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Enantioselective separations by capillary gas chromatography on derivatized cyclodextrins

III. Separation of some racemic 2,2-dialkyl-4-alkoxycarbonyl-1,3-dioxolane derivatives on 2,3-di-O-acetyl-6-O-*tert*.-butyldimethylsilyl-β- and -γ-cyclodextrins

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ABSTRACT

The enantioseparation of a set of 2,2-dialkyl-4-alkoxycarbonyl-1,3-dioxolane derivatives, which are important intermediates in the total synthesis of biologically active compounds, was studied by means of capillary gas chromatography (cGC). The chromatographic results, obtained on columns coated with 2,3-di-O-acetyl-6-O-*tert*.-butyldimethylsilyl-β- and -γ-cyclodextrins are reported. Most of the compounds could be separated with a resolution greater than 1.42. Considerations concerning the interaction mechanism are presented.

INTRODUCTION

Enantioselective separations by means of capillary GC on derivatized cyclodextrin stationary phases are of major importance and well documented [1–3]. It has been stated on several occasions that, in order to increase the understanding of the interactions between cyclodextrins and analytes, systematic studies are imperative [4–6].

In Part I, the separation of a set of 1,3-dioxolane derivatives on permethyl-α-, -β- and -γ-cyclodextrins was discussed [7]. These compounds are important intermediates in the total synthesis of biologically active compounds [8]. An attempt was made to describe the cyclodextrin–analyte complex structure starting from the dependence of enantioselectivity on the structural variations of the cyclodextrin and the analyte. In this contribution, we continue this approach by describing the enantioselectivity of the same set of 1,3-dioxolane derivatives on 2,3-di-O-acetyl-6-O-*tert*.-butyldimethylsilyl (TBDMS)-β- and -γ-cyclodextrins. The chromatographic behaviour of 2,3-di-O-acetyl-6-O-TBDMS-cyclodextrins was studied previously by Mosandl and co-workers [9–12]. Compared with permethyl-cyclodextrins, 2,3-di-O-acetyl-6-O-TBDMS-cyclodextrins differ in two respects: the substituent on C-6 is much larger and the C-2–C-3

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side of the cavity is fairly polar. It can be expected that those two differences will influence the enantioselectivity.

EXPERIMENTAL

Stationary phases

6-O-TBDMS-β- and -γ-cyclodextrins were synthesized according to the procedure described by Buda *et al.* [13] from the corresponding native cyclodextrins by reaction with TBDMS-Cl in imidazole and pyridine. The synthesis of 6-O-TBDMS cyclodextrins was described previously by Takeo *et al.* [14]. 2,3-Di-O-acetyl-6-O-TBDMS-β- and -γ-cyclodextrins were synthesized from 6-O-TBDMS-β- and -γ-cyclodextrins according to Buda *et al.*, [13] by reaction of 6-O-TBDMS-cyclodextrin with acetic anhydride in pyridine.

Column preparation

Fused-silica open tubular (FSOT) columns (25 m × 0.25 mm I.D.) were treated by static leaching (2% HCl) and Carbowax deactivation [15]. The columns were coated by the static method using cyclodextrin–OV-1701 (1:1, w/w) dissolved in dichloromethane, providing a film thickness of 0.25 μm.

Gas chromatographic conditions

Gas chromatography was performed on a Varian 3700 GC system, equipped with a split–splitless injector and flame ionization detector, both operated at 230°C. A 1-μl volume of a 0.1% (w/v) solution in dichloromethane was injected with a splitting ratio of 1:100. Hydrogen at a pressure of 70 kPa was used as the carrier gas. All analyses were performed isothermally.

Synthesis of analytes

All analytes were prepared as reported previously [7,8].

RESULTS AND DISCUSSION

The structures of the analytes studied are given in Table I. The chromatographic data obtained from the separation of the analytes on 2,3-di-O-acetyl-6-O-TBDMS-β- and -γ-cyclodextrin are given in Tables II and III.

All the selectivity factors display a consistent increase with decrease in temperature. In order to make the discussion clearer, only the data at 110°C (italic values in Tables II and III) will be discussed, as the data at other temperatures show the same tendencies. From Table I it can be seen that the analyte set can be divided into three groups: different substitution at C-4 and C-5 (compounds **1–8**); different substitution at C-2 (compounds **1** and **13–16**); and different ester alkyl chains (compounds **1** and **9–12**).

Effect of cyclodextrin C-6 substitution

When comparing the selectivity factors obtained for permethyl-α-, -β- and -γ-cyclodextrins [7], with only a few exceptions, the largest values are found for permethyl-β-cyclodextrin. However, for 2,3-di-O-acetyl-6-O-TBDMS-cyclodextrins, the largest enantioselectivity is observed on the γ-derivative in most instances. This shift of the optimum selectivity from permethyl-β-cyclodextrin to 2,3-di-O-acetyl-6-O-TBDMS-γ-cyclodextrin is probably a result of the cyclodextrin substitution pattern at the C-6 position. 6-O-TBDMS substitution requires much more space than 6-O-methyl substitution. This causes the cyclodextrin to rotate around the C-1–O–C-4 bonds of the glucose units, leading to a decrease of the ring opening at the C-2–C-3 side. Such a phenomenon has also been described for substitution of C-6-OH by C-6-OCH_3 [16]. The effects are shown in Fig. 1.

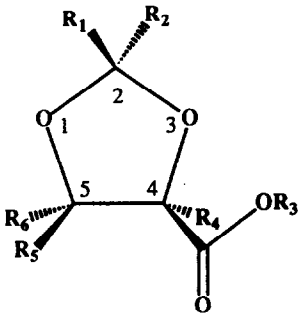
In view of the large effect of the nature of the cyclodextrin on selectivity, it can be concluded that the interaction mechanism is mainly steric in nature. Inclusion of the analyte in the cyclodextrin is to be expected from the C-2–C-3 side, as the bulky TBDMS groups will hamper entry from the C-6 side.

Effect of analyte acetal function

From Tables II and III, it can be observed that the enantioselectivity for analytes with a different substitution pattern on C-2 (acetal function) behaves totally differently for β- and γ-cyclodextrins. With 2,3-di-O-acetyl-6-O-TBDMS-β-cyclodextrin, the selectivity factor decreases to 1

TABLE I

STRUCTURES OF THE ANALYTES STUDIED



No.	R_1	R_2	R_3	R_4	R_5	R_6
1	CH_3	CH_3	n-C_4H_9	H	H	H
2	CH_3	CH_3	n-C_4H_9	H	CH_3	H
3	CH_3	CH_3	n-C_4H_9	H	H	CH_3
4	CH_3	CH_3	n-C_4H_9	CH_3	H	H
5	CH_3	CH_3	n-C_4H_9	CH_3	CH_3	H
6	CH_3	CH_3	n-C_4H_9	H	CH_3	CH_3
7	CH_3	CH_3	n-C_4H_9	CH_3	H	CH_3
8	CH_3	CH_3	n-C_4H_9	H	H	C_2H_5
9	CH_3	CH_3	CH_3	H	H	H
10	CH_3	CH_3	C_2H_5	H	H	H
11	CH_3	CH_3	n-C_3H_7	H	H	H
12	CH_3	CH_3	iso-C_3H_7	H	H	H
13	C_2H_5	C_2H_5	n-C_4H_9	H	H	H
14	n-C_3H_7	n-C_3H_7	n-C_4H_9	H	H	H
15	$-CH_2(CH_2)_2CH_2-$		n-C_4H_9	H	H	H
16	$-CH_2(CH_2)_3CH_2-$		n-C_4H_9	H	H	H

if the substituent on C-2 changes from dimethyl to larger alkyl groups. For the γ-cyclodextrin, however, a more complex behaviour is observed. Owing to its larger internal diameter, the γ-cyclodextrin is capable of accommodating larger analytes more effectively, which results in an increased enantioselectivity. The small selectivity decrease observed on replacing methyl with ethyl (compounds **1** and **13**) and when replacing cyclopentyl with cyclohexyl (compounds **15** and **16**) may be ascribed to polar effects on the C-2–C-3 rim.

Effect of analyte ester function

Fig. 2 shows the dependence of selectivity upon ester chain length on 2,3-di-O-acetyl-6-O-TBDMS-β-cyclodextrin. The decrease in selectivity on increasing the ester chain length (compounds **9–10–11–1**) for 2,3-di-O-acetyl-6-O-TBDMS-β-cyclodextrin is caused by the increase in the apolar character of the ester in the polar cyclodextrin environment. The effect is large and shows a clear dependence, because the β-cyclodextrin ring is small and the hydrocarbon chain has no freedom to avoid the unfavourable interaction with the polar C-2–C-3 rim. For 2,3-di-O-acetyl-6-O-TBDMS-γ-cyclodextrin, the change in selectivity on changing the ester chain length is less clear. The enantioselectivity decreases from Me to Et ester substitution and subsequently increases with increasing chain length of the ester function. No explanation can be presented based on the available data, al-

TABLE II

CHROMATOGRAPHIC RESULTS OF THE ISOTHERMAL ANALYSIS OF THE ANALYTES ON 2,3-DI-O-ACETYL-6-O-TBDMS-β-CYCLODEXTRIN

Compound	100°C			110°C			130°C			150°C		
	α	k'_2	R_s	α	k'_2	R_s	α	k'_2	R_s	α	k'_2	R_s
1	1.027	15.80	1.67	*1.021*	9.38	1.38	1.011	3.74	0.47	–[a]	1.67	–[a]
2	1.061	16.22	3.72	*1.043*	9.95	2.43	1.020	4.00	1.18	–[a]	1.80	–[a]
3	1.037	11.31	2.24	*1.025*	7.03	1.36	1.007	2.93	0.30	–[a]	1.36	–[a]
4	1.009	9.50	0.48	–[a]	6.07	–[a]	–[a]	2.67	–[a]	–[a]	1.28	–[a]
5	–[a]	10.72	–[a]	–[a]	6.88	–[a]	–[a]	3.01	–[a]	–[a]	1.43	–[a]
6	1.016	13.88	0.86	*1.012*	8.85	0.64	–[a]	3.69	–[a]	–[a]	1.69	–[a]
7	1.012	10.93	0.72	–[a]	6.85	–[a]	–[a]	3.00	–[a]	–[a]	1.42	–[a]
8	1.014	17.67	0.77	*1.008*	10.27	0.47	–[a]	4.25	–[a]	–[a]	1.94	–[a]
9	1.131	4.18	6.16	*1.093*	2.53	3.76	1.048	1.07	1.38	1.012	0.52	0.17
10	1.051	5.37	2.76	*1.039*	3.38	1.85	1.023	1.44	0.91	–[a]	0.68	–[a]
11	1.045	8.88	2.61	*1.034*	5.32	1.80	1.018	2.22	0.71	–[a]	1.00	–[a]
12	1.030	5.51	1.42	*1.020*	3.44	0.94	–[a]	1.51	–[a]	–[a]	0.72	–[a]
13				*1.010*	24.53	0.62	–[a]	9.16	–[a]	–[a]	3.59	–[a]
14				–[a]	60.69	–[a]	–[a]	20.39	–[a]	–[a]	7.11	–[a]
15				–[a]	52.75	–[a]	–[a]	17.68	–[a]	–[a]	6.34	–[a]
16				–[a]	86.39	–[a]	–[a]	27.36	–[a]	–[a]	10.01	–[a]

[a] No separation observed.

TABLE III

CHROMATOGRAPHIC RESULTS OF THE ISOTHERMAL ANALYSIS OF THE ANALYTES ON 2,3-DI-O-ACETYL-6-O-TBDMS-γ-CYCLODEXTRIN

Compound	100°C			110°C			130°C			150°C		
	α	k'_2	R_s	α	k'_2	R_s	α	k'_2	R_s	α	k'_2	R_s
1	1.026	15.88	1.35	*1.020*	9.90	0.91	–[a]	3.85	–[a]	–[a]	1.74	–[a]
2	1.069	21.79	3.64	*1.055*	12.60	2.84	1.036	4.72	1.62	1.020	2.03	0.62
3	1.099	15.23	4.91	*1.069*	8.82	3.38	1.032	3.41	1.25	–[a]	1.49	–[a]
4	1.220	13.46	10.05	*1.160*	7.90	6.99	1.082	3.25	3.05	1.042	1.41	1.22
5	1.065	16.62	3.20	*1.043*	9.43	2.02	1.018	3.56	0.66	–[a]	1.58	–[a]
6	1.179	24.20	8.45	*1.128*	11.95	6.20	1.066	4.42	3.02	1.035	1.92	1.10
7	1.646	22.33	26.33	*1.432*	11.71	17.46	1.188	3.94	7.39	1.082	1.65	2.39
8	1.017	19.09	0.78	*1.012*	11.20	0.54	–[a]	4.55	–[a]	–[a]	2.01	–[a]
9	1.050	5.65	1.17	*1.037*	3.31	0.93	–[a]	1.89	–[a]	–[a]	0.70	–[a]
10	–[a]	6.88	–[a]	–[a]	4.14	–[a]	–[a]	1.83	–[a]	–[a]	0.87	–[a]
11	1.017	11.80	0.50	*1.010*	7.10	0.31	–[a]	2.88	–[a]	–[a]	1.37	–[a]
12	1.040	6.94	1.26	*1.031*	4.30	0.93	1.014	1.84	0.33	–[a]	0.90	–[a]
13				*1.015*	26.62	0.75	–[a]	9.56	–[a]	–[a]	4.04	–[a]
14				*1.020*	66.95	0.48	1.010	20.93	0.43	–[a]	8.03	–[a]
15				*1.041*	58.19	2.23	1.023	19.33	1.16	1.009	7.71	0.32
16				*1.035*	95.84	1.77	1.019	33.30	0.95	–[a]	11.70	–[a]

[a] No separation observed.

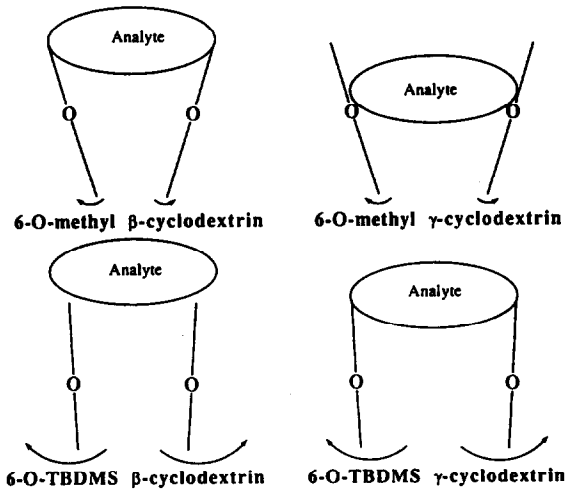


Fig. 1. Effect of C-6 substitution on cyclodextrin ring opening and analyte complexation.

though one cannot exclude inversion of elution order [17].

Effect of C-4–C-5 substitution

Fig. 3 shows the separation of compounds **1**, **3**, **4** and **7** on 2,3-di-O-acetyl-6-O-TBDMS-γ-cyclodextrin. For the methyl substituents on C-4 and C-5 the selectivity relationships, which are dependent on steric and polar effects from all interacting methyl functions, have become very complex. The effect of C-4 methyl substitution seems clear, however. On 2,3-di-O-acetyl-6-O-TBDMS-β-cyclodextrin, the selectivity decreases in all instances on addition of R_4 (compounds **4** and **1**, **5** and **2**, **7** and **3**) for steric reasons. For the γ-derivative, comparison of compounds **4** and **1**, **7** and **3** shows a strong increase in selectivity on addition of an R_4 methyl group.

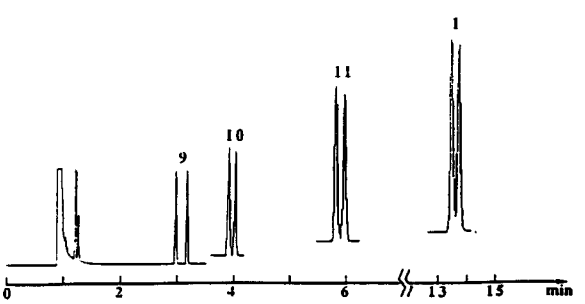


Fig. 2. Separation of compounds **9**, **10**, **11** and **1** on 2,3-di-O-acetyl-6-O-TBDMS-β-cyclodextrin at 110°C.

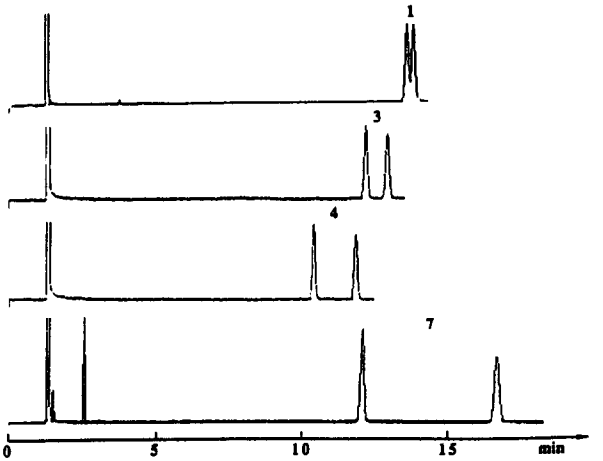


Fig. 3. Separation of compounds **1**, **2**, **3** and **7** on 2,3-di-O-acetyl-6-O-TBDMS-γ-cyclodextrin at 110°C.

It is remarkable that the largest selectivities in the series of compounds **1–8** are found for compound **7** on the γ-derivative (R_4 and R_6 = methyl), whereas for the β-derivative compound **2** gives the largest selectivity (R_5 = methyl). Increasing the R_6 chain length (compounds **1**, **3** and **8**) gives maximum selectivity for methyl substitution, for both 2,3-di-O-acetyl-6-O-TBDMS-β- and -γ-cyclodextrin.

CONCLUSIONS

The investigation of the enantioselectivity of a set of 2,2-dialkyl-4-alkoxycarbonyl-1,3-dioxolane derivatives on 2,3-di-O-acetyl-6-O-TBDMS-β- and -γ-cyclodextrins clearly demonstrates the importance of geometric factors. Small changes in the analyte structure have large effects on the selectivity factors. The same holds for the cyclodextrins: a very large difference in selectivity has been observed between 2,3-di-O-acetyl-6-O-TBDMS-β- and -γ-cyclodextrin.

The results obtained strongly support an inclusion type of interaction mechanism. Compared with permethyl cyclodextrins, 2,3-di-O-acetyl-6-O-TBDMS-cyclodextrins are less selective for the analytes. This can be ascribed to the polarity of the C-2–C-3 rim and/or to a diameter change at the C-2–C-3 side of the cyclodextrin owing to bulky C-6 substituents. Further study on the

chromatographic behaviour of the sixteen dioxolanes on 2,3-di-O-methyl-6-O-TBDMS-cyclodextrins is in progress.

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