Short Communication

Direct determination of enantiomeric excess of carbocyclic esters by chiral capillary gas chromatography

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ABSTRACT

Enantiomer separations of monocyclic and bicyclic esters (methyl and ethyl esters) were carried out directly by capillary gas chromatography (GC) using a chiral γ-cyclodextrin fused-silica capillary GC column. The direct determination of enantioselectivity of an asymmetric alkylation reaction was achieved. Larger enantiomer separations were found for the bicyclic esters ($\alpha = 1.038$–1.079) compared to the monocyclic esters ($\alpha = 1.013$–1.022). Molecular dimensions, derived from MM2 energy-minimized structures of a monocyclic ester and a bicyclic ester, correlate well with thermodynamic data and are consistent with more than one mechanism of enantio-differentiation.

INTRODUCTION

During the course of studies directed towards the enantioselective synthesis of bicyclic dienes, enantiomeric purity measurements of our reaction products were necessary. Chromatographic methods potentially offer both high precision and excellent reproducibility for enantiomeric purity determination, most commonly by derivatization to diastereomers and subsequent analysis on achiral chromatography columns or by the use of chiral chromatography columns [1–10]. O-Alkylated cyclodextrins have found use as chiral stationary phases in capillary gas chromatography (GC) for the enantiomeric separation of a wide variety of compounds [7–10] and offer

the possibility of reversing the order of enantiomer elution [11]. Herein, we report the first chromatographic enantiomeric separation and direct enantiomeric excess (ee) determination of diketoesters 1(S) and 1(R) (Figs. 1 and 2),
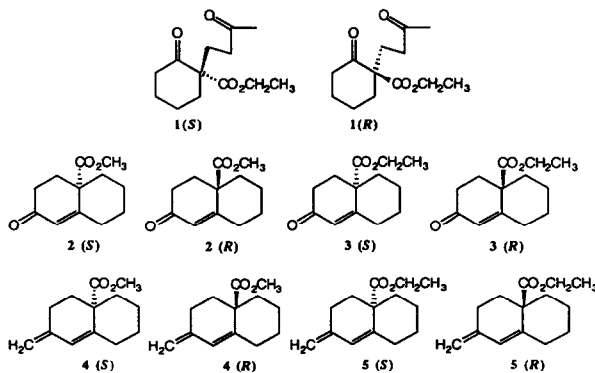

Fig. 1. Structures.

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Fig. 2. Enantiomer separation of diketoesters **1**(*S*) and **1**(*R*) on the FS-Lipodex E chiral phase capillary column (140°C); (a) predominantly (*R*)-enantiomer and (b) predominantly (*S*)-enantiomer.
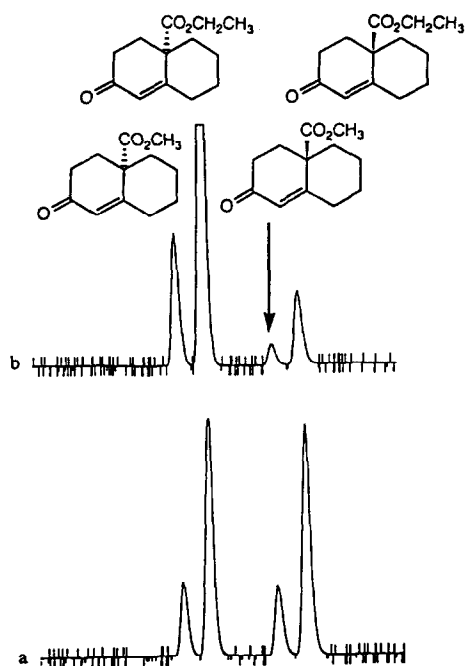

Fig. 3. Enantiomer separation of methylester enones **2**(*S*) and **2**(*R*) and ethylester enones **3**(*S*) and **3**(*R*) on the FS-Lipodex E chiral phase capillary column (150°C); (a) racemic mixture and (b) optically active mixture.

carbocyclic ester enones **2**(*S*), **2**(*R*), **3**(*S*) and **3**(*R*) (Fig. 3) and carbocyclic ester dienes **4**(*S*), **4**(*R*), **5**(*S*) and **5**(*R*) (Fig. 4)[a]. A brief discussion of enantio-differentiation of these compounds based on molecular size and thermodynamic parameters is presented.

EXPERIMENTAL

Racemic and optically active versions of compounds **1–5** were prepared from ethyl-2-cyclohexanone carboxylate, the details of which will be reported in a forthcoming publication. Chiral GC analyses were done with a Macherey-Nagel 50 m × 0.25 mm I.D. FS-Lipodex E fused-silica capillary column, a Hewlett-Packard 5890 instrument with flame ionization detector, and a Hewlett-Packard 3392A reporting integrator (helium column flow 51.7 ml/min, detector temperature 300°C, injector temperature 160°C, oven temperature 110–150°C).

RESULTS AND DISCUSSION

Quantitative separations of the carbocyclic esters were achieved on an octakis-(2,6-di-O-pentyl-3-O-butyl)-γ-cyclodextrin fused-silica capillary GC column (FS-Lipodex E) between 110 and 150°C (Table I, Figs. 2–4). Enantiomeric excesses of 72 and 71% ee were obtained for mixtures comprised predominantly of the (*S*)- and (*R*)-enantiomer, respectively. These values are similar to those reported previously for compounds **1** and **3**, in which an indirect method was utilized (polarimetry correlated with ^{13}C NMR) [12]. The chromatographic method employed here provides more precise results since, in all cases, complete resolution of enantiomers was achieved.

As evidenced in Table I, larger separation factors were obtained for the relatively compact bicyclic compounds **2–5** (Figs. 3 and 4), than the spatially more demanding monocyclic diketoester **1** (Fig. 2). The separation factor, *α*, is equal to the ratio of the retention times of the longer

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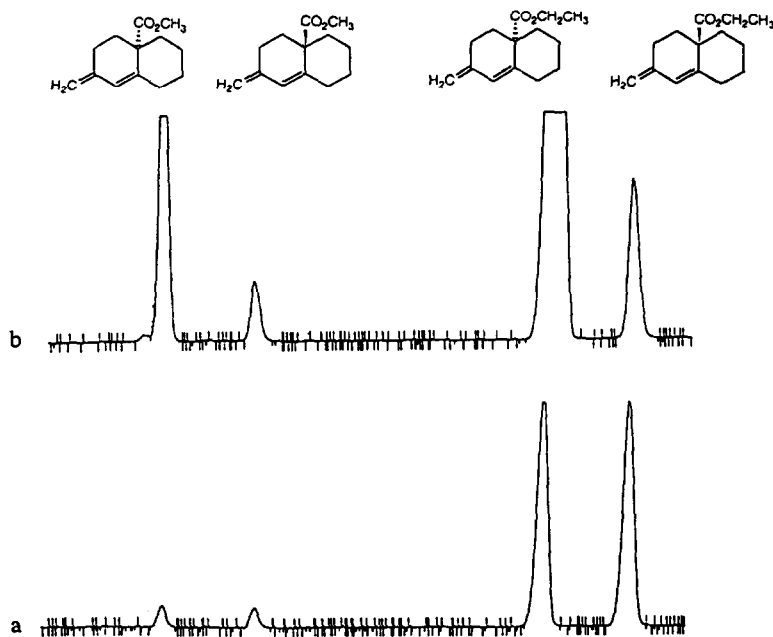[a] The asymmetric syntheses of these compounds will be reported by us elsewhere.

Fig. 4. Enantiomer separation of methylester dienes 4(S) and 4(R) and ethylester dienes 5(S) and 5(R) on the FS-Lipodex E chiral phase capillary column (110°C); (a) racemic mixture and (b) optically active mixture.

retained enantiomer (t_2) to the lesser retained enantiomer (t_1), i.e., $\alpha = t_2/t_1$. From the separation factor, the difference in free energy of association of an enantiomeric pair with the chiral stationary phase was estimated (Table II) [3]:

TABLE I

GAS CHROMATOGRAPHIC DATA FOR ENANTIOMERIC SEPARATION ON OCTAKIS-(2,6-DI-O-PENTYL-3-O-BUTYL)-γ-CYCLODEXTRIN FUSED-SILICA COLUMN (FS-LIPODEX E)

Compound[a]	T (°C)	α	Optical purity (% ee)
1(S)	140	1.013	72
1(R)	140	1.022	71
2(S)	150	1.079	72
3(S)	150	1.075	72
3(R)	150	1.074	71
4(S)	110	1.058	72
5(S)	110	1.038	72

[a] For optically active samples, tentative assignment of the absolute configuration of the predominant enantiomer is indicated.

$$-\Delta(\Delta G^0) = RT \ln \alpha$$

After obtaining chromatographic data at several temperatures, the following equation was used to afford a plot of $R \ln \alpha$ versus $1/T$ [7]:

$$R \ln \alpha = -\Delta(\Delta H^0)/T + \Delta(\Delta S^0)$$

From this plot, values of $\Delta(\Delta H^0)$ and $\Delta(\Delta S^0)$ were derived for the same enantiomeric pair (Table II). Straight-line plots were obtained in all cases, indicating that $\Delta(\Delta H^0)$ was constant

TABLE II

THERMODYNAMIC PARAMETERS DETERMINED BY CHIRAL CAPILLARY GC ON AN FS-LIPODEX E COLUMN

Compound	$-\Delta(\Delta G^0)$ (J/mol)	$-\Delta(\Delta H^0)$ (J/mol)	$-\Delta(\Delta S^0)$ (J/mol·K)
1	60 ± 21, 140°C	682	1.5
2	258 ± 7, 150°C	2731	5.8
3	248 ± 7, 150°C	3907	8.6

over the experimental temperature range. All three thermodynamic parameters, $\Delta(\Delta G^0)$, $\Delta(\Delta H^0)$ and $\Delta(\Delta S^0)$, were substantially larger for the more compact bicyclic esters relative to the monocyclic ester. The larger values of $\Delta(\Delta G^0)$ and $\Delta(\Delta H^0)$ are indicative of stronger enantioselective interactions for compounds 2 and 3, likely due, in part, to diffusion into the cyclodextrin cavity, as discussed below. A larger decrease in entropy is expected for cyclodextrin inclusion complex formation, possibly due to a decrease in degrees of freedom of the included molecule [7]. Larger negative values of $\Delta(\Delta S^0)$ were indeed obtained for bicyclic compounds 2 and 3 relative to monocyclic 1.

A preliminary assessment of the size and shape selectivities exhibited here can be made by comparison of the molecular dimensions of compounds 1 and 3, derived from the energy minimized structures calculated by the MM2 molecular mechanics program available in Chem 3D Plus (Cambridge Scientific Computing, Cambridge, MA, USA) with the reported cavity dimensions of underivatized γ-cyclodextrin (9.5 Å I.D. and 7.8 Å depth) [13][a]. The longest dimension of 3 was found to be 6.909 Å, small enough to fit into the cyclodextrin cavity. However, the 10.355 Å distance from the termini of the 2,2-substituents of 1 is large enough to be inhibited from diffusing fully into the cyclodextrin cavity.

The size/shape selectivity, based on molecular dimensions, parallels the thermodynamic parameters. These preliminary results support the possibility of more than one enantioselective retention mechanism, in accord with previously reported results [7]. The more compact molecules (2–5) may form a classic inclusion complex, while the more sterically demanding monocyclic enantiomers (1) may have limited interactions within the cavity but interact via weaker, external associations with the cyclodextrin.

Analysis of products from asymmetric alkylation reactions on an O-alkylated γ-cyclodextrin capillary GC column provides for fast, accurate, and reproducible determination of the enantioselectivity of the reaction. Thus, a level of accuracy hitherto unrealized for the enantiomeric purity evaluation of the aforementioned cyclic esters was realized. Further studies, directed towards optimizing asymmetric reactions, are expected to be expedited by employing this extremely versatile chiral chromatographic method.

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[a] It should be noted that the dimensions of the underivatized γ-cyclodextrin are used as an estimation only, due to lack of empirical data for the alkylated γ-cyclodextrin used in this study.