Synthesis of a New Enantiopure Chiral Aza Crown Ether and Its Application in Enantiomeric Separation

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A new enantiopure chiral aza crown ether (*S,S*)-1,7-bis(4-phenyl-5-hydroxy-2-oxo-3- zapentyl)-1,7-diaza-12-crown-4 ligand (1) has been synthesized and used as a chiral selector in the enantiomeric separation of D/L-carnitine by capillary electrophoresis.

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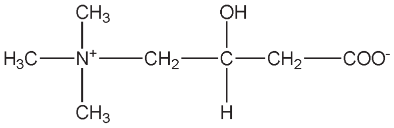
Introduction.

Since Pedersen first synthesized macrocyclic polyether compounds (crown ethers), a wide variety of crown ethers have been prepared and utilized in alkali and alkaline earth metal cation determination and separation due to their superior binding ability for these metal ions. Recently, a considerable number of studies on complexation of chiral alkylammonium salts [1] and chiral amino acids [2] by chiral crown ethers have been reported. Macrocyclic compounds containing nitrogen atoms, known as aza crown ethers, are of particular interest because one or more side arms can be attached to them, and these compounds have the ability to form strong and selective interactions with guest molecules, such as primary and quarternary alkylammonium salts. So, a number of aza crown ether analogues were used in chiral recognition [3]. In the present paper we report the synthesis and application of a new enantiopure chiral aza crown ether (*S,S*)-1,7-bis(4-phenyl-5- hydroxy-2-oxo-3-azapentyl)-1,7-diaza-12-crown-4 ligand (**1**) which was used successfully in the enantiomeric separation of D/L-carnitine by capillary zone electrophoresis.



$H_3C-N^+(CH_3)_2-CH_2-CH(OH)-CH_2-COO^-$

D/L-carnitine

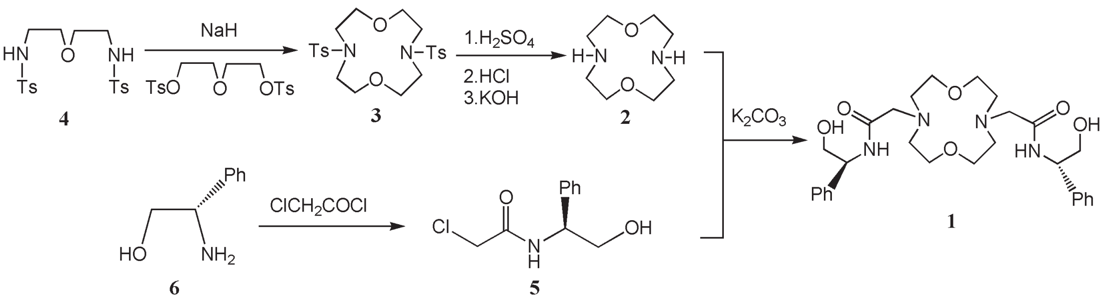
L-Carnitine plays an important role in the transport of fatty acids across the mitochondrial membrane by the transferase and translocase enzyme system [4]. Recently, L-carnitine and its derivatives have been proved to possess interesting pharmacological and nutritional properties [5], however D-carnitine has been shown to have a considerable toxic effect on biochemical processes [6].

Results and Discussion.

The synthesis is shown in Scheme 1. Compound **1** was prepared by alkylation of the diaza crown ether **2** with enantiopure chiral chloro compound **5** in the presence of anhydrous potassiun carbonate. 1,7-Diaza-12-crown-4 ligand (**2**) was obtained after acidic hydrolysis of the ditosyl derivative **3** followed by neutralization [7]. Ditosyl derivative **3** was obtained by cyclization of the disodium salt of bissulfonamide **4** [8] with diethylene glycol ditosylate in strong basic conditions. (2*S*)-*N*-(1-Phenyl-2-hydroxyethyl)- chloroacetamide (**5**) was prepared by the reaction of the amino alcohol **6** [9] with chloroacetyl chloride [10]. The structure of compound **1** was confirmed by elemental analysis, IR, MS, ^{1}H NMR and ^{13}C NMR spectra.

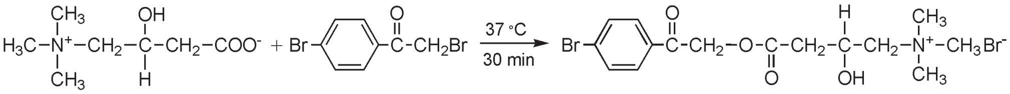
The use of enantiopure chiral aza crown ethers in the separation of enantiomers have scarcely been reported in the past. We have used the enantiopure chiral aza crown ether **1** as a chiral selector for the separation of enantiomers in capillary zone electrophoresis. The enantiomeric separation was performed using (*S,S*)-1,7-bis(4-phenyl-5-hydroxy-2-oxo-3-azapentyl)-1,7-diaza-12-crown-4 ligand (**1**) in the presence of sulfonated

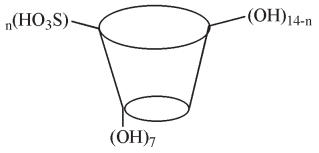
Scheme 1



β-cyclodextrin with a degree of substitution 3~4 (Sigma-Aldrich, USA). Under optimal conditions D- and L-carnitine derivatized with 4'-bromophenacyl bromide (according to the literature procedure [11], see Scheme 2) were separated completely (see Figure 1), whereas using only sulfonated β-cyclodextrin, enantiomeric separation was obtained with poor efficiency.

Scheme 2





n=3~4

Sulfated β-Cyclodextrin

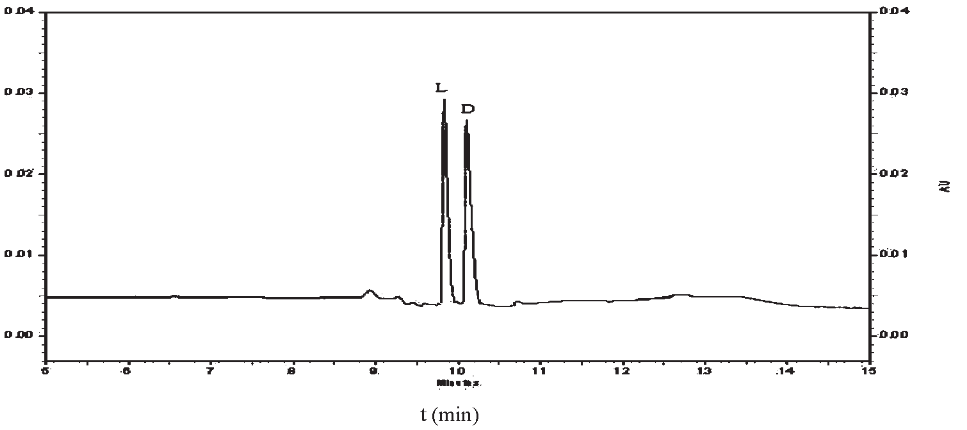


Figure 1. The electrophorogram of enantiomeric separation of D/L-carnitine derivatized with 4¡ä-bromophenacyl bromide

EXPERIMENTAL

Infrared spectra were recorded on a Nicolet spetrophotometer; ^{1}H NMR and ^{13}C NMR spectra were recorded on an Avance DMX 500 spectrometer and chemical shifts were reported relative to the solvent peak. MS spectra were obtained on a HP5989B instrument. Electrophorograms were recorded on P/ACE 2000 instrument with a 32 Karat software for data collection. A positive power supply of 25 kV was used with a constant current mode of operation. Capillaries of effective length of 60cmx75μm i.d. were used and the temperature was 25 °C. The buffer solution used for separation consisted of 50 mmol/L phosphoric acid, 1.25% (w/v) of sulfonated β-cyclodextrin, 0.94% (w/v) of compound **1** (in acetonitrile). The detection was carried out at 260 nm.

Compounds **3** and **4** were prepared according to the literature procedures [7,8]. Hydrolysis of **3** was performed with 97 % sulfuric acid at 95~100 °C for 48 hours, followed by work-up with 6 *N* hydrochloric acid. The acidic solution was made basic with saturated aqueous potassium hydroxide then extracted with chloroform to give 1,7-diaza-12-crown-4 ether (**2**) as a colorless solid (68.5%), mp: 84-85 °C (literature [12] mp: 83-84 °C); ^{1}H nmr (CDCl$_3$): δ 2.83 (8H, t, *J*=5.9, N-CH$_2$), 3.64 (8H, t, *J*=5.9, CH$_2$-O); ms m/z (%): 175 (M$^+$+1, 10.4), 113 (4), 106 (59), 100 (11), 88 (66), 57 (100),44 (46); ir ν_{max}: 3260, 2937, 1138, 1029, 916 cm^{-1}.

Enantiopure chiral amino alcohol **6** and enantiopure chiral chloro compound **5** were prepared following the literature procedures [9,10]. (2*S*)-*N*-(1-phenyl-2-hydroxyethyl)-chloroacetamide (**5**) is a colorless solid (82.4%), mp: 106-108 °C; $[\alpha]_D^{15}$ +44.78 (c 2.01, CH$_3$CN); ^{1}H nmr (CDCl$_3$): β 2.04 (1H, br, OH), 3.91-3.94 (2H, m, CH$_2$-O), 4.09-4.12 (2H, m, CH$_2$-Cl), 5.10-5.12 (1H, m, CH-N), 7.26-7.40 (6H, m, Ar and NH); ms m/z (%): 214 (M$^+$, 0.84), 182 (49), 106 (100), 91 (11), 77 (24), 51(15); ir ν_{max}: 3314, 1667, 1540, 1454, 1044, 756 cm^{-1}.

(*S,S*)-1,7-Bis(4-phenyl-5-hydroxy-2-oxo-3-azapentyl)-1,7-diaza-12-crown-4 Ligand (**1**).

A stirred mixture of 1,7-diaza-12-crown-4 ether (**2**) (0.35 g, 2.0 mmoles), anhydrous potassium carbonate (1.12 g, 8.1 mmoles) and (2*S*)-*N*-(1-phenyl-2-hydroxyethyl)- chloroacetamide (**5**) (0.88 g, 4.1 mmoles) in 30 ml of acetonitrile was heated under reflux for 12 hours. The reaction mixture was cooled and evaporated to dryness under reduced pressure. The residue separated into two layers after water was added. The organic layer was separated and the aqueous one was extracted by chloroform. The organic layers were combined and dried over anhydrous potassium carbonate. The solvent was evaporated under reduced pressure and the residual yellow oil was purified by chromatography on silica gel using a mixture of methylene chloride-methanol- 28% aq. ammonia (10:10:1) as eluent, to give the aza crown ether **1** as a pale yellow oil (0.81g, 76.7%). $[\alpha]_D^{15}$ +30.3 (c 0.846, CH_2Cl_2); ^1H nmr ($CDCl_3$): δ 1.88 (2H, br, -OH), 2.53 (8H, t, *J*=6.1, CH_2-N), 3.19 (4H, s, N-CH_2-CON), 3.45-3.49 (2H, m, CH_{2a}-O), 3.61-3.63 (8H, t, *J*=6.1, CH_2-O), 3.76-3.81 (2H, m, CH_{2b}-O), 4.98-5.01 (2H, m, CH-N), 7.27-7.37 (10H, m, Ar), 8.39-8.41 (2H, m, NH); ^{13}C nmr ($CDCl_3$): δ 172.0(C=O), 139.2(Ar, C_1), 129.2(Ar, C_3), 128.2(Ar, C_2), 127.0 (Ar, C_4), 66.8, 66.3, 62.5, 56.1, 54.3, 51.2; ms m/z (%): 529 ($M+1^+$, 2), 364 (14), 132 (25), 118 (37), 106 (75), 100 (78), 91 (43), 77 (48), 56 (71), 42 (100); ir ν_{max}: 3257, 2940, 1665, 1594, 1453, 1096, 701 cm^{-1}.

Anal. Calcd. for $C_{28}H_{40}N_4O_6$: C, 63.64; H, 7.58; N, 10.61. Found: C, 63.55; H, 7.60; N, 10.57.

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