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Journal of Chromatography A, 865 (1999) 201–210

JOURNAL OF CHROMATOGRAPHY A

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Enantiomer separation of α-ionone using gas chromatography with cyclodextrin derivatives as chiral stationary phases

Francesca Quattrini[a], Giovanni Biressi[a], Markus Juza[a], Marco Mazzotti[b], Claudio Fuganti[c], Massimo Morbidelli[a,*]

[a]*Laboratorium für Technische Chemie, ETH Zürich, Universitätstrasse 6, CH-8092 Zürich, Switzerland*
[b]*Institut für Verfahrenstechnik, ETH Zürich, Sonneggstrasse 3, CH-8092 Zürich, Switzerland*
[c]*Centro CNR per la Chimica delle Sostanze Organiche Naturali, Dipartimento di Chimica, Politecnico di Milano, Via Mancinelli 7, I-20131 Milan, Italy*

Abstract

The gas chromatographic enantiomer separation of α-ionone was studied with three different chiral stationary phases using as chiral selectors: (1) heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin, dissolved in polysiloxane PS-086, (2) octakis(2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin and (3) octakis(2,6-di-*O*-pentyl-3-*O*-butanoyl)-γ-cyclodextrin, both dissolved in polysiloxane SE-54. The influence of the concentration of the chiral selector in the polysiloxane, coated on Chromosorb P AW-DMCS 80–100 mesh, is described and discussed, as well as the effect of Chromosorb loading. The feasibility of the preparative gas chromatographic separation of the enantiomers of α-ionone is considered; in order to provide a term of comparison, the estimated performances are compared with those achieved in the separation of the enantiomers of the inhalation anaesthetic enflurane.

Keywords: Enantiomer separation; Chiral stationary phases, GC; Preparative chromatography; Ionones; Cyclodextrin

1. Introduction

Gas chromatography (GC) on chiral stationary phases (CSPs) is nowadays an essential tool for the determination of the enantiomeric purity in connection with organic synthesis and biological studies. Although chiral separation factors, α, are often low, a quantitative resolution is frequently achieved due to the large number of theoretical plates available in capillary GC. In particular, the gas chromatographic discrimination of enantiomers on alkylated/acylated cyclodextrins diluted in polysiloxanes is very well established [1–3].

In the last few years the chromatographic resolution of racemates has been developed also at the preparative scale, thus providing an important alternative for access to pure enantiomers.

In this context we have studied the separation of the enantiomers of α-ionone [1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one] (cf. Fig. 1), a C_{13}-cyclic norterpenoid ketone which is a key component in perfumery and in flavour and fragrance technology [4]. Its (+)-enantiomer, which was assigned the (*R*)

*Corresponding author. Tel.: +41-1-6323-034; fax: +41-1-6321-082.
E-mail addresses: mazzotti@ivuk.mavt.ethz.ch (M. Mazzotti), fuganti@dept.chem.polimi.it (C. Fuganti), morbidelli@tech.chem.ethz.ch (M. Morbidelli)

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PII: S0021-9673(99)00998-X

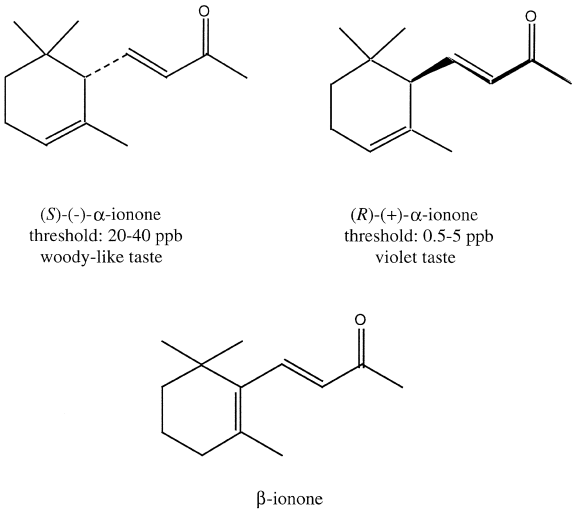

Fig. 1. Structures of α-ionone enantiomers and their isomer, β-ionone.

absolute configuration through correlation with manool [5], has been detected as a natural constituent of raspberries [6], black tea [7], violet flowers [8] and carrots [9]. Racemic α-ionone has an interesting strong sweet-floral odour, reminiscent of violets. Its synthesis is performed industrially by rearrangement of pseudoionone under acidic conditions; this reaction always yields some amounts of the isomeric β-ionone (cf. Fig. 1) [10,11].

Since (*S*)-(−)-α-ionone and (*R*)-(+)-α-ionone possess different olfactory properties [12] their synthesis has attracted considerable attention. The pure enantiomers have been used or proposed as building blocks for the synthesis of carotenes [13] and drimanes [14].

The first historically important separation of the enantiomers of α-ionone, described 40 years ago [15,16], is based on the fractional crystallisation of the menthylhydrazones of the racemic ketone. Recently a multistep synthesis of the enantiomers with 48% yield via enone transposition from (*R*)- and (*S*)-damascone was reported [17]. Despite its elegance, this method requires a quite precious starting material such as α-damascone and several steps with delicate reaction conditions. Even more laborious is the synthesis leading from (*S*)-(−)-4-hydroxy-2,6,6-trimethylcyclohex-2-enone to (*R*)-(+)-α-ionone, with 85% of enantiomeric excess (e.e.) [18].

Two new ways to access enantiomerically pure (*S*)- and (*R*)-α-ionone using enzymatic reactions have been described recently. The first one is based on the preparation of enantiomerically pure diastereoisomers of α-ionol via lipase-mediated selective acetylation of the racemic mixture, followed by MnO_2 oxidation [19]. The second one exploits the lipase-mediated esterification of *cis*-4,5-epoxy-α-ionol, obtained by epoxidation of racemic α-ionol, followed by oxidation of the corresponding enantiomerically pure epoxy-α-ionol and cleavage of the epoxy group under mild conditions [20]. Both these methods lead to e.e.>99% for the two enantiomers starting from rather inexpensive materials and require simple reaction conditions, thus they actually represent the easiest access to the pure enantiomers. However, up-scaling these methods is not straightforward, due to the high number of reaction steps. An effective chromatographic enantiomer separation of racemic α-ionone at the preparative scale would overcome these limitations.

The analytical gas chromatographic separation of racemic α-ionone using various cyclodextrin derivatives is well documented [21–25]. In this work the feasibility of the scale up to a preparative separation is investigated, by first finding a suitable chiral stationary phase and then evaluating its performance in a preparative process. For this aim, a comparison has been made between the performance of the GC separation of α-ionone and the one of the anaesthetic enflurane, whose enantiomers have been separated on a preparative scale using two different cyclodextrin derivatives as chiral selectors [26,27].

2. Experimental

2.1. Analytical equipment

Six different glass columns were used (see Table 1). Columns 3 and 6 were installed in a HP-6890 gas chromatograph (Hewlett-Packard, Wilmington, DE, USA). The other columns were installed in a Fractovap C gas chromatograph (Carlo Erba, Milan, Italy). Nitrogen was always used as carrier gas.

2.2. Materials

Racemic α-ionone (purity 90–95%) and β-cyclodextrin (purity 99%) were obtained from Fluka

Table 1
Composition of stationary phases tested for the gas chromatographic enantiomer separation of α-ionone[a]

Column	Chiral selector	Loading (%, w/w)	CSP (g)	CD in PS (%)	ϵ^*	V (ml)
1	B	23	11.2	10	0.90	23.7
2	B	19	9.9	20	0.89	21.1
3	B	19	13.5	50	0.87	27.6
4	GF	19	11.4	10	0.75	23.7
5	GF	20	11.3	20	0.72	23.7
6	GB	17	13.8	20	0.86	27.9

[a] B is heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin; GF is octakis(2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin; GB is octakis(3-*O*-butanoyl-2,6-di-*O*-pentyl)-γ-cyclodextrin. CD and PS are, respectively, the cyclodextrin and the corresponding polysiloxane. % Loading is the percentage of solution CD–PS coated on Chromosorb.

(Buchs, Switzerland). γ-Cyclodextrin (purity 98%) was a courtesy from Wacker Chemie (Munich, Germany).

The following polysiloxanes were used: PS-086 (85–88%)-dimethyl-(15–12%)-diphenylsiloxane copolymer, silanol terminated (ABCR, Karlsruhe, Germany), SE-54 dimethyl-methylphenyl-vinylmethyl-copolymer, methoxyterminated (Supelco, Bellefonte, PA, USA).

Chromosorb P AW-DMCS, 80–100 mesh, was obtained from Macherey–Nagel (Düren, Germany).

2.3. Synthesis of cyclodextrin derivatives

A 20-g amount of heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (type B in Table 1) was synthesised according to Ref. [28].

Octakis(2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin, (type GF in Table 1) was synthesised according to the procedure described by Li et al. [29] except that the acylation was accomplished in a mixture of trifluoroacetic anhydride and chloroform by refluxing the reaction at 50°C as proposed in Ref. [30]. After hot filtration to remove unreacted sodium trifluoroacetate the unpurified crude product was filtered over a small amount of silica-gel and dried at 60°C and 0.016 Torr for 16 h (1 Torr=133.322 Pa).

Octakis(3-*O*-butanoyl-2,6-di-*O*-pentyl)-γ-cyclodextrin (type GB in Table 1) was synthesised as reported in Ref. [31].

All synthesised cyclodextrin derivatives were identified by thin-layer chromatography (TLC), ^{1}H-, ^{13}C- and ^{19}F-nuclear magnetic resonance (NMR) spectroscopy and by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS).

2.4. Preparation of the packing

The polysiloxane and the relevant cyclodextrin derivative were dissolved in dry chloroform using an ultrasonic bath. Chromosorb P, AW-DMCS, 80–100 mesh, was poured into the mixture. The slurry was manually agitated until it became homogeneous. The solvent was evaporated using a rotavapor at 30°C under moderate vacuum.

All the stationary phases were prepared analogously, using the amounts and ratios of chiral selectors and polysiloxanes reported in Table 1. The percentage of solution cyclodextrin–polysiloxane coated on Chromosorb was in all cases about 20%, which leads to the optimal loading, as reported in Ref. [30].

2.5. Preparation of the packed columns

Before the columns were filled, the packing was sieved (mesh 100) to exclude lumps and to ensure a homogeneous flow through the column. Six glass columns were packed under moderate vacuum. Afterwards an ultrasonic bath was applied to achieve a dense, homogeneous bed.

3. Results

3.1. Analytical chromatography

The analytical GC separation of α-ionone enantio-

mers can be performed with several cyclodextrin derivatives [21,24,25], however only heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin [22] and octakis(2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin [23] have been reported to show high selectivities. Therefore, these two cyclodextrins have been selected for our investigation, together with octakis(3-*O*-butanoyl-2,6-di-*O*-pentyl)-γ-cyclodextrin, which has already been employed in our laboratory for the GC simulated moving bed (SMB) separation of the enantiomers of the volatile anaesthetic enflurane [31].

The first cyclodextrin derivative considered, i.e., heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin, is a colourless crystalline compound with a high melting point. Recently Fuchs and Perrut tried to employ heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin as a chiral selector (10%, w/w, coated directly on Chromosorb P NAW) for the gas chromatographic preparative enantiomer separation of 1-octenyl-3-acetate, however they were unable to obtain either baseline separation or pure enantiomers (e.e.<60%) [32]. A more flexible approach was demonstrated by Schurig and Novotny, who successfully dissolved permethylated β-cyclodextrin in the moderately polar polysiloxane OV-1701 in order to increase the range of operating temperatures for analytical and preparative applications and to achieve better peak shapes and higher coating efficiencies [1,2]. Following this approach, we coated Chromosorb P (AW-DMCS) particles (size 80–100 mesh) with various concentrations of heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin dissolved in a polysiloxane matrix. To overcome the problem of the limited solubility of permethylated β-cyclodextrin in OV-1701 we used as an alternative the relatively apolar polysiloxane PS-086, as proposed by Bicchi et al. [33]. Solubility tests showed that up to 50% of permethylated β-cyclodextrin could be dissolved without precipitation in the polysiloxane PS-086.

The second chiral selector, i.e., octakis(2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin, is a slightly coloured relatively polar compound that is often obtained as a mixture of homologues and isomers [30]. The gas chromatographic properties of this cyclodextrin derivative coated in capillary columns were investigated for more than 120 racemates [29]. In spite of the high enantioselectivity reported for the analytic separation of α-ionone, this cyclodextrin derivative has a tendency to hydrolyse in contact with moisture or during chromatographic purification in contact with silica gel; moreover, at more than 180°C an irreversible decrease in enantioselectivity is observed.

Octakis(2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin readily dissolves in the moderately polar polysiloxane SE-54, and so does also the last chiral selector considered, i.e., octakis(3-*O*-butanoyl-2,6-di-*O*-pentyl)-γ-cyclodextrin, which exhibits an analogous substitution pattern and a comparable enantioselectivity for a broad range of racemates [34]. The butanoyl moiety of the latter cyclodextrin is more stable to hydrolysis than the trifluoroacetyl group. Octakis(3-*O*-butanoyl-2,6-di-*O*-pentyl)-γ-cyclodextrin is also more stable to high temperature.

In order to investigate the effect of the chiral selector concentration on the separation performance a series of semi-preparative glass columns were packed containing various concentrations of the chiral selectors dissolved in different polysiloxanes (cf. Table 1).

The efficiency of the columns, in terms of height equivalent to a theoretical plate (HETP) was determined at different flow-rates, and all further injections were performed at a flow-rate near to the Van Deemter minimum. The overall void fraction ϵ^* reported in Table 1 was obtained from the retention time t_0 of a non-retained species (methane), using the following equation:

$$t_0 = \frac{V\epsilon^*}{Q_o J} \tag{1}$$

where V is the volume of the column, Q_o is the outlet volumetric flow-rate and J is the James and Martin factor, which corrects the flow-rate so as to account for the pressure drop variation along the column and is defined as:

$$J = \frac{3}{2} \cdot \frac{\left(\frac{P_i}{P_o}\right)^2 - 1}{\left(\frac{P_i}{P_o}\right)^3 - 1} \tag{2}$$

where P_i and P_o are the inlet and outlet pressures, respectively.

A volume of 1 μl of a 50% (v/v) solution of

α-ionone in diethyl ether (corresponding to 0.46 μg of α-ionone, close to the minimum detectable amount) was injected at 120, 130 and 140°C in order to study the effect of temperature on selectivity. From the observed retention times of the two enantiomers of α-ionone the Henry constants H_i were calculated using the following equation:

$$t_{R,i} = t_0\left(1 + \frac{1-\epsilon^*}{\epsilon^*}\cdot H_i\right) \quad (3)$$

For columns 3, 5 and 6, where separation has been achieved, the operating temperatures and the retention times of the three species are reported in Table 2, together with the calculated Henry constants and selectivity factors. In the Table indices 1 and 2 refer to (*S*)-(−)-α-ionone and (*R*)-(+)-α-ionone, respectively, whereas index 3 indicates β-ionone; accordingly $\alpha_{21} = H_2/H_1$ represents the measured enantioselectivitiy, whereas $\alpha_{32} = H_3/H_2$ represents the selectivity of β-ionone with respect to the more retained α-ionone enantiomer, i.e., (*R*)-(+)-α-ionone.

In all tests performed with the first two columns, where the concentration of cyclodextrin in polysiloxane was 10% and 20% (w/w), only one, very broad peak was observed. This is contradictory to what reported by Lindström [22], who achieved a separation on CSPs made of 20% solution of heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin in polydimethylsiloxane in an analytical capillary column. This might be due to different interaction of the analyte with the different polysiloxanes used in the two studies and to the lower column efficiency in the case of packed columns with respect to capillary GC.

Column 3 (concentration of cyclodextrin in polysiloxane: 50%, w/w) allowed the separation of the two enantiomers and β-ionone as reported in Table 2. However the performance of this stationary phase is not satisfactory, due to very high retention times and the low enantioselectivity, which is not higher than 1.1 at all temperatures. The long retention times can be explained with reference to the retention mechanism, which involves two steps, a non-selective vapour–liquid equilibrium and an enantioselective interaction with the cyclodextrin in the liquid phase: α-ionone is an apolar high boiling oil (T_b = 132°C) and therefore strongly interacts with the polysiloxane liquid film. The results obtained with a newly synthesised heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin and a newly coated stationary phase were very similar.

In the case of octakis(2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin (columns 4 and 5 in Table 1), going from 10% to 20% loading allows to achieve a rather good separation factor, actually the best one observed in this study, i.e., $\alpha_{21} = 1.37$ at $T = 120$°C (see Table 2). Unfortunately this cyclodextrin appeared to be highly unstable. The same stationary phase, tested eight months later, did not reproduce the same performance: the selectivity at 120°C was reduced to a value of 1.02. A new

Table 2
Experimental determination of the Henry constants for the columns 3, 4, 5[a]

Column	T (°C)	t_0 (min)	t_{R1} (min)	t_{R2} (min)	t_{R3} (min)	H_1	H_2	H_3	α_{21}	α_{32}
3	140	0.38	61.3	64.5	98.4	1060	1110	1700	1.05	1.53
3	130	0.39	99.6	107.4	168.1	1720	1850	2900	1.08	1.57
3	120	0.42	170	187.9	302.6	2730	3020	4870	1.11	1.61
5	140	0.45	62.4	80.4	156.4	354	456	890	1.19	1.95
5	130	0.45	73.6	97.5	194.6	419	556	1110	1.33	2.00
5	120	0.45	82.4	112.4	229.4	468	640	1310	1.37	2.05
6	100	0.49	42.8	46.6	61.7	536	584	775	1.09	1.33
6	90	0.50	58.2	64.2	87.4	711	785	1070	1.10	1.36
6	75	0.52	78.4	88.6	122.6	920	1040	1440	1.13	1.39

[a] H_1, H_2, H_3 are the Henry constants of (*S*)-(+)-α-ionone, (*R*)-(−)-α-ionone and β-ionone, respectively. α_{21} is the selectivity for the separation of the enantiomers. α_{32} is the selectivity for the separation of the more retained enantiomer, (*R*)-(−)-α-ionone, and β-ionone.

^{19}F-NMR analysis of the cyclodextrin revealed that the trifluoroacetyl group was hydrolysed. Hence, we have not attempted higher concentrations of this cyclodextrin derivative in the polysiloxane.

Octakis(3-*O*-butanoyl-2,6-di-*O*-pentyl)-γ-cyclodextrin, showed optimum performance for other separations when dissolved in SE-54 even at a concentration as low as 20% [31]. Based on this we tested only one column, adopting this optimal composition of the CSP (cf. Table 2, column 6). With this stationary phase we were able to separate the enantiomers of α-ionone with intermediate selectivity and reasonable retention times even at a lower temperature, namely $\alpha_{21}=1.13$ with retention times of the two enantiomers of about 80 min at $T=75$°C.

Thus, also due to its higher stability, this cyclodextrin appears to be the best chiral selector for the separation of the α-ionone enantiomers.

The β-isomer of ionone, which is always found as an impurity in synthetic racemic α-ionone (ranging from 4% to 15%), was eluted as third peak from all tested columns.

3.2. Preparative chromatography

In view of the potential use of this chromatographic method for preparative purposes it is important to identify the optimal operating temperature. In all cases enantioselectivity is increased when the separation is performed at lower temperatures. This behaviour implies that lower temperatures will allow for larger injected amounts to be separated; however, the retention times of the analytes will also increase, thus leading to a low throughput of injected material per day. Thus a compromise has to be found.

In all cases the temperature dependence of the selectivity was interpolated through linear regression, according to the Van 't Hoff equation, as illustrated in Fig. 2. This allows us to predict the value of selectivity at different temperatures. At 75°C a good compromise seems to be reached for column 6, since, as it can be seen in Fig. 2, the predicted increase of selectivity at lower temperatures is small.

Under these operating conditions (i.e., using a flow-rate corresponding to the Van Deemter optimum at 75°C) various injections of α-ionone were made in order to determine the maximum amount that can be baseline separated in our semipreparative column. As can be seen in Fig. 3, under these conditions up to 0.3 mg of α-ionone could be baseline separated, with a time span of 42 min between the breakthrough of the first eluted α-ionone enantiomer and the tail of

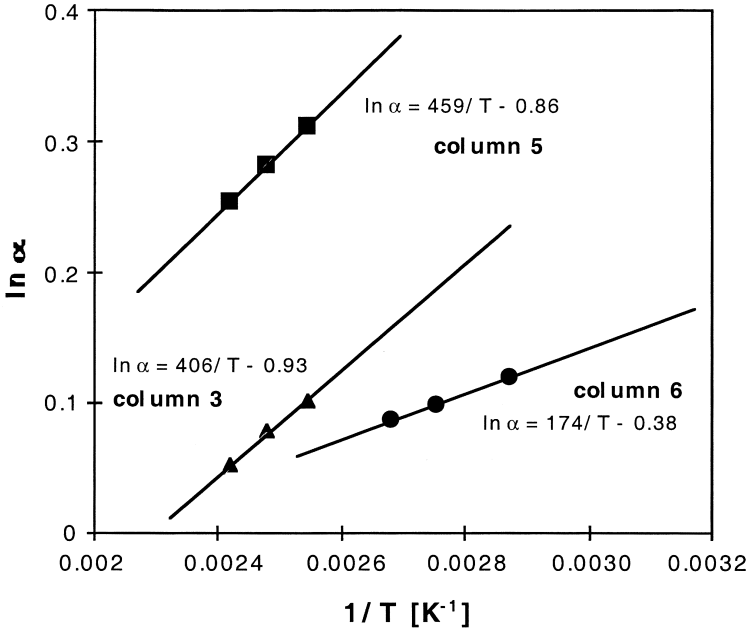

Fig. 2. Van 't Hoff plots of enantioselectivity vs. temperature for columns 3, 5 and 6 in Table 1.

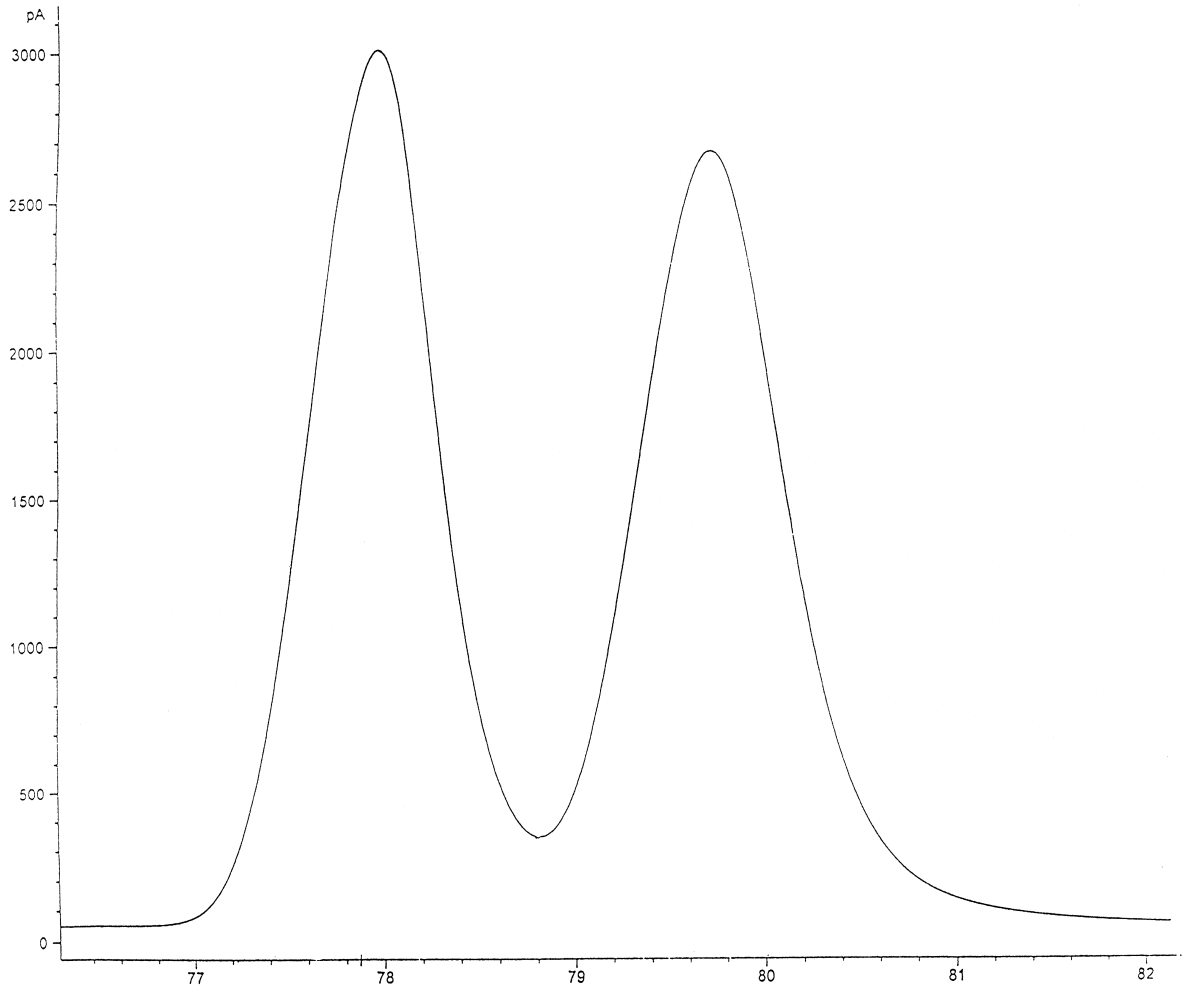

Fig. 3. Semipreparative GC separation of α-ionone enantiomers. Column: 0.2 m×4 mm I.D. filled with Chromosorb P AW-DMCS, coated with 17% of the solution 20% octakis(3-*O*-butanoyl 2,6-di-*O*-pentyl)-γ-cyclodextrin in the polysiloxane SE-54; carrier gas: nitrogen; 75°C, 90 ml/min; injected amount: 0.3 mg. The retention times corresponding to the maximum of the peaks of the two enantiomers are, respectively, 77.8 min and 79.9 min. The peak of β-ionone is not shown. Time scale in min.

β-ionone. The separated amount corresponds to a specific CSP utilisation of 93 ml/mg. This parameter is defined as the ratio between the volume of CSP employed and the maximum amount which can be baseline separated.

For the sake of comparison, increasing amounts of racemic enflurane were also injected in column 6 at the Van Deemter optimum at 26°C, which is a good operating temperature for the preparative batch chromatography of this racemate. Under these conditions it is possible to separate up to 3.0 mg of enflurane, with a lag of 30 min between the breakthrough of the first peak and the tail of the second peak, as can be observed in Fig. 4. The resulting specific CSP utilisation is 9 ml/mg, as can be seen in Table 3. This result is consistent with what reported in [35], where 1.5 mg of enflurane could be baseline separated in a 16 ml packed column containing a CSP of analogous composition, leading to a specific CSP utilisation of 10.5 ml/mg. In the same work the effect of the CSP composition on the selectivity and the loading capacity was investigated, showing that increasing the percentage of octakis(3-*O*-butanoyl-2,6-di-*O*-pentyl)-γ-cyclodextrin dissolved in SE-54,

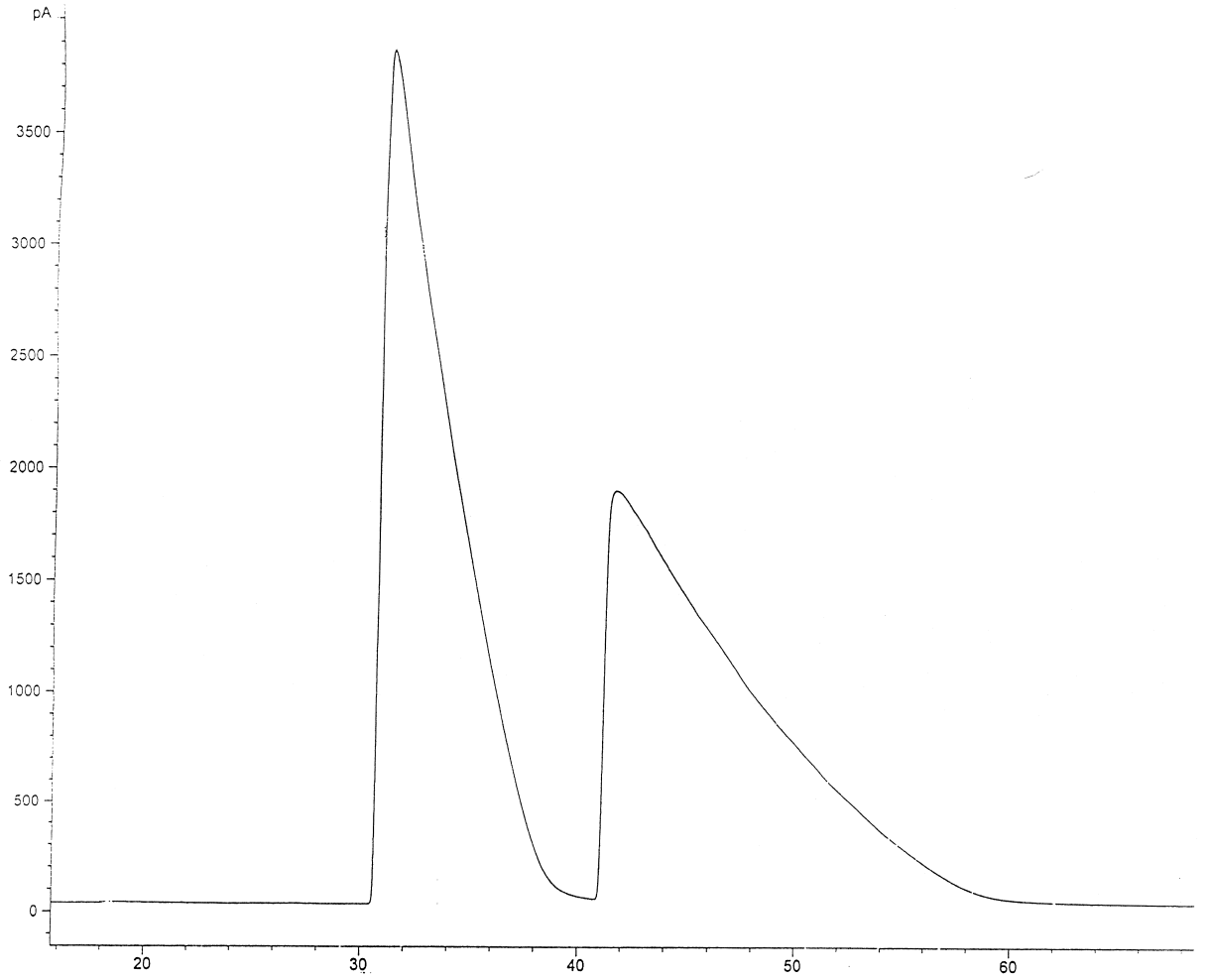

Fig. 4. Semipreparative GC separation of enflurane enantiomers. Column: 0.2 m×4 mm I.D. filled with Chromosorb P AW-DMCS, coated with 17% of the solution 20% octakis(3-*O*-butanoyl 2,6-di-*O*-pentyl)-γ-cyclodextrin in the polysiloxane SE-54; carrier gas: nitrogen; 26°C, 30 ml/min; injected amount: 3.0 mg. The retention times corresponding to the maximum of the peaks are, respectively, 31.8 min and 42.3 min. Time scale in min.

the specific CSP utilisation decreases from the value of 27 ml/mg to the value of 6 ml/mg. Unfortunately, it is not possible to compare the productivity of the different systems because data about elution times were not reported [35].

However, based on our data it is possible to

Table 3
Comparison between the batch GC separation of enflurane and α-ionone

	T (°C)	Max. injected amount (mg)	Δ*t* for the elution of peaks (min)	Specific CSP utilisation (ml_{CSP}/mg)	Specific theoretical productivity ($mg/ml_{CSP}\cdot day$)
Enflurane	26	3.0	30	9	5.1
α-Ionone	75	0.3	5.5	93	2.8
α-Ionone + β-ionone	75	0.3	42	93	0.37

compare the enantiomer separation of α-ionone and enflurane, in terms not only of CSP utilisation, but also of the specific productivities, i.e., the amount of racemate that can be separated per unit time and volume of the column.

As far as α-ionone is concerned two entries are reported in Table 3. The first refers to the elution of the peaks of the α-ionone enantiomers ignoring the presence of β-ionone. The second accounts for the presence of β-ionone, in such a way that pure α-ionone enantiomers can be collected. In the former case, the time period between breakthrough of the first peak and complete elution of the second is only 5.5 min, as illustrated in Fig. 3, whereas in the latter 42 min are necessary to elute also β-ionone from the column. In the first, more favourable case, the specific theoretical productivity for α-ionone is only half that for enflurane. On the contrary, in the less favourable case, where β-ionone must be absent from α-ionone enantiomers fractions enflurane productivity is 14-times larger than the α-ionone one. This is not only due to the lower selectivity, but also to the fact that α-ionone is severely penalised by the necessity to let the slow β-ionone peak elute before injecting a new pulse.

4. Conclusions

In this work we have reported the chromatographic enantioseparation of α-ionone through gas chromatography, using three different cyclodextrin derivatives dissolved in polysiloxane and coated on Chromosorb. Among these, octakis(3-*O*-butanoyl-2,6-di-*O*-pentyl)-γ-cyclodextrin has proved to achieve performances which make its use possible not only for analytical purposes, but also for preparative separations.

The feasibility of the latter has been investigated by measuring the maximum loading capacity of a semipreparative column and by comparing the results with the ones obtained for the enantiomers of enflurane (see Refs. [26,27] for its preparative GC separation). This shows that α-ionone enantiomers have larger retention times and smaller selectivity than enflurane. In addition the period between two following injections has to be significantly enlarged when the impurity β-ionone has to be eliminated. However, neglecting the peak of β-ionone and repeating injections with a period corresponding to the time span between the front of the first enantiomer peak and the tail of the second enantiomer peak, it is possible to obtain productivities of the same order of magnitude as for enflurane.

Acknowledgements

We thank Wacker Chemie, Munich, Germany, for a generous gift of γ-cyclodextrin. We would also like to thank F. Mayer, ETH Zürich, Switzerland for his technical assistance during the course of this work.

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