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Synthesis of Polymerized N-Undecylenyl-L-Aminoacid and N-Undecylenyl-L-Peptide Derivatives

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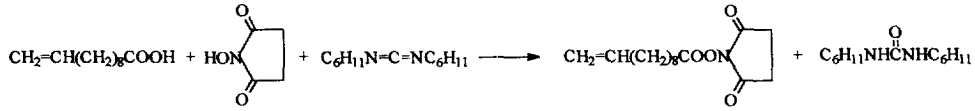
Abstract: Micelle forming polymerized N-Undecylenyl-L-aminoacid and N-Undecylenyl-L-peptide derivatives have been obtained. These compounds are effective as pseudostationary phases in electrokinetic capillary electrophoresis for racemate resolution. Synthetic procedures are described in detail, as well as preliminary analytical data comparing aminoacid derivatives and an aminoacid derivative with a peptide derivative.

Analytical separations of enantiomers through the use of capillary electrophoresis (CE) is an area that has been the objective of a significant number of researchers in the last decade.[1-8] This type of separations can be accomplished using immobilized chiral phases or chiral mobile phase additives, such as: (1) cyclodextrins,[2,8] (2) chiral metal complexes,[3] (3) crown ethers,[4] (4) calixarenes,[5] and (5) chiral surfactants.[6,7] The latter technique is referred as micellar electrokinetic capillary chromatography (MECC), where the micelle forming chiral surfactants act as pseudostationary phases to resolve efficiently enantiomers. The first report in the literature on the synthesis of polymerized N-Undecylenyl-L-valine and its proven ability as an effective mobile phase additive in CE was originated in our laboratory,[9] with another publication following it.[10] The success obtained with this compound for chiral separations encouraged our laboratory to pursue the synthesis of different N-Undecylenyl-L-aminoacid derivatives for their evaluation as pseudophases in electrokinetic chromatography. Furthermore, in order to study the effects, such as resolution and retention time, that one additional chiral center might have upon chiral separation, we have synthesized the Undecylenyl-L-peptide analogues for comparison with the Undecylenyl-L-aminoacid derivatives. The present manuscript describes the synthetic methodology to obtain these compounds, which involves methods commonly utilized in peptide chemistry,[11] as well as preliminary analytical data on chiral resolution.

Undecylenic acid (1) is reacted with N-Hydroxysuccinimide (NHS) (2) in the presence of Dicyclohexylcarbodiimide (DCC) (3) to produce an Ester (4) and Dicyclohexylurea (DCU) (5). The Ester (4), which is the common intermediate for all the compounds obtained, is then reacted with L-alanine, L-valine, L-leucine, L-isoleucine, L-alanine-L-alanine, L-valine-L-valine, and L-leucine-L-leucine (6) to give the respective compound in good yields.[15-17] These monomers (7) are then polymerized at 0.1M aqueous solutions in a ^{60}Co source,[12] to give the respective polymerized surfactant (8).[15]



(1) (2) (3) (4) (5)

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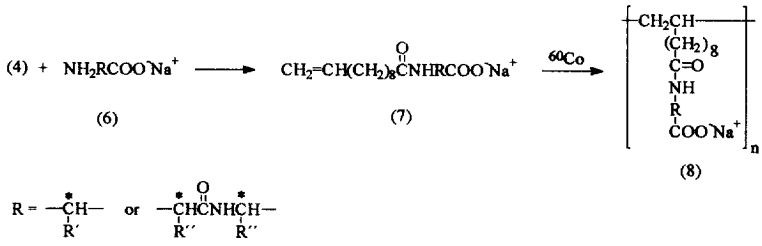

Fig. 1 shows racemate separation of (±) 1,1′-bi-2-naphthol and (±) 1,1′-binaphthyl-2,2′-diamine utilizing polymerized Undecylenyl-L-alaninate, Undecylenyl-L-valinate, Undecylenyl-L-leucinate, and Undecylenyl-L-isoleucinate sodium salts. [18] A series of cationic, anionic, and neutral enantiomers have been resolved successfully using these polymers.[13]

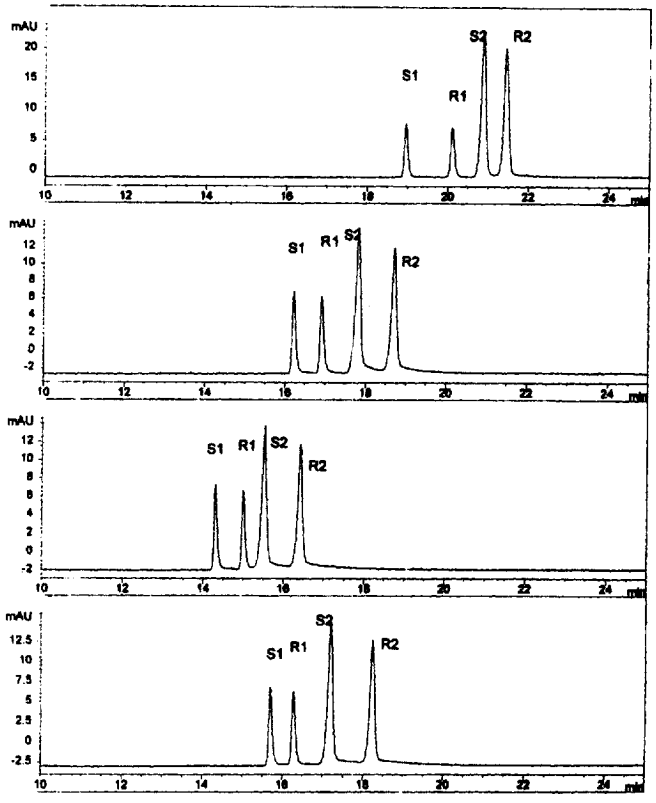

Fig. 1. Separation of (±)-1,1′-bi-2-naphthol (S1/R1) and (±)-1,1′-binaphthyl-2,2′-diamine (S2/R2) utilizing poly(undecylenyl-L-alaninate), poly(undecylenyl-L-valinate), poly(undecylenyl-L-leucinate), and poly(undecylenyl-L-isoleucinate) (in order from top to bottom electropherogram).

A comparison between poly(undecylenyl-L-valinate) and poly(undecylenyl-L-valine-L-valinate) for the enantiomeric resolution of (±)-1,1 of ′-binaphthyl-2,2′-diyl hydrogen phosphate, (±)-1,1′-binaphthyl-2,2′-diamine and (±)-1,1′-bi-2-naphthol is presented in Fig. 2. [18] The results show that the latter polymer decreases the time required for analysis, while at the same time resolves more efficiently the first couple of enantiomers mentioned. Several enantiomers are currently being investigated.[13,14]

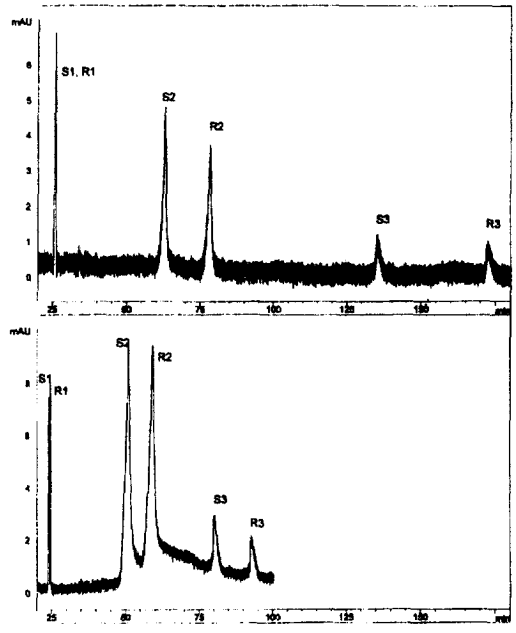

Fig. 2. Separation of (±)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (S1/R1), (±)-1,1′-binaphthyl-2,2′-diamine (S2/R2) and (±)-1,1′-bi-2-naphthol (S3/R3) utilizing poly(undecylenyl-L-valinate) (top electropherogram) and poly(undecylenyl-L-valine-L-valinate) (bottom electropherogram).

In conclusion, this work reports detailed synthetic procedures with good yields[15] of efficient chiral pseudostationary phases for electrokinetic capillary chromatography. These compounds contain undecylenic acid as the common moiety, and different aminoacids and peptides to render chirality to the molecule. To the best of our knowledge, this is the first report on the synthesis of these molecules, which is followed by their application in the analytical area. Further studies on the analytical separations of several analytes are currently being performed in our laboratory.[13,14]

Acknowledgments

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15.- **Synthesis of N-Hydroxysuccinimide ester of Undecylenic acid (4):** NHS (125 mmols) is dissolved in dry ethyl acetate (542 mL), followed by the addition of Undecylenic acid (125 mmols). A solution of DCC (1M, 125 mmols) in dry ethyl acetate is then added. The reaction is run at room temperature for at least 16 hours under anhydrous conditions. The resulting byproduct, DCU, is removed by filtration, followed by evaporation of the solvent under reduced pressure. The resulting white waxy product is recrystallized from 100 mL of isopropyl alcohol and rinsed with water. The product is vacuum dried overnight. **Synthesis of N-Undecylenyl aminoacid derivatives and N-Undecylenyl peptide derivatives (7):** Sodium bicarbonate (20 mmols) is dissolved in water (200 mL), followed by the addition of the corresponding aminoacid, L-alanine, L-valine, L-leucine and L-isoleucine or peptide, L-alanine-L-alanine, L-valine-L-valine, and L-leucine-L-leucine (20 mmols). Then, a solution of the N-Hydroxysuccinimide ester of Undecylenic acid (20 mmols) in tetrahydrofuran (THF) (200 mL) is added to the reaction flask. The reaction proceeds for at least 16 hours at room temperature. The pH is dropped to 2 with 1M HCl, followed by evaporation of the solvent under vacuum for the aminoacid derivatives, and rinsing with water and evaporation of the solvent under vacuum for the peptide derivatives. The aminoacid products are dissolved in dichloromethane (DCM) (15 mL for L-alanine, and L-valine, 20 mL for L-leucine, and L-isoleucine) and reprecipitated by the addition of 100 mL of petroleum ether. Likewise, the peptide compounds are dissolved and reprecipitated (30mL DCM-20mL THF to dissolve L-alanine-L-alanine and reprecipitated with 100 mL of petroleum ether, 100 mL to dissolve L-valine-L-valine and reprecipitated with 200 mL of petroleum ether, 30 mL THF to dissolve L-leucine-L-leucine, and reprecipitated with 200 mL of petroleum ether). Then, the product is filtered and dried under vacuum overnight. **Sodium salt formation of N-Undecylenyl aminoacid derivatives and N-Undecylenyl peptide derivatives (7):** The corresponding N-Undecylenyl amino acid derivative (20 mmols) is dissolved in THF (200 mL), while the corresponding N-Undecylenyl peptide derivative (20 mmols) is dissolved in THF (250 mL). These compounds are reacted overnight at room temperature with a sodium bicarbonate (20 mmols) solution in water (200 mL), followed by evaporation of the solvent under vacuum, and freeze drying of the material. **Polymerization of N-Undecylenyl sodium salt derivatives (8):** The corresponding N-Undecylenyl amino acidate sodium salts and N-Undecylenyl peptide sodium salts are dissolved in water (1M), and polymerized by the use of a ^{60}Co source for 72 hours. The product is dialyzed against water in cellulosic membranes with 2000 MWCO, and freeze dried. The resulting polymer is analyzed by NMR for the abscence of residual double bonds.
16.- **Characterization**: N-Hydroxysuccinimide ester of Undecylenic acid - m.p.: 53-54 °C, yield: 46%; Undecylenyl-L-Alanine - m.p.: 54-55 °C, yield: 79%, $[\alpha]^{20}_D$: -10.03, CMC: 21; Undecylenyl-L-Valine - m.p.: 94-95 °C, yield: 64%, $[\alpha]^{20}_D$: -5.29, CMC: 13; Undecylenyl-L-Leucine - m.p.: 99-100 °C, yield: 65%, $[\alpha]^{20}_D$: -15.71, CMC: 11; Undecylenyl-L-Isoleucine - m.p.: 99-100 °C, yield: 76%, $[\alpha]^{20}_D$: 2.14; CMC: 11; Undecylenyl-L-Alanine-L-Alanine - m.p.: 139-140 °C, yield: 83%, $[\alpha]^{20}_D$: -32.17, CMC: 12; Undecylenyl-L-Valine-L-Valine - m.p.: 124-125 °C, yield: 82%, $[\alpha]^{20}_D$: -26.14, CMC: 10; Undecylenyl-L-Leucine-L-Leucine - m.p.: 141-142 °C, yield: 90%, $[\alpha]^{20}_D$: -31.50, CMC: 9.
17.- $[\alpha]^{20}_D$ and CMC determinations correspond to the sodium salts dissolved in water, except for Undecylenyl-L-Isoleucine sodium salt (dissolved in MetOH); concentration for optical rotations = 1% wt/v.; Analytical data (Elemental Analysis, FAB-MS, IR, ^1H NMR) are available from the author on request.
18.- **CE conditions:** Aminoacid derivatives - 17mM equivalent monomer concentrations of surfactants with 25mM $Na_2B_4O_7$ at pH 10.2; capillary 50 μm x 64.5 cm (56 cm effective length); applied voltage +30kV; current +74-80 μA; Peptide derivatives - 17mM equivalent monomer concentrations of surfactants with 50mM each of NaH_2PO_4 and $Na_2B_4O_7$ at pH 7.2; capillary 50 μm x 64.5 cm (56 cm effective length); applied voltage +20kV; current +80-90 μA.