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Note

High-performance liquid chromatographic separation of chiral alcohols on chiral stationary phases

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The high-performance liquid chromatographic (HPLC) separation of enantiomers has been achieved by the use of chiral stationary phases. Pirkle and Finn[1] accomplished the direct separation of racemic arylalkylcarbinols upon N-(R)-3,5-dinitrobenzoylphenylglycine bonded to aminopropyl silanized silica, but the solutes to which the method could be applied were limited.

In general, enantiomer separation in liquid chromatography is affected not only by the enantioselectivity of the stationary phase but also by the type of derivatives employed. Pirkle and House[2] reported that some racemic arylalkylcarbinols were separated in the form of their 3,5-dinitrobenzoyl derivatives on a stationary phase comprised of chiral 2,2,2-trifluoro-1-(9-anthryl)ethanol bonded to silanized silica. In this instance, the incorporation of the 3,5-dinitrobenzoyl group as a π-acid may contribute to a charge transfer interaction in the enantiomer separation.

In this work we demonstrate that various chiral alcohols can be separated efficiently by HPLC upon chiral stationary phases after conversion of the solutes into their 3,5-dinitrophenylurethane derivatives.

EXPERIMENTAL

Formation of derivatives

The alcohol solutes were reagent-grade chemicals. Allethrolone was provided by colleagues in our laboratory. 3,5-Dinitrophenyl isocyanate was prepared from 3,5-dinitroaniline (Aldrich, Milwaukee, WI, U.S.A.) (0.005 mol) by reaction with phosgene (0.05 mol) in a mixture of toluene (20 ml) and ethyl acetate (15 ml) at 80°C for 2 h.

Samples of 5 mg or less of chiral alcohols were dissolved in 0.5 ml of dry toluene and 5–20 mg of 3,5-dinitrophenyl isocyanate were added. The mixture was heated at 60–70°C for 1 h in the presence of 0.05 ml of dry pyridine. After cooling, 2 ml of methanol were added and the solvent was removed at 50°C under reduced pressure. The derivatives were dissolved in 2 ml of chloroform for liquid chromatography.

Liquid chromatography

The experiments were carried out using a Shimadzu LC-3A high-performance

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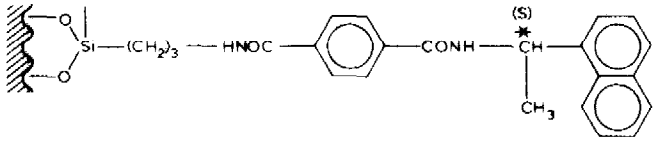

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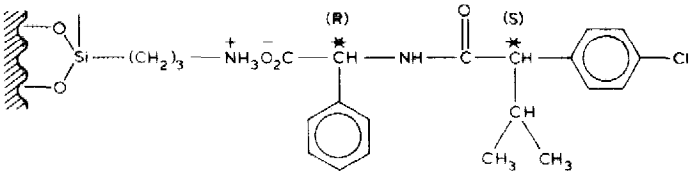

II

liquid chromatograph equipped with a UVD-2 ultra-violet (UV) detector (254 nm). The chiral stationary phases I and II were prepared as described previously[3,4].

Steel columns (250 × 4 mm I.D.) were slurry packed with these phases using conventional techniques.

RESULTS AND DISCUSSION

Recently we[3,4] developed some novel optically active stationary phases consisting of chiral 1-(α-naphthyl)ethylamine, 2-(4-chlorophenyl)isovaleric acid and its amide derivatives bonded to aminopropyl silanized silica, such as I and II. These phases proved to be excellent for the separation of enantiomers of 3,5-dinitrobenzoyl

TABLE I

SEPARATION OF ALCOHOL ENANTIOMERS AS 3,5-DINITROPHENYLURETHANES ON CHIRAL STATIONARY PHASES

The separation factor of the enantiomers, α, is the ratio of the capacity ratios of the enantiomers. k'_1 is the capacity ratio for the first enantiomer eluted. Mobile phases: *n*-hexane–1,2-dichloroethane-ethanol, 20:6:1 (A), 48:15:1 (B) and 100:20:1 (C). Flow-rates of 1 ml/min were typically used for the 250 × 4 mm I.D. columns at room temperature.

Racemate	*Phase I*			*Phase II*		
	α	k'_1	*Mobile phase*	α	k'_1	*Mobile phase*
2-Hexanol	1.08	2.37	A	1.11	2.85	C
2-Octanol	1.07	1.83	A	1.22	3.46	C
2-Decanol	1.10	1.72	A	1.21	2.72	C
1-Methoxy-2-propanol	1.15	3.40	A	1.06	4.54	C
4-Methyl-2-pentanol	1.07	2.32	A	1.14	2.75	C
1-Phenylethanol	1.22	4.27	A	1.13	7.08	C
1-(α-Naphthyl)ethanol	1.27	5.21	A	1.15	8.46	C
Menthol	1.07	4.40	B	1.04	5.29	C
Borneol	1.00	5.11	B	1.13	6.24	C
Pantoyl lactone	1.22	8.62	A	1.53	1.58	B
Allethrolone	1.00	7.90	A	1.33	4.60	B

derivatives of amines or amino acid esters, and 3,5-dinitroanilide derivatives of carboxylic acids, but unfortunately have no enantioselectivity for 3,5-dinitrobenzoyl derivatives of various chiral alcohols, except for some arylalkylcarbinols. The lack of enantioselectivity may be attributed to the fact that no functional group containing a hydrogen atom is available for hydrogen bonding interaction with the stationary phase.

In gas chromatography, there are few examples of the separation of chiral alcohols in the form of their O-acyl derivatives[5], but many alcohols were well separated in the form of isopropylurethane derivatives[6,7] on OA-300 and XE-60–S-valine-S-α-phenylethylamide as chiral stationary phases. We therefore introduced a NH group as well as a 3,5-dinitrobenzoyl group by the reaction of alcohols with 3,5-dinitrophenyl isocyanate, yielding the corresponding urethanes.

The HPLC results are shown in Table I. Several aliphatic and aromatic alcohol enantiomers were separated with good separation factors. Typical chromatograms are shown in Figs. 1 and 2.

The influence of the 3,5-dinitrophenylaminocarbonyl group in the solutes suggests contributions from both a hydrogen-bonding association and a π–π donor–acceptor interaction in the separation of alcohol enantiomers.

We expect that this new procedure using 3,5-dinitrophenylisocyanate will be applied for HPLC analysis of various chiral alcohols on these chiral stationary phases.

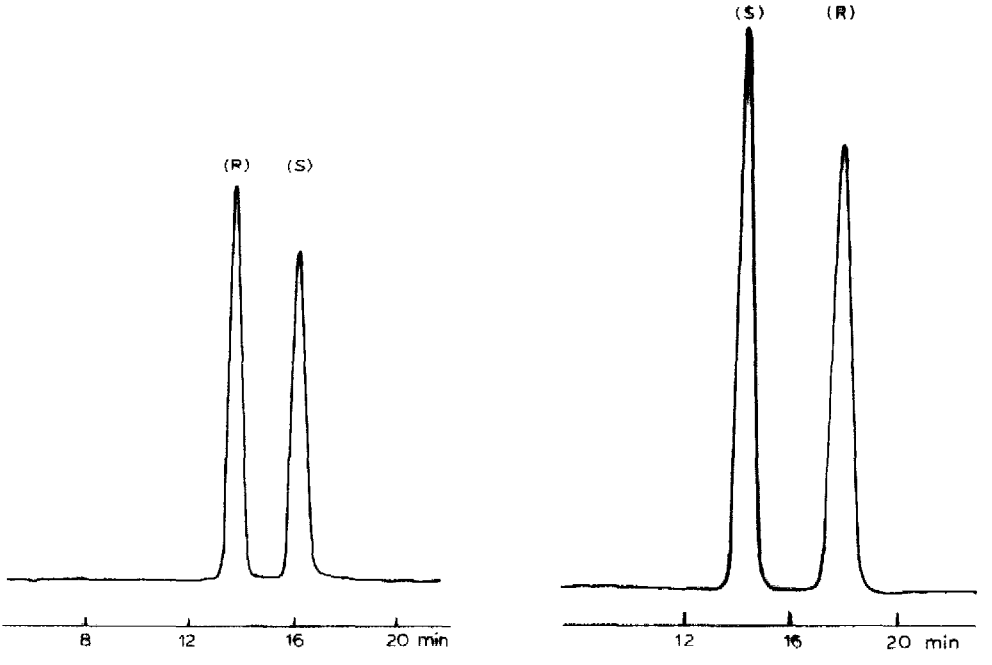

Fig. 1. Separation of the enantiomers of racemic 1-phenylethanol as 3,5-dinitrophenylurethanes on chiral stationary phase I. Chromatographic conditions as in Table I.

Fig. 2. Separation of the enantiomers of racemic allethrolone as 3,5-dinitrophenylurethanes on chiral stationary phase II. Chromatographic conditions as in Table I.

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