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OPTICAL RESOLUTION OF FERROCENE DERIVATIVES BY LIQUID CHROMATOGRAPHY USING AQUEOUS CYCLOMALTOHEXAOSE AS THE MOBILE PHASE AND POLYAMIDE AS THE STATIONARY PHASE

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ABSTRACT

1-Ferrocenylethanol and its analogues were completely resolved into their enantiomers by liquid chromatography on a polyamide column using aqueous cyclomaltohexaose (α-cyclodextrin, αCD) as the mobile phase. The stability constants (K_c) for the inclusion complexes of αCD with each enantiomer of 1-ferrocenylethanol, determined by liquid chromatography with various concentrations of αCD, were 104M^{-1} for (*S*)-ferrocenylethanol and 79M^{-1} for the (*R*) isomer. The temperature dependence of the resolution has been studied.

INTRODUCTION

The optical resolution of racemates by liquid chromatography has been investigated extensively[1] and several useful systems have been reported[2]. In the field of host–guest chemistry, optical resolution using asymmetric cavities has attracted attention. Optically active crown ethers, for example, have been used for resolution of amino acid derivatives[3].

Cyclodextrins (CDs), which are cyclic (1→4)-linked α-D-gluco-oligosaccharides, form inclusion complexes with various organic compounds[4] and can induce stereospecific precipitation. Although CDs have been used for the fractional precipitation of racemates, only partial resolution has been attained[5]. This technique is not suitable for resolutions on a preparative scale because it is incomplete and laborious. In principle, such a preparative resolution could be carried out by liquid chromatography.

The first optical resolution by liquid chromatography was reported[6] using cross-linked CDs, and the resolution of racemic metallocenes using a chiral αCD-bonded stationary phase has been described[7]. The use of CD in the mobile phase and polyamide as the stationary phase in the t.l.c. of *ortho-*, *meta-*, and *para*-disubstituted benzenes has been reported[8]. Racemates have been resolved by using

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aqueous cyclomaltoheptaose (βCD) as the mobile phase[9], but αCD was much less effective.

During a study of the inclusion compounds of organotransition metal complexes with CDs, αCD was found to be effective for the optical resolution of 1-ferrocenylethanol by fractional precipitation. Previously, we reported the complete optical resolution of 1-ferrocenylethanol by liquid chromatography using aqueous αCD as the mobile phase and polyamide as the stationary phase[10]. We now report on the optical resolution of some ferrocene derivatives in detail and on the mechanism of the optical resolution of ferrocenylethanol. This system may be applied on a preparative scale and in physicochemical studies of the interaction of CDs with enantiomers.

EXPERIMENTAL

A glass column (50 × 0.8 cm) was packed with polyamide 6 (Baker, for t.l.c., 250–400 mesh) by the slurry technique. A medium-pressure liquid chromatography system was equipped with a u.v. detector. The column has 2,000 theoretical plates when aqueous αCD was used as eluent. The flow rate was 0.56 mL/min and 5–30 mg of racemic compounds were used.

Determination of stability constants. — The stability constants for the inclusion complex of a guest [G] with αCD were based on the literature[11]. The retention behavior of the G and its inclusion complex [G–CD] in a column can be depicted as follows.

$$\begin{tikzcd}
{[\mathrm{G}]_m} \arrow[d, shift left] & {+\ [\mathrm{CD}]_m} \arrow[r, shift left, "K_c"] & {[\mathrm{G{-}CD}]_m} \arrow[l, shift left] \arrow[d, shift left] & \text{mobile phase} \\
{[\mathrm{G}]_s} \arrow[u, shift left, "D_0"'] & & {[\mathrm{G{-}CD}]_s} \arrow[u, shift left, "D_c"'] & \text{stationary phase}
\end{tikzcd}$$

where D_0, D_c, and K_c are the concentration distribution of G, that of G–CD, and the stability constant of the 1:1 complex, respectively, as defined by the following equations.

$$D_0 = \frac{[\mathrm{G}]_s}{[\mathrm{G}]_m} = \frac{V_{RO} - V_0}{V_0} \cdot \frac{V_m}{V_s},$$

$$D_c = \frac{[\mathrm{G{-}CD}]_s}{[\mathrm{G{-}CD}]_m} = \frac{V_{RC} - V_0}{V_0} \cdot \frac{V_m}{V_s},$$

and

$$K_c = \frac{[\mathrm{G{-}CD}]_m}{[\mathrm{G}]_m[\mathrm{CD}]_m},$$

where s and m connote the stationary phase and mobile phase, respectively, V_m and V_s are the volumes of mobile phase and stationary phase, respectively, and V_0 is the dead volume.

The apparent concentration distribution ratio D_{obs} for this system can be expressed as follows,

$$D_{obs} = \frac{[G]_s + [G\text{–}CD]_s}{[G]_m\,[G\text{–}CD]_m} = \frac{D_0 + D_c K_c [CD]_m}{1 + K_c [CD]_m} = \frac{V_{Robs} - V_0}{V_0} \cdot \frac{V_m}{V_s},$$

According to the literature[11],

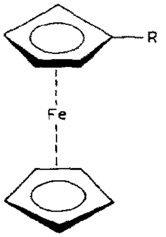
$$\frac{[CD]_m}{V_{non} - V_{obs}} = \frac{1}{V_{non} - V_{inc}}[CD]_m + \frac{1}{K_c[V_{non} - V_{inc}]},$$

where V_{non} and V_{inc} are the retention volumes of the guest and the complex, respectively. A plot of the left-hand term *versus* $[CD]_m$ gives both the K_c and V_{inc} values from the slope and intercept.

RESULTS AND DISCUSSION

Fig. 1. shows the chromatograms of the optical resolution of 1-ferrocenylethanol (**1**) and 1-ferrocenylpropanol (**2**), using 0.05M αCD (pH 11.4, carbonate buffer) as eluent. 1-Ferrocenylethanol was completely resolved by this column, and the (*S*)-(+) enantiomer interacted more strongly with αCD than the (*R*)-(−)-isomer. Base-line separation of 1-ferrocenylpropanol was achieved also (Fig. 1b), for which the (−)-isomer was eluted first. Thus, the (−)-isomer interacted more strongly with αCD than the (+)-isomer. 1-Ferrocenylbutanol (**3**) was almost completely resolved under the same conditions and the (−)-isomer was eluted first. The $[\alpha]_{589}$ values (*c*, 0.01) of (*S*)-(+)- and *R*-(−)-1-ferrocenylethanol were +36° and −34°, respectively. The value for the (*S*) isomer is higher than that reported[12].

Table I summarizes the results of the resolution of racemic ferrocene deriva-



1 R = —CH(OH)Me
2 R = —CH(OH)Et
3 R = —CH(OH)Pr

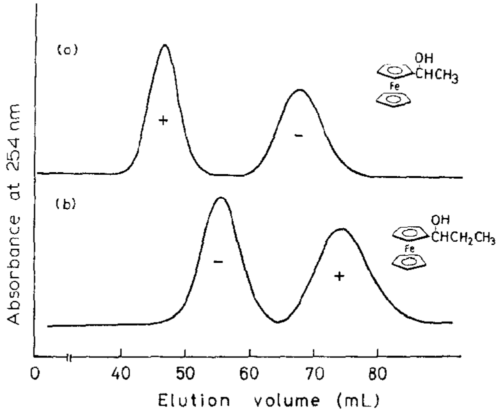


Fig. 1. Chromatograms of the optical resolution of (*a*) 1-ferrocenylethanol and (*b*) 1-ferrocenylpropanol, using 0.05M αCD (pH 11.4, carbonate buffer) as eluent, and a column (50 × 0.8 cm) of polyamide 6 (250–400 mesh) with a flow rate of 0.56 mL/min and a pressure of 20 p.s.i.

tives. Since racemic 1-ferrocenylpropanol was resolved completely under the conditions employed, the resolution factors (Rs) were >1. The separation factor (α) was 1.64 and Rs was 1.81.

The resolution factor increases with decrease in the number of carbons in the substituents, which indicates that the chiral discrimination probably involves the formation of inclusion complexes. Inclusion complexes of ferrocene derivatives with CDs have been isolated[13].

Fig. 2. shows the elution diagrams of 1-ferrocenylethanol as a function of the concentration of αCD. The retention volumes of 1-ferrocenylethanol decrease with increase in the concentration of αCD, indicating the formation of inclusion complexes. The resolution factor was optimized at 0.03–0.05M αCD. The plots of $[CD]_m \times 10^4/(V_{non} - V_{obs})$ *versus* [αCD] (Fig. 3) gave a straight line for each enantiomer, indicating that there is no adsorption of αCD on the polyamide stationary phase. The association constants were calculated from the slope and the intersect (see Experimental). The slopes for each enantiomer are almost the same, indicating

TABLE I

RESOLUTION OF RACEMIC FERROCENE DERIVATIVES[a]

Racemate	$k_1'^{b}$	$k_2'^{c}$	α^{d}	Rs^{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 Fig. 1. [b]Capacity factor for the less-retained enantiomer = (retention volume − void volume)/(void volume). [c]Capacity factor for the more-retained enantiomer. [d]Separation factor = k_2'/k_1'. [e]Resolution factor = 2 × (distance of the two peaks)/(sum of bandwidths of the two peaks). [f]Configuration of the enantiomer is *S*.

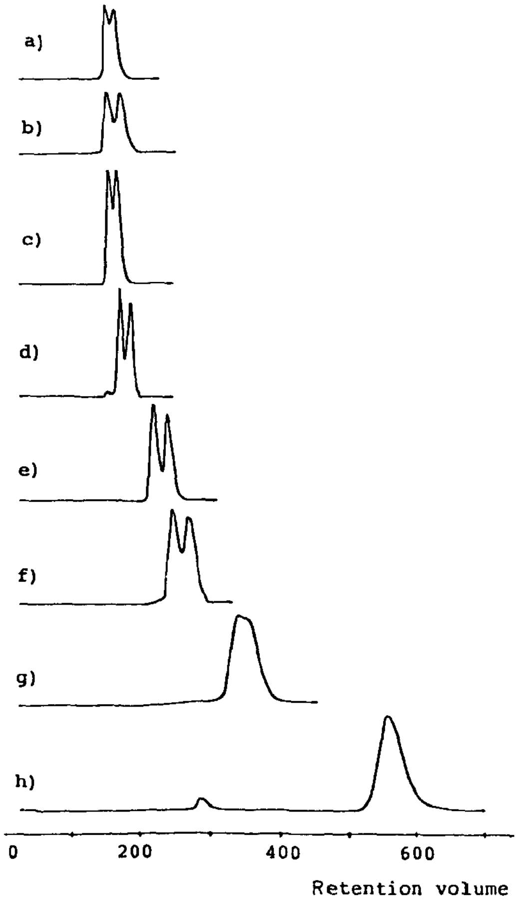


Fig. 2. Elution diagrams of 1-ferrocenylethanol as a function of the concentration of αCD: (*a*) 0.10M, (*b*) 0.09M, (*c*) 0.08M, (*d*) 0.05M, (*e*) 0.03M, (*f*) 0.02M, (*g*) 0.01M, (*h*) zero.

similar retention volumes. Therefore, the optical resolution might be achieved by the difference of the stability of the inclusion complexes. The values of K_c for (*S*)- and (*R*)-1-ferrocenylethanol were $104M^{-1}$ and $79M^{-1}$, respectively.

Fig. 4 shows the temperature dependence of K_c for the inclusion complex of 1-ferrocenylethanol with αCD. Plots of ln K_c *versus* 1/T gave straight lines for each enantiomer, indicating homogeneous binding over the range of temperature examined. Thermodynamic parameters for the inclusion are shown in Table II. The inclusion process of 1-ferrocenylethanol by αCD was associated with negative changes in entropy and enthalpy. These results accord with those[14] for a series of inclusion complexes with αCD. The change in entropy is more negative for the (*S*) than for the (*R*) isomer, indicating that the (*S*) isomer is bound more tightly to αCD. However, the change in enthalpy is more favorable for the (*S*) isomer. The

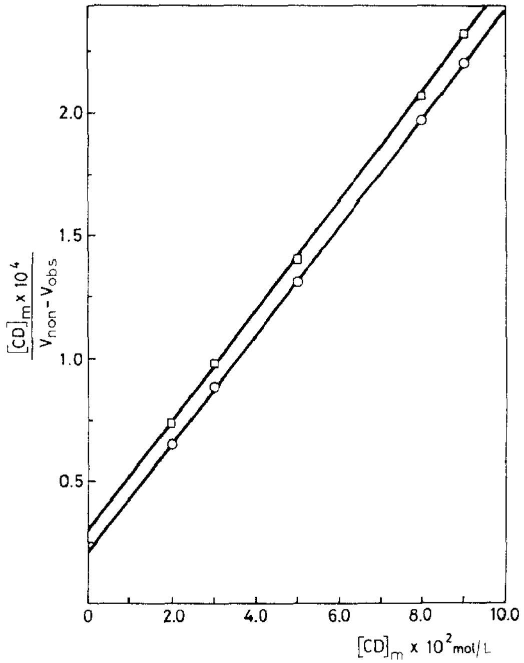


Fig. 3. Effects of concentration of αCD on $[CD]_m \times 10^4/(V_{non} - V_{obs})$ of 1-ferrocenylethanol.

contribution of a negative change in enthalpy is the driving force for the optical resolution of 1-ferrocenylethanol.

The column used in this work could be used repeatedly without change in characteristics and could be applied on a preparative scale. The enantiomers eluted could be isolated readily by extraction with organic solvents, and the αCD could be recovered easily and re-used repeatedly.

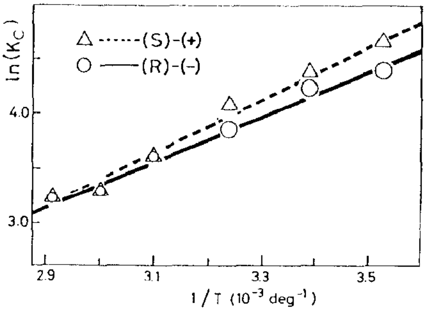


Fig. 4. Temperature dependence of K_c for the inclusion complex of 1-ferrocenylethanol with αCD.

TABLE II

THERMODYNAMIC PARAMETERS FOR THE FORMATION OF INCLUSION COMPLEXES

	ΔH *(kcal/mole)*	ΔS *(e.u.)*
(*S*) Isomer	−5.0	−8.2
(*R*) Isomer	−4.0	−5.5

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