

Liquid Chromatographic Separation of Enantiomeric α -Hydroxycarboxylic Acids on a Chiral Stationary Phase

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Optically active α -hydroxycarboxylic acids are important as biologically active substances, chiral building blocks or intermediates for the asymmetric synthesis of natural products.¹ Various methods such as chemical² and enzymatic methods³ are currently available for the preparation of optically active α -hydroxycarboxylic acids. However, the methods for the determination of enantiomeric composition of chiral α -hydroxycarboxylic acids prepared chemically or enzymatically are not general. Usually, NMR chemical shift reagent methods³, polarimetric methods and/or chromatographic separation of diastereomers^{2,4} have been used for the determination of enantiomeric composition of chiral α -hydroxycarboxylic acids. Gas chromatographic separation of racemic α -hydroxycarboxylic acids as their volatile derivatives on chiral stationary phases has also been used for the determination of enantiomeric purity.⁵ However, liquid chromatographic direct separation of enantiomeric α -hydroxycarboxylic acids had not been fully investigated.⁶ Liquid chromatographic direct separation of enantiomeric α -hydroxycarboxylic acids may provide quite a useful technique for solving three common stereochemical problems simultaneously such as the determination of enantiomeric purity, the determination of absolute configuration and the obtainment of optically pure two enantiomers at the same time.

Previously we developed chiral stationary phase 1 (CSP 1) derived from (S)-1-[1-(6,7-dimethylnaphthyl)]isobutylamine.⁷ CSP 1 has been reported to separate various racemates such as amino acids, amino alcohols, chiral amines, chiral alcohols, chiral carboxylic acids, dipeptides, chiral ketones and racemic drugs as their appropriate derivatives.⁷ However, separation of two enantiomers of α -hydroxycarboxylic acids on CSP 1 has not yet been studied. In this communication, we report that the enantiomers of derivatized α -hydroxycarboxylic acids can be separated on CSP 1.

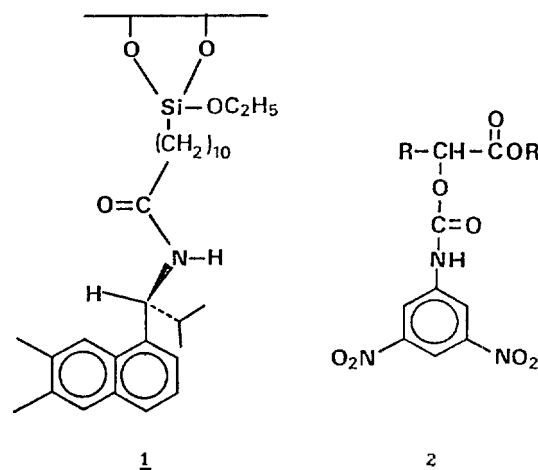
CSP 1 has been known to separate various racemates through a minimum of three simultaneous interactions with at least one of the two enantiomers.⁸ Especially, the π - π interaction between CSP 1 and analytes has been known to be very important.⁷ However, α -hydroxycarboxylic acids do not have any π -acidic site while CSP 1 has 6,7-dimethylnaphthyl group as a π -basic site. Previously racemic alcohols and racemic diols have been resolved as their 3,5-dinitrophenylcarbamates.^{7c,7d} Based on this prior study, we planned to derivatize α -hydroxycarboxylic acids by the action of 3,5-dinitrophenylisocyanate.

α -Hydroxycarboxylic acids were first converted into their esters by the usual method to improve the chromatographic behavior. And then these esters were treated with 3,5-dinitrophenylisocyanate obtained in situ from 3,5-dinitrobenzoyl azide to afford 3,5-dinitrophenylcarbamates 2 of α -hydroxycarboxylic acid esters as described for the derivatization of alcohols and diols.^{7c,7d} Via this process, various 3,5-dinitro-

Table 1. The Resolution of 3,5-Dinitrophenylcarbamates 2 of α -Hydroxycarboxylic Acid Esters on CSP 1^a

Analytes 2		k_1^b	α^c	Conf. ^d
R	R'			
Methyl	Methyl	4.91	1.90	S
Methyl	Ethyl	3.40	1.94	S
Methyl	n-Propyl	2.87	1.94	S
Methyl	n-Butyl	2.43	1.95	S
Methyl	n-Octyl	1.91	1.99	S
Methyl	n-Dodecyl	1.57	2.10	S
Ethyl	Ethyl	3.13	2.11	
n-Hexyl	Ethyl	2.03	1.96	
Phenyl	Methyl	4.87	1.94	S
Phenyl	Ethyl	3.73	1.98	S
Phenyl	Isopropyl	3.00	1.98	S
Phenyl	n-Butyl	3.00	2.00	S
Phenyl	n-Octyl	2.32	2.04	S
Phenyl	n-Dodecyl	2.05	2.21	S
Phenyl	Benzyl	4.81	2.06	

^aThe chromatographic system used consists of Waters Model 510 pump, Waters Model U6k Liquid Chromatographic Injector, Waters Model 441 Absorbance Detector and Waters Model 740 Data Module Recorder. All data were obtained by using 10% isopropyl alcohol in n-hexane as a mobile phase with flow rate of 2 ml/min at 254 nm UV. ^bCapacity factor for the first eluted enantiomer. ^cSeparability factor. ^dAbsolute configuration of the second eluted enantiomer. For blanks, elution orders have not been established.



phenylcarbamates 2 were prepared and identified by their satisfactory spectroscopic data.

Table I lists data obtained for the resolution of α -hydroxycarboxylic acid derivatives on CSP 1 and Figure 1 shows the representative chromatogram. The elution orders shown in

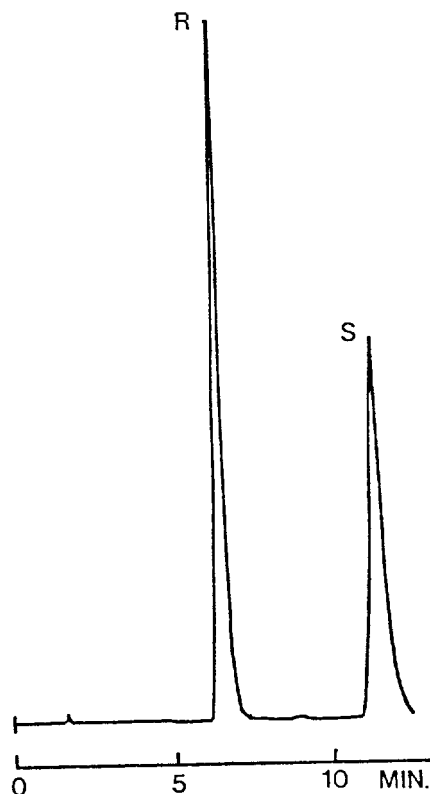


Figure 1. Liquid chromatographic resolution of 3,5-dinitrophenyl-carbamate of lactic acid ethyl ester (R = Methyl, R' = Ethyl) on CSP 1. All chromatographic conditions are given in Table 1.

Table I were determined by chromatographing samples prepared from optically pure α -hydroxycarboxylic acids. In every case, the optical resolution of α -hydroxycarboxylic acid derivatives on CSP 1 is excellent and it is shown that (S)-enantiomer eluted second. One interesting observation is that the separation factor, α values increase slightly as the ester alkyl groups increase in length. However, the size of R group of analytes 2 seems not to affect much the resolution behaviors.

In this communication, we do not rationalize these experimental results in mechanistic terms. We only assume from the resolution behaviors that the intercalation of the ester alkyl group of 2 between the two connecting arms of CSP may do important role in determining the resolution beha-

viors of 2 on CSP 1 and we want to mention that the efforts to rationalize the chromatographic resolution results are still in progress.

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Reaction of O,S-Acetals and Phosphites in the Presence of Lewis Acids: Chemoselectivity in the Cleavage of the Acetals

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The synthetic utility of α -heterosubstituted methanephosphonate carbanions in the Wittig-Horner reaction has been a

subject of interest in organic synthesis. 1-Alkoxy (or 1-aryltio) methanephosphonates are useful reagents for ke-