas [10]. The alcohols used were: *n*-octanol, *n*-nonanol, *n*-decanol, *n*-undecanol and *n*-dodecanol. The reactions were followed by thin-layer chromatography (see preparation of complexes). Two products were observed, γ-ester hydrochlorides and diester hydrochlorides. Small quantities of glutamic acid hydrochlorides were also observed. The spots were detected by spraying the plates with a solution of ninhydrin, which is converted to: a pale purple color for glutamic acid hydrochlorides, a red color for γ-ester hydrochlorides and a yellow color for diester hydrochlorides. The γ-ester hydrochlorides were obtained by decomposition of the copper (II) complexes with 6 M hydrochloric acid. The acid was added until the color of the solid changed from purple to white. Water (5 mL) was added and the resulting white precipitates were filtered off,

washed with water and then dried in a drying pistol (110 °C) for 12 h. Yields were calculated based on the quantity of the complexes used in the decompositions.

■ *S-Glutamic acid 5-octyl ester hydrochloride (n-oct glu)*

72%, Mp 184–186 °C, R_F: 0.30.

IR: 1 740 (ν_a C=O ester); 1 720 (ν_a C=O acid); 1 600 (δ_a NH_3^+); 1 490 (δ_s NH_3^+); 1 230 (ν_s C–O ester); 1 200 (ν_s C–O acid).

^{1}H NMR: 0.9 (t, 3H, CH_3, J = 6.96); 1.4–1.7 (m, 12H, $(CH_2)_6$); 2.6 (m, 2H, CH_2–H_β); 2.9 (t, 2H, CH_2–H_γ, J = 6.34); 4.6 (t, 1H, CH); 4.2 (t, 2H, CH_2–O, J = 6.45); 11.6 (s, 1H, COOH).

^{13}C NMR: 14.5 (CH_3), 24.1–31.1 (CH_2 aliph), 32.3 (CH_2–C_β), 33.6 (CH_2–C_γ), 55.7 (CH), 69.7 (CH_2OOC), 174.3 (COOR), 178.8 (COOH).

MS (m/z, %): (260, 13.6); (130, 27.2); (102, 30.4); (84, 100.0); (57, 40.5).

Anal calc for $C_{13}ClH_{26}NO_4$ (295.60): C 52.82, H 8.80, N 4.74; found: C 52.20, H 8.54, N 4.70.

■ *S-Glutamic acid 5-nonyl ester hydrochloride (n-non glu)*

30%, Mp 184.1–185.7 °C, R_F: 0.40.

IR: 1 740 (ν_a C=O ester); 1 730 (ν_a C=O acid); 1 600 (δ_a NH_3^+); 1 500 (δ_s NH_3^+); 1 230 (ν_s C–O ester); 1 190 (ν_s C–O acid).

^{1}H NMR: 0.9 (t, 3H, CH_3, J = 6.89); 1.3–1.7 (m, 14H, $(CH_2)_7$); 2.6 (m, 2H, CH_2–H_β); 2.9 (t, 2H, CH_2–H_γ, J = 6.32); 4.6 (t, 1H, CH); 4.2 (t, 2H, CH_2–O, J = 6.46); 11.5 (s, 1H, COOH).

^{13}C NMR: 14.5 (CH_3), 24.2–30.9 (CH_2 aliph), 32.4 (CH_2–C_β), 33.6 (CH_2–C_γ), 55.8 (CH), 70.0 (CH_2OOC), 174.6 (COOR), 178.8 (COOH).

MS (m/z, %): (274, 15.6); (130, 32.1); (102, 35.4); (84, 100.0); (57, 58.0).

Anal calc for $C_{14}ClH_{28}NO_4$ (309.61): C 54.26, H 8.72, N 4.52; found: C 55.64, H 8.49, N 4.54.

■ *S-Glutamic acid 5-decyl ester hydrochloride (n-dec glu)*

60%, Mp 183.8–185.3 °C, R_F: 0.45.

IR: 1 740 (ν_a C=O ester); 1 700 (ν_a C=O acid); 1 590 (δ_a NH_3^+); 1 480 (δ_s NH_3^+); 1 230 (ν_s C–O ester); 1 180 (ν_s C–O acid).

^{1}H NMR: 0.9 (t, 3H, CH_3, J = 6.93); 1.3–1.7 (m, 16H, $(CH_2)_8$); 2.6 (m, 2H, CH_2–H_β); 2.9 (t, 2H, CH_2–H_γ, J = 6.64); 4.6 (t, 1H, CH); 4.2 (t, 2H, CH_2–O, J = 6.48); 11.6 (s, 1H, COOH).

^{13}C NMR: 14.5 (CH_3), 20.1–31.0 (CH_2 aliph), 32.31 (CH_2–C_β), 33.5 (CH_2–C_γ), 55.7 (CH), 69.7 (CH_2OOC), 174.3 (COOR), 178.7 (COOH).

MS (m/z, %): (288, 10.5); (130, 30.2); (102, 32.3); (84, 100.0); (57, 53.7).

Anal calc for $C_{15}ClH_{30}NO_4$ (323.62): C 55.62, H 9.27, N 4.33; found: C 55.34, H 8.99, N 4.28.

■ *S-Glutamic acid 5-undecyl ester hydrochloride (n-und glu)*

68%, Mp 180.9–182.6 °C, R_F: 0.47.

IR: 1 740 (ν_a C=O ester); 1 730 (ν_a C=O acid); 1 500 (δ_a NH_3^+); 1 500 (δ_s NH_3^+); 1 230 (ν_s C–O ester); 1 190 (ν_s C–O acid).

^{1}H NMR: 0.9 (t, 3H, CH_3, J = 6.89); 1.3–1.6 (m, 18H, $(CH_2)_9$); 2.6 (m, 2H, CH_2–H_β); 2.9 (t, 2H, CH_2–H_γ, J = 6.34); 4.6 (t, 1H, CH); 4.2 (t, 2H, CH_2–O, J = 6.40); 11.6 (s, 1H, COOH).

^{13}C NMR: 14.5 (CH_3), 22.3–30.9 (CH_2 aliph), 32.6 (CH_2–C_β), 33.6 (CH_2–C_γ), 55.8 (CH), 69.9 (CH_2OOC), 174.6 (COOR), 178.8 (COOH).

MS (m/z, %): (302, 12.1); (130, 28.5); (102, 30.1); (84, 100.0); (57, 55.8).

Anal calc for $C_{16}ClH_{32}NO_4$ (337.63): C 56.91, H 9.48, N 4.15; found: C 56.15, H 9.62, N 4.04.

■ *S-Glutamic acid 5-dodecyl ester hydrochloride (n-dod glu)*

57%, Mp 177.2–179.2 °C, R_F: 0.50.

IR: 1 740 (ν_a C=O ester); 1 730 (ν_a C=O acid); 1 590 (δ_a NH_3^+); 1 510 (δ_s NH_3^+); 1 250 (ν_s C–O ester); 1 200 (ν_s C–O acid).

^{1}H NMR: 0.9 (t, 3H, CH_3, J = 6.88); 1.4–1.7 (m, 20H, $(CH_2)_{10}$); 2.6 (m, 2H, CH_2–H_β); 2.9 (t, 2H, CH_2–H_γ, J = 6.34); 4.6 (t, 1H, CH); 4.2 (t, 2H, CH_2–O, J = 6.40); 11.6 (s, 1H, COOH).

^{13}C NMR: 14.6 (CH_3), 24.2–31.2 (CH_2 aliph), 32.4 (CH_2–C_β), 33.7 (CH_2–C_γ), 55.8 (CH), 69.9 (CH_2OOC), 174.6 (COOR), 178.9 (COOH).

MS (m/z, %): (316, 10.3); (130, 30.9); (102, 36.4); (84, 100.0); (57, 54.8).

Anal calc for $C_{17}ClH_{34}NO_4$ (351.64): C 59.36, H 9.84, N 3.88; found: C 58.63, H 9.67, N 3.98.

Preparation of complexes

• *trans-bis-[(S)-2-Amino-3-(4-alkoxyphenyl)-propanoate]copper (II)*

A suspension of 7×10^{-4} mol of the ligands in mixed solvent (ethanol, water, ether – 2:2:3) was stirred for 30 min at room temperature. Aqueous copper sulfate (3×10^{-4} mol) was added, and the reaction was then stirred for 15 min. Solid sodium acetate was added until a pale purple coloring was observed. The resulting pale purple precipitate was filtered off, washed with water and then refluxed in hexane for 2 h. The precipitate was then filtered off, washed with water, diethyl ether and dried in a drying pistol (110 °C) for 6 h.

■ *[Cu(n-oct tyr)$_2$]*

99.87%, Mp 207.9 °C (dec).

IR: 3 400, 3 200 (ν NH_2·); 2 980–2 860 (δ C–H aliph); 1 650 (ν_a C=O); 1 380 (ν_s C–O); 1 230 (δ_a CH_2–O–Ph); 360 (ν Cu–N); 330 (ν Cu–O).

Anal calc for $C_{34}CuH_{52}N_2O_6$ (647.82): C 63.03, H 8.34, N 4.32, Cu 9.81; found: C 63.89, H 8.23, N 4.50, Cu 10.17.

■ *[Cu(n-non tyr)$_2$]*

53.27%, Mp 202.2 °C (dec).

IR: 3 410, 3 210 (ν NH_2·); 2 940–2 860 (δ C–H aliph); 1 630 (ν_a C=O); 1 370 (ν_s C–O); 1 240 (δ_a CH_2–O–Ph); 360 (ν Cu–N); 305 (ν Cu–O).

Anal calc for $C_{36}CuH_{56}N_2O_6$ (675.84): C 63.95, H 8.29, N 4.14, Cu 9.40; found: C 62.93, H 8.16, N 4.20, Cu 9.07.

■ *[Cu(n-dec tyr)$_2$]*

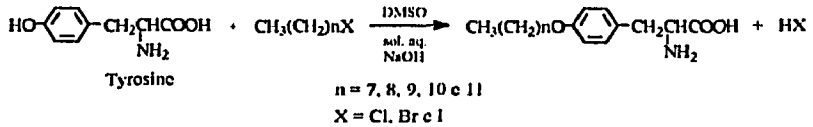
73.0%, Mp 211–213 °C.

IR: 3 400, 3 200 (ν NH_2·); 2 960–2 860 (δ C–H aliph); 1 650 (ν_a C=O); 1 380 (ν_s C–O); 1 240 (δ_a CH_2–O–Ph); 360 (ν Cu–N); 330 (ν Cu–O).

Anal calc for $C_{38}CuH_{60}N_2O_6$ (703.86): C 64.84, H 8.52, N 3.98, Cu 9.02; found: C 64.19, H 8.58, N 4.02, Cu 9.27.

■ *[Cu(n-und tyr)$_2$]*

48.68%, Mp 212.1–214 °C.



Scheme 1

IR: 3 400, 3 200 (ν NH_2·); 2 960–2 860 (δ C–H aliph); 1 650 (ν_a C=O); 1 370 (ν_s C–O); 1 250 (δ_a CH_2–O–Ph); 370 (ν Cu–N); 299 (ν Cu–O).

Anal calc for $C_{40}CuH_{64}N_2O_6$ (731.88): C 65.62, H 8.75, N 3.83, Cu 8.68; found: C 66.74, H 8.87, N 3.94, Cu 8.79.

■ *[Cu(n-doc tyr)$_2$]*

80.0%, Mp 219–221 °C.

IR: 3 420, 3 200 (ν NH_2·); 2 960–2 860 (δ C–H aliph); 1 640 (ν_a C=O); 1 370 (ν_s C–O); 1 240 (δ_a CH_2–O–Ph); 370 (ν Cu–N); 300 (ν Cu–O).

Anal calc for $C_{42}CuH_{68}N_2O_6$ (759.90): C 66.38, H 8.95, N 3.68, Cu 8.36; found: C 65.32, H 8.77, N 3.60, Cu 8.50.

• *trans-bis-[(S)-5-n-Alkyl ester glutamate]copper (II)*

Hydrogen chloride was bubbled into appropriate dry alcohol. *S*-glutamic acid was added and the reaction was then stirred at room temperature for several hours (see table I). The reactions were monitored by thin-layer chromatography (silica gel as adsorbent, butanol/acetone/water – 5:5:3 as eluent and ninhydrin as developer). The R_F values are cited below. An equimolar quantity of copper sulfate pentahydrate was added to the resulting compounds produced in situ. The pH of the mixture was then adjusted to 8 by slow addition of 10% NaOH with stirring. The formation of two phases was observed, and a color change from green to purple occurred during the neutralization. A purple precipitate was observed at the alcohol/water interface. The resulting purple precipitate was filtered off, washed with water, ethanol, diethyl ether and then refluxed in toluene for 2 h. Finally, the precipitate was again filtered off, washed with ethanol, diethyl ether and then dried in a drying pistol (110 °C) for 12 h.

Table I. Reagent quantities utilized in the esterification reaction of glutamic acid and reaction time.

Esters	*GluH*[a] × 10^{-3} *(mole)*	*Alcohol (mol)*	*HCl (mol)*	*Reaction time (h)*
n-oct glu	3.39	10.19×10^{-1}	10.19×10^{-1}	12
n-non glu	1.70	5.09×10^{-2}	5.09×10^{-2}	17
n-dec glu	6.79	1.36×10^{-1}	1.36×10^{-1}	11
n-und glu	1.70	5.04×10^{-2}	5.04×10^{-2}	24
n-dod glu	1.70	5.09×10^{-2}	5.09×10^{-2}	24

[a] GluH = glutamic acid.

■ *[Cu(n-oct glu)$_2$]*

78%, Mp 241.3 °C (dec).

IR: 3 360, 3 250 (ν NH_2·); 2 980–2 860 (δ C–H aliph); 1 730 (ν_a C=O ester); 1 620 (ν_a C=O acid); 1 380 (ν_s C–O acid); 1 210 (ν_s C–O ester); Cu–N and Cu–O (unresolved bands).

Anal calc for $C_{26}CuH_{48}N_2O_8$ (579.72): C 53.86, H 8.28, N 4.83, Cu 10.96; found: C 52.98, H 8.31, N 4.73, Cu 10.01.

■ *[Cu(n-non glu)$_2$]*

67%, Mp 246 °C (dec).

IR: 3 400, 3 290 (ν NH_2·); 2 980–2 880 (δ C–H aliph); 1 740 (ν_a C=O ester); 1 630 (ν_a C=O acid); 1 390 (ν_s C–O acid); 1 210 (ν_s C–O ester); 390 (ν Cu–N); 310 (ν Cu–O).

Anal calc for $C_{28}CuH_{52}N_2O_8$ (607.74): C 55.33, H 8.56, N 4.61, Cu 10.45; found: C 54.44, H 8.45, N 4.56, Cu 9.98.

■ *[Cu(n-dec glu)$_2$]*

58%, Mp 235–236 °C (dec).

IR: 3 410, 3 250 (ν NH_2·); 2 910–2 850 (δ C–H aliph); 1 730 (ν_a C=O ester); 1 620 (ν_a C=O acid); 1 380 (ν_s C–O acid); 1 240 (ν_s C–O ester); 390 (ν Cu–N); 310 (ν Cu–O).

Anal calc for $C_{30}CuH_{56}N_2O_8$ (635.76): C 56.67, H 8.81, N 4.40, Cu 9.99; found: C 55.88, H 8.80, N 4.43, Cu 9.86.

■ *[Cu(n-und glu)$_2$]*

72%, Mp 236.4 °C (dec).

IR: 3 410, 3 280 (ν NH_2·); 2 980–2 860 (δ C–H aliph); 1 740 (ν_a C=O ester); 1 630 (ν_a C=O acid); 1 390 (ν_s C–O acid); 1 210 (ν_s C–O ester); Cu–N and Cu–O (unresolved bands).

Anal calc for $C_{32}CuH_{60}N_2O_8$ (663.78): C 57.89, H 9.04, N 4.22, Cu 9.57; found: C 57.10, H 8.84, N 4.31, Cu 9.25.

■ *[Cu(n-dod glu)$_2$]*

84%, Mp 237.2 °C (dec).

IR: 3 320, 3 280 (ν NH_2·); 2 960–2 880 (δ C–H aliph); 1 730 (ν_a C=O ester); 1 620 (ν_a C=O acid); 1 380 (ν_s C–O acid); 1 210 (ν_s C–O ester); 410 (ν Cu–N); 310 (ν Cu–O).

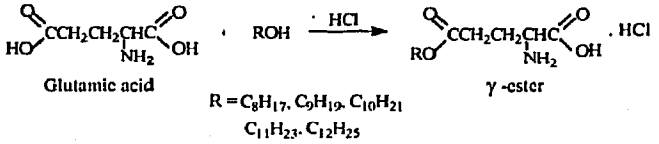
Anal calc for $C_{34}CuH_{64}N_2O_8$ (691.80): C 59.03, H 9.25, N 4.05, Cu 9.18; found: C 58.91, H 9.45, N 3.97, Cu 8.93.

Results and discussion

The ethers derived from tyrosine were prepared by nucleophilic substitution by the phenol group of this amino acid. The synthesis of alkyl ethers of tyrosine has been reported previously. One method requires the protection of the amino group by formylation, however, Solar [1] has reported that dimethyl sulfoxide was particularly effective in promoting *O*-*n*-alkylation of tyrosine. The Solar method was utilized by us, and confirmed the effectiveness of dimethyl sulfoxide in promoting the selective *O*-*n*-alkylation of tyrosine without prior protection of the amino group.

Concerning the γ-esters, our attempts toward the conversion of the hydrochlorides into free esters by the Coleman method were unsuccessful.

The etherification and esterification can be accounted for by scheme 1 and 2 respectively.



Scheme 2

Vibrational spectroscopy

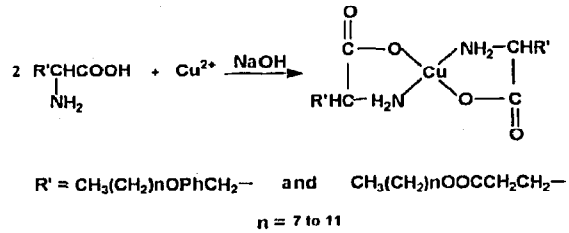
• *Ligands*

The vibrational spectra of the alkyl ethers of *S*-(−)-tyrosine are empirically assigned by comparison with the spectrum of *S*-(−)-tyrosine. In tyrosine, the NH_3^+ and OH bands coalesce in the 3 400–2 200 cm^{-1} region. In alkyl ethers, the NH_3^+ band is well defined in the 3 220–3 190 cm^{-1} region. The COO^- asymmetric stretching bands in alkyl ethers of *S*-(−)-tyrosine are at ca 1 600 cm^{-1}, while in tyrosine this band is at 1 590 cm^{-1}. The COO^- stretching symmetric absorption frequencies are in the 1 390–1 380 cm^{-1} region in the alkyl ethers of *S*-(−)-tyrosine, while in tyrosine this band is at 1 420 cm^{-1}. For the five ethers synthesized, the strong bands in the 1 260–1 250 cm^{-1} region may be attributed to CH_2–O–Ph groups. These bands and the bands in the 2 960–2 950 cm^{-1} region due to the C–H aliphatic stretching are clear evidence for the etherification of tyrosine since they are absent in the tyrosine IR spectrum.

The IR spectra of the γ-ester hydrochlorides are empirically assigned by comparison with the spectrum of *S*-(+)-glutamic acid hydrochloride. The COO^- asymmetric stretching absorption frequency in *S*-(+)-glutamic acid hydrochloride is a strong band at 1 728 cm^{-1}. For the five esters synthesized, the spectra reveal two coupled absorptions: one of these at ca 1 740–1 730 cm^{-1} is due to the asymmetric stretching absorption of the ester carboxylate group and the other absorption in the 1 730–1 700 cm^{-1} region is due to the asymmetric stretching vibration of the COOH group. The spectra of the γ-ester hydrochlorides also have characteristic absorption peaks in the 3 000–2 800 cm^{-1} region due to the added aliphatic chain. These C–H peaks indicate that the compounds are esterified.

• *Complexes*

The complexation reaction of these tyrosine and glutamic acid derivatives are shown in scheme 3. The shift of the stretching vibrations of the carboxylate and amino groups of the complexes and the metal–ligand stretchings are analysed below.



Scheme 3

■ *COO^- stretching vibration*

The COO^- group stretching frequencies are affected by coordination as well as by intermolecular interaction. In the free ligands of the alkyl ethers of tyrosine, the carboxylate group asymmetric stretching absorptions are at ca 1 600 cm^{-1}, and the stretching symmetric vibrations are in the 1 380–1 390 cm^{-1} region. In the infrared absorption spectra of the complexes the absorptions due to the asymmetric stretching of the carboxylate group are in the 1 640–1 650 cm^{-1} region and those of the symmetric stretching at 1 370–1 380 cm^{-1}. The increase in the frequency of the COO^- asymmetric stretching absorption and the decrease in the frequency of the COO^- stretching symmetric absorption may be attributed to an interference of the metal–ligand bond in the resonance of the carboxylate ion [11]. Unidentate complexes of the carboxylate ion show an increase in double-bond character of one of the C–O bonds. This is evidenced by the increase of one C–O stretching frequency (COO asymmetric stretching vibration). Consequently, a decrease in the frequency is expected of the COO stretching symmetric bands owing to a smaller bond order. The infrared data for the carboxylate ion indicate that the COO^- group is a unidentate ligand in all of the tyrosine derivatives synthesized.

For the γ-alkyl ester hydrochlorides, the absorption maxima associated with the asymmetric and symmetric COOH stretching occur respectively at 1 700–1 730 cm^{-1} and 1 180–1 200 cm^{-1}. For the corresponding complexes with copper (II) ion, these absorptions occur at 1 620–1 630 cm^{-1} and at 1 370–1 390 cm^{-1}. It is observed therefore, that there is a decrease in the frequency of the asymmetric stretching absorption, and an increase in the frequency of the symmetric stretching absorption after coordination compared with the corresponding γ-alkyl ester hydrochlorides. This indicates that carboxylate group is also a unidentate ligand in all of the alkyl glutamate complexes synthesized.

■ *NH_2 stretching vibrations*

The NH_2 and OH stretching absorptions in the ligands appear as a wide band due to hydrogen bonding. The spectra of all the complexes investigated do not show decreases in the NH_2 stretching frequencies compared to the free ligands. We expected that chelation would be accompanied by a decrease in the NH_2 stretching absorption. If this does not occur and if the NH_2 are sharp peaks in the complexes we assume the nonexistence of hydrogen bonding in the complexes.

■ *Metal–ligand stretching*

Square-planar bis(*n*-alkyl tyrosine) and bis(γ-alkyl glutamate)copper (II) complexes can exhibit *cis* or *trans* local geometries. The activity of the copper–ligand stretching vibrations may be utilized to make the distinction between the *cis* or *trans*-isomers. The *trans*-isomers exhibit only asymmetric Cu–N and Cu–O stretching modes, while the spectra of the *cis*-isomers exhibit two Cu–N and two Cu–O stretching modes, namely the Cu–N asymmetric and symmetric stretching modes and the Cu–O asymmetric and symmetric modes respectively. Thus, for the *trans*-isomers only the asymmetric stretching modes are expected to be infrared-active. Our complexes exhibit only one absorption for each of these modes. This suggests that the complexes studied exhibit the *trans*-configuration. This criterion has also been used to predict the geometrical isomerism in bis(amino acidato) copper (II) complexes. It is a vibrational criterion that permits distinction between the *cis* and *trans* geometries of the several copper complexes and has been already described [12].

Nuclear magnetic resonance spectrometry

Two absorptions observed in the ^1H NMR spectra of the alkyl ethers of tyrosine are important: one is the peak at 3.3–3.6 ppm, attributed to the hydrogens of the CH_2 groups attached to a phenolic oxygen, and the other at 1.1–1.3 ppm attributed to the methylene hydrogens of the aliphatic carbon chain. These absorptions offer supporting evidence for the *O*-alkylation of tyrosine. In the ^{13}C NMR spectra the absorptions attributed to the methylene carbon attached to the phenolic oxygen occur at 18.2–36.2 ppm and 103.9–112.7 ppm. The signal attributed to the carboxylic hydrogen does not appear because these derivatives are in the zwitterion form.

For the γ-alkyl glutamate ester hydrochloride, we emphasize the peaks that support the esterification and the peaks that exclude the formation of the diester hydrochlorides. These are the peaks due to the methylenic group of the aliphatic chain in the 1.3–1.7 ppm region, and the unique peak in the 11.54–11.64 ppm region due to the absorption of the hydrogen of the carboxylic acid respectively. In the ^{13}C NMR spectra, two signals attributable to carbonyl carbons are observed. One at ca 178 ppm due to carboxylic acid and another at ca 174 ppm due to aliphatic esters. In the ^1H spectrum, at ca 8 ppm a broad peak is also observed due to the protons of the NH_3^+ group. The chemical shift of the absorption signals of these hydrogen atoms occurs due to the influence of the electronegativity of the chlorine atom, in these compounds.

The NMR spectra of the aminoacids are affected by variations in pH. The hydrogen absorption signals are more sensitive to this variation than the ^{13}C absorption peaks. The results of these investigations reveal that protons become more shielded as the pH is raised, while ^{13}C nuclei generally become less shielded [13]. Also the multiplicity of the signals is significantly altered when the pH is raised. This is due to the formation of the $RCH_2CH(NH_2)CO_2^-$ species. It is also important to observe, that in ^1H NMR spectra of the γ-alkyl glutamate ester hydrochloride the hydrogens of the $CH(H_\alpha)$ group are shifted to greater δ values, compared to H_α of the alkyl ethers of *S*-(−)-tyrosine. These chemical shifts are in good agreement with previously published work [14, 15].

Mass spectrometry

Table II exhibits most of the prominent fragments in the mass spectrum of one tyrosine derivative, *n*-octyl tyrosine, taken as a representative example of this group. The last four fragments are present in all tyrosine derivatives. Other important peaks are the $(M + H)^+$ peak and the M-107 peak, probably due to the recombination of $CH_3(CH_2)_n^+$ and $^+CH_2CH(NH_2)COOH$.

Table III lists the principal fragments for one γ-*n*-alkyl ester hydrochloride derivative. The M–Cl peak is indicative of the hydrochloride formation, and the peaks due to a loss of mass attributed to the $C_nH_{2n+1}O$ and $C_nH_{2n+1}OOC$ fragments, present in all spectra, are in good agreement with our proposed hypothesis of esterification of the *S*-(+)-glutamic acid.

Table II. Mass spectrum of [(*S*)-2-amino-3-[4-(octyloxy)-phenyl]propanoic acid].

m/z	*Rel Abund*	*Species*
294	6.7	$(M + H)^+$ [a]
248	6.9	$CH_3(CH_2)_7$-O-$(C_6H_4)CH_2CH{=}NH_2^+$
186	66.2	$CH_3(CH_2)_7C{\cdot}(NH_2)COOH$
136	9.9	HO-(C_6H_4)-$CH_2CH{=}NH_2^+$
107	6.5	HO-(C_6H_4)-$CH_2{\cdot}$
88	100.0	$^+CH_2CH(NH_2)COOH$
57	21.5	$C_4H_9^+$

[a] M = molecular ion.

Table III. Mass spectrum of *S*-glutamic acid 5-undecyl ester hydrochloride.

m/z	*Rel Abund*	*Species*
302	12.2	M–Cl[a]
256	29.3	$CH_3(CH_2)_{10}OOCCH_2CH_2CH{=}NH_2^+$
130	24.4	$^+OCCH_2CH_2CH(NH_2)COOH$
102	31.7	$^+CH_2CH_2CH(NH_2)COOH$
84	100.0	$^+OCCH_2CH_2CH{=}NH$
57	25.0	$C_4H_9^+$

[a] M = molecular ion.

We observed only the $(M + H)^+$ ion in our compounds. The $[(M + H) - 46]^+$ peaks (table II) correspond to the loss of formic acid from the $(M + H)^+$ ion. In previously reported studies the EI spectra of amino acids show weak or nonexistent molecular ion peaks [14]. The weak molecular ion peak occurs because the amino acids easily lose their carboxyl group upon electron impact.

Acknowledgment

The authors are indebted to the Brazilian agencies CNPq and FAPEMIG which financially supported this work. We also thank Dr Richard Michael Grazul for his helpful discussions, comments and suggestions.

References

1 Solar SL, Schumaker RR, *J Org Chem* (1966) 31, 1996
2 Cantacuzène D, Pascal F, Guerreiro C, *Tetrahedron* (1987) 43, 8, 1823
3 Coleman D, *J Chem Soc* (1966) 2294
4 Jouin P, Castro B, Zeggaf C, Pantaloni A, *Tetrahedron Lett* (1987) 28, 15, 1665
5 Baillie AJ, Florence AT, Hume LR, Muirhead GT, Rogerson A, *J Pharm Pharmacol* (1985) 37, 863
6 Angelici RJ, Leach BE, *J Am Chem Soc* (1968) 90, 2504
7 Herlinger AW, Wenhold SL, Long TV, *J Am Chem Soc* (1970) 90, 6474
8 Cotton FA, Wilkinson G, In: *Advanced Inorganic Chemistry*, John Wiley, New York, 1988, p 1334
9 Silva MLA, MSc thesis, Belo Horizonte, Brazil, 1991, p 22–29
10 Dantas TNC, Dsc thesis, Toulouse, France, 1983, p 93

11 Nakamoto K, Morimoto Y, Martell AE, *J Am Chem Soc* (1961) 83, 4528

12 Misra BN, Kripal R, *Acta Phys Polon* (1981) 59A, 4, 425

13 Bovey FA, Jelinsk L, Mirau PA, In: *Nuclear Magnetic Resonance Spectroscopy*, Academic, San Diego, 1987, p 381

14 Silverstein RM, Bassler GC, Morrill TC, In: *Spectrometric Identification of Organic Compounds*, John Wiley, New York, 1991

15 Prestsch E, Clerc T, Seibl J, Simon W, In: *Tables of Spectral Data for Structure Determination of Organic Compounds*, Springer, New York, 1989, p H-351