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Gas Chromatographic Enantioseparation and Thermodynamic Parameters of Bicyclic Diketones

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The analytical separation of the enantiomers of seven bicyclic bridgehead diketones of varying ring size and molecular shape has been studied by gas chromatography on permethylated α- and β-cyclodextrin columns. Factors influencing the enantiomer separation are discussed. Thermodynamic parameters ΔG, ΔH and ΔS were determined from variable temperature measurements in order to investigate the mode of interaction of enantiomers with the chiral stationary phase. The enantiodifferentiations are accounted for, at least in part, by reversible inclusion complex formation between guest molecules and the stationary phase during the chromatographic process.

The problem of determining enantiomeric composition frequently arises in the characterization and use of chiral compounds. Chiral separation by high-resolution gas chromatography (GC) represents a versatile method for enantiomer analysis. In recent years permethylated cyclodextrins have proved to be highly efficient chiral discriminating stationary phases for the separation of the enantiomers of a wide range of racemic mixtures.[1–4] Despite a large amount of work in this area there is a continuing discussion as to whether inclusion complexation plays a major role in GC enantioseparations,[5–11] and a universal model that explains enantiomer separation has still to be put forward. Suitable model molecules for chiral guests are sought in order to shed light on the mechanism of enantiomer separation.

Recently, we reported a preparative enantiomer separation of various bicyclic structures by liquid chromatography on swollen microcrystalline triacetylcellulose (TAC) columns.[12–14] The interaction between several of these structures and α- and β-cyclodextrins (CD) in solution has been studied by ^{1}H NMR spectroscopy.[15] We therefore considered the application of chiral GC for the separation of racemic mixtures of bridgehead bicyclic diketones and comparison of the mode of their interaction with the same CDs in the gas phase to be of interest. We here report such a study. The molecular structures of the compounds investigated are shown in Fig. 1.

Experimental

Investigated compounds. Compounds **1–7** were synthesised according to known methods.[12,16,17] The order of elution of the enantiomers was determined by comparison with enantiomerically enriched reference compounds obtained by preparative high performance liquid chromatography on a microcrystalline triacetylcellulose column using the equipment described previously.[18]

Instrumentation. A Perkin Elmer Autosystem gas chromatograph, equipped with split/splitless injector and flame ionization detector, was used. Helium served as the carrier gas (6.0 bar) with split ratio 1:100, in isothermal elution. Alpha-Dex 120 and Beta-Dex 120 fused silica capillary columns of 0.25 μm film thickness, 30 m × 0.25 mm i.d., were used (Supelco). The stationary phase was 20% permethylated CD in poly(35% diphenyl–65% dimethylsiloxane), SPB-35. The columns were conditioned at 200 °C for 2 h. The various compounds were run on different days and the results were reproducible.

Data evaluation. The chiral resolution R_s given in the tables was calculated according to eqn. (1),

$$R_s = 1.177 \frac{t_{R(2)} - t_{R(1)}}{w_{h(1)} + w_{h(2)}} \quad (1)$$

where indices 1 and 2 refer to the first- and second-eluting enantiomer, respectively. The capacity factors, k', were calculated from the retention times of the enantiomers and the dead time of a non-retained compound.

Enthalpic and entropic contributions to $\Delta\Delta G$, i.e., $\Delta\Delta H$ and $\Delta\Delta S$, were determined from the Gibbs–

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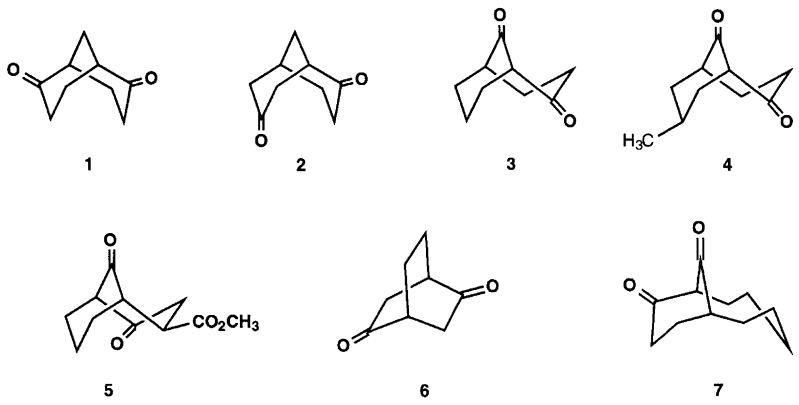

Fig. 1. Molecular structures of bicyclo[3.3.1]nonane-2,6-dione **1**, -2,7-dione **2**, -2,9-dione **3**, 7-methylbicyclo[3.3.1]nonane-2,9-dione **4**, methyl 4,9-dioxobicyclo[3.3.1]nonane-2-carboxylate **5**, bicyclo[2.2.2]octane-2,5-dione **6** and bicyclo[5.3.1]undecane-8,11-dione **7**. The configuration of the first eluted enantiomer is given in Table 2.

Helmholz relationship (van't Hoff plot) according to eqn. (2),

$$\Delta\Delta G = \Delta\Delta H - T\Delta\Delta S \qquad (2)$$

manipulating the data by the least squares method.

Results and discussion

The chromatographic enantiomer separation investigated herein includes chiral structures of bicyclo[3.3.1]nonane-2,6-, -2,7-, -2,9-diones, 7-methylbicyclo[3.3.1]nonane-2,9-dione, methyl 4,9-dioxobicyclo[3.3.1]nonane-2-carboxylate, bicyclo[2.2.2]octane-2,5-dione and bicyclo[5.3.1]-undecane-8,11-dione **1–7**, respectively (Fig. 1). The structures studied show variation in ring size and position of the carbonyl groups, and in their molecular symmetry. Thus, they may prove useful for the investigation of structure–retention relationships. The difference in Gibbs free energies of the interaction as well as the difference in free enthalpies and entropies were determined from chromatographic parameters.

The interaction between stationary phases containing permethylated α- and β-cyclodextrins and substrates **1–7** showed considerable differences. Separation on permethylated α-CD was achieved only for 2,6-dione **1** at different temperatures (100–140 °C). The first eluted enantiomer was the enantiomer with a negative rotation, i.e., (1*R*,5*R*)-**1**.[12] Other compounds were not resolved in the temperature range studied (100–140 °C), and although characteristic peak broadening was observed at lower temperatures the significantly increased elution time, e.g., ca. 2 h for **2** and **3**, and >3 h for compound **7**, made further resolution attempts meaningless (Table 1).

Considering the size of the molecules and the dimensions of the cyclodextrin cavities, the interaction of the β-CD phase with the bicyclic structures was expected to give better resolution. Indeed, for all these racemates baseline resolution was achieved, and for some substrates over a rather wide range of temperature in isothermal mode. However, a decrease in the separation factor, α, was always observed on increasing the temperature. The values for chiral resolution, R_s, also decreased similarly as the temperature increased (Table 2). The separation factors, α for enantiomers separated on β-CD phase are low, as they are generally low for CD-derived chiral stationary phases.[2,19] A representative gas chromatogram of the enantiomer separation on the β-cyclodextrin column is shown in Fig. 2.

High elution temperatures were required for the separation of all the bicyclic chiral compounds investigated. In general, retention times were governed by the molecular weight of the compounds. Peak broadening and partial overlapping was observed in many cases at lower

Table 1. Gas-chromatographic data on the separation of enantiomers on an α-cyclodextrin column.

Compound	T/K	Capacity ratios k_1	k_2	α	R_s
1	373	176.2	181.4	1.030	2.2
	383	107.4	110.1	1.025	1.8
	393	54.5	56.1	1.029	1.4
	413	30.1	30.6	1.016	0.7
2	383	108.8		0	
	393	65.0		0	
	413	28.7		0	
3	373	109.3		0	
	383	68.4		0	
	393	44.4		0	
	403	29.8		0	
	413	20.8		0	
4	373	108.8		0	
	393	46.6		0	
6	383	57.9		0	
	393	38.9		0	
7	383	215.4		0	
	393	136.6		0	
	413	56.5		0	

Table 2. Capacity factors, k, separation factors, α, chiral resolution, R_s, and thermodynamic parameters for the compounds **1–7** on a β-cyclodextrin column.

Compound	T/K	Capacity ratios k_1	k_2	α	R_s	$\Delta\Delta G°$/J mol^{-1}	$\Delta\Delta H°$/J mol^{-1}	$\Delta\Delta S°$/J mol^{-1} K^{-1}
1	403	60.8	64.2	1.056	2.9	182	1390±150[b]	3.0±0.5[b]
(−)-(1*R*,5*R*)	413	39.0	40.8	1.046	3.0	154		
	423	25.7	26.5	1.031	1.8	117		
	433	17.8	18.2	1.022	1.7	86		
	443	12.9	13.1	1.018	1.3	66		
2	393	93.3	96.3	1.032	1.2	103	533±250	1.1±1.5
(−)-(1*S*,5*S*)	403	57.8	59.3	1.026	1.4	86		
	413	37.1	38.0	1.024	1.5	81		
3	383	98.9	100.9	1.020	1.2	63	577±200	1.3±1.0
(+)-(1*S*,5*R*)	393	58.5	59.5	1.017	0.8	55		
	398	46.1	46.7	1.013	0.5	43		
	403	37.1	37.5	1.011	[a]	37		
4	443	88.8	90.3	1.017	1.5	62	590±100	1.2±0.5
(+)-(1*S*,5*S*,7*S*)	453	58.5	59.3	1.014	1.2	52		
	463	39.8	40.2	1.010	0.8	38		
	473	28.0	28.2	1.007	[a]	27		
5	413	112.5	114.2	1.015	1.1	52	308±150	0.6±0.5
(−)-(1*S*,2*R*,5*R*)	418	89.0	90.2	1.013	0.8	47		
	423	70.9	71.8	1.013	0.7	45		
	433	46.2	46.7	1.011	[a]	39		
6	383	73.9	75.9	1.027	1.9	85	814±150	1.9±0.5
(−)-(1*R*,4*R*)	393	45.2	46.2	1.022	1.5	71		
	403	27.9	28.3	1.014	0.9	47		
7	403	102.4	103.9	1.015	1.1	50	1092±200	2.6±1.0
(−)-(1*R*,7*S*)	408	81.0	81.9	1.011	0.8	37		
	413	64.5	65.1	1.009	0.7	32		
	423	42.3	42.4	1.002	[a]	[a]		

[a]Because of peak overlap, a reliable value could not be obtained. [b]Maximum estimated error is given.

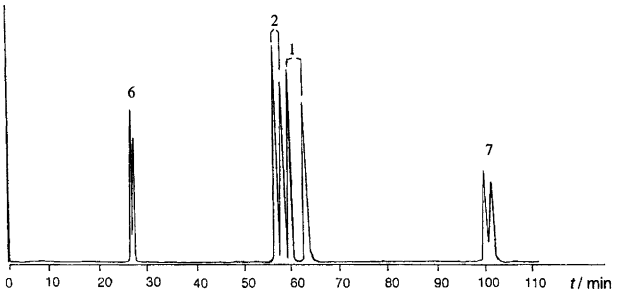

Fig. 2. Enantiomer separation of 2,5-dione **6**, 2,7-dione **2**, 2,6-dione **1**, and undecadione **7** on a permethylated β-cyclodextrin column (30 m × 0.25 μm) at 130 °C in isothermal mode, inlet pressure 6 bar of helium. Some compounds did not give baseline separation at this temperature.

temperatures with the retention times increasing nearly exponentially. However, almost no peak broadening occurred for enantiomers of 2,6-dione **1**. This structure, together with 2,5-dione **6**, for which the peaks were also rather symmetrical, is of C_2-symmetry. Less effective separation was achieved for the other bicyclic structures, which are molecules of C_1-symmetry. The best resolved among those compounds were the enantiomers of the 2,7-dione **2**; however, the retention times were over 90 min at 120 °C. Much higher temperatures were used to resolve 7-methyl dione **4** and a good separation was achieved only at 170 °C, although the retention times were again over 90 min. Separation of racemic diones became increasingly poor with the presence of a methyl or ester group in the bicyclic framework and with increasing ring size: compounds **4**, **5** and **7**, respectively. Only partial enantiomer separation was achieved for racemates of dioxo ester **5** and undecadione **7**. The rather poor separation of undecadione **7** indicates that the ring size has a large influence on the enantiomer separation of this series of diketones. The boat conformation of one of the six-membered rings in structures **3–5** also is connected with inferior separability of enantiomers.

Interestingly, the order of the elution of enantiomers from the permethylated β-CD column is the same as from the TAC column except for the diones **3** and **4**. The first eluted enantiomer from the GC column was established by the injection of enantiomerically enriched samples after separation on the TAC column connected

to the polarimeter. The sign of rotation and the absolute configuration of the first eluted enantiomer of racemates **1–7** are indicated in Table 2.

The observed dependence of the separation parameters on the relative size and shape of the molecules reinforces the concept of an inclusion mechanism of enantiodifferentiation on cyclodextrin columns. Cyclodextrin as a chiral molecule is able to interact enantioselectively with molecules by inclusion into the cavity or by adsorption on the top or bottom of the torus. However, whereas external interactions are quite similar for α-CD and β-CD, the observed variation in enantiodifferentiation follows the size consistency between guest and host. We see this as a support for an inclusion mechanism. Furthermore, it has been shown that the interaction between 2,6-dione **1** and α-CD is rather weak ($K=$ 60 M^{-1}), but stronger with β-CD ($K=345$ M^{-1}) in water solution.[15] The same effect was observed on cyclodextrin columns in the gas phase. According to ROESY NMR experiments molecules of **1** penetrate into the cavity of β-CD.[15] Consequently, since the corresponding internal diameter of the α-CD is appreciably smaller compared with that of β-CD, the former material proved to be less efficient for enantiomer separation of the structures studied. The analogous conclusion has been made for separation of some other alicyclic ketones.[20] This supports the proposed inclusion effect of the interaction between the stationary phase and the substrate molecules. While most cyclodextrin inclusion complexes formed in aqueous or mixed solutions are broken at temperatures over 90 °C, enantioselectivity is observed at higher temperatures in the GC experiments. Each racemic mixture studied herein has a characteristic temperature above which enantioselectivity is lost, and also a temperature below which the retention times increase very sharply together with broadening of the peaks. When strong inclusion complexes are formed, there is often broadening due to slow mass transfer on the stationary phase. Thus, the results obtained in this work support inclusion complex formation on GC with a β-CD column for the compounds in this study.

Gas chromatography retention parameters are the source of data for determination of thermodynamic parameters. The latter could be used to evaluate the degree of association between the enantiomers and cyclodextrin. ΔH values are a direct measure of the interaction energies and were verified by independent methods, e.g., NMR spectroscopy[21,22] and molecular modelling.[23,24] The lower limit for enantiomer differentiation, which still yields peak separation in gas chromatography, was estimated to be 40 J mol^{-1} (10 cal mol^{-1}) for $\Delta\Delta G$.[25] Values of $\Delta\Delta G$ in the range 30–180 J mol^{-1} were obtained for the resolution of the bicyclic diketones. A linear relationship was observed between ln α and $1/T$, and between $\Delta\Delta G/T$ and $1/T$ for the resolution of enantiomers on β-cyclodextrin column. Thus, the Gibbs–Helmholz parameters of enantiomer discrimination could be determined according to the eqn. (2).[26]

The calculated energies indicate that the differences between the thermodynamic parameters of two enantiomers are small. From the data in Table 2 it is clear that there is a relationship between the separation efficiency and the enthalpy and entropy difference. As $\Delta\Delta H$ increases, the entropy difference, $\Delta\Delta S$, also increases slightly, in agreement with the enthalpy–entropy compensation effect. A good correlation between $\Delta\Delta H$ and the separation efficiency is found for all the compounds except for **7**. A strong host–guest interaction is no guarantee of good separation of the enantiomers as is shown for the undecadione **7**. Of course, the retention time is also determined by interactions with the SPB part of the stationary phase and the volatility of the compound.

Conclusions

Enantiomer separation of a series of bicyclic diketones was achieved by GC on a permethylated β-cyclodextrin column, which proved to be a highly selective chiral stationary phase. The order of enantiomeric elution for compounds **1–7** was determined by comparison with enantiomerically enriched samples. Thermodynamic parameters ΔG, ΔH and ΔS were determined from variable temperature measurements in order to investigate the mode of interaction of enantiomers with the chiral stationary phase. The enantiodifferentiation results obtained here could be accounted for, at least in part, by the intermolecular inclusion complexes formed between guest molecules and stationary phase during the chromatographic process.

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