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# Short Communication

# Optical resolution of 2-chloro-3-phenylmethoxypropanoic acid after derivatization with (*S*)-2-octanol by high-performance liquid chromatography

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ABSTRACT

A simple chromatographic method is described to resolve the enantiomers of 2-chloro-3-phenylmethoxypropanoic acid. The optical resolution is achieved by applying a silica phase with 0.4% tetrahydrofuran in *n*-hexane as eluent, after derivatization of the sample with (*S*)-2-octanol in the presence of dicyclohexylcarbodiimmide.

## INTRODUCTION

2-Chloro-3-phenylmethoxypropanoic acid [$C_6H_5CH_2OCH_2CH(Cl)COOH$ (**1**)] is a key intermediate in the synthesis of polyaminopolycarboxylic ligands, like diethylenetriamine-N,N,N′,N″,N″-pentaacetic acid (linear) [1,2] and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (cyclic) [3,4], whose gadolinium-complexes are used as contrast agents for magnetic resonance imaging (MRI) [5]. The presence of the phenylmethoxymethyl group in the structure makes these gadolinium complexes particularly attractive for imaging of the hepatobiliary system and the myocardium.

The chemical resolution of **1** by formation of the diastereoisomeric salts with enantiomerically pure 1-phenylethylamine has recently been reported [6]. The optical purity of (+)- and (−)-**1** cannot be precisely determined by polarimetry owing to the very low specific rotation values shown by the pure enantiomers in all common solvents.

This paper describes a chemical derivatization method that allows the high-performance liquid chromatographic (HPLC) separation of the optical isomers of **1**. The mixture of enantiomers of **1** was derivatized with (*S*)-2-octanol using the esterification conditions [N,N′-dicyclohexylcarbodiimide, 4-(N,N-dimethylamino)pyridine, chloroform] reported by Felder *et al.* [7].

## EXPERIMENTAL

### *Chemicals*

N,N′-Dicyclohexylcarbodiimide, 4-(N,N-dimethylamino)pyridine, analytical-reagent grade chloroform, chromatographic grade *n*-hexane and tetrahydrofuran (THF) were obtained from E. Merck (Darmstadt, Germany) and (*S*)-2-octanol from Aldrich (Milwaukee, WI, USA). (*S*)- and (*R*)-2-chloro-3-phenylmethoxypropanoic acid were synthesized as described previously [6].

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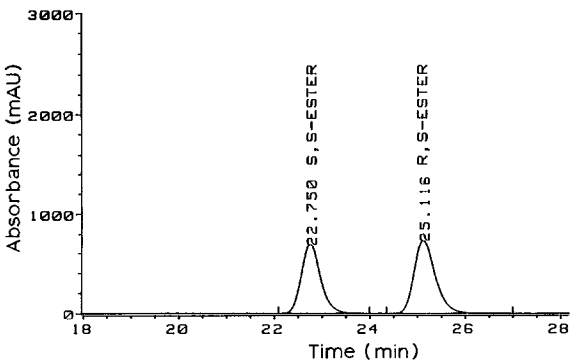


Fig. 1. Resolution of 2-chloro-3-phenylmethoxypropanoic acid after derivatization with (*S*)-2-octanol.

*High-performance liquid chromatography*

A Hewlett-Packard HP 1090M liquid chromatograph, equipped with an autosampler, a diode-array detector set at 210 nm and a Merck LiChrosorb Si 60 (5 μm) column (250 × 4 mm I.D.) thermostated at 37°C, was used. The column was eluted with 0.4% THF in *n*-hexane at a flow rate of 1 ml $min^{-1}$.

*Procedure*

An exactly weighed sample of **1** (about 25 mg; 0.116 mmol) was placed in a 10-ml volumetric flask containing (*S*)-2-octanol (100 μl; 82.7 mg; 0.635 mmol), N,N′-dicyclohexylcarbodiimide (500 μl of a 0.762 *M* solution in chloroform) and 4-(N,N-dimethylamino)pyridine (100 μl of a 0.123 *M* solution in chloroform). The mixture was sonicated for 1 h at 25°C and then diluted to 10 ml by addition of *n*-hexane. The precipitated N,N′-dicyclohexylurea was filtered through an HV 0.45-μm Millipore filter and a sample (15 μl) of the solution was injected for HPLC analysis.

## RESULTS AND DISCUSSION

Preliminary attempts to obtain a good resolution of diastereoisomeric mixtures of **1**, esterified with optically active alcohols [*e.g.*, (*S*)-2-butanol, (*S*)-2-octanol, (−)-menthol], by either gas chromatography or reversed-phase failed, despite the wide range of achiral stationary phases tested. As emphasized by other workers [8,9] we obtained much better results using HPLC with a normal silica phase. The use of (*S*)-2-octanol for the preparation of diastereoisomeric derivatives for analytical purposes has already been reported [10].

TABLE I

CALCULATED *vs.* EXPERIMENTAL (*S,S*)-ESTER CONTENT IN NON-RACEMIC MIXTURES OF (*R*)- and (*S*)-2-CHLORO-3-PHENYLMETHOXYPROPANOIC ACID AFTER DERIVATIZATION WITH (*S*)-2-OCTANOL

| Sample composition (mg) | | (*S,S*)-Ester (%) | |
|---|---|---|---|
| (*R*)-Acid | (*S*)-Acid | Calculated | Found |
| 24.494 | 0.225 | 0.91 | 0.89 |
| 21.953 | 3.396 | 13.40 | 14.31 |
| 20.122 | 6.187 | 23.52 | 22.86 |
| 16.557 | 8.050 | 32.71 | 32.17 |
| 13.568 | 11.924 | 46.78 | 46.30 |
| 10.005 | 15.519 | 60.80 | 60.03 |
| 7.141 | 18.900 | 72.64 | 72.34 |
| 5.581 | 19.122 | 77.41 | 76.80 |
| 2.538 | 22.347 | 89.80 | 89.50 |
| 0.356 | 22.219 | 98.49 | 98.52 |

The resolution of the two diastereoisomeric esters of **1** with (*S*)-2-octanol, under our experimental conditions, is shown in Fig. 1. The (*S,S*)- and the (*R,S*)-esters elute with retention times of 22.75 and 25.12 min, respectively, and the chromatographic resolution is always better than 2.

Ten suitable samples of (*R*)- and (*S*)-**1** mixtures were analysed and the experimental enantiomeric percentages are reported, together with the calculated values, in Table I. The derivatization procedure proved to be very easy and highly reproducible. Modifying the reaction conditions, *i.e.*, temperature (within the range 20–40°C), concentration of the reagents and time (up to 24 h) did not result in any detectable racemization of either the acids **1** or their corresponding esters. It is noteworthy that even when the derivatization was performed at temperatures up to 40°C we did not observe the formation of any N-acylurea as a side-product [11]. The method described provides a reliable and practical means for the determination of the optical purity of **1**.

## REFERENCES

1 E. Felder, L. Fumagalli, F. Uggeri and G. Vittadini, *Eur. Pat. Appl.*, EP 230893 (1987); *Ital. Pat. Appl.* (1986).
2 G. Vittadini, E. Felder, P. Tirone and V. Lorusso, *Invest. Radiol.*, 23 (1988) S246.

3 E. Felder, L. Fumagalli, C. Musu and F. Uggeri, *PCT Int. Appl.*, WO 8905802 (1989); *Ital. Pat. Appl.*, 87/23217 (1987).
4 C. Musu, E. Felder, L. Fumagalli, P. Tirone and G. Vittadini, presented at the *7th Annual Meeting of the Society of Magnetic Resonance in Medicine, San Francisco, CA, August 22–26, 1988.*
5 R. B. Lauffer, *Chem. Rev.*, 87 (1987) 901.
6 S. Aime, P. L. Anelli, M. Botta, M. Grandi, P. Paoli and F. Uggeri, *Inorg. Chem.*, submitted for publication.
7 E. Felder, U. Tiepolo and A. Mengassini, *J. Chromatogr.*, 82 (1973) 291.
8 L. R. Snyder and J. J. Kirkland, *Introduction to Modern Liquid Chromatography*, Wiley-Interscience, New York, 2nd ed., 1979, pp. 359-360.
9 L. R. Snyder, K. Glajch and J. J. Kirkland, *Practical HPLC Method Development*, Wiley-Interscience, New York, 1988, p. 8.
10 B. Halpern, in K. Blau and G. S. King (Editors), *Handbook of Derivatives for Chromatography*, Heyden, London, 1978, p. 482.
11 B. Helferich and H. Böshagen, *Chem. Ber.*, 92 (1959) 2813.