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THERMODYNAMIC PROPERTIES OF ENANTIOMERS OF UNDERIVATIZED DIOLS *VERSUS* THE CYCLIC CARBONATES IN GAS CHROMATOGRAPHY ON CHIRASIL-VAL

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SUMMARY

Enantiomers of underivatized vicinal alkyl diols are resolved by capillary gas chromatography on the polymeric chiral stationary phase Chirasil-Val. Owing to intramolecular hydrogen bonding of the type O–H···O, aliphatic 1,2-diols are far less polar than 1,3-diols, and can be separated with only moderate peak tailing on deactivated glass capillaries. Thermodynamic measurements reveal a fairly large difference in the enthalpy of interaction of the enantiomers ($\Delta\Delta H$) but also an unusual high negative (unfavourable) value for the entropy difference) ($\Delta\Delta S$). Hence the extrapolated isoselective temperature (T_s) is intriguingly low, but the resolution is thereby also restricted to the low-temperature range. The corresponding cyclic carbonates, formed by reaction with phosgen in toluene, are also fairly polar and therefore do not offer any significant advantage in terms of peak tailing. The resolution factors (α) are apparently small, owing to the very low values of $-\Delta\Delta H$ and $\Delta\Delta S$, but the isoselective temperature is usually much higher than for the diols.

INTRODUCTION

Chiral aliphatic compounds with several hydroxy groups[1–12] are important as starting compounds for the synthesis of natural products. Diols are formed in high enantiomeric purity by enzymatic conversion of suitable precursors[13–17]. Among different techniques for the determination of the enantiomeric excess (e.e.)[18–20], enantiomer resolution by gas chromatography (GC) of the underivatized hydroxy compounds on a chiral stationary phase[21–23] is the most convenient approach.

However, even on the particularly versatile polymeric phase L-[24] or D-Chirasil-Val[25,a], binaphthol[26], aryl-1,2-ethanediols[26] and aliphatic triols[11] are only separated after perfluoroacylation. Accordingly, trifluoracylation has been applied

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[a] Fused-silica capillary columns coated with either L- or D-Chirasil-Val are commercially available from Chrompack (Middelburg, The Netherlands).

prior to enantiomer resolution of polyols, such as sugar alcohols, on the stationary phase XE-60-L-Val-(*R*)-α-pea[27] and for diols and polyols on modified cyclodextrins[28]. Other methods involve conversion with phosgene or ethyl chloroformate into cyclic carbonates that are separated on XE-60-L-Val-(*R*)-α-pea[27], and the formation of either cyclic boronates or acetals that are separated by complexation GC[29]. N-Trifluoroacetylglycyl chloride has also been used as a promising achiral auxiliary to convert aliphatic 1,2- and 1,3-diols into monoesters with good enantiomer resolution factors (α) on Chirasil-Val[1]. However, all of these approaches have certain drawbacks. Apart from the additional time consumption and safety problems (*e.g.*, with phosgene) during sample preparation, the derivatization reactions may be accompanied by side-reations and racemization.

The purpose of this work was to extend the scope of the direct separation on well deactivated borosilicate glass capillaries coated with Chirasil-Val, previously reported briefly for *trans*-cyclohexane-1,2-diol[23], to other aliphatic diols, and to compare the chromatographic properties of the underivatized diols with those of the corresponding cyclic carbonates in terms of peak resolution and thermodynamic behaviour.

EXPERIMENTAL

Reference compounds

Racemic 1,2-propanediol, 1,2-hexanediol, *trans*-cyclohexanediol and *trans*-cycloheptanediol were purchased from Aldrich and 1,2-butanediol from Fluka. Mixtures of the three stereoisomers of 2,3-butanediol and 2,4-pentanediol were obtained from Fluka and Aldrich, respectively. (2*R*,4*R*)-Pentanediol was purchased from Aldrich. (2*S*,3*S*)-2,3-Butanediol[30] and (*S*)-1,2-propanediol[31] were synthesized according to literature procedures.

Cyclic carbonates

In a 1-ml Reactivial (Macherey, Nagel & Co.), 50 μl of a solution of phosgene in toluene (20%, 1.93 *M*; Fluka) were added to a sample of the diol (1–2 mg). After 1 h at ambient temperature, the reaction mixture was slowly concentrated in a gentle stream of nitrogen. Care should be taken to prevent the loss of volatile cyclic carbonates. Eventually, the oily residue was dissolved in 50 μl of dichloromethane.

Gas chromatography

Samples were eluted from a borosilicate glass (Duran 50; Schott, Mainz, F.R.G.) capillary column (M 174, 22 m × 0.28 mm I.D.), deactivated with diphenyltetramethyldisilazane (DPTMDS)[32], and coated with L-Chirasil-Val (film thickness 0.3 μm). Gas chromatography was performed on a Carlo-Erba Model 2001 AC gas chromatograph with hydrogen as the carrier gas at a constant inlet pressure (typically 0.4 kg cm^{-2}, splitting ratio 1:50) with flame ionization detection. Net retention times (from methane) were measured with a Trivector Trilab II laboratory computer. Calculations were run on an IBM XT computer.

RESULTS AND DISCUSSION

The free vicinal diols were injected on to a well deactivated borosilicate glass column, coated with L-Chirasil-Val. It was found that the peak resolution is strongly temperature dependent. For short-chain compounds, a good compromise between peak resolution and peak retention was reached at *ca.* 50°C. Within the series of terminal diols investigated (up to 1,2-hexanediol, **4a**), the peak resolution of the enantiomeric pairs increased with increasing chain length as a rule, for two reasons. First, as indicated in Table I, the resolution factors (α) are significantly increased in this order. Second, the influence of peak tailing on resolution vanishes for large capacity factors (k'). Similar trends are seen with the alicyclic compounds **5** and **6**, but they can be resolved at much higher temperatures.

The absolute configurations were assigned by using diols of high enantiomeric purity, *i.e.*, (*S*)-1,2-propanediol (**1a**) and (2*S*,3*S*)-butanediol, [(*S*,*S*)-**2a**] [synthesized in six steps from (*R*,*R*)-tartaric acid[30]]. (*R*,*R*)-**2a** and (*R*,*S*)-**2a** were assigned by comparison of the relative peak areas obtained from a synthetic mixture of the three stereoisomers.

The only 1,3-diol investigated, 2,4-pentanediol (**7**), was separated into the diastereoisomers with unlike (*R*,*S*) and like (*S*,*S* and *R*,*R*) configurations. However, the enantiomers of the latter were not resolved. This interesting observation deserves further comment (see below).

TABLE I

ENANTIOMER RESOLUTION OF ALIPHATIC DIOLS ON L-CHIRASIL-VAL

Conditions: capillary column (M 174, 22 m × 0.28 mm I.D., film thickness 0.3 μm); 0.4 kg cm^{-2} hydrogen; U = 28 m min^{-1}; t_0 = 55.5 s at 52°C; flame ionization detection.

No.	*Compound*	*Temperature (°C)*	*Stereo-isomer*	k'	α
1a	1,2-Propanediol	52	*S*	6.16	1.023
			R	6.30	
2a	2,3-Butanediol	52	*S,S*	5.07	1.046
			R,R	5.30	
			R,S	6.17	
3a	1,2-Butanediol	52	(1)[a]	12.30	1.056
			(2)[a]	12.99	
4a	1,2-Hexanediol	52	(1)[a]	67.7	1.062
			(2)[a]	71.9	
		72	(1)[a]	14.15	1.032
			(2)[a]	14.60	
5	*trans*-1,2-Cyclohexanediol	72	(1)[a]	14.63	1.030
			(2)[a]	15.07	
6	*trans*-1,2-Cycloheptanediol	92	(1)[a]	14.62	1.030
			(2)[a]	15.06	
7	2,4-Pentanediol	52	*S,S*/*R,R*	15.16	1[b]
			R,S	17.77	

[a] First and second peaks, absolute configuration not assigned.

[b] Not resolved.

TABLE II

ENANTIOMER RESOLUTION OF CYCLIC CARBONATES ON L-CHIRASIL-VAL

Conditions as in Table I.

No.	*Compound*	*Temperature (°C)*	*Stereo-isomer*	*k'*	*α*
1b	1,2-Propylene carbonate	52	*S*	5.90	1.015
			R	5.99	
2b	2,3-Butylene carbonate	52	*S,S*	6.32	1.037
			R,R	6.55	
			R,S	9.04	
3b	1,2-Butylene carbonate	52	(1)[a]	10.98	1.020
			(2)[a]	11.20	
4b	1,2-Hexylene carbonate	72	(1)[a]	15.03	1.028
			(2)[a]	15.45	

[a] First and second peaks, absolute configuration not assigned.

The resolution factors for vicinal diols are comparable to or even better than those of the corresponding carbonates formed by a derivatization reaction with phosgene or ethyl chloroformate, as determined on XE-60–L-Val-(*R*)-α-pea[27]. In order to make a fair comparison, some carbonates were prepared by reaction with a solution of phosgene in toluene and injected on to the same Chirasil-Val column. The chromatographic data are given in Table II. All carbonates investigated could be separated on Chirasil-Val, but in terms of resolution factors and capacity factors there is no point in resorting to this derivatization method. As shown in Fig. 1 for a typical example, **3a** *versus* **3b**, there is no striking advantage in peak shape, and thus peak resolution, of the carbonate on well deactivated Chirasil-Val columns.

In order to gain a better understanding of the chromatographic behaviour, the temperature coefficients of the Kováts retention indices of the diols **1a**–**4a** were

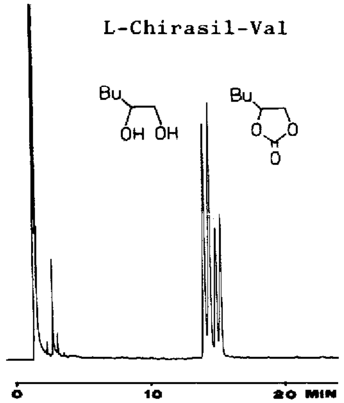

Fig. 1. Comparison of the enantiomer resolution of 1,2-hexanediol **4a** and the corresponding cyclic carbonate **4b** on L-Chirasil-Val with a DPTMDS-deactivated borosilicate glass column (22 m × 0.28 mm I.D.). Conditions: 0.4 kg cm^{-2} hydrogen, 72°C (isothermal), flame ionization detection. Bu = Butyl.

determined and compared with those of the carbonates **1b–3b**. Differences in the retention index–temperature relationship between the two classes of compounds are demonstrated in Fig. 2. In general, the slopes for the cyclic carbonates exceed those for the corresponding diols, thus reflecting the differences in entropy and enthalpy of interaction for the two classes of compounds, as compared with the coeluted hydrocarbons. The lines for the open-chain diols are rather flat; in other words, their enthalpies of interaction are approximately similar to those of the straight-chain hydrocarbons of comparable free enthalpy of interaction. In contrast, the lines for the carbonates are biased considerably. All carbonates have a positive temperature coefficient. Hence, on decreasing the oven temperature they are not retained as much as the coeluted hydrocarbons, owing to their smaller enthalpies of interaction. For a given temperature, they are coeluted with hydrocarbons with much higher $-\Delta H$ values, as the ΔS values are particularly small. In our experience with Chirasil-Val, such a behaviour is typical of cyclic compounds with little capability of hydrogen bonding to the stationary phase.

This interpretation is corroborated by the thermodynamic parameters of interaction of butanediols and the corresponding cyclic carbonates with L-Chirasil-Val, as given in Tables III and IV, respectively. Because of the hydrogen-bonding capability of the hydroxy groups, the enthalpies of interaction between the diols and the stationary phase are larger than those of the corresponding cyclic carbonates. However, owing to the influence of entropy, the free energies of the diols are usually lower than those of the corresponding derivatives, which are therefore eluted later within the temperature range investigated.

Striking dissimilarities between the two classes of compounds are also found in the differences in the thermodynamic parameters $-\Delta\Delta H$, $\Delta\Delta S$ and $-\Delta\Delta G$ (*cf.*, Tables V and VI). In general, the contributions of the (favourable) enthalpy and (unfavourable) entropy of interaction are much larger for the diols than the corresponding carbonates, owing to the contribution of hydrogen bonding to chiral recognition[26]. The differences in the free enthalpy values ($-\Delta\Delta G$), and hence the resolution factors

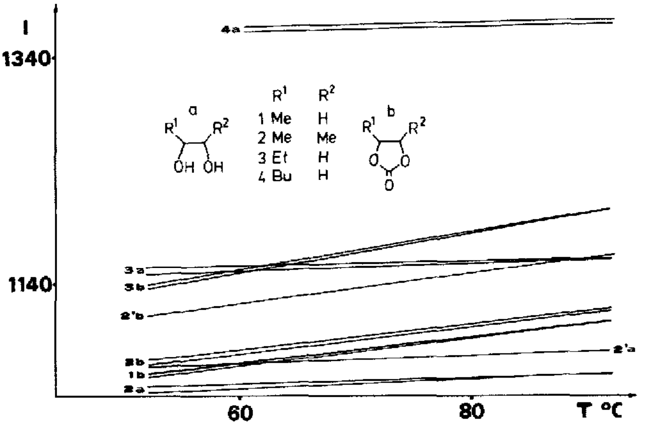

Fig. 2. Comparison of the temperature dependence of the Kováts retention indices of some aliphatic diols and the corresponding cyclic carbonates on L-Chirasil-Val. The notation **2'** refers to the achiral *meso* compound (*R*,*S*)-**2**.

TABLE III

THERMODYNAMIC PARAMETERS OF INTERACTION OF SOME ALIPHATIC DIOLS WITH L-CHIRASIL-VAL

No.	*Compound*	*Stereo-isomer*	$-\Delta H$ *(kcal mol^{-1})*	$-\Delta S$ *(cal mol^{-1} K^{-1})*	$-\Delta G_{298}$ *(kcal mol^{-1})*	$-\Delta G_{323}$ *(kcal mol^{-1})*	$-\Delta G_{373}$ *(kcal mol^{-1})*
2a	2,3-Butanediol	*S,S*	13.29	27.05	5.23	4.55	3.20
		R,R	13.60	27.93	5.28	4.58	3.18
		R,S	13.77	28.14	5.38	4.68	3.27
3a	1,2-Butanediol	(1)[a]	14.99	30.52	5.90	5.13	3.60
		(2)[a]	15.29	31.37	5.94	5.15	3.58

[a] First and second peak, absolute configuration not assigned.

TABLE IV

THERMODYNAMIC PARAMETERS OF INTERACTION OF SOME CYCLIC CARBONATES WITH L-CHIRASIL-VAL

No.	*Compound*	*Stereo-isomer*	$-\Delta H$ *(kcal mol^{-1})*	$-\Delta S$ *(cal mol^{-1} K^{-1})*	$-\Delta G_{298}$ *(kcal mol^{-1})*	$-\Delta G_{323}$ *(kcal mol^{-1})*	$-\Delta G_{373}$ *(kcal mol^{-1})*
2b	2,3-Butylene carbonate	*S,S*	12.59	24.47	4.69	3.46	2.24
		R,R	12.63	24.52	4.71	3.48	2.26
		R,S	12.75	24.23	5.52	4.92	3.71
3b	1,2-Butylene carbonate	(1)[a]	12.30	22.46	5.04	3.92	2.80
		(2)[a]	12.33	22.53	5.05	3.93	2.80

[a] First and second peak, absolute configuration not assigned.

TABLE V

ENANTIOMER DIFFERENCES IN THERMODYNAMIC PARAMETERS FOR SOME ALIPHATIC DIOLS WITH L-CHIRASIL-VAL

No.	$-\Delta\Delta H$ (*kcal mol*$^{-1}$)	$-\Delta\Delta S$ (*cal mol*$^{-1}$ *K*$^{-1}$)	$-\Delta\Delta G_{298}$ (*kcal mol*$^{-1}$)	$-\Delta\Delta G_{323}$ (*kcal mol*$^{-1}$)	α_{298}	α_{323}	T_s (°*C*)
2a	227.4	0.6090	45.8	30.6	1.080	1.049	100
	±53.8[a]	±0.1632	±7.5	±3.7	±0.014	±0.006	±14
3a	336.7	0.9277	60.1	36.9	1.107	1.059	90
	±43.8	±0.1336	±7.5	±3.7	±0.014	±0.006	±6
4a	287.7	0.7679	58.8	39.6	1.104	1.063	102
	±33.3	±0.0977	±5.4	±3.1	±0.010	±0.005	±5

[a] Standard deviations after ± signs.

(α), are much higher for the diols at 50°C and even more pronounced at 25°C, but not at elevated temperatures. The reason becomes obvious from the van't Hoff plot of ln α *versus* $1/T$ for the most striking example of **3a** versus **3b** (see Fig. 3). As the ratio of the enthalpy difference and entropy difference, $\Delta\Delta H/\Delta\Delta S$, is particularly small for the free diol **3a**, the isoselective temperature, T_s at which the selectivity is similar for a pair of compounds out of a multitude of sample components, depicted in Fig. 3 as the cross-section of the straight line with the abscissa, is unusually low. Further experiments with extra-long Chirasil-Val columns are in progress in order to demonstrate the expected peak reversal of the enantiomers of **3a** above 90 ± 6°C. Similar phenomena were predicted several years ago[26,33], and independently observed recently in three laboratories[34–36]. The extrapolated isoselective temperature (T_s) for the carbonate **3b** is considerably higher, *i.e.*, 252 ± 36°C, although both $-\Delta\Delta H$ and $\Delta\Delta S$ are much smaller. As expected, the ratio $T_s = \Delta\Delta H/\Delta\Delta S$ is larger for the interaction of the rigid carbonate with the chiral polysiloxane. In view of the different possible conformations of the free diols (see Fig. 4), one can presume in this instance that there is a dedicated change in conformation population during solute–solvent interaction. Such a significant change in the average conformation has been termed "induced fit"[37], in analogy with similar phenomena in enzyme–substrate recognition processes[38]. One should bear in mind, however, that such a change in average conformation, although it may increase the difference in the interaction enthalpies

TABLE VI

ENANTIOMER DIFFERENCES IN THERMODYNAMIC PARAMETERS FOR SOME CYCLIC CARBONATES WITH L-CHIRASIL-VAL

No.	$-\Delta\Delta H$ (*kcal mol*$^{-1}$)	$-\Delta\Delta S$ (*cal mol*$^{-1}$ *K*$^{-1}$)	$-\Delta\Delta G_{298}$ (*kcal mol*$^{-1}$)	$-\Delta\Delta G_{323}$ (*kcal mol*$^{-1}$)	α_{298}	α_{323}	T_s (°*C*)
3b	37.7	0.0437	24.7	23.6	1.0425	1.0374	589
	±0.7[a]	±0.0021	±0.1	±0.1	±0.0002	±0.0001	±7
4b	33.1	0.0631	14.3	12.7	1.0245	1.0200	252
	±3.6	±0.0109	±0.5	±0.3	±0.0009	±0.0004	±36

[a] Standard deviations after ± signs.

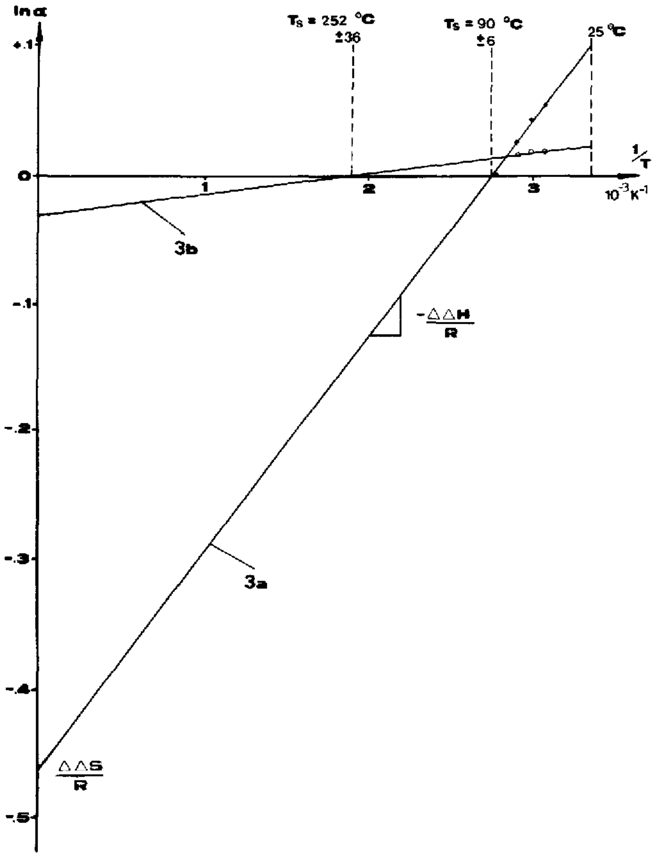

Fig. 3. Comparison of the van't Hoff plots of 1,2-butanediol (**3a**) and the corresponding cyclic carbonate **3b** for enantiomer resolution on L-Chirasil-Val. The extrapolated isoselective temperature, where peak inversion occurs, is marked T_s.

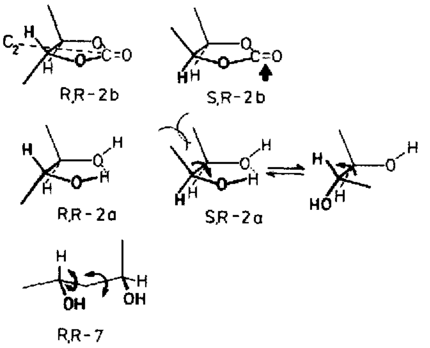

Fig. 4. Possible conformations for the cyclic carbonate **2b** and the free diols **2a** and **7**.

($-\Delta\Delta H$) of the two enantiomers, is very unfortunate in terms of the entropy difference ($\Delta\Delta S$), in particular at elevated temperature. Too much flexibility may even cancel possible differences in the interaction energies of the two enantiomers with the chiral stationary phase, as demonstrated by the non-resolved enantiomeric pair (*S*,*S*)/(*R*,*R*)-2,4-pentanediol.

Differences in conformation populations may also account for the relative retentivity of the diastereoisomers of **2a** and **2b**. As demonstrated by IR spectroscopy, the free diol **2a** with *like* configuration of the two stereogenic centres is more likely to undergo intramolecular hydrogen bonding[39] (see Fig. 4). Hence one can conclude that the *unlike* diastereoisomer is more prone to undergo intermolecular hydrogen bonding, and thus is retained more strongly by the stationary phase, which is indeed observed (see Table I). For the cyclic carbonate **2b**, a similar order of the diastereoisomers is found, but the explanation is completely different. The *unlike* diastereoisomer with a *cis* configuration is more readily accessible to the hydrogen-bonding amide moieties of the stationary phase (see arrow in Fig. 4) than the respective like diastereoisomer with a *trans* configuration, and is therefore more strongly retained.

It is noted with interest that the order of emergence of the enantiomers of the diols **1a** and **2a** from L-Chirasil-Val (see Table I) can be correlated with the corresponding simple alcohols[40] formed by replacement of one hydroxy function by an alkyl residue, leaving one residual hydroxy function at the stereogenic centre. Likewise, the derivative **2b** is eluted with an enantiomeric order that is comparable to that of perfluoroacylated arylethanediols[26] and vinyltriols[11].

CONCLUSION

Enantiomers of aliphatic 1,2-diols, in contrast to 1,3-diols, can be separated by gas chromatography on well deactivated glass capillaries coated with L-Chirasil-Val. At low temperature, the resolution factors (α) are even higher than for the corresponding cyclic carbonates. Although the properties of the two classes of compounds seem to be similar around 70°C, detailed studies reveal intriguing differences in their thermodynamic properties, according to the pronounced differences in conformational flexibility and in the mode of the solute–solvent interaction. The surprisingly low isoselective temperature (T_s) found for simple aliphatic 1,2-diols may shed new light on the strong influence of interaction entropy on the separation mechanism. Obviously, rigidity of either the solute or solvent molecules is not a prerequisite for separation, although it may help to keep the resolution at a high level at elevated temperatures. At low temperatures, on the other hand, well designed flexibility may give rise to a good balance between enthalpy and entropy of interaction, and thus to relatively high α values.

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