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Enantiomeric resolution of axially chiral compounds and interconvertible enantiomers by high-performance liquid chromatography

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Abstract

Racemic benzylidene cyclohexane derivatives and related compounds were successfully resolved into their enantiomers by HPLC using cellulose and amylose stationary phases. The effect of polar modifiers in the mobile phase on optical resolution on Chiralcel OD-H was studied. Hexane alone as the eluent provided excellent results in many cases; addition of small amounts of alcohols reduced the efficiency drastically. The influence of structural differences of interconvertible enantiomers on the chromatographic resolution was studied.

Keywords: Enantiomer separation; Chiral stationary phases, LC; Mobile phase composition; Benzylidene cyclohexane derivatives

1. Introduction

Chromatographic methods are particularly useful for checking the optical purity of compounds prepared by asymmetric synthesis. Owing to the development of a wide variety of chiral stationary phases, many of which are now commercially available, a large number of substrates of different structures and compositions have been made accessible for chiral analysis. Enantiomeric resolution of some benzylidene cyclohexane derivatives by gas chromatography has, for example, been achieved using an octakis(6-O-methyl-2,3-di-O-pentyl)-γ-cyclodextrin phase [1]; cellulose-based materials as stationary phases are more or less generally suitable for the enantiomeric resolution of a broad range of compounds by HPLC.

2. Experimental

The experiments were performed with a Model 1090 Series II liquid chromatograph, equipped with a diode-array detector (Hewlett-Packard) and a Chiralyser (IBZ Messtechnik, Hannover, Germany). Separations were carried out on Chiralcel OD-H, Chiralcel OB, Chiralcel OF and Chiralpak AD analytical columns (250 × 4.6 mm I.D.) (Daicel). Cellulose tribenzoate (10–

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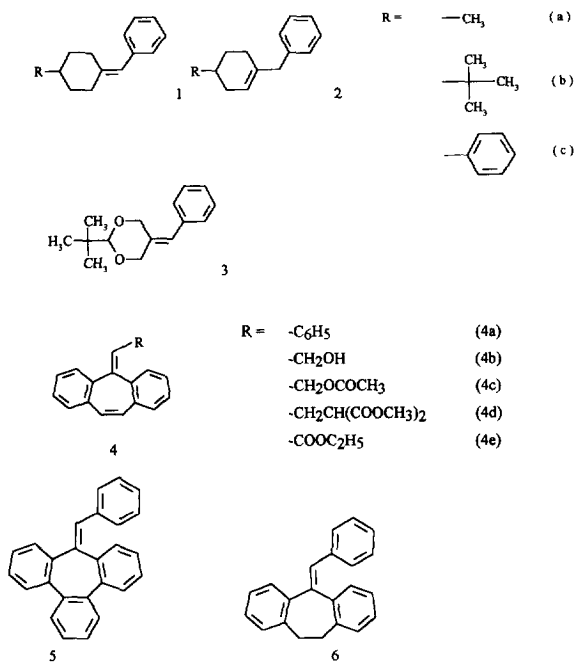


Fig. 1. Structures of the compounds studied.

20 μm) was purchased from Riedel-de Haën and packed into a stainless-steel column (250 × 8 mm I.D.) by the slurry technique in methanol. Hexane, *tert.*-butyl methyl ether and alcohols were purchased from Merck.

3. Results and discussion

Substrates **1a–c** and **3** with axial chirality and the isomers **2a** and **c** (see Fig. 1) with centres of asymmetry were subjected to chiral resolutions using several HPLC systems.

Compounds **1–3** have phenyl groups as substituents, but no polar functional groups by which asymmetric interactions may be effected. We therefore utilized chiral stationary phases (CSPs) whose effectiveness in many cases arises in part from interactions of the substrate with its carbamate or ester groups, but also from the chiral polymeric structure itself. Currently the chiral efficiencies of large number of cellulose and amylose derivatives, bound on silica gel, are under investigation by many groups; Okamoto and Kaida have collected the most important results in a recent review [2].

In addition to microcrystalline cellulose tribenzoate, we utilized several CSPs, as developed by Okamoto et al. [3], which contain cellulose and amylose derivatives bound on macroporous silica-gel, and compounds **1–3** as substrates.

Table 1 gives the capacity factors (k') of the first-eluted enantiomers, relative retentions α (k'_2/k'_1) and resolution factors R_S $\{1.18[t_2 - t_1 / w_{1/2(1)} + w_{1/2(2)}]\}$ for the CSPs of the Okamoto type with hexane as eluent; in the case of cellulose tribenzoate, methanol was used as the eluent.

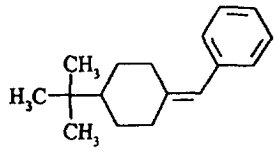
The axially chiral compounds **1a** and **c** are, with all CSPs, better resolved than **2a** and **c** having centres of asymmetry. All CSPs show enantioselectivity towards **1c** and **3**; only Chiralcel OF [cellulose tris(4-chlorophenylcarbamate)] is reluctant to separate the enantiomers of **1a** and only Chiralcel OD-H [cellulose tris(3,5-dimethylphenyl carbamate)] and cellulose tribenzoate were found to be suitable to separate **1b**. The heterocycle **3** is more polar than **1b** (which also has a *tert.*-butyl group as substituent), and hence more easily resolved by Chiralcel OB (cellulose tribenzoate on silica gel) and Chiralpak AD [amylose tris(3,5-dimethylphenyl carbamate)]; separation by means of Chiralcel OD-H works well with both substrates (Fig. 2).

Chiralcel OD-H, having electron-donating methyl groups on the phenyl substituents, is the best CSP to separate **1b** and **1c**; **1a** is most readily separated by Chiralcel OB. Chiralcel OF, having electron-withdrawing chlorine substituents on the phenyl groups, shows only a low efficiency towards **1c** and **3**; the other substrates remain unresolved.

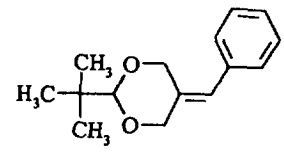
Microcrystalline cellulose tribenzoate is efficient towards almost all substrates. Compound **1a** is particularly well separated whereas with **1b** we observed no baseline separation. Heterocycle **3**, however, is readily separated, thus showing the effect of a more polar molecular structure. The retention time with this CSP, however, are very long in all cases.

Table 1
Chromatographic results

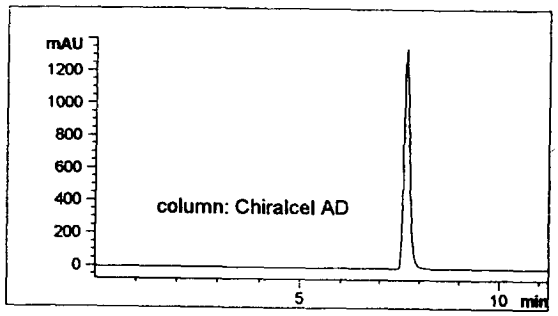
CSP	Mobile phase	**1a**			**1b**			**1c**			**2a**			**2c**			**3**		
		k'_1	α	E_S	k'_1	α	R_S	k'_1	α	R_S	k'_1	α	R_S	k'_1	α	R_S	k'_1	α	R_S
Chiralcel OD-H	Hexane	0.67	1.81	6.69	0.78	1.54	4.96	3.19	1.45	4.49	0.49	1.00	–	2.47	1.06	0.85	1.66	1.35	3.67
Chiralcel OB	Hexane	0.45	2.6	3.5	0.3	1.00	–	2.75	1.41	1.76	0.64	1.55	1.92	2.66	1.00	–	1.16	3.0	3.00
Chiralpak AD	Hexane	0.19	1.21	1.37	1.38	1.00	–	1.17	1.27	2.18	0.16	1.00	–	1.02	1.09	0.57	1.1	2.49	5.48
Chiralcel OF	Hexane	0.30	1.00	–	0.28	1.00	–	1.78	1.13	1.14	0.23	1.00	–	1.46	1.00	–	3.54	1.07	0.67
Cellulose tribenzoate	MeOH	0.79	2.63	9.0	1.08	1.17	1.04	2.83	1.16	1.45	1.48	1.38	1.64	2.83	1.16	1.22	0.86	2.91	6.32

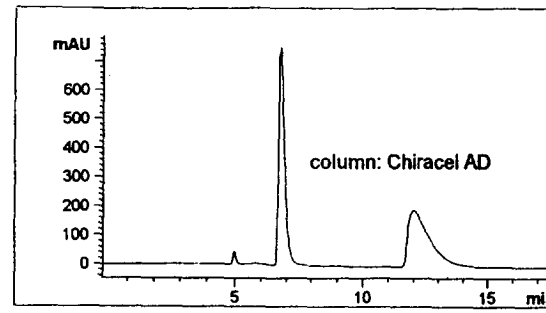


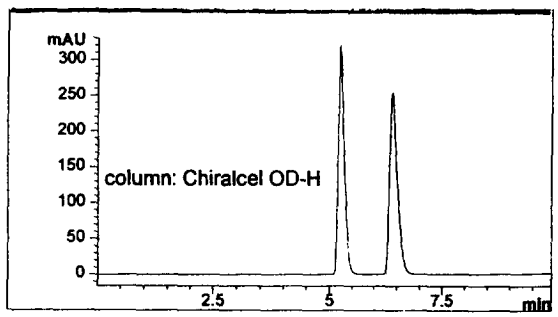
1b

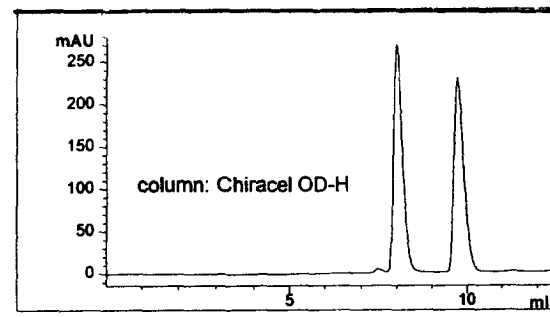


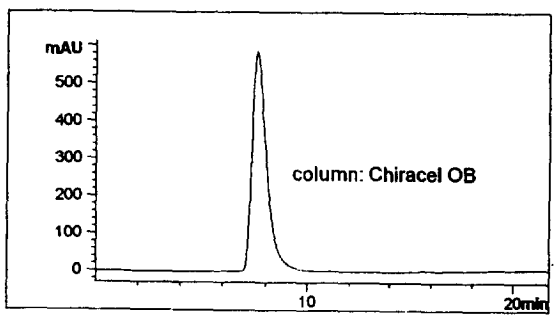
3











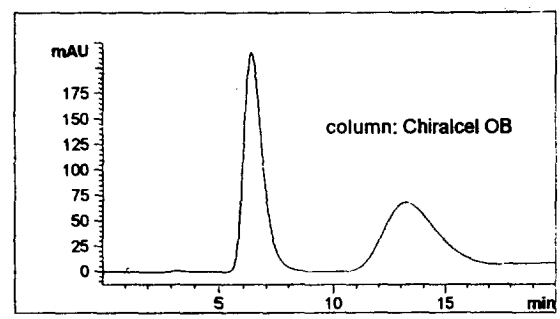


Fig. 2. Enantiomeric resolution of **1b** and **3** on different CSPs.

3.1. Effect of composition of the mobile phase on optical resolution on Chiralcel OD-H

In the case of Chiralcel OD-H, mixtures of hexane with smaller amounts of alcohols are usually applied as eluents. We studied the influence of the addition of different alcohols in various amounts to hexane on the retention times and chiral efficiencies. When separating a series of more than 35 substrates at Chiralcel OD, Dingenen [4] observed, on varying the concentrations of polar modifiers (i.e., alcohols) between 5 and 30%, a lowering of the k' values, but only small changes in the α-values. The values listed in Table 1 for Chiralcel OD-H refer to experiments with pure hexane as the eluent. The retention times may be shortened by addition of *tert.*-butyl methyl ether to hexane, an eluent which has been used, e.g., by Huffer and Schreier [5] for the enantiomeric separation of γ-lactones on a chiral polyacrylamide phase. As Fig. 3a shows, the α values for **1b** and **c** change only slightly and, in case of **1a**, become smaller.

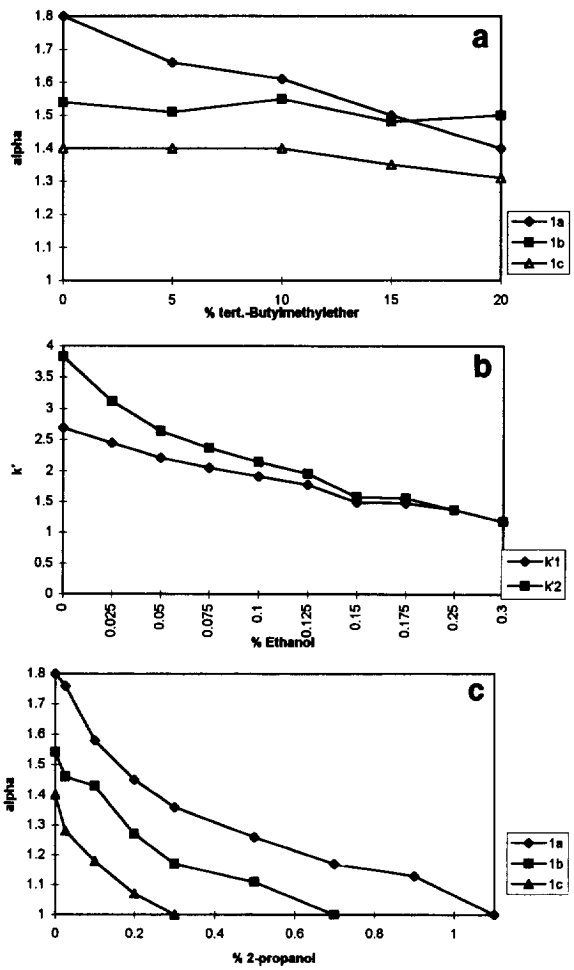


Fig. 3. (a) Influence of *tert.*-butyl methyl ether addition to hexane eluent on α-values (compounds **1a–c**). (b) Influence of ethanol addition to hexane–*tert.*-butyl methyl ether (98.5:1.5, v/v) eluent on k' values of **1c**. (c) Influence of 2-propanol addition to hexane eluent on α-values (compounds **1a–c**).

Addition of small amounts of ethanol to a hexane–tert.-butyl methyl ether (98.5:1.5, v/v) eluent causes (for compounds **1a–c**) the complete loss of enantioselectivity of the Chiralcel OD-H CSP. Fig. 3b shows the effect of very small amounts of ethanol on the k' values of **1c**. Likewise, even very small amounts of 1- or 2-propanol when added to hexane as the eluent cause a drastic decrease in enantioselectivity. As indicated in Fig. 3c, hexane–2-propanol (99:1, v/v) is completely ineffective for the separation of **1a–c**. This may be explained by the binding of the alcohols to the active centres of the CSP, thus preventing their interaction with the substrates.

3.2. Separation of thermally interconvertible enantiomers

Thermal enantiomeric interconversions of compounds have been studied by several groups. e.g., by Mannschreck [6] and Cuyegkeng and Mannschreck [7] by HPLC and Jung and Schurig [8] and König et al. [9] by gas chromatography. We investigated compounds **4** by HPLC on Chiralcel OD-H at temperatures from −30 to +60°C. All species of type **4** (see Fig. 1) show the typical chromatographic behavior of compounds with thermal interconversion (Fig. 4).

If R remains unchanged, and the seven-membered ring of **4a** is benzo-annellated with a further benzene ring as in **5**, an enhanced stability of the enantiomers results and below 60°C no interconversion could be observed. If, instead, the double bond of the seven-membered ring of **4a** is changed to a single bond as in **6**, a lowering of the barrier of interconversion is observed, i.e.,

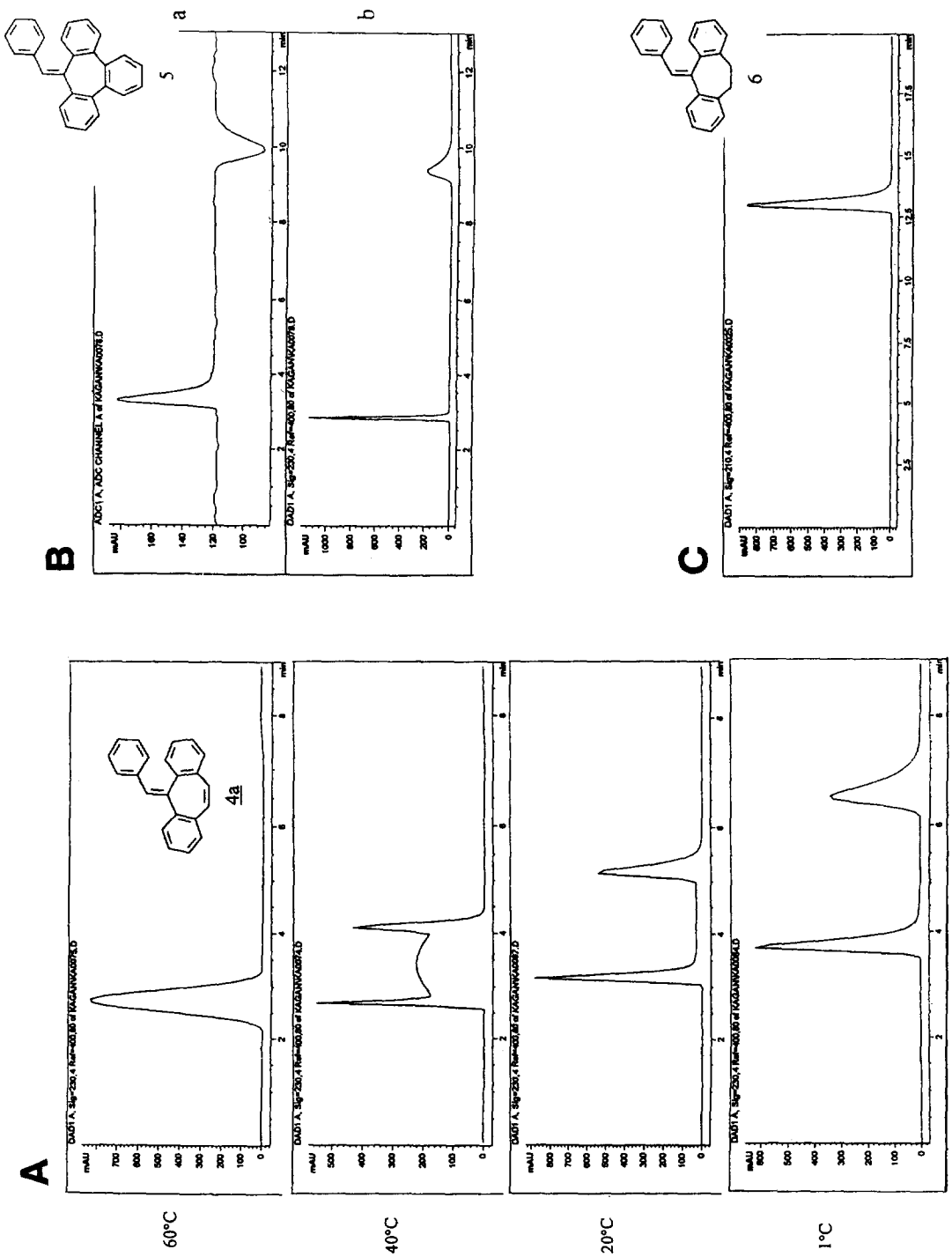


Fig. 4. (A) Separation and enantiomerization of **4a** as a function of temperature: column, Chiralcel OD-H; eluent, *n*-hexane–*tert.*-butyl methyl ether (9:1, v/v); flow-rate, 2 ml/min. (B) Separation of **5**: column, Chiralcel OD-H (15 cm × 4.6 mm I.D.); eluent, *n*-hexane–*tert.*-butyl methyl ether (1:1, v/v); temperature 60°C; flow-rate, 1 ml/min; (a) detector Chiralyser; (b) UV detection. (C) Separation of **6**: column, Chiralcel OD-H (25 cm × 4.6 mm I.D.); eluent, *n*-hexane–*tert.*-butyl methyl ether (98,5:1.5, v/v); temperature −30°C; flow-rate, 1 ml/min.

even at −30°C the chromatographic curve consists of only one peak (Fig. 4).

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