Journal of Chromatography, 552 (1991) 43–57
Elsevier Science Publishers B.V., Amsterdam

CHROMSYMP. 2165

Theoretical approach to the gas chromatographic separation of enantiomers on dissolved cyclodextrin derivatives

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ABSTRACT

The theoretical concept described previously for enantiomer separation by complexation gas chromatography was extended to polysiloxane stationary phases containing dissolved cyclodextrin derivatives. A relationship between the chiral separation factor α and the cyclodextrin molality was derived. The theory was verified by comparing the predicted and measured dependence of α on the cyclodextrin molality for various racemates. Retention increases R' were determined as a measure of the enantiomer–cyclodextrin interactions and of the contribution of these interactions to the total retention time. By measuring R' at different temperatures, Gibbs-Helmholtz parameters ($\Delta_{R,S}\Delta G$, $\Delta_{R,S}\Delta H$ and $\Delta_{R,S}\Delta S$) of enantiomer discrimination were obtained from the ln (R'_R/R'_S) *vs.* $1/T$ plots. Because of the difficulty of finding a truly inert reference standard, these data are affected by a systematic error which restricts the interpretation of the observed enantioselectivities to a qualitative manner.

INTRODUCTION

Enantiomer separation by gas chromatography on chiral stationary phases is based on the different stabilities of diastereomeric 1:1 associates formed rapidly and reversibly. In complexation gas–liquid chromatography (GLC) employing stationary phases containing dissolved transition metal β-diketonates, extensive studies on the thermodynamics of molecular association including enantioselectivity have been performed [1–7]. For derivatized cyclodextrin stationary phases, which have become increasingly important for enantiomer separation by GLC in the last few years [8–13], there are still only a few theoretical investigations available [14,15]. It was therefore of interest to investigate systematically whether the model developed for complexation GLC can also be applied to dissolved cyclodextrin stationary phases.

The consideration of retention increases R' (or retention increments, a quantitative measure of the interactions between solute and cyclodextrin) and the relationship between the chiral separation factor α and the cyclodextrin molality m allows a better understanding of enantioselectivity and it may guide the optimization of enantiomer separations.

0021-9673/91/$03.50

EXPERIMENTAL

Instrumentation

A Carlo Erba Fractovap 2101 instrument equipped with a flame ionization detector was used. Retention times were determined using a Shimadzu C-R 3A integrator.

Column preparation and gas chromatographic procedure

Cyclodextrin derivatives and capillary columns were prepared and used as described previously [9]. Fused-silica columns (25 m × 0.25 mm I.D.) with a film thickness of 0.2 μm (permethylated β-cyclodextrin dissolved in OV-1701) were employed. The inlet pressure was 1.0 bar hydrogen.

Determination of net retention times and retention increases, R'

Retention increases were determined as described for complexation GLC [6]; all measurements were performed at least three times. Net retention times t' were measured from the methane peak. The relative net retention r_0 of a solute with respect to a reference standard was calculated from the ratio t'_0(solute)/t'^*_0(standard) obtained on an achiral reference column (eqn. 10). The relative net retention r of a solute with respect to a reference standard was calculated from the ratio t'(solute)/t'^*(standard) obtained on the chiral, cyclodextrin-containing column (eqn. 9). The retention increase R' was calculated according to $R' = (r/r_0) - 1$ (eqn. 8).

In order to study systematically the influence of the choice of the standard, all relative retention data were determined with respect to four different commercial *n*-alkanes (hereafter abbreviated C_7, C_8, etc.) as standards ($k' \approx 0.4$–0.8 for the smallest).

THEORETICAL

Consider a volatile solute B eluting through a column containing a dilute solution of a cyclodextrin derivative A (*e.g.*, permethylated β-cyclodextrin) in an (achiral) solvent S (*e.g.*, a polysiloxane such as OV-1701).

In analogy with the theory advanced for complexation GLC [1–4], the present derivation is based on two equilibria:

$$B_{(g)} \overset{K_L^0}{\rightleftharpoons} B_{(l)}$$

$$B_{(l)} + A \overset{K}{\rightleftharpoons} AB$$

The partition coefficient K_L^0 of B between the gaseous and pure liquid phase is

$$K_L^0 = \frac{a_{B_{(l)}}}{a_{B_{(g)}}} \tag{1}$$

and the thermodynamic stability constant K of AB in the given solvent S is

$$K = \frac{a_{AB}}{a_A a_{B_{(l)}}} \tag{2}$$

As the total amount of solute present in the liquid phase is $a_{B_{(l)}} + a_{AB}$, the apparent partition coefficient is

$$K_L = \frac{a_{B_{(l)}} + a_{AB}}{a_{B_{(g)}}} \tag{3}$$

Using eqns. 1 and 2, this can be rewritten as [1,2]

$$K_L = K_L^0(1 + Ka_A) \tag{4}$$

Employing the fundamental equation of chromatography

$$t' = \frac{K_L}{\beta} \cdot t'_m \tag{5}$$

where t'_m = dead time, t' = net retention time, K_L = partition coefficient between mobile and stationary phases and β = phase ratio, an analogous equation can be written for the net retention time:

$$t' = t'_0(\underbrace{1}_{\text{physical}} + \underbrace{Ka_A}_{\text{chemical contribution}}) \tag{6}$$

where t_0 is the (experimentally not available) net retention time on a totally identical reference column devoid of the cyclodextrin derivative A.

In eqn. 6, the retention increase (or retention increment) R' is defined as [4]

$$R' = Ka_A \tag{7}$$

R' is a quantitative measure of the increase in the retention of B caused by the addition of the cyclodextrin derivative A to the achiral solvent S. Hence the determination of R' allows one to quantify the "physical" (K_L^0) and "chemical" (K) contributions to the total retention.

As it is experimentally impossible to determine t' and t'_0 with strictly identical column parameters such as column length, diameter, film thickness or flow-rate, it is useful, according to Schurig *et al.* [4], to rewrite eqn. 6 in terms of *relative retention data* in order to obtain an equation that is independent of these parameters:

$$r = r_0(1 + R')$$

or (8)

$$R' = \frac{r}{r_0} - 1$$

where r is the relative net retention of solute B with respect to an inert reference standard B* (*e.g.*, a small *n*-alkane):

$$r = \frac{t'}{t'^*} \qquad \text{[chiral column (A in S)]} \tag{9}$$

$$r_0 = \frac{t'_0}{t'^*_0} \qquad \text{[achiral reference column (only S)]} \tag{10}$$

The chiral separation factor α

Suppose solute B is a racemic mixture of the enantiomers B_R and B_S. Since $K^0_{LR} = K^0_{LS}$, enantiomer separation of B_R and B_S must be due to different values of K_R and K_S. The chiral separation factor is given by[a]

$$\alpha = \frac{K_{LR}}{K_{LS}} = \frac{t'_R}{t'_S} = \frac{r_R}{r_S} \tag{11}$$

Using eqns. 4 and 7, a very useful relationship is obtained:

$$\alpha = \frac{K_R a_A + 1}{K_S a_A + 1} = \frac{R'_R + 1}{R'_S + 1} \tag{12}$$

Enantiomer separation ($\alpha > 1$) requires retention increases R' of the two enantiomers being R'_R, $R'_S > 0$ and $R'_R \neq R'_S$.

Thermodynamic data

Applying the thermodynamic relationship

$$\Delta G = -RT \ln K \tag{13}$$

the ratio of the thermodynamic stability constants

$$\frac{K_R}{K_S} = \frac{R'_R}{R'_S} = \frac{r_R - r_0}{r_S - r_0} \tag{14}$$

yields the difference in the free enthalpies of formation of the diastereomeric associates[b,c]:

$$\Delta\Delta G = \Delta G_R - \Delta G_S = -RT \ln \frac{R'_R}{R'_S} \tag{15}$$

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[a] Where R arbitrarily represents the enantiomer eluted later so that $\alpha \geqslant 1$.

[b] Where R arbitrarily represents the chemically more strongly bonded enantiomer (more negative ΔH).

[c] Note that only for large R' values does R'_R/R'_S approach $(R'_R + 1)/(R'_S + 1) = \alpha$ (*cf.*, eqn. 12 and eqn. 15 becomes $\Delta\Delta G = -RT \ln \alpha$. The latter equation is sometimes used instead of eqn. 15 as a measure of the chiral recognition $\Delta\Delta G$.

The ratio R'_R/R'_S and thus $\Delta\Delta G$ are independent of the cyclodextrin activity a_A in the solvent S.

It is further possible [16,17] to determine enthalpic and entropic contributions to $\Delta\Delta G$, *i.e.*, $\Delta\Delta H$ and $\Delta\Delta S$, from the Gibbs–Helmholtz relationship (Van 't Hoff plot):

$$\frac{\Delta\Delta G}{T} = f\left(\frac{1}{T}\right) = \Delta\Delta H \cdot \frac{1}{T} - \Delta\Delta S \tag{16}$$

RESULTS AND DISCUSSION

n-Alkanes and the reference standard problem

n-Alkanes (hereafter abbreviated C_7, C_8, etc.) have been used in complexation GLC as inert reference standards for the determination of relative retention data (*r* values, see eqns. 8–10) as they are not capable of coordinating with transition metal ions. For cyclodextrins, unfortunately, we cannot find any reference standard that would be totally inert toward molecular association.

In order to test the suitability of *n*-alkanes as "inert" reference standards employing cyclodextrin derivatives, log *t' versus n* (number of carbon atoms) curves were recorded and compared with those obtained on a reference column containing the pure polysiloxane without cyclodextrin (see Fig. 1). There are still straight lines for permethylated β-cyclodextrin and for heptakis(3-trifluoroacetyl-2,6-dimethyl)-β-cyclodextrin, but the slopes are slightly steeper than on the achiral reference column. As the slope is independent of the experimental parameters (flow-rate, column length, etc., only affect the intercept at $n = 0$ in the logarithmic diagram), this means that there is some interaction between alkane and cyclodextrin, increasing with the carbon number *n*, *i.e.*, *n*-alkanes do not represent totally inert reference standards for cyclodextrin phases. However, the best results should be obtained if a small *n*-alkane ($k' \approx 0.4$–0.8) is used as a standard. The retention increases R' of all solutes were calculated with respect to four different *n*-alkane standards, and indeed the smallest standard always yielded the largest R' value (which is still considered to be too small, *cf.*, Table I; note that between the use of the standards C_9 and C_{12} an error in R' of *ca.* 10% is introduced).

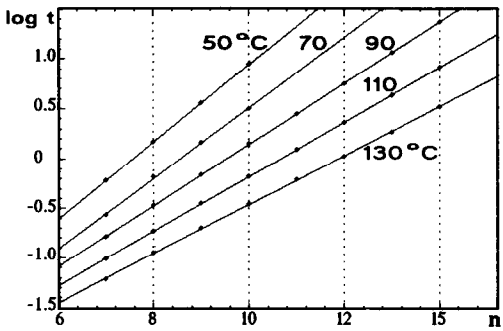


Fig. 1. Log *t' vs. n* (number of C atoms) for the homologous series of *n*-alkanes on permethylated β-cyclodextrin in OV-1701 at different temperatures.

TABLE I

INFLUENCE OF THE CHOICE OF THE *n*-ALKANE STANDARD, DEMONSTRATED FOR A TYPICAL EXAMPLE: SOLUTE I FROM TABLE II, T = 100°C, MOLALITY OF PERMETHYLATED β-CYCLODEXTRIN m_A = 0.065.

Enantiomer	Standard	k'	r[a]	r_0[a]	R'[b]	$\Delta\Delta G$ (J/mol)[c]
First eluted	C_9	12.87	19.51	12.74	0.531	
	C_{10}		10.04	6.62	0.518	
	C_{11}		5.19	3.48	0.491	1006
	C_{12}		2.70	1.84	0.464	1020
Second eluted	C_9	14.58	22.10	12.74	0.734	1051
	C_{10}		11.37	6.62	0.719	1086
	C_{11}		5.88	3.48	0.689	
	C_{12}		3.05	1.84	0.658	

[a] ±1%.
[b] ±2%.
[c] ±10.

Suppose the standard itself had a small retention increase R'_0 (with respect to a hypothetical ideal standard). A relationship between the measured $R' = (r/r_0) - 1$ values and the ideal, true $R'_{true} = (r_{true}/r_0) - 1$ values can be derived; the r values (but not r_0) must be corrected in analogy with eqn. 8:

$$r_{true} = (1 + R'_0)r$$

$$R'_{true} = \frac{r_{true}}{r_0} - 1 = (1 + R'_0)\frac{r}{r_0} - (1 + R'_0) + R'_0 \tag{17}$$

$$= (1 + R'_0)R' + R'_0$$

R'_0 is not an inaccessible quantity. The comparison of calculated and measured α *vs.* molality curves (see below) allows R'_0 to be estimated.

It may be noted that, in contrast to *n*-alkanes, the homologous series of γ-lactones do not yield a straight log t' *vs.* n line (see Fig. 2, top).

Dependence of the chiral separation factor α on the cyclodextrin molality m_A

Eqn. 7 allows the calculation of the retention increase R' at a molality m_A[a], *i.e.*, $R'(m_A)$, if R' at a molality m_A^0, *i.e.*, $R'(m_A^0)$, is known:

$$\frac{R'(m_A)}{m_A} = \frac{R'(m_A^0)}{m_A^0} \tag{18}$$

[a] Eqn. (7) can also be written in the form

$$R' = K_{(m)}m_A \tag{7a}$$

Here, the molality concentration scale m_A is used instead of the unknown activity a_A because m_A is independent of temperature and the weight rather than the volume is determined for practical reasons when preparing GLC columns.

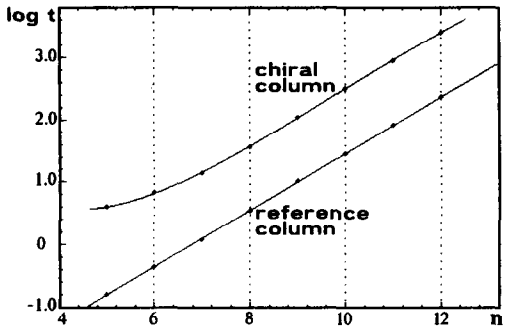


Fig. 2. Log t' *vs.* n (number of C atoms) for the homologous series of γ-lactones (enantiomer eluted later) on heptakis(3-trifluoroacetyl-2,6-dimethyl)-β-cyclodextrin in OV-1701 (top) and on pure OV-1701 (bottom) at 170°C.

Thus a complete α *vs.* m_A curve can be calculated, using eqns. 12 and 18, if the $R'_R(m_A^0)$ and $R'_S(m_A^0)$ values at a single molality m_A^0 are provided:

$$\alpha(m_A) = \frac{m_A R'_R(m_A^0) + m_A^0}{m_A R'_S(m_A^0) + m_A^0} \tag{19}$$

Eqn. 19 shows that the α *vs.* m_A curve levels off as m_A increases, and Fig. 3 clearly shows how this is influenced by the retention increase R'_R (R'_S being calculated from eqn. 19).

Figs. 4 and 5 show some measured α *vs.* m_A curves (all data are listed in Table II). In Figs. 6–9 the measured α values (independent of any standard!) are compared with the calculated curves for some racemates.

There is good agreement between the calculated and measured curves, which is a clear support for the validity of our approach. Further, it can be seen that the finite retention increase R'_0 of the standard should in no case be above 0.1 (according to eqn. 17, this would lead, for example, to an error of 0.2 for a measured R' value of 1.0).

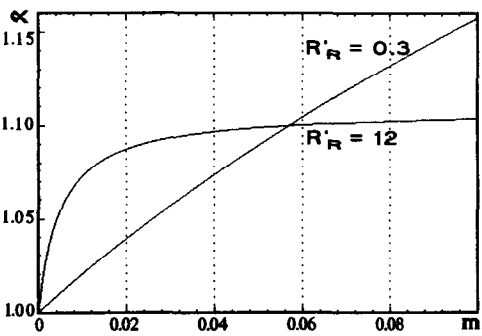
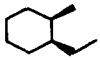
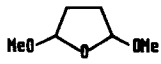
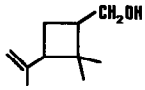
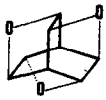
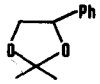
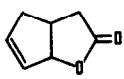


Fig. 3. Simulated α *vs.* m_A curves, assuming $\alpha = 1.10$ for $m_A^0 = 0.057$ and retention increases $R'_R(m_A^0)$ of 0.3 and 12, respectively.

TABLE II

RETENTION INCREASES R'_R AND R'_S (±2%), SEPARATION FACTORS α AND $\Delta\Delta G$ (IN J/mol, ±10) FOR TWELVE CHIRAL SOLUTES ON OV-1701 CONTAINING DIFFERENT MOLALITIES OF PERMETHYLATED β-CYCLODEXTRIN

Me = Methyl; Ph = phenyl.

Solute	Temperature and standard	Parameter	Cyclodextrin molality, m_A					
			0.027	0.042	0.057	0.065	0.088	0.096
A 	40°C, C_7	R'	0.195	0.334	0.413	0.530	0.637	0.655
			0.221	0.388	0.480	0.609	0.725	0.757
		α	1.022	1.041	1.047	1.051	1.054	1.061
		$\Delta\Delta G$	330	390	390	360	340	380
B 	40°C, C_7	R'	0.263	0.464	0.578	0.729	0.889	0.918
			0.294	0.523	0.650	0.815	0.998	1.038
		α	1.025	1.040	1.045	1.050	1.057	1.063
		$\Delta\Delta G$	290	310	300	290	300	320
C 	40°C, C_7	R'	0.427	0.773	0.971	1.227	1.505	1.556
			0.509	0.931	1.164	1.462	1.796	1.857
		α	1.057	1.089	1.098	1.105	1.116	1.118
		$\Delta\Delta G$	450	480	470	460	460	460
D 	50°C, C_7	R'	0.102	0.326	0.320	0.338	0.485	0.527
			0.165	0.434	0.469	0.500	0.719	0.765
		α	1.058	1.082	1.113	1.122	1.158	1.158
		$\Delta\Delta G$	1310	770	1030	1060	1060	1010
E 	50°C, C_7	R'	0.187	0.382	0.513	0.551	0.790	0.804
			0.230	0.461	0.613	0.659	0.947	0.961
		α	1.037	1.058	1.066	1.070	1.088	1.087
		$\Delta\Delta G$	560	510	480	480	490	480
F 	75°C, C_8	R'	−0.002	0.041	0.007	0.001	0.003	0.030
			0.056	0.125	0.113	0.115	0.162	0.193
		α	1.058	1.080	1.105	1.113	1.159	1.159
		$\Delta\Delta G$	—	—	—	—	—	—
G 	75°C, C_8	R'	0.542	0.843	1.005	1.048	1.530	1.685
			0.764	1.172	1.422	1.492	2.202	2.383
		α	1.144	1.178	1.208	1.217	1.266	1.260
		$\Delta\Delta G$	1000	950	1010	1020	1050	1000
H 	75°C, C_8	R'	0.167	0.265	0.319	0.323	0.445	0.484
			0.236	0.353	0.433	0.442	0.588	0.636
		α	1.059	1.069	1.087	1.090	1.099	1.102
		$\Delta\Delta G$	1010	830	890	910	810	790
I 	100°C, C_9	R'	0.199	0.410	0.502	0.531	0.784	0.826
			0.290	0.560	0.689	0.734	1.083	1.137
		α	1.077	1.106	1.124	1.113	1.168	1.171
		$\Delta\Delta G$	1180	970	980	1010	1000	990
K 	115°C, C_9	R'	0.763	1.061	1.381	1.510	2.211	2.261
			0.851	1.185	1.551	1.702	2.484	2.539
		α	1.050	1.060	1.071	1.077	1.085	1.085
		$\Delta\Delta G$	350	360	370	390	380	380
L 	115°C, C_9	R'	0.091	0.081	0.141	0.152	0.204	0.166
			0.132	0.138	0.219	0.239	0.328	0.291
		α	1.038	1.053	1.069	1.075	1.103	1.107
		$\Delta\Delta G$	1220	1720	1430	1450	1530	1810
M 	115°C, C_9	R'	0.219	0.292	0.362	0.392	0.506	0.506
			0.285	0.373	0.472	0.510	0.660	0.664
		α	1.053	1.063	1.081	1.085	1.102	1.105
		$\Delta\Delta G$	840	790	860	850	860	880

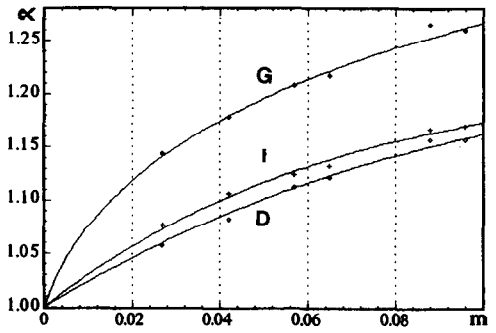


Fig. 4. Measured α *vs.* molality m_A curves for solutes G, I and D (data from Table II).

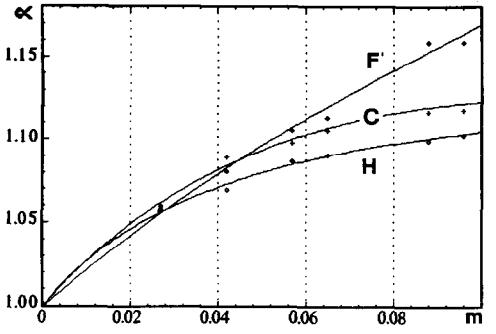


Fig. 5. Measured α *vs.* molality m_A curves for solutes F, C and H (data from Table II).

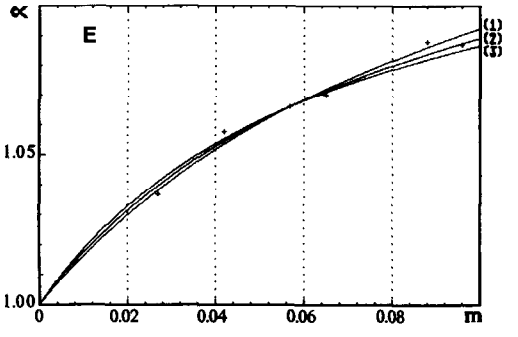


Fig. 6. Comparison of measured α values and calculated α *vs.* m_A curves for the typical solute E from Table II. The calculations are based on the R' values for $m_A^0 = 0.057$: (1) measured R' values; (2) and (3) measured R' values correlated for the retention increase R'_0 of the standard according to eqn. 17, assuming (2) $R'_0 = 0.1$ and (3) $R'_0 = 0.2$ for $m_A^0 = 0.057$.

A practical aspect of these investigations is that for most solutes (except those with very small R' values) it is not useful to increase the cyclodextrin molality m_A above 0.1. The retention increase R' and analysis time would also increase without much improvement in α.

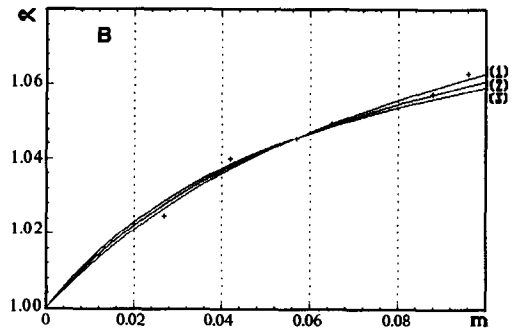


Fig. 7. Comparison of measured α values and calculated α *vs.* m_A curves for the typical solute B from Table II. The calculations are based on the R' values for $m_A^0 = 0.057$: (1) measured R' values; (2) and (3) measured R' values corrected for the retention increase R'_0 of the standard according to eqn. 17, assuming (2) $R'_0 = 0.1$ and (3) $R'_0 = 0.2$ for $m_A^0 = 0.057$.

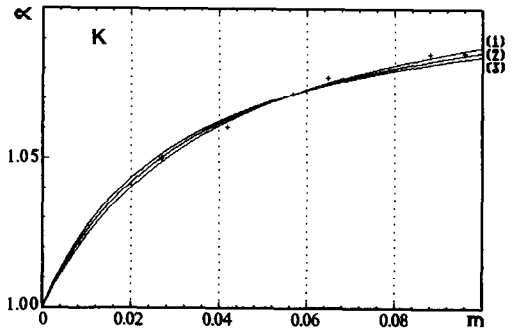


Fig. 8. Comparison of measured α values and calculated α *vs.* m_A curves for the typical solute K from Table II. The calculations are based on the R' values for $m_A^0 = 0.057$: (1) measured R' values; (2) and (3) measured R' values corrected for the retention increase R'_0 of the standard according to eqn. 17, assuming (2) $R'_0 = 0.1$ and (3) $R'_0 = 0.2$ for $m_A^0 = 0.057$.

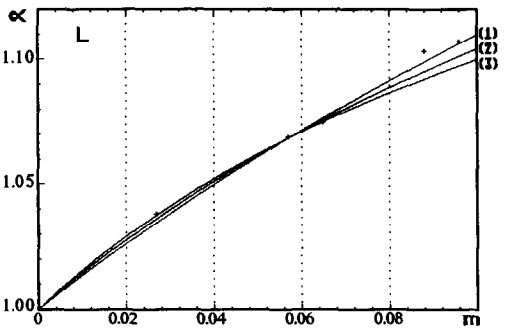


Fig. 9. Comparison of measured α values and calculated α *vs.* m_A curves for the typical solute L from Table II. The calculations are based on the R' values for $m_A^0 = 0.057$: (1) measured R' values; (2) and (3) measured R' values corrected for the retention increase R'_0 of the standard according to eqn. 17, assuming (2) $R'_0 = 0.1$ and (3) $R'_0 = 0.2$ for $m_A^0 = 0.057$.

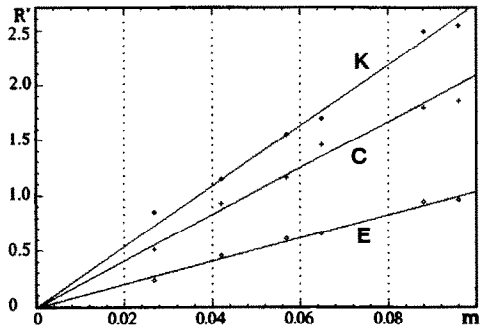


Fig. 10. Measured retention increase R'_R *vs.* cyclodextrin molality m_A curves for solutes K, C and E from Table II.

Retention increase R'

Some R'_R *vs.* m curves (data from Table II) are shown in Figs. 10 and 11. The slight deviation from the expected straight lines (*cf.*, eqn. 7 and the footnote with eqn. 7a) can be explained by the systematic error caused by the finite retention increase R'_0 of the standard itself (*cf.*, eqn. 17; note that also R'_0 itself depends on m_A; the deviation is more obvious for weakly complexing solutes, *e.g.*, solute H in Fig. 11).

The R' values rarely exceed 1.5 (the same was found for 3-perfluoroacylated 2,6-dimethyl-β-cyclodextrins), whereas in complexation GLC [17–19] often values around or above 20 are observed. This demonstrates how weak the solute–cyclodextrin interactions are (*cf.*, racemate F) and that the contribution of these interactions to the total retention time (*cf.*, eqn. 6) is not dominant.

Measurements of R' values on heptakis(3-heptafluorobutanoyl-2,6-dimethyl)-β-cyclodextrin in OV-1701 [14] indicate that in case of failure of enantiomer separation the R' values are relatively small or intermediate and equal for both enantiomers.

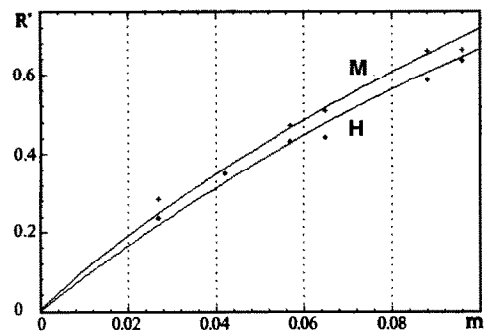


Fig. 11. Measured retention increase R'_R *vs.* cyclodextrin molality m_A curves for solutes M and H from Table II.

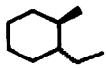
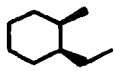
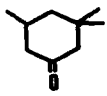
Thermodynamic data: $\Delta\Delta G$, $\Delta\Delta H$ and $\Delta\Delta S$

For some racemates, $\Delta\Delta H$ and $\Delta\Delta S$ were determined in addition to $\Delta\Delta G$ by temperature-dependent studies according to eqn. 16, still using four different *n*-alkanes as reference standards. The results are listed in Table III and shown in Figs. 12–17. It should be noted that, because of the reference standard problem described above, the figures are affected by a systematic error restricting the interpretation of the observed enantioselectivities to a qualitative manner. However, they clearly show that a temperature-dependent reversal of the elution order due to an isoenantioselective temperature ($T_{iso} = \Delta\Delta H/\Delta\Delta S$) [16,17] will not be observed within the temperature range of the experiment. By extrapolation of the straight lines in Figs. 12–17, T_{iso} was calculated to be above 450°C, and in the case of the racemate C (*cis*-pinane) it was even found to be outside the range of positive absolute temperatures. Ln α *vs.* $1/T$ plots for several racemates on heptakis(3-trifluoroacetyl-2,6-dimethyl)-β-cyclodextrin indicate that lower isoenantioselective temperatures are also possible (*e.g.*, for 1-phenyl-2,6-dimethyloxirane at 150°C, for isomenthol at 180°C and for a series of γ-penta- to γ-decalactones at 210–230°C), the temperatures being still too high to be verified experimentally. These results are in contrast to complexation GLC, where isoenantioselective temperatures between 15 and 100°C have often been observed [17–19].

There is no direct relationship between $\Delta\Delta G$ on the one hand and favourable values of the chiral separation factor α or the peak resolution on the other. According to eqns. 12 and 15, a certain $\Delta\Delta G$ value can result either from a large α and small R' values or *vice versa*.

TABLE III

GIBBS–HELMHOLTZ PARAMETERS CALCULATED BY LINEAR REGRESSION ACCORDING TO EQN. 16 FOR THE STRAIGHT LINES OF VAN 'T HOFF PLOTS IN FIGS. 12–17

Solute	Cyclodextrin molality, m_A	Standard	$\Delta\Delta H$ (J/mol)[a]	$\Delta\Delta S$ (J/K · mol)[b]
A 	0.065	C_7	−390	−0.11
	0.057	C_7	−420	−0.15
	0.042	C_7	−410	−0.11
B 	0.065	C_7	−330	−0.13
		C_8	−380	−0.22
		C_9	−420	−0.29
		C_{10}	−410	−0.20
C 	0.065	C_7	−320	0.44
		C_8	−350	0.39
		C_9	−360	0.40
		C_{10}	−330	0.55
G 	0.065	C_8	−4570	−10.22
		C_9	−4530	−10.05
		C_{10}	−4560	−10.09
		C_{11}	−4650	−10.26
H 	0.065	C_8	−3350	−7.22
		C_9	−3150	−6.51
		C_{10}	−3100	−6.22
		C_{11}	−3180	−6.20

[a] ±40.
[b] ±0.3.

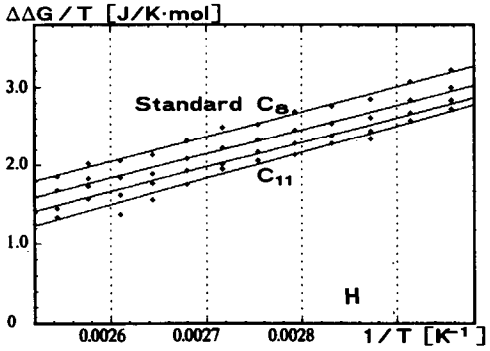


Fig. 12. Van 't Hoff plots for solute H (*cf.*, Tables II and III) (calculations of $\Delta\Delta G$ with respect to four different *n*-alkanes as reference standards), obtained on OV-1701 containing 0.065 *m* permethylated β-cyclodextrin.

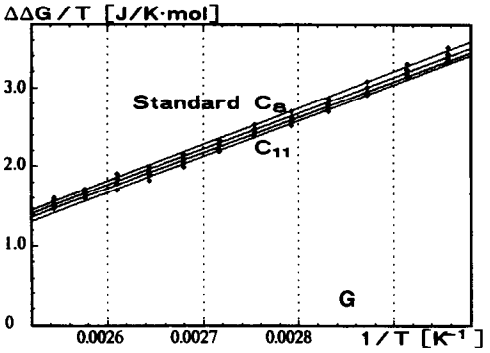


Fig. 13. Van 't Hoff plots for solute G (*cf.*, Tables II and III) (calculations of $\Delta\Delta G$ with respect to four different *n*-alkanes as reference standards), obtained on OV-1701 containing 0.065 *m* permethylated β-cyclodextrin.

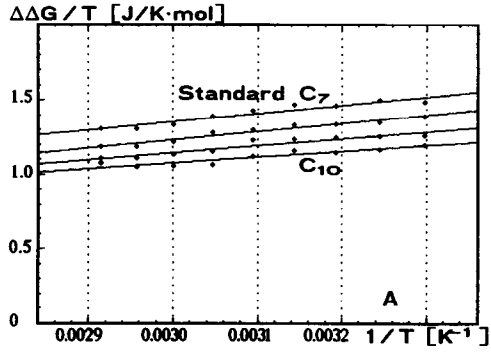


Fig. 14. Van 't Hoff plots for solute A (*cf.*, Tables II and III) (calculations of $\Delta\Delta G$ with respect to four different *n*-alkanes as reference standards), obtained on OV-1701 containing 0.065 *m* permethylated β-cyclodextrin.

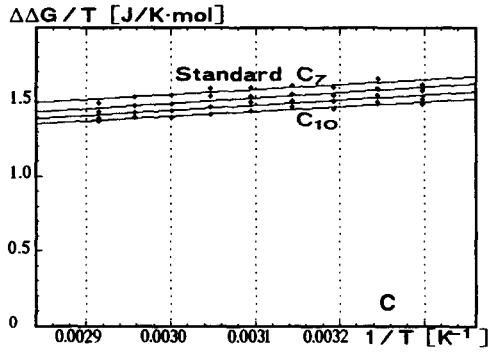


Fig. 15. Van 't Hoff plots for solute C (*cf.*, Tables II and III) (calculations of $\Delta\Delta G$ with respect to four different *n*-alkanes as reference standards), obtained on OV-1701 containing 0.065 *m* permethylated β-cyclodextrin.

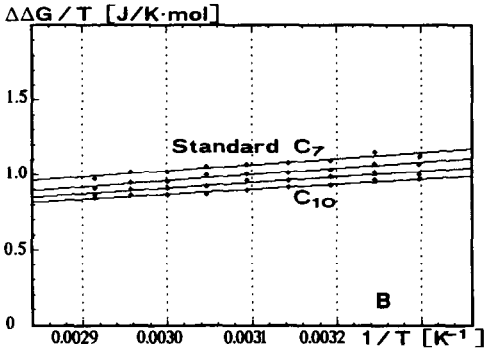


Fig. 16. Van 't Hoff plots for solute B (*cf.*, Tables II and III) (calculations of $\Delta\Delta G$ with respect to four different *n*-alkanes as reference standards), obtained on OV-1701 containing 0.065 *m* permethylated β-cyclodextrin.

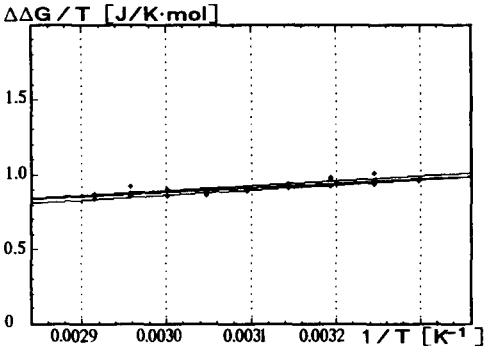


Fig. 17. Van 't Hoff plots for solute B, obtained on OV-1701 containing different molalities (0.042, 0.057 or 0.065 *m*) of permethylated β-cyclodextrin (standard: C_7). $\Delta\Delta G$ does not depend on the cyclodextrin molality m_A.

In contrast to α, $\Delta\Delta G$ is independent of the cyclodextrin molality m_A (*cf.*, Fig. 17 and eqn. 15).

Further observations

Changing the polysiloxane solvent might result in different K_L^0 (or K) and thus in different α values (owing to polarity or solvation effects). However, the replacement of OV-1701 with PS-086, a polysiloxane solvent of similar polarity, did not affect α or R' appreciably. Also, the replacement of all methyl protons with deuterium in permethylated β-cyclodextrin did not have a significant effect on the values of α, R' or $\Delta\Delta G$.

CONCLUSION

It could be shown that the theoretical treatment of enantioselectivity advanced in complexation GLC can also be applied to dissolved cyclodextrin stationary phases. However, there is no totally inert reference standard available for the determination of relative retention data, and therefore a small systematic error is introduced into the calculation of the retention increase R'. Yet, the good agreement of calculated and measured α *vs.* molality m_A curves supports the validity of our approach. The slight deviation from the expected linearity of the R' *vs.* m_A relationship is due to the systematic error mentioned above. The molecular association between the racemates and the cyclodextrin derivative is relatively weak, which results in small values of R'. Hence its contribution to the total retention time is not dominant. In contrast to complexation GLC, temperature-dependent reversals of the elution order (isoenantioselective temperatures) were extrapolated to occur only at temperatures too high to be measured or to be non-existent.

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