

A New Semi-Preparative Liquid Chromatographic Optical Resolution of Ferrocene Derivatives by the Use of Aqueous Solution of α -Cyclodextrin as a Mobile Phase and Polyamide as a Stationary Phase

AKIRA HARADA, KOHJI SAEKI, and SHIGETOSHI TAKAHASHI*
The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan

(Received: 2 September 1986; in final form: 13 October 1986)

Abstract. 1-Ferrocenylethanol and its analogues were completely resolved into their enantiomers by liquid chromatography on a polyamide column using an aqueous solution of α -cyclodextrin as a mobile phase.

Key words: α -cyclodextrin, optical resolution, polyamide

1. Introduction

Recently, direct optical resolution of racemic compounds by liquid chromatography has been extensively investigated [1] and several practically useful systems have been reported [2]. The use of cyclodextrins in separations has been reviewed by Hinze [3]. He and co-workers reported the first use of CD mobile phases and polyamide stationary phases in the TLC separation of ortho, meta, and para disubstituted benzenes [4]. Although cyclodextrins have been often used as reagents for fractional precipitation of racemates, only partial resolution has so far been attained [5]. Moreover, optical resolution of mandelic acid derivatives was studied by column chromatography on immobilized cyclodextrins [6] and the first separation of the enantiomers was reported by using an aqueous solution of β -cyclodextrin as a mobile phase [7]. However, complete resolution has not been achieved [6] and α -cyclodextrin was found to be much less effective for the optical resolution [7]. Recently, liquid chromatographic separation of enantiomers including racemic metallocenes using a chiral β -cyclodextrin-bonded stationary phase has been reported [8]. In the course of our study on a series of inclusion compounds of organotransition metal complexes with cyclodextrins, we found that α -cyclodextrin is very effective for the optical resolution of 1-ferrocenylethanol by fractional precipitation. In this communication, we report the complete optical resolution of some ferrocene derivatives by liquid chromatography using an aqueous solution of α -cyclodextrin as a mobile phase and polyamide as a stationary phase. This system may provide a useful method for the resolution because it can be applied on a preparative scale due to its simple operation and the low cost of polyamides.

* Author for correspondence.

2. Experimental

A glass-column (50 × 0.8 cm (i.d.)) was packed with polyamide 6 (Baker, for TLC, 250–400 mesh) by the slurry technique. The chromatography was performed on a medium pressure liquid chromatography system equipped with a UV detector. The theoretical plate number of the packed column was about 2000 when an aqueous α -CD solution was used as eluent. The flow rate was 0.56 ml/min and 5 to 30 mg of racemic compounds were used.

3. Results and Discussion

Figure 1 shows the chromatogram of the optical resolution of 1-ferrocenylethanol (**1**) and that of 1-ferrocenylpropanol (**2**) using an aqueous solution of α -cyclodextrin (0.05 M, pH 11.4

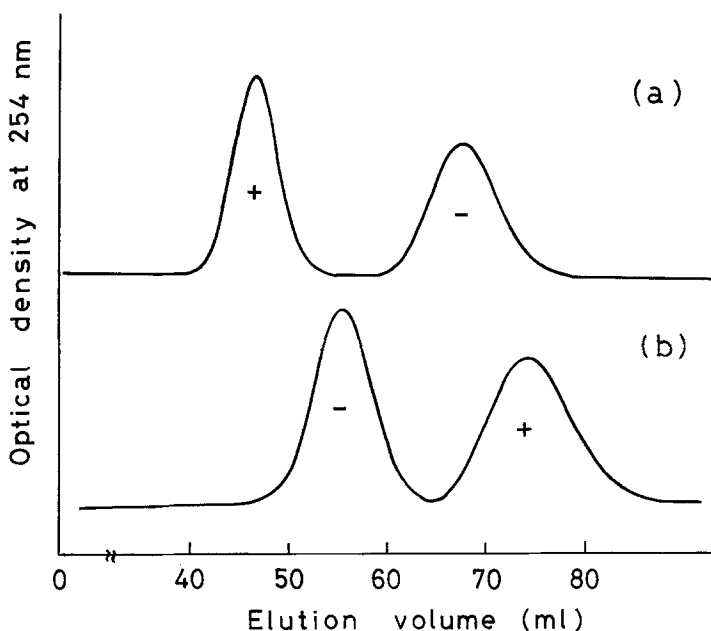
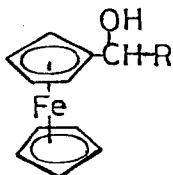


Fig. 1. Chromatographic separation of the enantiomers of (a) 1-ferrocenylethanol and (b) 1-ferrocenylpropanol using an aqueous solution of α -cyclodextrin (0.05 M, carbonate buffer) as eluent. Column, 50 × 0.8 cm (i.d.).

carbonate buffer) as eluent. 1-Ferrocenylethanol was completely resolved by this column. The first eluted isomer was found to be the (S)-(+)-enantiomer, indicating that the (S)-(+)-isomer interacts more strongly with α -cyclodextrin than the (R)-(-)-isomer. Baseline separation was also accomplished for the optical resolution of 1-ferrocenylpropanol (Figure 1(b)). In this case, the (-)-isomer was eluted first, and followed by the (+)-isomer, contrary to the case of 1-ferrocenylethanol. This result indicates that the (-)-isomer interacts more strongly with



- (1) R = CH₃-
- (2) R = CH₃CH₂-
- (3) R = CH₃(CH₂)₂

α -cyclodextrin than the (+)-isomer. 1-Ferrocenylbutanol (**3**) was almost completely resolved under the same conditions. The (-)-isomer was eluted first, and then followed by the (+)-isomer in the same order as that of 1-ferrocenylpropanol. The specific rotation of the optically pure (S)-(+)-isomer of 1-ferrocenylethanol was $+36^\circ$ (589 nm) in benzene ($c = 0.01$ g/dl). This rotation value is higher than the value found in the literature [9].

Table I. Resolution of racemic ferrocene derivatives^a

Racemate	k_1^b	k_2^c	α^d	R_s^e
(1)	1.98 ^f	3.24	1.64	1.81
(2)	2.61	3.82	1.46	1.28
(3)	1.67	2.13	1.28	0.88

^a Conditions are shown in Figure 1.

^b Capacity factor for less retained enantiomer = (retention volume - void volume)/(void volume).

^c Capacity factor for more retained enantiomer.

^d Separation factor = k_2/k_1 .

^e Resolution factor = $2 \times$ (distance between the two peaks)/(sum of bandwidths of the two peaks).

^f Configuration of the enantiomer is S.

Table I summarizes the results of the resolution of racemic ferrocene derivatives. Optical isomers of 1-ferrocenylethanol and 1-ferrocenylpropanol were completely resolved under the conditions employed, that is, the resolution factors R_s were greater than unity. The separation factor, α , was 1.64, which corresponds to the resolution factor of 1.81 (the ratio $(V_A - V_0)/(V_B - V_0)$; V_A = retention volume of less mobile enantiomer, V_B = retention volume of more mobile enantiomer, and V_0 = dead volume).

The resolution factor increases with the decrease of the carbon number of the substituents. This indicates that the chiral discrimination is probably achieved through the inclusion complex formation with α -CD. We have already reported the isolation of the inclusion complexes of ferrocene derivatives with cyclodextrin [10].

The column used in this work can be used repeatedly. The theoretical plate number of this column, the separation factor, and the resolution factor did not change after continuous use for at least several months. This system seems to be useful for the resolution of many racemic compounds, particularly ferrocene derivatives, since it may be applied on a preparative scale. The enantiomers eluted are readily isolated by extraction with organic solvents and cyclodextrin can be easily recovered and used repeatedly.

References

1. V. A. Davankov, A. A. Kurganov, and A. S. Bochkov: *Adv. Chromatogr.* **22**, 71 (1983).
2. Y. Okamoto, S. Honda, I. Okamoto, H. Yuki, S. Murata, R. Noyori, and H. Takaya: *J. Am. Chem. Soc.* **103**, 6971 (1981);
Y. Okamoto, M. Kawashima, and K. Hatada: *J. Am. Chem. Soc.* **106**, 5357 (1984);
W. H. Pirkle, J. M. Finn, J. L. Schreiner, and B. C. Hamper: *J. Am. Chem. Soc.* **103**, 3964 (1981);
L. R. Sousa, G. D. Y. Sogah, D. H. Hoffman, and D. J. Cram: *J. Am. Chem. Soc.* **100**, 4569 (1978).
3. W. L. Hinze: *Sep. Purif. Methods* **10**, 159 (1981).
4. W. L. Hinze and D. W. Armstrong: *Anal. Lett.* **13**, 1093 (1980);
D. W. Armstrong: *J. Liq. Chromatogr.* **3**, 895 (1980).

5. F. Cramer and W. Dietsch: *Chem. Ber.* **92**, 378 (1959);
H. P. Benschop and G. R. J. Van den Berg: *J. Chem. Soc., Chem. Commun.* 1431 (1970);
M. Mikolajczyk, J. Drabowicz, and F. Cramer: *J. Chem. Soc., Chem. Commun.* 317 (1971);
M. Mikolajczyk and J. Drabowicz: *J. Am. Chem. Soc.* **100**, 2510 (1978).
6. A. Harada, M. Furue, and S. Nozakura: *J. Polym. Sci., Polym. Chem. Ed.* **16**, 189 (1978).
7. J. Debowski, D. Sybilska, and J. Jurczak: *J. Chromatogr.* **237**, 303 (1982);
J. Debowski, J. Jurczak, and D. Sybilska: *J. Chromatogr.* **282**, 83 (1983).
8. W. L. Hinze, T. E. Riehl, D. W. Armstrong, W. DeMond, A. Alak, and T. Ward: *Anal. Chem.* **57**, 237 (1985);
D. W. Armstrong, W. DeMond, and B. P. Czech: *Anal. Chem.* **57**, 481 (1985).
9. A. Ratajczak and B. Misterkiewicz: *J. Organomet. Chem.* **91**, 73 (1975).
10. A. Harada and S. Takahashi: *J. Chem. Soc., Chem. Commun.* 645 (1984).