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A direct HPLC method for the resolution of glycidyl tosylate and glycidyl 3-nitrobenzenesulphonate enantiomers*

CHARLES J. SHAW† and DONALD L. BARTON

R.W. Johnson Pharmaceutical Research Institute, Route 202, P.O. Box 300, Raritan, NJ 08869, USA

Abstract: The enantiomeric composition of glycidyl tosylate and glycidyl 3-nitrobenzenesulphonate is obtained using an enantiomeric HPLC column. The chiral oxiranes were resolved on a cellulose carbamate column using a mobile phase of hexane:2-propanol. The method is simple, sensitive and does not require derivatization.

Keywords: *HPLC; glycidyl tosylate; glycidyl 3-nitrobenzenesulphonate; enantiomers.*

Introduction

The utility of enantiomerically enriched glycidyl tosylate and glycidyl 3-nitrobenzenesulphonate as synthons in synthesis has been described by Sharpless and co-workers [1]. The (*R*)- and (*S*)-enantiomers have been used in the synthesis of cardiovascular agents [2], 1,2-cytoxic phospholipids [3] and platelet activating factor [4].

The direct determination of enantiomeric purity of the glycidyl sulphonates is of particular interest since they are such useful synthons and because the published method of analysis utilizes a derivatization technique and subsequent separation of the diastereomers [5]. In an industrial setting it is desirable and often necessary to have a rapid and easily performed method of analysis for purchased intermediates. This was particularly true for the glycidyl sulphonates, which at the time of our initial work were not supplied with certificates of analysis specifying their enantio-enrichment. In addition, polarimetric measurement of their optical rotations is not a precise enough method since the rotation values are relatively small.

Although chromatographic methods for the resolution of a variety of chiral compounds are becoming more abundant, little has been published on the chromatographic separation of epoxides. Most of the literature deals with the epoxide metabolites of polycyclic aromatic hydrocarbons (PAH). The indirect HPLC method for PAH epoxides involves derivatization with glutathione followed by separation of the diastereoisomers using commercially available reversed-phase columns [6]. Gal described a simple and convenient two reaction derivatization sequence for the enantiomeric analysis of chiral epoxides. The resulting diastereomeric thioureas were resolved on C_{18} columns [7]. Recently, Dougherty *et al.* resolved short-chain aliphatic epoxy alcohols without derivatization using a gas chromatographic method which used a capillary column coated with the permethylated hydroxypropyl derivative of alpha cyclodextrin [8].

Determination of the enantiomeric composition of the glycidyl tosylates and the glycidyl 3-nitrobenzenesulphonates using the indirect HPLC methods or the direct gas chromatographic method were not successful in our laboratory. The chiral epoxides were separated on a cellulose carbamate adsorbent coated on silica gel. The direct HPLC method is simple, sensitive and does not require derivatization.

Experimental

Chemicals

The epoxides were obtained from Aldrich Chemical Co. (Milwaukee, WI, USA),

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† Author to whom correspondence should be addressed.

Andeno B.V. (Grubbenvorsterweg 8 — 5928 NX Venlo, The Netherlands), and Genzyme (Haverhill, Suffolk, UK): (2*R*)-(−)-glycidyl tosylate, (2*S*)-(+)-glycidyl tosylate, (2*R*)-(−)-glycidyl 3-nitrobenzenesulphonate, and the (2*S*)-(+)-glycidyl 3-nitrobenzenesulphonate. Hexane and 2-propanol were Fischer OPTIMA solvents (Springfield, NJ, USA).

Chromatography

A Perkin–Elmer series 410 pump was used for solvent delivery with a Hewlett–Packard series 1050 auto-injector and 1040A diode array detection system. Separations were obtained on a Daicel Inc. (Fort Lee, NJ, USA) OD chiral HPLC column, 0.46 × 25 cm, packed with cellulose carbamate coated on silica gel of 10 μm particle size. The composition of the mobile phases was delivered by the solvent delivery system after degassing with helium for 10 min. The mobile phase flow rates and detection wavelengths are found in Table 1. The detector output was recorded using the Hewlett–Packard laboratory automation system and Think Jet printer plotter.

Results

Chromatograms showing the enantiomeric resolution of glycidyl tosylate and glycidyl 3-nitrobenzenesulphonate are shown in Figs 1–3. The *R* and *S* enantiomers were resolved using a single enantiomeric column with isocratic conditions. The separation factor, peak resolution and conditions for obtaining the chromatograms are shown in Table 1. The degree of resolution, less than 1.5, is not a serious deficiency since detection of 0.5% was obtained. The individual enantiomers were first used to determine the elution order of the enantiomers. Calibration curves were prepared using synthetic mixtures of the enantiomers. The response curve for the per cent (*R*)-(−) spiked into (2*S*)-(+)-glycidyl 3-nitrobenzenesulphonate consisted of five standards with a concentration range of 2.6–50.0% weight *R* enantiomer. The standard error of slope was 0.984 with a correlation coefficient of 0.9996. The concentration range for the per cent (*S*)-(+)-enantiomer spiked into (2*R*)-(−)-glycidyl tosylate also consisted of five standards ranging from 1.1 to 50.0% weight *S* enantiomer. This calibration curve had a 2.18 standard error of slope and a correlation coefficient equal to 0.9985.

Discussion

The direct HPLC method, which uses the Daicel OD column, for the resolution of glycidyl tosylate and glycidyl 3-nitrobenzenesulphonate is simple, quantitative and does not require derivatization. The total elution time is not a drawback if one considers additional time-consuming steps are not required in order to obtain resolution of these epoxides.

The determination of enantiomeric composition of glycidyl tosylate and glycidyl 3-nitrobenzenesulphonate using the indirect HPLC methods was not successful in our laboratory. Additional peaks due to interferences from impurities introduced during derivatization and less than 100% enantiomeric purity of derivatization agents complicated the chromatographic resolution of these epoxides. Although the diastereomeric derivatives of chiral epoxides are generally resolvable by reversed-phase liquid chromatography, the problem of regioselectivity of the ring-opening reaction remains with certain epoxides. The gas chromatographic determination of enantiomeric composition was investigated for these epoxides. Fused silica capillary columns coated with the permethylated hydroxypropyl derivative of alpha cyclodextrin and L-valine-*S*-α-phenethylamide coupled to methyl-cyanoethyl-polysiloxane were investigated. In all cases, only a single peak was observed in the gas chromatograms for racemic mixtures of these epoxides.

Table 1
Resolution of glycidyl tosylate and glycidyl 3-nitrobenzenesulphonate enantiomers using cellulose carbamate HPLC column

Epoxide	wavelength (mm)	Flow rate (ml min^{-1})	Mobile phase (Hex:IPA)	α[9]	R[9]	*t* (min)	Faster eluting enantiomer
1	230	0.7	99:1	1.06	1.48	51.2;53.9	*S*
2	220	0.4	80:20	1.05	1.45	58.4;61.5	*R*

Legend: 1 — Glycidyl tosylate; 2 — glycidyl 3-nitrobenzenesulphonate; α — separation factor; R — resolution.

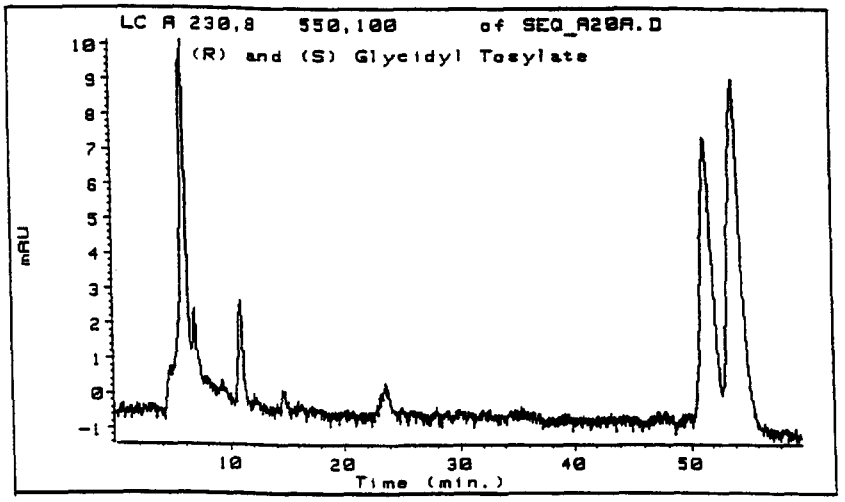

Figure 1
Chromatogram of glycidyl tosylate (20% enantiomeric excess) favouring the (*R*)-(−) configuration.

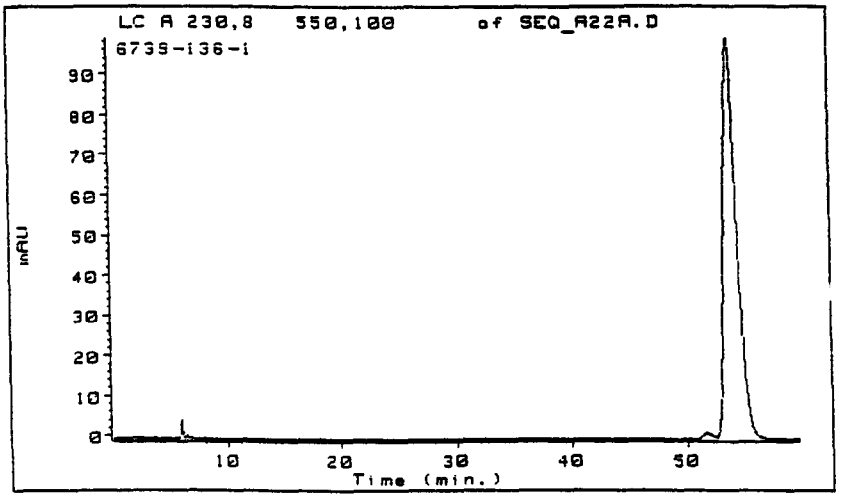

Figure 2
Chromatogram of glycidyl tosylate (98% enantiomeric excess) favouring the (*R*)-(−) configuration.

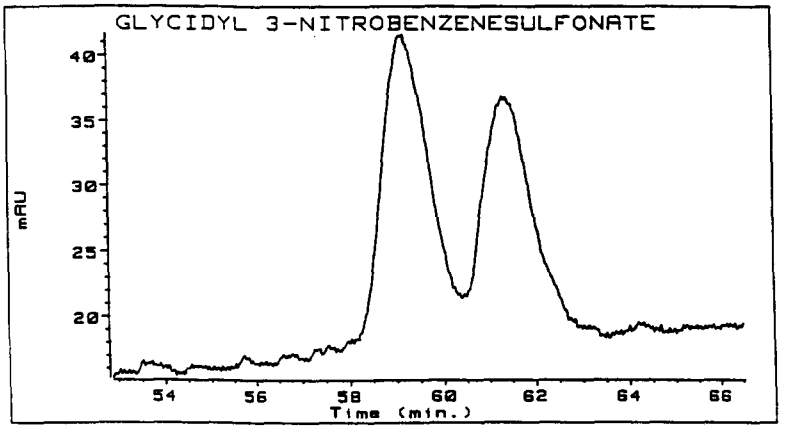

Figure 3
Chromatogram of glycidyl 3-nitrobenzenesulphonate (20% enantiomeric excess) favouring the (*R*)-(−) configuration.

The interaction between glycidyl tosylate and glycidyl 3-nitrobenzenesulphonate with the cellulose carbamate stationary phase is significant. This phenomenon is manifested by the observed retention times and the amount of polar modifier necessary for elution. It is not clear why there is a reversal in the elution order for the enantiomers of the two sulphonates (Table 1). Gradient elution, achiral derivatization (ring opening followed by acetylation), and two OD columns in series were investigated to obtain peak resolution greater than 1.5. These experiments resulted in longer retention times and/or peaks with greater than 10% valley.

Conclusions

The resolution and quantitative measurement of the enantiomeric composition of glycidyl tosylate and glycidyl 3-nitrobenzenesulphonate has been achieved, without the need for derivatization, using a commercially-available cellulose carbamate HPLC column. The method is simple, uses isocratic conditions with hexane:2-propanol mobile phases, and is able to measure 0.5% of one enantiomer in the presence of the other.

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