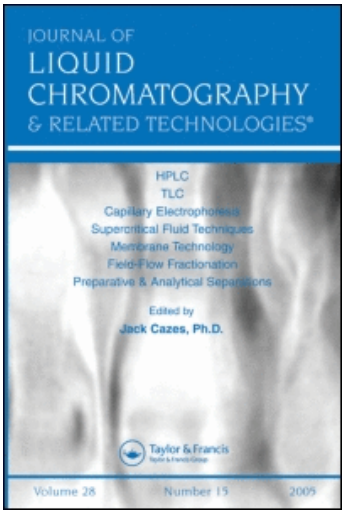


Journal of Liquid Chromatography & Related Technologies

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

Direct Chiral High Performance Liquid Chromatography Separation of O,O-Diethyl-(p-methyl-benzene-sulfonamido)- Aryl (Alkyl)-Methylphosphonate

R. Y. Gao[a]; G. S. Yang[b]; H. X. Shen[b]; R. Y. Chen[a]; Q. Dai[a]; Q. S. Wang[a]
[a] National Laboratory of Elemento-Organic Chemistry, Tianjin, People's Republic of China [b] Department of Chemistry, Nankai university, Tianjin, People's Republic of China

To cite this Article Gao, R. Y. , Yang, G. S. , Shen, H. X. , Chen, R. Y. , Dai, Q. and Wang, Q. S.(1996) 'Direct Chiral High Performance Liquid Chromatography Separation of O,O-Diethyl-(p-methyl-benzene-sulfonamido)- Aryl (Alkyl)-Methylphosphonate', Journal of Liquid Chromatography & Related Technologies, 19: 2, 171 — 178
To link to this Article: DOI: 10.1080/10826079608005503
URL: http://dx.doi.org/10.1080/10826079608005503

J. LIQ. CHROM. & REL. TECHNOL., 19(2), 171–178 (1996)

DIRECT CHIRAL HIGH PERFORMANCE LIQUID CHROMATOGRAPHY SEPARATION OF O,O-DIETHYL-(p-METHYL-BENZENE-SULFONAMIDO)- ARYL (ALKYL)-METHYLPHOSPHONATE

R. Y. Gao,[1] G. S. Yang,[2] H. X. Shen,[2]
R. Y. Chen,[1] Q. Dai[1], Q. S. Wang*[1]

[1]National Laboratory of Elemento-Organic Chemistry
[2]Department of Chemistry
Nankai university
Tianjin, 300071
People's Republic of China

ABSTRACT

The enantiomers of a series of twelve O,O-diethyl, (p-methyl-benzenesulfonamido), aryl(alkyl)-methylphosphonates have been separated by high performance liquid chromatography on a Pirkle model chiral stationary phase. Chromatographic data and a chiral recognition model are presented for the separation of these organic phosphorus enantiomers on the chiral phase. The influence of column temperature and flow rate of mobile phase has been described.

INTRODUCTION

Optical resolution methods using high performance liquid chromatography (HPLC) have been extensively developed. There are three

methods of separation available in liquid chromatography. 1. Formation of diasteroisomeric derivatives; 2. addition of chiral discriminating agents to the mobile phase and, 3. use of chiral stationary phases (CSP). In particular, CSP methods have become of interest.

For the direct HPLC resolution of enantiomers, various kinds of enantioselective chiral stationary phases (CSP's) and packings have been developed. They are described comprehensively in several recent reviews and books.[1-5]

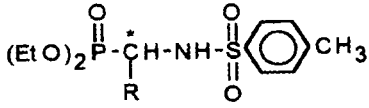
Separation based on complementary donor-acceptor rearrangements such as π-donor-acceptor, dipole-dipole (dipole-stacking), hydrogen bonding and steric interaction have been investigated. π-Donor-acceptor type phases, which also contain amide functionalities, are especially successful, and highly efficient HPLC columns can be obtained. These have been rationally designed by Pirkle and co-workers utilizing chiral recognition models.[4]

In this paper, we descibe the synthesis of a chiral, L-leucine tert-butylamide bonded phase. This synthesized phase has been used in the resolution of enantiomers of a series of twelve O,O-diethyl, (p-methyl-benzenesulfonamido)-, aryl (alkyl)-methylphosphonates. We discuss how column temperature, volume fraction of mobile phase and flow rate variation affect retention and selectivety for chiral resolution.

EXPERIMENTAL

Materials

The study was performed with a series of twelve O,O-diethyl, (p-methyl-benzenesulfonamido)-, aryl (alkyl)-methylphosphonates, prepared by us; the spectra and elemental analyses were recorded. The general formula of the compounds is



The structures of the substituents " R " are (1) C_6H_5, (2) p-$CH_3OC_6H_4$, (3) p-ClC_6H_4, (4) p-$NO_2C_6H_4$, (5) p-$CH_3C_6H_4$,, (6) m-$NO_2C_6H_4$, (7) m-ClC_6H_4, (8) o-$NO_2C_6H_4$, (9) o-$CH_3C_6H_4$, (10) 2,4-$Cl_2C_6H_3$, (11) ET and (12) i-Pr. These compounds were dissolved in acetone, then diluted with eluent solvent. Solutions with approximate concentration of 0.1 mg/mL in eluent solvent were used for injection. All solvents were redistilled and filtered through a 0.45 μ filter and degassed in vacuo before use.

Apparatus

The HPLC system was composed of a Model 2010 liquid chromatograph (Varian, Northeast Florham Park, NJ, USA) with a Model 2050 UV detector and HP-3392 integrator (Hewlett packard, Palo Alto, CA USA).

Chromatography

During the chromatographic runs, all experimental variables, except those being investigated, were carefully controlled at fixed values. The variables held constant included the sample size (2 μL) and UV detector wavelength (230 nm). The range of the mobile phase compositions were 15, 20, 25 and 30 % of isopropyl alcohol-water, the column temperatures were 16, 25 and 35 °C and the flow rates were 1.0, 1.5 and 2.0 mL/min.

Pirkle-Type Column Preparation

For 3,5-Dinitrobenzoylleucine preparation refer to Reference 6. A solution of 3.5 g of L-3,5-dinitrobenzoylleucine in 200 ml of dry THF was poured over 5 g of dry aminopropyl silica gel, YWG-NH (Second Reagent Factory, Tianjin, P. R. China) and 3 g of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) was added with swirling. After 8 h at room temperature, the silica was isolated by filtration and washed repeatedly with methanol, acetone and ether. These last washings employed centrifugation-decantation and some fines were thus removed. After drying, ca. 5.6 g of silica bonded phase was obtained. Anal. Found: C, 10.10; H, 1.80; N, 2.5 %.

RESULTS AND DISCUSSION

In order to optimize separation, the experiment was under various mobile phase compositions. The separation data, capacity factor k', and α values, are indicated in Table 1. These results evidently prove that 15% isopropyl alcohol mobile phase gave the best α values for O,O-diethyl, (p-methyl-benzenesulfonamido)-, aryl-methylphosphonate enantiomers on the CSP, which all gave baseline separation of compounds 11 and 12 (R all is aliphatic group). Isopropyl alcohol, in the concentration range 15 - 30 %, produced α values for the enantiomers which decrease with increasing concentration of isopropyl alcohol. But the effect was not large. The maximum α value was obtained with 15% isopropyl alcohol and minimum analytical time with 30 % in all the enantiomers. The result is listed in Table 1. Chromatograms of compounds Nos. 1 and 2 are shown in Figure 1.

Table 1

k'_2 , k'_1 and α Values of Twelve O,O-Diethyl, (p-Methyl-Benzenesulfonamido)-, Aryl (alkyl)-Methylphosphonate at Different Mobile Phase Compositions (Column Temperature: 16°C, Flow Rate: 1.0 ml/min)

No*	15 % i-PrOH			20 % i-PrOH			25 % i-PrOH			30 % i-PrOH		
	k'_2	k'_1	α	k'_2	k'_1	α	k'_2	k'_1	α	k'_2	k'_1	α
1	4.307	2.702	1.591	3.042	1.924	1.572	2.329	1.517	1.535	1.863	1.23	1.508
2	7.610	3.750	2.209	5.075	2.592	1.959	3.969	2.070	1.917	3.184	1.656	1.889
3	4.281	2.302	1.860	2.983	1.657	1.799	2.462	1.381	1.782	2.011	1.146	1.754
4	6.712	3.949	1.700	4.779	2.879	1.660	3.860	2.357	1.638	3.102	1.926	1.611
5	4.376	2.483	1.763	3.569	2.026	1.762	2.769	1.609	1.720	2.415	1.417	1.705
6	8.094	5.493	1.621	6.498	4.069	1.597	4.822	3.052	1.580	3.484	2.477	1.552
7	3.682	2.623	1.404	2.751	1.974	1.393	2.129	1.549	1.375	1.746	1.279	1.365
8	9.541	5.445	1.752	6.493	3.782	1.717	4.902	2.944	1.665	3.809	2.329	1.636
9	5.839	4.007	1.457	4.126	2.857	1.445	2.997	2.115	1.417	2.300	1.654	1.391
10	3.348	1.827	1.832	2.724	1.519	1.794	2.196	1.257	1.747	1.975	1.133	1.744
11	1.720	1.569	1.096	1.404	1.293	1.086	1.105	1.026	1.077	0.965	0.908	1.063
12	1.457	1.261	1.156	1.201	1.048	1.145	0.932	0.819	1.139	0.859	0.760	1.130

* Substituents R number (see text).

The efficiency of column temperatures was investigated in all the compounds for the range of 16 - 35 °C. The capacity factor , k', decreased with

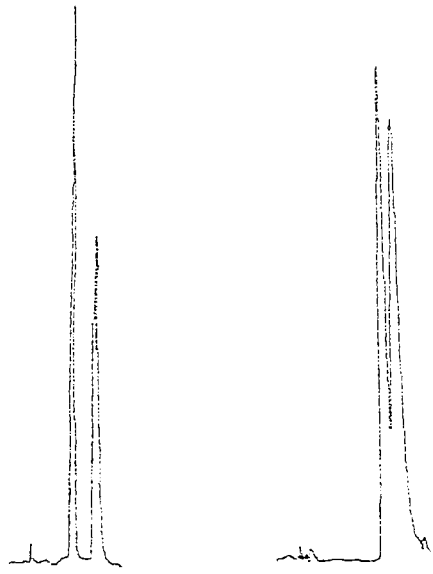


Figure 1. Chromatogram for compounds 1 (left) and 12 (right) enantiomers (mobile phase: 20 % isopropyl alcohol-water, column temperature: 16°C, flow rate: 1mL/min).

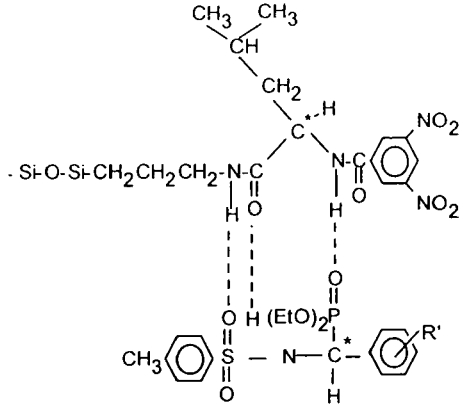


Figure 2. Proposed mechanism for chiral recognition.

Table 2

k'_2 k'_1 and α Values of Twelve O,O-Diethyl, (p-Methyl-Benzenesulfonamido)-Aryl (Alkyl)-Methylphosphonate at Different Column Temperatures (Mobile Phase: 20 % Isopropyl Alcohol, Flow Rate : 1.0 ml/min)

No*	16°C			25°C			35°C		
	k'_2	k'_1	α	k'_2	k'_1	α	k'_2	k'_1	α
1	3.024	1.924	1.572	2.893	1.886	1.534	2.266	1.536	1.475
2	5.075	2.592	1.959	5.000	2.624	1.905	3.730	2.080	1.794
3	2.983	1.657	1.799	2.910	1.652	1.762	2.218	1.336	1.660
4	4.779	2.879	1.660	4.586	2.841	1.614	3.474	2.263	1.535
5	3.569	2.026	1.762	3.248	1.893	1.716	2.588	1.564	1.655
6	6.498	4.069	1.597	5.948	3.790	1.570	4.533	2.972	1.525
7	2.751	1.974	1.393	2.586	1.886	1.371	2.028	1.526	1.329
8	6.493	3.782	1.717	6.270	3.759	1.652	4.696	2.990	1.571
9	4.126	2.857	1.445	3.941	2.690	1.413	3.059	2.246	1.362
10	2.724	1.519	1.794	2.597	1.466	1.771	2.048	1.218	1.682
11	1.404	1.293	1.086	1.338	1.238	1.081	1.118	1.038	1.077
12	1.201	1.048	1.145	1.152	1.003	1.148	0.962	0.848	1.135

* same as Table 1.

a rise in temperature, but the separation factor, α, was small decreased, the result was shown in Table 2. The effect of mobile phase flow rate was investigaed in the range of 1 - 2 ml / min in step of 0.5 mL / min. for all compounds. The result of separation was hardly affected which was listed in Table 3.

The results suggest the mechanism for chiral recognition depicted in Figure 2. This model involves the formation of a charge-transfer complex between the π-electron acceptor 3,5-dinitrobenzoyl group of the CSP and the π-electron donor aryl substitument R of the organic phosphorus compounds and three hydrogen bonding of the 3,5-dinitrobenzamide hydrogen of the CSP and the phosphorous compounds. Obviously the π-bonding is more important, so the enantiomers of a series ten compounds (No. 1-10) have good separation. When R is an aliphatic group (No. 11-12), the π-bond disappears and the results of separation are not as good as with an aromatic group.

Table 3

k'_2 k'_1 and α Values of Twelve O,O-Diethyl, (p-Methyl-Benzenesulfonamido)-Aryl (Alkyl)-Methylphosphonate at Different Mobile Phase Flow Rate (Mobile Phase: 20 % Isopropyl Alcohol, Column Temperture:16^{0}C)

No*	1.0 mL/min			1.5 mL/min			2.0 mL/min		
	k'_2	k'_1	α	k'_2	k'_1	α	k'_2	k'_1	α
1	3.024	1.924	1.572	3.383	2.150	1.573	3.188	2.049	1.556
2	5.075	2.592	1.959	6.047	3.047	1,985	5.583	2.861	1.951
3	2.983	1.657	1.799	3.466	1.902	1.823	3.215	1.799	1.788
4	4.779	2.879	1.660	5.528	3.321	1.665	5.049	3.083	1.637
5	3.569	2.026	1.762	3.736	2.130	1.754	3.576	2.056	1.740
6	6.498	4.069	1.597	6.943	4.347	1.597	6.528	4.118	1.585
7	2.751	1.974	1.393	3.026	2.171	1.394	2.840	2.046	1.382
8	6.493	3.782	1.717	7.591	4.389	1.730	6.993	4.118	1.698
9	4.126	2.857	1.445	4.554	3.161	1.441	4.306	3.014	1.429
10	2.724	1.519	1.794	2.886	1.606	1.797	2.813	1.576	1.784
11	1.404	1.293	1.086	1.497	1.378	1.806	1.451	1.340	1.083
12	1.201	1.048	1.145	1.285	1.114	1.153	1.250	1.087	1.153

*Same as Table 1

REFERENCES

1. S. Ahuja (Editor), **Chiral Separation by Liquid Chromatography** (ACSSymposium Series. No.471) American Chemical Society, Washington, DC. 1991.

2. S. G. Allenmark, **Chromatographic Enantioseparation**, Ellis Horwood, Chichester, 1988

3. A. M. Krstulovic (Editor) **Chiral Separation by HPLC**, Ellis Horwood, Chichester, 1988

4. C. J. Welch, J. Chromatogr. A, **666**, 3 (1994).

5. K. B. Lipkowitz, J. Chromatogr., A, **666**, 493 (1994).

6. W. H. Pirkle, D. M. Alessi, M. Ho Hyun, T. C. Pochapsky, J. Chromatogr., **398**, 203 (1987).

Received April 16, 1995
Accepted August 23, 1995
Manuscript 1052