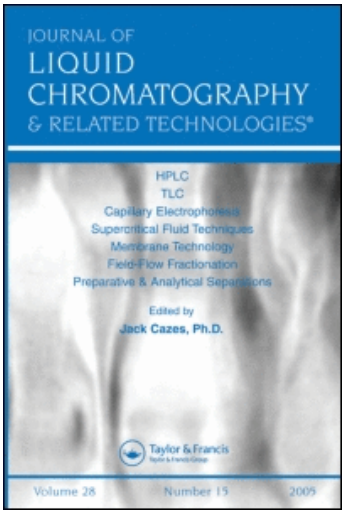

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Study of Elution Order in Chiral Separation of Organophosphonate Esters Using Tris-(3,5-dimethylphenyl Carbamate) Cellulose Chiral Stationary Phase by HPLC

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Abstract: It is known that the separation of several organic phosphonate esters using a tris(3,5-dimethylphenyl carbamate) cellulose (Chiralcel OD) column are better than the separation obtained using the Pirkle type chiral stationary phase (CSP), namely the N-(3,5-dinitrobenzoyl) leucine column. However, the elution order of the organic phosphonate esters enantiomers separated on tris(3,5-dimethylphenyl carbamate) cellulose chiral stationary phase is not known. The tandem use of these two CSPs together showed that the R-enantiomer had shorter retention time than S-enantiomer when tris(3,5-dimethylphenyl carbamate) cellulose chiral stationary phase was used.

Keywords: Chiral separation, Elution order, Tandem use of chiral stationary phases, Tris(3,5-dimethylphenyl carbamate) cellulose (Chiralcel OD) chiral stationary phase

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INTRODUCTION

Chirality has been thrust to the scientific forefront in several disciplines of the chemical sciences, particularly in organic, biological, and pharmaceutical chemistry.[1,2] Several chiral stationary phases (CSPs) are available to allow the direct separation and determination of drug enantiomers and racemates.[3] Cellulose CSPs are these commonly employed phases used for the separation and enantiomeric purity determination,[4,5] especially if derivatized to give tris(3,5-dimethylphenyl carbamate) cellulose, a chiral stationary phase known as the Chiralcel OD column, which exhibits excellent resolution properties.[6]

However, sometimes it is difficult to know the elution order of enantiomers when using these polysaccharide CSPs unless one of the enantiomers is available. Lipkowitz and coworkers[7–10] were able to predict the correct elution order using Pirkle's type chiral stationary phases with MM2. Yang et al.[11] studied the chiral discrimination of diniconazole using a Sumichiral OA4700 column (Pirkle type column) and predicted the elution order of diniconazole enantiomers. In another study, the elution order of several organophosphonate derivatives were predicted using *N*-(3,5-dinitrobenzoyl)-*S*-leucine chiral stationary phase and the results were supported by molecular modeling.[12] Both of those two CSPs are Pirkle's type chiral phases. However, we failed to predict the elution order of several oraganophosphonate esters enantiomers using tris (3, 5-dimethylphenyl carbamate) cellulose CSP.[13]

This paper describes a simple method to predict the elution order of enantiomers using tris (3,5-dimethylphenyl carbamate) cellulose CSP using Pirkle's type chiral phases in tandem with tris (3,5-dimethylphenyl carbamate) cellulose CSP. The details are described herein.

EXPERIMENTAL

Apparatus

The chromatography was performed with Shimadzu (Japan) modular liquid chromatography equipped with CR-6A integrator, SPD-10A UV-Vis detector, and LC-10AD solvent delivery system.

Chromatography Conditions

N-(3,5-dinitrobenzoyl)-l-leucine chiral stationary phase (CSP1) was synthesized according to Gao et al.[14] cellulose tris (3,5-dimethylphenyl

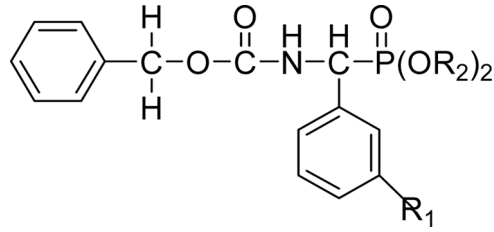

Figure 1. The general structure of the organophosphonate esters used in this study.

carbamate) CSP (CSP2) was synthesized according to Okamoto et al.[15] and Chassaing et al.[16] and packed into a 250 mm × 4.6 mm i.d. stainless steel column. The mobile phase consisted of 10% of isopropanol in *n*-hexane. The flow rate was maintained at 1 mL min^{-1}. The SPD-10A UV-Vis detector was at 230 nm.

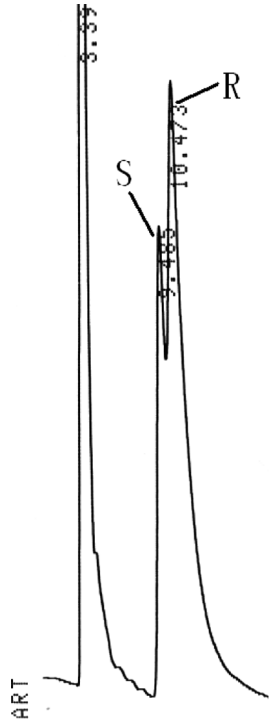

Figure 2. The chiral separation result of compound No. 4 by CSP1.

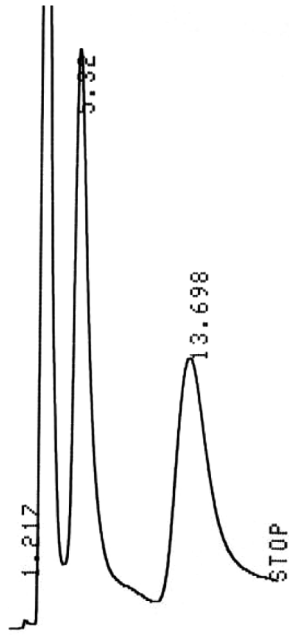

Figure 3. The chiral separation result of compound No. 4 by CSP2.

Materials

Seven dialkyl benzyloxycarbonyl-aminoaryl-methyl phosphonate esters (Figure 1) used in this study were provided by the National Laboratory of Elemento-Organic Chemistry, Nankai, P. R. China.[17]

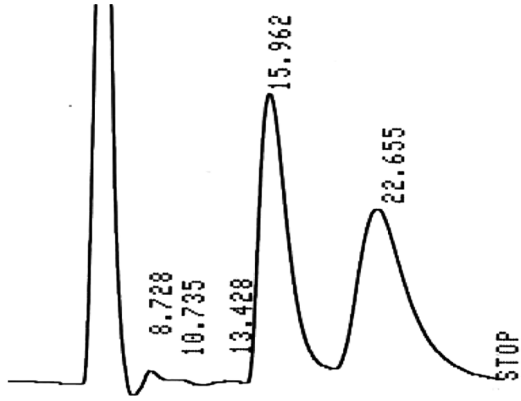

Figure 4. The chiral separation result of compound No. 4 by CSP1 + CSP2.

Table 1. Chromatographic parameters of the chiral separation of orgnaophosphonate esters using CSP1, CSP2 and CSP1 + CSP2

			CSP1			CSP2			CSP1 + CSP2		
No.	R_1	R_2	k_1	k_2	α	k_1	k_2	α	k_1	k_2	α
1	H	Et	1.108	1.443	1.302	0.775	1.567	2.022	1.340	0.000	1.000
2	*p*-OMe	Et	1.866	2.837	1.520	1.290	1.920	1.488	2.236	0.000	1.000
3	*p*-Cl	Et	0.846	1.199	1.417	0.766	1.134	1.480	1.153	0.000	1.000
4	*o*-OMe	Et	1.872	2.169	1.159	1.150	4.554	3.960	1.941	3.175	1.636
5	*p*-Me	Et	0.937	1.280	1.366	0.715	1.107	1.548	1.144	0.000	1.000
6	H	Me	2.302	2.717	1.180	1.674	2.257	1.348	2.490	0.000	1.000
7	H	Pr	0.641	0.863	1.346	0.478	1.048	2.192	0.876	0.000	1.000

RESULTS AND DISCUSSION

The results obtained from our previous study[12] indicated that the *R*-enantiomer of these organophosphonate esters had longer retention time than the *S*-enantiomer. This data was also supported by molecular modeling. Table 1 shows the chiral separation results of seven organophosphonanate esters using *N*-(3,5-dinitrobenzoyl)-l-leucine chiral stationary phase (CSP1), cellulose tris-(3,5-dimethylphenyl carbamate) CSP (CSP2), and the tandem CSP1 and CSP2. The results from Table 1 indicate that both CSP1 and CSP2 provided good chiral separation for those compounds. After tandem CSP1 and CSP2, the separation factor of all of the compounds decreased. Therefore, one can conclude that the elution order of the enantiomers using CSP1 were different from those using CSP2. In CSP1, the *R*-enantiomer had longer retention time than *S*-enantiomer, while using CSP2 the *R*-enantiomer had shorter retention time than the *S*-enantiomer. Figures 2–4 show the chiral separation results of compound No. 4 on CSP1, CSP2, and CSP1 + CSP2, respectively. From the data, one can predict the elution order of the chiral separation when it is not possible to have a single enantiomer of the separated racemic compounds.

CONCLUSION

This study shows that one can predict the elution order of enantiomers separated on polysaccharide type CSPs when the elution order of the enantiomers are separated on a Pirkle type CSP, when these columns are used in tandem and the separation factors are compared.

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