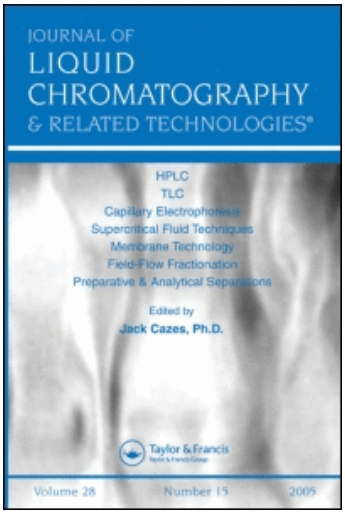

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Enantioseparation of Organophosphonate Derivatives on Amylose *Tris*(3,5-Dimethylphenylcarbamate) Chiral Stationary Phase by HPLC

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ABSTRACT

The enantiomers of fourteen *O,O*-dialkyl-2-benzyl-oxycarbonyl-aminoaryl-methyl-phosphonates are directly separated on *tris*(3,5-dimethyl-phenylcarbamate) amylose chiral stationary phases, known as Chiralcel AD.

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All of the selected compounds are baseline separated. The influence of the position and properties of substituents in benzene rings, the length and steric hindrance of alkoxyl groups of the phosphonate ester on the chiral separation are discussed. When the substituents are in the para-position of the benzene ring, the separation factor is in the following order $\alpha_{p\text{-}NO_2} \gg \alpha_{p\text{-}Cl} > \alpha_{p\text{-}CH_3} > \alpha_{p\text{-}H} > \alpha_{p\text{-}OCH_3}$. When the same substituent is in a different position of the benzene ring, the order of the separation factor is $\alpha_{p\text{-}Cl} > \alpha_{m\text{-}Cl}$ and $\alpha_{p\text{-}NO_2} \gg \alpha_{m\text{-}NO_2}$. The values of the separation factor α of the enantiomers where R_1 substituent is a hydrogen ($R_1 = H$) are always smaller than those of the enantiomers with *p*-Cl substituent, whether R_2 was Me, Et, Pr or *i*-Pr. Compounds with different substituent R_2 and R_1 where the substituent is H or *p*-Cl, the α values always show an order of $\alpha_{Pr} > \alpha_{Et} > \alpha_{Me} > \alpha_{i\text{-}Pr}$. The chiral discrimination in the amylose *tris*(3,5-dimethyl-phenylcarbamate) was based on π–π interaction and H-bond interaction.

Key Words: Organophosphonate derivatives; Chiral separation; Chiral discrimination mechanisms; Amylose *tris*(3,5-dimethylphenylcarbamate) chiral stationary phase.

INTRODUCTION

Numerous chiral stationary phases (CSPs) had been developed in the last few decades to provide an efficient method for separation of optical isomers.[1,2] Among these CSPs, Pirkle's and polysaccharide-based CSPs, have proven to be very effective for the determination of the enantiomeric purity, and absolute configuration of a variety of enantiomers.[3,4] Recently, the chiral separations of some organo-phosphorus compounds were reported on different Pirkle's CSPs, for example the separation of the enantiomers of a series of diethyl *N*-(aryl)-1-arylmethanephosphonates on a Whelk-O-column.[5] It showed that the C-aryl substituents play an important role on both the retention and the enantioselectivity. Selim[6] separated a series of enantiomers of dimethyl *N*-3,5-dinitrobenzoyl-α-amino substituted-benzyl phosphonate derivatives on the (*R*)-2,2,2-trifluoro-1-(9-anthryl) ethanol derivative chiral stationary phase. Pirkle also reported the separation of the enantiomers of a variety of *N*-DNB-amino-phosphonic acids derivatives on the (*R*)-2,2,2-trifluoro-1-(9-anthryl) ethanol derivative,[7] (*R*)-*N*-(2-naphthyl)-D-alanine,[8,9] (*S*)-*N*-(1-naphthyl)-leucine[9,10] and *N*-[11-(dimethylethoxysilyl)undecanoyl]-L-proline-3,5-dimethylanilide[11,12] chiral stationary phases. The separation of several 3,5-dinitrobenzenzyloxycarbonyl-amino-phosphonic acid derivatives were successfully resolved on the quinine carbamate CSP.[13] Liu reported the separation of the enantiomers of α-amino-alkylphosphonic acid derivatives on

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the (L,L) valinyl-valine-tert-butylamide CSP.[14] Grassert[15] described the separation of the enantiomers of α-amino-phosphonic acid derivatives on polysaccharide-types, namely Chiralpak AD and Chiralcel OD-H CSPs. Kuwano reported the separation of the enantiomers of dimethyl-1 (*N*-acetylamino)-2-oxo-2-phenyl-1-*E*-3-phenyl-2-propenyl-ethyl phosphonate on Chiralpak AD.[16] We also reported the resolution of a series of racemic *O*,*O*-diethyl, (*p*-methyl-benzenesulfonamido), aryl(alkyl)-methylphosphonates and *O*,*O*-dialkyl-1-benzyloxycarbonyl-aminoarylmethyl phosphonates on the *N*-(3,5-dinitrobenzoyl) leucine (DNB-leu) CSP and polysaccharide-based CSP.[17–21] The compounds in this study were selected from a pesticide research and develpment program.[22]

In this paper, we describe the separation of a series of racemic *O*,*O*-dialkyl-1-benzyloxycarbonyl-aminoarylmethyl phosphonates enantiomers on amylose *tris*(3,5-dimethylphenyl carbamate) chiral stationary phase, Chiralpak AD. The chiral recognition mechanisms involved between those analytes and the chiral selector used in this study are discussed.

EXPERIMENTAL

Materials

A series of fourteen dialkyl-benzyloxycarbonyl-aminoaryl methyl-phosphonate compounds were synthesized by the National Laboratory of Elemento-Organic Chemistry, Nankai University Tianjin, China.[22] The general structure of the compounds is presented in Fig. 1. The structures of the substituents "R_1" are H, $-CH_3$, $-OCH_3$, $-NO_2$, and $-Cl$, respectively. The substituents "R_2" are Me, Et, Pr, and *i*-Pr, respectively. These compounds were dissolved in ethanol and then diluted with the mobile phase. Solutions with approximate concentrations of 0.1 mg mL^{-1} in eluent solvent were used

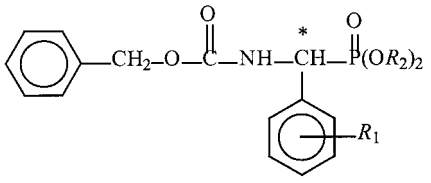

Figure 1. The general structure of *O*,*O*-dialkyl-1-benzyloxycarbanyl-aminoaryl-methyl phosphonates used in this study. Asterisk denotes the position of the chiral carbon.

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for injection. All solvents were filtered by a 0.5 μm filter and degassed in helium.

Apparatus

The chromatography was performed with a Waters liquid chromatograph equipped with Millenium 32 software program. Chromatography working station, Waters 2996 Photodiode Array detector, Waters 600E system controller, and 600E solvent delivery system.

Chromatographic Conditions

Amylose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phase known as Chiralpak AD (250 × 2 mm ID) was purchased from GROM (Herrenberg-Kayh, Germany). The mobile phase composition was 20% of ethanol in *n*-hexane. The flow-rate was maintained at 0.3 mL min^{-1}.

RESULTS AND DISCUSSION

We have separated the enantiomers of these compounds with cellulose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phase known Chiralcel OD.[20–21] The stereochemistry of the glycosidic linkage of compared to amylose cellulose is different which imparts different characteristics between the two polysaccharides. The chiral separation results show a difference between cellulose *tris*(3,5-dimethyl-phenylcarbamate) and amylose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phases. With amylose *tris*-

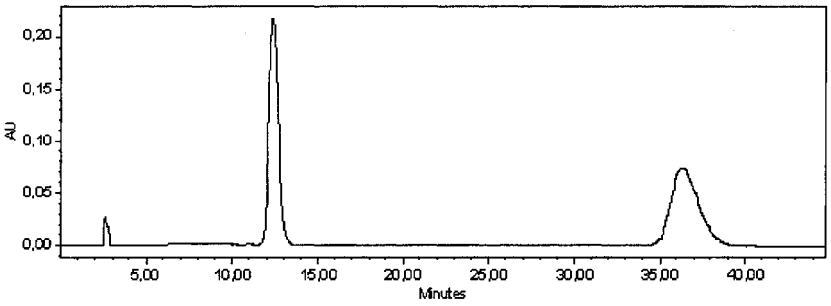

Figure 2. Chromatogram of chiral separation of Compound 3. Chromatographic conditions: see Experimental.

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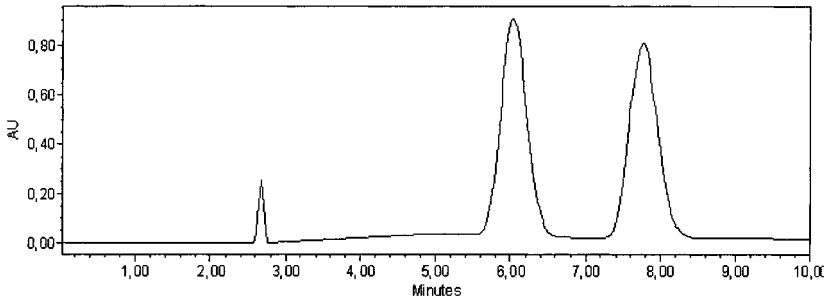

Figure 3. Chromatograms of chiral separation of Compound 7. Chromatographic conditions: see Experimental.

(3,5-dimethyl-phenylcarbamate) chiral stationary phases, all of the selected compounds could be easily baseline separated. The chromatographic parameters, resolution factor (*Rs*), capacity factor (k), and separation factor (α) obtained by Chiracel AD are indicated in Table 1. Typical chromatograms are shown in Figs. 2 and 3. It is of interest to mention from the Table, that the enantiomers of compound 3, with the substituent of *p*-NO_2, gives the best

Table 1. Chromatographic parameters capacity factor (k), separation factor (α) and resolution factor (*Rs*) of the chiral separation of organic phosphonate by Chiralpak AD.

Compared no.	R_1	R_2	k_2	k_1	α	*Rs*
1	H	Et	2.81	1.67	1.68	3.86
2	*p*-OMe	Et	5.57	3.42	1.63	3.42
3	*p*-NO_2	Et	12.45	3.59	3.47	10.47
4	*p*-Cl	Et	4.68	2.26	2.07	5.75
5	*p*-Me	Et	4.09	2.40	1.71	2.09
6	*o*-OMe	Et	3.24	1.77	1.83	4.26
7	*m*-Cl	Et	1.88	1.23	1.52	2.25
8	*m*-NO_2	Et	4.28	2.55	1.68	4.32
9	H	*i*-Pr	1.69	1.04	1.62	2.89
10	*p*-Cl	*i*-Pr	1.17	0.67	1.76	2.83
11	H	Me	4.64	2.64	1.76	4.26
12	*p*-Cl	Me	6.52	3.54	1.84	4.78
13	H	Pr	2.59	1.40	1.85	4.10
14	*p*-Cl	Pr	3.26	1.53	2.13	5.16

Note: Chromatographic conditions: see Experimental section.

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separation. While the same compound gave the worst separation with cellulose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phase, Chiralcel OD, it is almost the worst one.[20] With Chiralcel OD, the enantiomers of compound 6, with the substituent of *o*-OMe, gave the best separation. Although both stationary phases belongs to the polysaccharides-based group with the same substituted namely *tris*(3,5-dimethyl-phenylcarbamate), yet they show different chiral separation characteristics. This is to due to (a) the difference in glycosidic linkage between cellulose (β-1,4) and amylose (α-1,4), (b) the difference in the configuration between cellulose, which is linear and rigid and amylose, which is more helical in configuration.

Influence of the Substituents on the Chiral Separation

When the substituents are in the para-position of the benzene ring, with amylose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phases, most of the chiral separations were better than unsubstituted analogs, except *p*-OMe. The chiral separation factor were in the following order $\alpha_{p\text{-}NO_2} \gg \alpha_{p\text{-}Cl} > \alpha_{p\text{-}CH_3} > \alpha_{p\text{-}H} > \alpha_{p\text{-}OCH_3}$. It indicates that the best chiral separation occurs when there is a strong π-acceptor substituent in the para-position of the benzene ring.

When the substituents are in the para-position of the benzene ring, with cellulose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phase, the chiral separation was worse than unsubstituted analogs, no matter whether the substituent was a π-donor or π-acceptor group. The order of chiral separation factor of the para-substituted phosphonate analogs was $\alpha_{p\text{-}H} \gg \alpha_{p\text{-}CH_3} \approx \alpha_{p\text{-}OCH_3} > \alpha_{p\text{-}Cl} \gg \alpha_{p\text{-}NO_2}$.[20]

When the same substituent is in a different position of the benzene ring, with amylose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phases, the chiral separation of the para-position substituted analogs are much better than that in the meta-position. The order of the chiral separation was $\alpha_{p\text{-}Cl} > \alpha_{m\text{-}Cl}$ and $\alpha_{p\text{-}NO_2} > \alpha_{m\text{-}NO_2}$. The chiral separation of compounds with substituents in the para-position are slightly different from that in the ortho-position.

When the same substituent is in a different position of the benzene ring, with cellulose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phase, the chiral separation of the ortho-position substituted analogs are much better than that in the meta- or para-position. The order of the chiral separation was $\alpha_{p\text{-}Cl} > \alpha_{m\text{-}Cl}$ and $\alpha_{o\text{-}OCH_3} \gg \alpha_{p\text{-}OCH_3}$. The chiral separation of compounds with substituents in the para-position are slightly different from that in the meta position. The chiral separation factors were in the order $\alpha_H \gg \alpha_{m\text{-}NO_2} > \alpha_{p\text{-}NO_2}$ and $\alpha_H \gg \alpha_{p\text{-}Cl} \gg \alpha_{m\text{-}Cl}$.[20]

When the substituents are in the same position, the π-acceptor substituted compounds achieve better chiral separation than that of π-donor compounds,

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unlike the chiral separation obtained with cellulose *tris*(3,5-dimethyl-phenyl-carbamate) chiral stationary phase.

Compounds 1, 9, 11, 13, and 4, 10, 12, 14 have same substituent (R_1) and different substituents (R_2). The values of the separation factor α of the enantiomers, where R_1 substituent is a hydrogen ($R_1 = H$), are always smaller than those of the enantiomers with *p*-Cl substituent, whether the R_2 was Me, Et, Pr, or *i*-Pr. Compounds with different substituents R_2, and R_1 substituents are H or *p*-Cl, the α values always show an order of $\alpha_{Pr} > \alpha_{Et} > \alpha_{Me} > \alpha_{i\text{-}Pr}$. This result is different from the order of $\alpha_{i\text{-}Pr} > \alpha_{Pr} \approx \alpha_{Et} > \alpha_{Me}$ obtained with cellulose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phase.[21]

The k values are found to be in the order $k_{Me} > k_{Et} > k_{Pr} > k_{i\text{-}Pr}$. This result indicates that the k values increased while the α values decreased with increasing the length of alkoxyl groups of the phosphonate esters.

From these results, it can be concluded that the property (π-donor or π-acceptor) of substituents in the benzene ring was important when performing the chiral separation amylose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phase. It is quite different with the chiral separation by cellulose *tris*(3,5-dimethylphenyl carbamate) CSP, in which the position of substituents in the benzene ring was important.[20]

Possible Chiral Discrimination of *Tris*(3,5-Dimethyl-Phenylcarbamate) Amylose Chiral Stationary Phases

Amylose and cellulose are the most important polysaccharides polymers of D-glucose. The primary difference between cellulose and amylose is the nature of the glycosidic linkage. In cellulose it is a β-1,4 linkage, while in amylose the D-glucose units are joined together by α-1,4 linkages. While this is a seemingly small difference, it has a major impact on the shapes and functions of these two polymers. Unlike cellulose, the polymer strands of amylose do not assemble in planar sheets. They adopt a helical structure similar to that found in nucleic acids. This is the reason why those two kinds of chiral stationary phases possess different chiral separation characteristics, even though they have same substituent, *tris*(3,5-dimethyl-phenylcarbamate). With cellulose *tris*(3,5-dimethyl-phenyl carbamate) CSP, the position of substituents in a benzene ring of the organo phosphonate derivative studied played an essential role in chiral separation. While with amylose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phase, the property (π-donor or π-acceptor) of substituents in the benzene ring was more important than the position in chiral separation.

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CONCLUSION

In this study, using amylose *tris*(3,5-dimethyl-phenylcarbamate) chiral stationary phase. all of the organo phosphonate compounds could be easily baseline separated. When the substituents are in the para-position of the benzene ring, it shows the order of the chiral separation is in $\alpha_{p\text{-}NO_2} \gg \alpha_{p\text{-}Cl} > \alpha_{p\text{-}CH_3} > \alpha_{p\text{-}H} > \alpha_{p\text{-}OCH_3}$. When the same substituent is in a different position of the benzene ring, the order of the chiral separation was $\alpha_{p\text{-}Cl} > \alpha_{m\text{-}Cl}$ and $\alpha_{p\text{-}NO_2} > \alpha_{m\text{-}NO_2}$. The values of the separation factor, α, of the enantiomers where R_1 substituent is a hydrogen ($R_1 = H$) are always smaller than those of the enantiomers with *p*-Cl substituent, whether the R_2 was Me, Et, Pr, or *i*-Pr. Compounds with different substituents, R_2 and R_1 substitutent is H or *p*-Cl, the α values always show an order of $\alpha_{Pr} > \alpha_{Et} > \alpha_{Me} > \alpha_{i\text{-}Pr}$. The chiral discrimination in the amylose *tris*(3,5-dimethyl-phenylcarbamate) was based on π–π interaction and H-bond interaction. Although both of the chiral stationary phases, Chiralcel AD and Chiralcel OD, are polysaccharides with the same substituent, namely *tris*(3,5-dimethyl-phenylcarbamate), they show quite different chiral separation ability.

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