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Synthesis of a Water-Soluble Chiral *N*-acylcalix(4)arene Amino Acid Derivative

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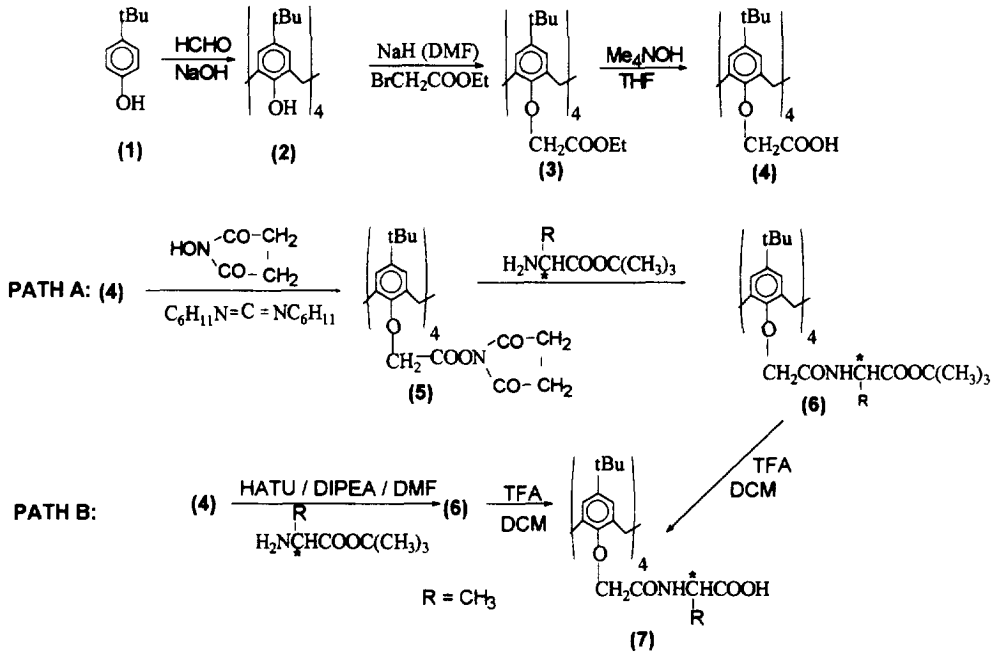
Abstract: The synthesis of a novel water-soluble chiral *N*-acylcalix(4)arene amino acid derivative has been achieved. The chiral calix(4)arene is in a "cone" conformation according to NMR spectroscopy. We report preliminary results using this chiral calixarene derivative as a mobile phase additive in capillary electrophoresis.

Calixarenes are macrocyclic compounds with defined cavities, having host-guest complexation properties similar to cyclodextrins.[1,2] Functionalization of their upper and lower rims provides the calixarenes with variable solubilities and variable complexation characteristics.[1-4] Such systems have been proposed as possible enzyme mimics. However, unlike cyclodextrins, the most common forms of calixarenes are not water-soluble and do not have chiral recognition ability. To enhance calixarene derivatives as water-soluble enzyme mimics and to catalyze enantioselective reactions, chiral centers have been attached to the rims of calixarenes.[5,6,7] For example, Shinkai *et al.* have recently reported the synthesis of a chiral calixarene bearing aliphatic chains[5] and amino acid moieties[7] on the lower and upper rim, respectively. In addition, Bayard has modified the upper rim of calixarene by introduction of two chiral units of 2-(methoxymethyl) pyrrolidine.[6] However, molecular asymmetry can be generated not only by different substituents but also by conformational isomerism.[8] Herein, we report the synthesis of a water-soluble *N*-acylcalix(4)arene amino acid derivative and its use in the resolution of racemic (±)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BNHP), using capillary electrophoresis (CE). The synthetic route to this class of calix(4)arenes allows derivatization with chiral amines in general and is especially well suited to the synthesis of water-soluble calix(4)arenes by reaction with amino acid derivatives. The synthesis of (**4**) was done according to the literature.[9-12] The tetra(acid) (**4**) was transformed into the activated ester derivatives by two pathways.[13] The tetra(acid) was treated with dicyclohexylcarbodiimide (DCC), and *N*-hydroxysuccinimide to

prepare (**5**). The calixarene derivative (**5**) reacts with L-alanine t-butyl ester to give (**6**) in good yield. Alternatively, (**4**) can be activated in situ and coupled with L-alanine t-butyl ester to give (**6**) using HATU, O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate. HATU is an excellent peptide coupling reagent recently reported by Carpino *et al.*.[14] The t-butyl esters are readily hydrolized using trifluoroacetic acid (TFA), in dichloromethane (DCM), to form (7). The ^{1}H NMR splitting pattern of the $ArCH_2Ar$ methylene protons and the singlet peak for the aromatic protons suggest a "cone" conformation.[15] The amino acids are attached to the lower rim of calix(4)arene. This places the chiral groups distant from the internal aromatic cavity of calix(4)arene but there is likely to be secondary interactions of the amino acid functional groups with a homochiral guest.



The focus of our work was to synthesize a calixarene with new ligands for chiral recognition as well as to improve its water solubility. In CE, chiral separation is often achieved through the addition of chiral selectors as mobile phase additives. Chiral separations by capillary electrophoresis (CE) have been accomplished by use of cyclodextrins[16] polymerized micelles[17] , and crown ethers.[18] The calixarene derivative (**7**) is added to the buffered CE solution allowing the enantiomeric resolution of racemic (±)- 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, (BNHP), (Resolution = 1.0, other conditions in Fig. 1). To the best of our knowledge this is the first report of

chiral separation using a chiral calixarene as a chiral medium in CE.

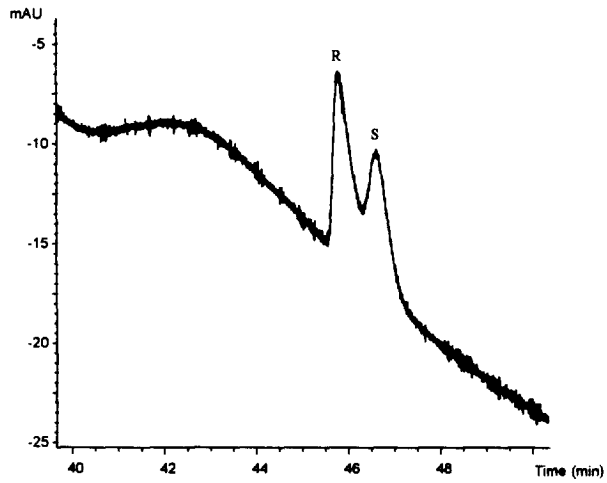


Fig. 1. Separation of (±)-BNHP, CE conditions: 40 mM Na_2HPO_4 (pH = 11, adjusted by addition of NaOH); applied voltage, 15 kV; UV detection, 280 nm).

In summary, the synthesis of *N-p*-t-butylcalix[4]arene tetracarboxyloyl-L-alanine t-butyl ester and its acid have been accomplished. Path b has a shorter pathway and reaction times, and higher yields than path a. Other calixarene derivatives, such as calixarene (**6**) with different amino acid derivative groups, will be synthesized according to the procedure that we report here. These chiral calixarenes, including water-soluble and non-water-soluble calixarenes, will be used to separate and detect chiral molecules by use of membrane transport, HPLC and/or capillary electrophoresis. Other studies using these molecules are presently being conducted in our lab with encouraging preliminary results.

Acknowledgements

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13. **Synthesis of chiral calixarenes (6) using DCC/NHS (path a):** The compound (**4**) (1 mmol) was added to a solution of *N*-hydroxysuccinimide (4 mmol) in dry ethyl acetate. A solution of dicyclohexylcarbodiimide (4 mmol) in dry ethyl acetate was added and left overnight at room temperature under anhydrous conditions. The resulting precipitate was filtered and the filtrate was concentrated in vacuo to give (**5**) in a 68 % yield as white product. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 36H, $ArCMe_3$), 2.8 (s, 16H, $C(O)CH_2CH_2C(O)$), 3.24 (d, 4H, $ArCH_2Ar$), 4.76 (d, 4H, $ArCH_2Ar$), 5.16 (s, 8H, CH_2CO_2), 6.79 (s, 8H, ArH); FAB-MS ($M+Na^+$): 1291. (Found: C, 63.88; H, 6.28; N, 4.24. $C_{68}H_{80}N_4O_{20}$ requires: C, 64.12; H, 6.34; N, 4.40). The calixarene (**5**) was suspended in dry dichloromethane in a flask equipped with a drying tube containing anhydrous calcium sulphate. A solution of L-alanine t-butyl ester (4 mmol) and *N,N*-diisopropylethylamine (4 mmol) in dry dichloromethane was added, and the mixture was stirred at room temperature for 24 h. After addition of water, the product was extracted with dichloromethane. The combined organic extracts were washed with water and dried. The dichloromethane solution was evaporated to give a white pure product (crystalline) (77 %) (**6**). 1H NMR (200 MHz, $CDCl_3$) δ 1.08 (s, 36H, $ArCMe_3$), 1.33 (s, 36 H, CO_2CMe_3), 1.52 (d, 12H, $CHCH_3$), 3.13 (d, 4H, $ArCH_2Ar$), 4.50-4.67 (m, 16H, $CHCO_2$ CH_2CON and $ArCH_2Ar$), 6.84 (s, 8H, ArH); FAB-MS ($M+Na^+$): 1411. (Found: C, 69.28; H, 8.39; N, 4.13. $C_{80}H_{116}N_4O_{16}$ requires: C, 69.12; H, 8.42; N, 4.03). **Synthesis of chiral calixarenes (6) using HATU (path b):** To a solution containing (**4**) (0.5 mmol), protected L-amino acid (L-amino t-butyl ester·HCl (2 mmol)) and *N,N*-diisopropylethylamine (4.4 mmol) in dimethylformamide (22 ml), HATU (2.2 mmol) was added. The mixture was stirred at 0°C during the first hour and at room temperature for the next four hours. The reaction was stopped, and water was added. The white precipitate (**6**) was filtered off, washed thoroughly with water, and dried. The yield was greater than 86 %. The results of ^{1}H NMR were the same for compound **6** (path a). (Found: C, 69.15; H, 8.38; N, 4.08. $C_{80}H_{116}N_4O_{16}$ requires: C, 69.12; H, 8.42; N, 4.03). $[\alpha]^{25}$ (c =1 in methanol) -18.93. **Hydrolysis of the ester:** Hydrolysis of the ester (**6**) to the acid (**7**) was achieved by use of TFA and dichloromethane at room temperature. The four carboxylic groups can be converted to the salt form with little difficulty, providing water-soluble calixarene.
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