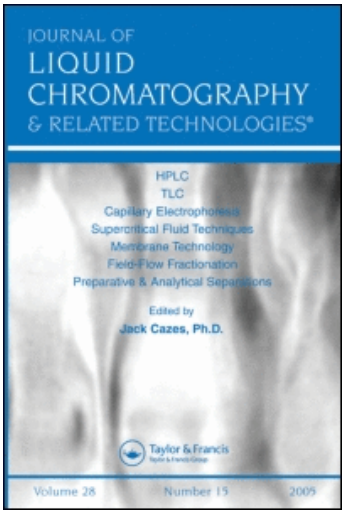

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SEPARATION OF D AND L ENANTIOMERS OF [(PHENYLSULFONYL)AMINO]-3-OXO-1-OCTADECANOL BY CHIRAL HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A convenient and rapid method has been developed for the separation of the D and L enantiomers of [(phenylsulfonyl)amino]-3-oxo-octadecanol using chiral High Performance Liquid Chromatography (HPLC). An amylose tris(3,5-dimethylphenylcarbamate) chiral HPLC column was used for the separation. The two enantiomers were fully resolved from each other with approximate retention times of 11 and 13 minutes for the L and the D forms respectively. The total run time per sample was 30 minutes.

INTRODUCTION

The chiral separation of the two enantiomers of [(phenylsulfonyl)amino]-3-oxo-1-octadecanol was necessary in order to obtain information regarding the enantiomeric purity of the product during synthesis.[2] Chiral HPLC was found

to be an appropriate analytical technique to monitor the synthesis and to determine the enantiomeric purity of the final product. The synthetic challenge was to synthesize exclusively the L enantiomer. The analytical challenge was to develop a method for the separation of the two enantiomers. The developed analytical method provided the required information for the optimization of synthetic conditions as well as the basis to demonstrate the enantiomeric purity of the final product.

Purified enantiomers and a racemic mixture of [(phenylsulfonyl)amino]-3-oxo-octadecanol[1] were provided by our Chemical Development group for method development. The HPLC method is very simple, fast, and convenient for the intended purposes. The structures of the two enantiomers are presented in Figure 1.

MATERIALS AND METHODS

Equipment

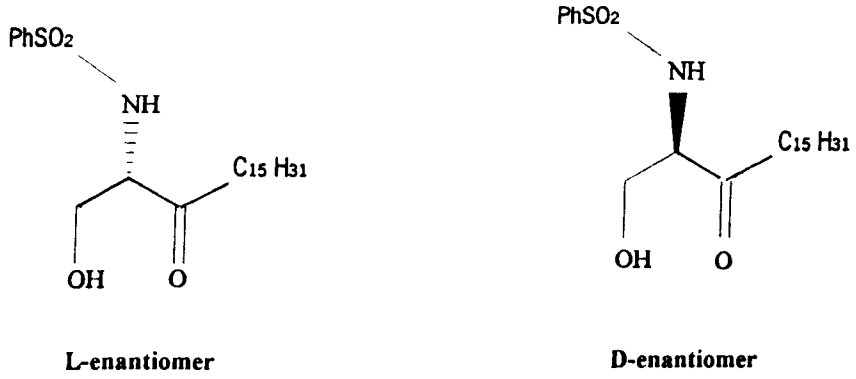
The high performance liquid chromatograph (HPLC) consisted of a Spectra-Physics P2000 pump, a Thermo Separations Products AS3000 autoinjector, and a Spectra-Physics UV2000 variable wavelength ultraviolet detector. The analytical column was an amylose tris(3,5-dimethyl-phenylcarbamate) or Chiralpack AD, 25 cm x 4.6 mm I.D., obtained from Regis Chemical Company, Morton Grove, Illinois 60053, USA.

Reagents

Hexane and isopropanol, both Liquid Chromatography Grade, were obtained from EM Science, 480 S. Democrat Road, Gibbstown, New Jersey 08027, USA., and used to make the mobile phase. The D and L enantiomers of [(phenylsulfonyl)amino]-3-oxo-1-octadecanol[3] were made by our Chemical Development group, and the structures confirmed by high resolution nmr, mass spectroscopy, and infrared spectroscopy.

Mobile Phase and Analysis

The mobile phase consisted of a mixture of hexane and isopropanol at a ratio of 9:1 respectively. The mobile phase was pumped at a flow rate of 1.0 mL per minute. The column temperature was maintained at approximately 25



L-enantiomer **D-enantiomer**

Figure 1. Structures of the two enantiomers of [(phenylsulfonyl)amino]-3-oxo-1-octadecanol.

degrees Centigrade using a temperature controlled HPLC column heater. Injections into the chromatographic system were performed using the HPLC auto-injector with a set injection volume of 50 microliters. The detection was made at 254 nm using the ultraviolet HPLC detector at a range of 0.1 AUFS. The sample was prepared by weighing 100 mg of sample into a 100 mL volumetric flask, dissolved, and then diluted to the mark with mobile phase. Injections were made from this preparation. Sample chromatograms are shown in the Results section below.

RESULTS AND DISCUSSION

During method development, several Pirkle concept type of chiral columns (Phenylglycine, Naphthylleucine, and Naphthylalanine obtained from Regis Technologies, Inc.) were evaluated without success. There were restrictions on the composition of the mobile phase due to the solubility of the compound. At this point, derivatized cellulose and amylose (3,5-dimethylphenylcarbamate) chiral columns were evaluated. The cellulose type gave us some retention, but no separation, while the amylose type column fully resolved the two enantiomers under the same conditions. Theoretically, the difference in results between the cellulose and the amylose type of columns may be attributed to structural differences between cellulose and the amylose. Cellulose and amylose differ in the way glucose is linked together, and the type of conformation which results from this linking. In cellulose, the linkage is of the $\beta(1\rightarrow4)$ type, while in amylose the linkage is of the $\alpha(1\rightarrow4)$ type.[3]

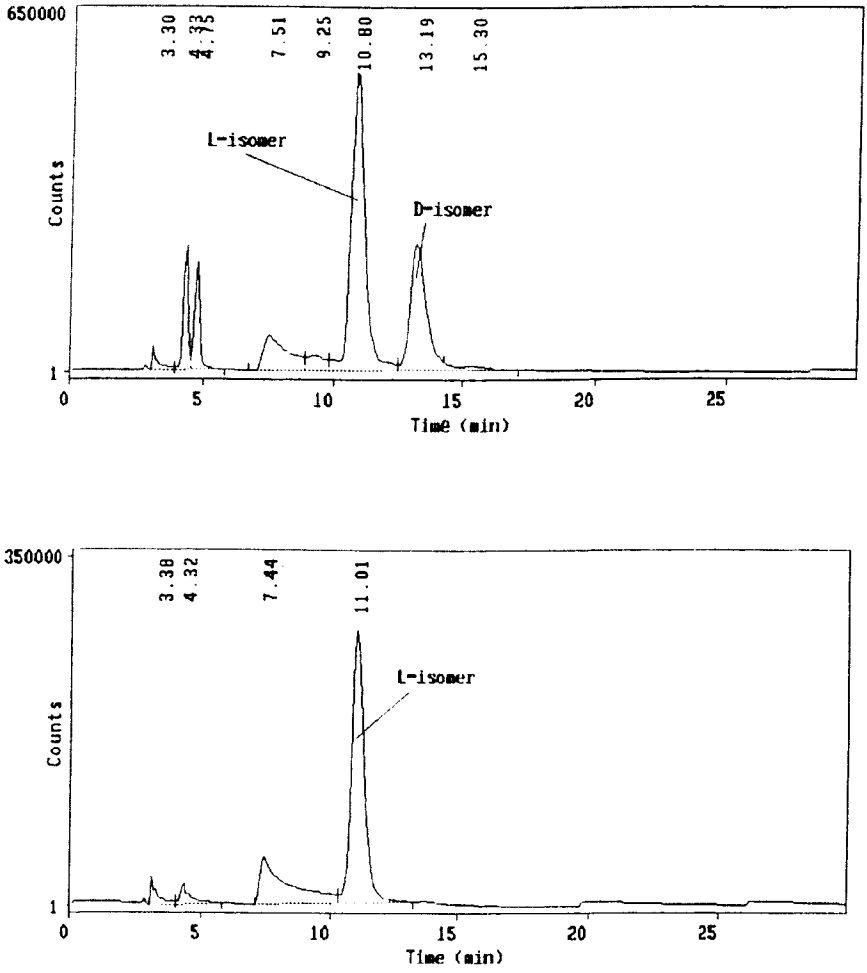


Figure 2. Sample chromatograms of a racemic mixture and the L-isomer.

This difference accounts for the difference in conformation: cellulose has a linear type of conformation, while amylose has a helical type of conformation. Since both types of columns are derivatized as the 3,5-dimethylphenylcarbamate, it is then the type of conformation which provides the basis for the separation of [(phenylsulfonyl)amino]-3-oxo1-octadecanol. In addition, both enantiomers contain a 15 carbon aliphatic chain with a phenylsulfonyl end. It is likely that the helical conformation of the amylose

provides the right geometry for the aliphatic chain of the enantiomers to interact with the helical frame of amylose, while the phenylsulfonyl end of the enantiomers interacts with the dimethylphenyl portion of the derivatized amylose. The phenylsulfonyl portion of the molecule interacts with the dimethylphenylcarbamate portion of the solid substrate through a π-π type of interation of the corresponding benzene rings. It is therefore, the orientation of the phenylsulfonyl group of the particular enantiomer, with respect to the dimethylphenyl group of the derivatized amylose, that determines which enantiomer is retained more or less than the other.

Based on the chromatographic retention times, one concludes that the D enantiomer's phenylsulfonyl portion has stronger interaction than the L enantiomer's. It also appears that for this interction to take place, the helical conformation is required as the cellulose counterpart failed to achieve resolution.

CONCLUSIONS

A convenient and rapid chiral chromatographic method has been developed (Figure 2) for the separation of the D and L enantiomers of [(phenylsulfonyl)amino]-3-oxo-1-octadecanol. Full baseline resolution was achieved. The absolute retention times for the two enantiomers were 11 and 13 minutes for the L and D forms respectively.

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