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# Synthesis of novel chiral Schiff base and amino alcohol derivatives of calix[4]arene and chiral recognition properties

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ABSTRACT

In the present study, the synthesis and liquid phase extraction properties towards some amino acid methylesters and amino alcohols of Schiff base and amino alcohol substituted calix[4]arene are reported. The Schiff base substituted calix[4]arene **5** has been synthesized via condensation reaction involving 5,17-diformyl-11,23-di-*tert*-butyl-25,27-di[3-(4-formylphenoxy)propoxy]-26,28 dihydroxycalix[4]arene **4** and (*R*)-(−)-2-phenylglycine methyl ester in $CHCl_3$:MeOH. To give the amino alcohol substituted calix[4]arene **6**, the synthesized chiral compound **5** was reduced by $LiAlH_4$. The new chiral Schiff base and amino alcohol derivatives of calix[4]arene have been characterized by a combination of FT-IR, $^1H$ NMR, $^{13}C$ NMR, FAB-MS and elemental analysis. Also, the extraction behaviors of **5** and **6** towards some selected amino acid methylesters and amino alcohols have been studied by liquid–liquid extraction.



## 1. Introduction

Calixarenes, cyclic oligomers of phenolic units linked through the ortho positions, are a fascinating class of macrocycles. They are synthetic macrocycles readily available by condensation of *p*-*tert*-butylphenol with formaldehyde under alkaline conditions. From these starting materials, a large number of sophisticated compounds have been prepared. To date, various calixarenes that possess ketone, amine, ester, amide, carboxylic acid or other functional groups have been synthesized for separation, recognition, discrimination and catalysis. A number of books were published concerning synthesis, structural features and host–guest interactions [1]. More specifically, the subject of chemical recognition and separation of ions was addressed in several publications [2]. On the other hand, only few reviews concerning calixarenes for biochemical recognition are available, e.g. on peptido- and glycoconjugates and the role of hydrogen-bonding interactions [3], on neoglyco conjugates with large rigidified cavities [4] and on synthetic receptors [5]. Among them, chiral recognition, the process in which an enantiomerically pure host molecule, such as a chiral calixarene, selectively binds one of the enantiomers, is one of the most essential reaction processes occurring in living systems [6]. Therefore chiral calixarenes [7] have attracted increasing research interest because of their potential in enantio discrimination processes. They can be obtained either by attaching chiral moieties at one of the calix rims (upper or lower) [1] or by synthesizing inherently chiral derivatives [8] in which an asymmetric substitution of the macrocycle is associated to its intrinsic three-dimensional nature. From a practical point of view, the first approach appears to be preferable because inherent chirality always requires a difficult resolution on an appropriate scale [9]. Therefore, a large number of chiral calixarenes have been prepared by using chiral units, such as single amino acids [10], peptides [11], amino alcohols [12], sugars [13], tartaric acid esters [14], binaphthyl [15], glycidyl [16], menthone [17], and guanidinium groups [18].

Herein we report the synthesis of novel chiral calix[4]arene platform with Schiff base and amino alcohol derivatives on their lower and upper rim for quantitative extraction of some amino acid methylesters and amino alcohols in a liquid–liquid extraction system.

## 2. Experimental

### 2.1. Materials and general methods

Melting points were determined on a Gallenkamp apparatus in a sealed capillary and are uncorrected. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Varian 400 MHz spectrometer in $CDCl_3$. FT-IR spectra were recorded on a Perkin Elmer spectrum 100. UV–vis spectra were obtained on a Shimadzu 160A UV–visible recording spectrophotometer. FAB-MS spectra were taken on a Varian MAT 312 spectrometer. Elemental analyses were performed on a Leco CHNS-932 analyzer. Optical rotations were measured on an Atago AP-100 digital polarimeter. Analytical TLC was performed on precoated silica gel plates ($SiO_2$, Merck PF254), while silica gel 60

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(Merck, particle size 0.040–0.063 mm, 230–240 mesh) was used for preparative column chromatography. Generally, solvents were dried by storing them over molecular sieves (Aldrich; 4 Å, 8–12 mesh). Acetone and $CHCl_3$ were distilled from $CaSO_4$ and $CaCl_2$, respectively. All aqueous solutions were prepared with deionized water that had been passed through a Millipore Milli-Q Plus water purification system.

The following amino acid methylester hydrochlorides and amino alcohols obtained from Aldrich or Merck at the highest commercially available purity were used in this study: L-phenylalanine methylester hydrochloride (L-Phe-OMe), D-phenylalanine methylester hydrochloride (D-Phe-OMe), L-alanine methylester hydrochloride (L-AlaOMe), D-alanine methylester hydrochloride (D-AlaOMe), L-tryptophan methylester hydrochloride (L-TrpOMe), D-tryptophan methylester hydrochloride (D-TrpOMe), L-phenylglycinol (L Phegly), D-phenylglycinol (L-Phegly), (R)-(5)-(hydroxymethyl)-2-pyrolidinone [(R)-Hyd-Me-Pyr], (S)-(5)-(hydroxymethyl)-2-pyrolidinone [(S)-Hyd-Me-Pyr] (Figs. 1 and 2).

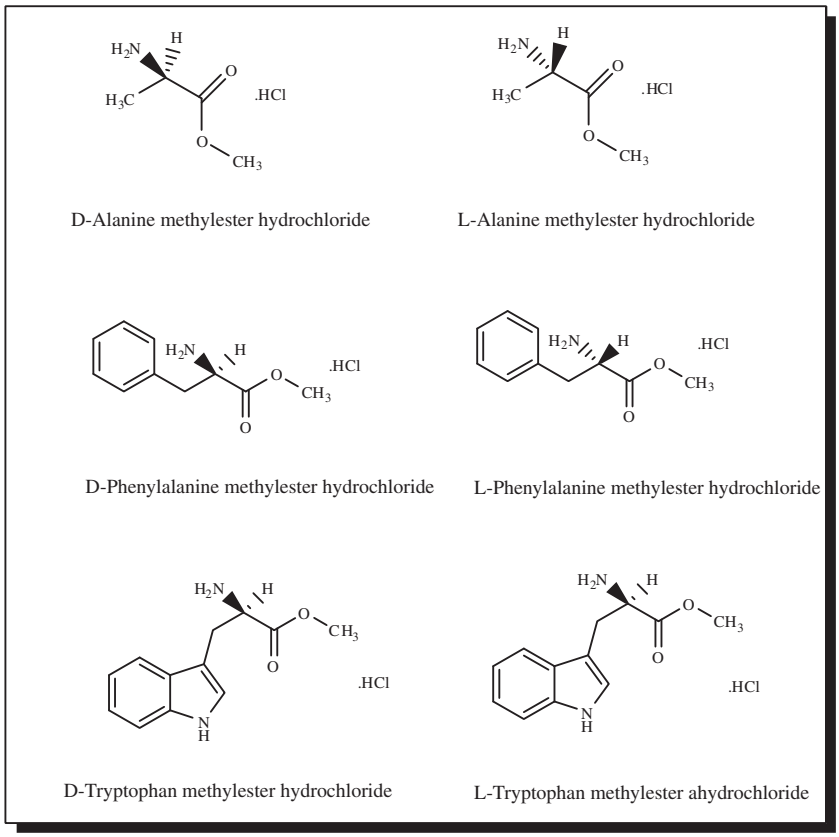


**Fig. 1.** The chemical structures of amino acid methylesters used in experiments.

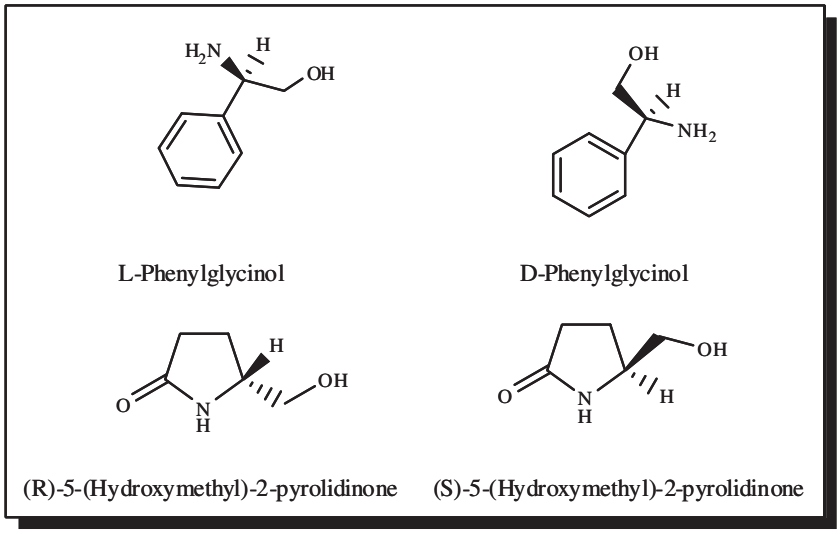


**Fig. 2.** The chemical structures of amino alcohols used in experiments.