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A Maltooctaose Derivative ("Acyclodextrin") as a Chiral Stationary Phase for Enantioselective Gas Chromatography

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The enantiorecognition mechanism of several cyclodextrin derivatives is still not completely rationalized, and the application of acyclic selectors may aid to explain the role of the cavity (typical of the underivatized cyclic selectors) combined with the functional groups introduced by multistep synthesis. Octakis[(3-*O*,-4′′*O*)-butanoyl-(1′-*O*,2,6-di-*O*)-*n*-pentyl]maltooctaose was applied as a chiral stationary phase for gas chromatographic enantioseparation. Selected racemic compounds were enantioseparated also on the acyclic phase. The promising results of this chiral selector [and its direct comparison with the cyclic counterpart octakis(2,6-di-*O*-*n*-pentyl-3-*O*-butanoyl)-γ-cyclodextrin (Lipodex E)] suggest the application of other well-known spectroscopic techniques (CD, NMR) to point out further details on the mechanism of enantiorecognition.

Introduction

The elucidation of the mechanism of enantiorecognition[1] and the assignment of absolute configuration[2] are still open challenges, especially with respect to cyclodextrin-based chiral selectors. The cyclic selector [octakis(2,6-di-O-*n*-pentyl-3-O-butanoyl)-γ-cyclodextrin (Lipodex E, CD8)] represents one of the most common and versatile cyclodextrin derivatives used as a chiral stationary phase (CSP) in enantioselective gas chromatography.[3–5] The comprehensive NMR spectroscopic characterization of this cyclic host molecule revealed the self-inclusion of a 6-O-*n*-pentyl group into the molecular cavity, which may reduce the propensity of potential guest molecules for inclusion by steric constraint.[6] The application of an *acyclic* carbohydrate selector can be used to probe the role of the cavity for enantiorecognition of modified cyclodextrins.[7] Previously, linear oligosaccharides with different derivatization patterns have been applied as CSPs for enantioselective GC, for example, per-*n*-pentylated amylose,[8] amylose tris(*n*-butylcarbamate),[9] and a maltoheptaose derivative.[10,11] Acyclic dextrin derivatives carrying *tert*-butyldimethylsilyl groups at the primary hydroxy sites and acetyl groups at the secondary hydroxy sites showed indeed an unexpected ability for the enantioseparation of α-amino acid derivatives and halogenated compounds reinforcing the role of the polar external surface of derivatized oligosaccharides in enantiorecognition.[11] Also, in capillary zone electrophoresis, underivatized maltoheptaose has been applied as chiral selector for the enantioseparation of racemic compounds.[12,13] The application of maltooligosaccharides was also extended to enantioselective HPLC.[14] In general, the extensive derivatization of cyclic and acyclic dextrins usually results in the formation of a more flexible structure relative to that of the native oligosaccharides, which renders the elucidation of the mechanisms of enantiorecognition more difficult. In the present work, the enantioselectivity of the acyclic selector octakis[(3-*O*,-4′′*O*)-butanoyl-(1′-*O*,2,6-di-*O*)-*n*-pentyl]maltooctaose (G8, **1**) toward selected racemic compounds is compared with that of the cyclic counterpart octakis(3-O-butanoyl-2,6-di-O-*n*-pentyl)-γ-cyclodextrin (Lipodex E, CD8).

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Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Results and Discussion

Linear maltooctaose derivative **1** was synthesized according to the multistep procedure employed for CD8 by *n*-pentylation, carried out with *n*-pentyl bromide in dry DMSO, followed by acylation with butyric anhydride in dry pyridine (Figure 1). Details regarding the synthesis of selector **1** are described in the Supporting Information (S1). As in the case of cyclic selector CD8,[3] maltooctaose derivative G8 (**1**) was dissolved in a semipolar polysiloxane (PS 255) by adopting the general procedure of Schurig and

Nowotny[15] for diluted permethylated cyclodextrins, followed by the static coating of a fused silica capillary column.[16] The highest gas chromatographic enantioseparation factor ever achieved in enantioselective GC was observed for the chiral degradation product of the achiral halogenated anaesthetic sevoflurane, that is, 2-(fluoromethoxy)-3-methoxy-1,1,1,3,3-pentafluoropropane (**2**), CD8 (Lipodex E).[3] Surprisingly, the enantioseparation of **2** occurs also on acyclic G8 (**1**), although with a very significant reduction in the enantioselectivity (α = 1.06 on G8 vs. α = 10.6 on CD8, at 26 °C; Figure 2). It is interesting to point out that a remarkable difference in enantioselectivity is also observed for the cyclic selectors CD6, CD7, and CD8 with the same *n*-pentyl/butanoyl derivatization pattern (Table 1).[2] This leads to the unexpected finding that enantioselectivity is still displayed by acyclic G8 (**1**) but is totally lost by cyclic CD6 (Table 1). Although devoid of a molecular cavity, the acyclic maltooctaose derivative G8 (**1**) is able to enantioseparate different classes of compounds ranging from pentafluoropropyl derivatives of amines to heptafluorobutanoyl derivatives of alcohols, including underivatized diols and trifluoroacetyl derivatives of diols (Supporting Information, S2). For the racemic compounds listed in S2 of the Supporting Information, cyclic CD8 usually exhibits a better enantioseparation ability relative to that of acyclic G8 (**1**). This trend holds also true for the enantioseparation of racemic *N*-trifluoroacetyl-*O*-methyl esters of selected α-amino acids (Supporting Information, S3). However, an unexpected trend is observed for the enantioseparation of halogenated compounds **3**–**5**. Whereas a higher enantioseparation ability and a significant retention factor is observed for methyl 2-chloropropionate (**3**; Figure 3a) on the cyclic selector CD8 relative to that of acyclic G8 (**1**), the same enantioseparation factor α is obtained for racemic 2,4-dibromobutane (**5**; Figure 3c and Table 2), a result which clearly challenges the role of the cavity in the case of CD8. The diastereoselectivity may also differ between CD8 and G8 (**1**) (Figure 3b). Thus, for the three stereoisomers of 2,3-dibromobutane (**4**), the *meso* compound is eluted before the two enantiomers on acyclic G8 (**1**) but between the two enantiomers on cyclic CD8. The propensity of linear acyclic dextrins to separate enantiomers of various classes of compounds requires a reappraisal of the role of the cavity of cyclodextrins in enantioselective gas chromatography, notably when enantioseparation factors are low ($\alpha < 1.05$, the usual trend) and thus comparable to those observed with modified dextrins.

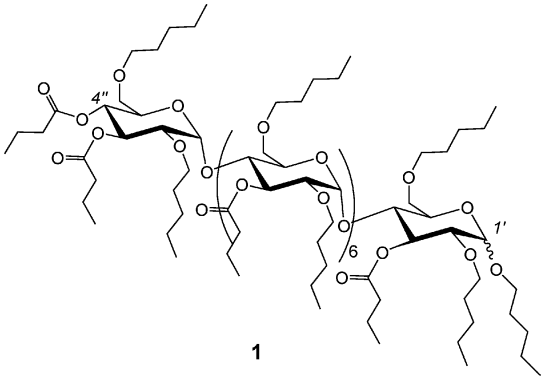


Figure 1. Acyclic G8 (**1**).

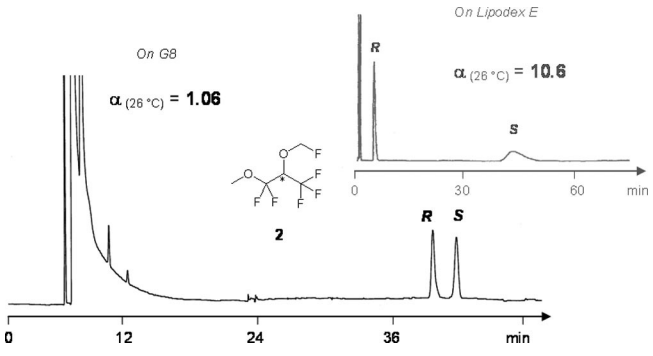


Figure 2. Gas chromatographic separation of racemic **2** on octakis-[(3-*O*,-4′′*O*)-butanoyl-(1′-*O*,2,6-di-O)-*n*-pentyl]maltooctaose (**1**), 30% (w/w) in PS 255. Column: 20 m × 0.25 mm i.d. fused-silica capillary, film thickness 0.25 μm. Carrier gas: 30 kPa helium; oven temperature: 26 °C. Octakis(2,6-di-*O*-*n*-pentyl-3-*O*-butanoyl)-γ-cyclodextrin (CD8) 30% in PS 255. Column: 5 m × 0.25 mm i.d., film thickness: 0.25 μm. Carrier gas: 12 kPa H_2; oven temperature: 26 °C.

Table 1. Enantioseparation factor α of **2** on modified *n*-pentyl/butanoyl cyclic (CD8) and acyclic (G8) dextrins [each 30% (w/w) in PS 255]. Carrier gas: 30 kPa (H_2), oven temperature: 30 °C.

CSP	α
CD6	1.00
CD7	2.08
CD8	9.70
G8	1.06

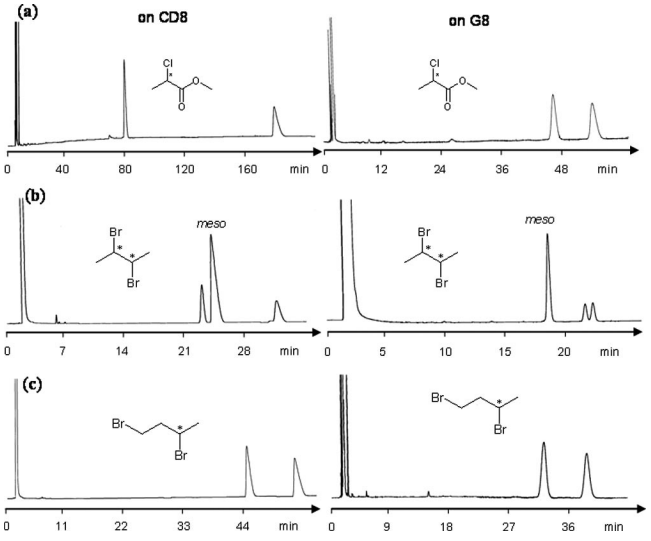
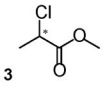
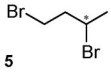


Figure 3. Gas chromatographic enantioseparation of racemic **3**, **4**, and **5** on CD8 (left) and on G8 (**1**) (right) [each 30% (w/w) in PS 255]. Columns: 25 m × 0.25 mm i.d. fused-silica capillary, film thickness: 0.25 μm. For other experimental conditions, see S4 of the Supporting Information.

Table 2. Retention factor k_1 (first eluted enantiomer), enantioseparation factor α, and resolution factor R_s for racemic **3**, **4**, and **5**. Experimental conditions: a) 40 °C, 50 kPa (H_2); b) 40 °C, 50 kPa (H_2). Columns: 25 m × 0.25 mm i.d. fused-silica capillary, film thickness: 0.25 μm.

	CD8			G8 (1)		
	k_1	α	R_s	k_1	α	R_s
 **3**	39.8	2.38	25.3	22.7	1.18	3.89
 **4**	11.1	1.38	9.44	8.54	1.02	0.91
	11.6 (*meso*)	–	–	7.84 (*meso*)	–	
 **5**	21.9	1.19	5.59	14.9	1.17	8.85

Conclusions

Derivatized acyclic dextrins ("acyclodextrins") represent a new class of carbohydrate-based selectors for gas chromatographic enantioseparation amenable to the investigations of the role of molecular inclusion. Thus, for derivatized carbohydrates, the presence of a molecular cavity is not a prerequisite for gas chromatographic separation of enantiomers; an observation that has some important bearings on the elucidation of the mechanisms of enantiorecognition by comparative studies between G8 (**1**) and CD8. The enantioseparation obtained for all of the above-mentioned racemic compounds on the linear chiral stationary phase G8 (**1**), albeit with lower separation factors, clearly demonstrates the role of the *n*-pentyl and butanoyl groups in the enantiorecognition process, which may, in the future, be further probed by NMR spectroscopic studies. An avenue has been opened for further screening of different derivatization patterns in an effort to increase the enantioselectivity of acyclic dextrin selectors. Another variable is the degree of oligomerization of the linear oligosaccharides including the parent derivatized glucose building block, as demonstrated previously for another derivatization pattern.[11] The incentive to employ acyclic carbohydrates rests on the possibility to obtain the selectors in the natural all-D- and in the unnatural all-L-configurations, which is important for peak switching scenarios precluded for cyclodextrins that are readily available only in the all-D-configuration. Furthermore, these novel acyclic selectors may also be applied as chiral solvating agents (CSAs) in solution for the determination of chemical shift nonequivalencies of chiral compounds by NMR spectroscopic analysis, which has previously been performed with cyclic CD8 (Supporting Information, S5–S7).

Experimental Section

Maltooctaose derivative **1** was synthesized according to the following multistep procedure: To a solution of the native maltooctaose (0.5 g, 0.38 mmol) in dry DMSO (14 mL) was added pulverized NaOH (0.55 g, 13.8 mmol) and 1-bromopentane (1.7 mL, 13.8 mmol), and the mixture was stirred at room temperature. A white precipitate of NaBr was formed. After stirring for 2 d, an additional amount of pulverized NaOH (0.55 g 13.8 mmol) was added, followed by the addition of 1-bromopentane (1.7 mL, 13.8 mmol). After a total of 5 d, the mixture was poured in water and extracted with diethyl ether (2×). The organic phase was washed with water, dried with Na_2SO_4, and the solvent was evaporated. The raw product was characterized by maltooctaose bearing sixteen (M_1), seventeen (M_2), or eighteen (M_3) *n*-pentyl functional groups due to the excess amount of 1-bromopentane (1:1.4) used for the alkylation. MS (ESI): m/z = 2348 $[M_1 + H]^+$, 2508 $[M_2 + H]^+$, 2578 $[M_3 + H]^+$; this mixture was used for the subsequent acylation reaction without further purification.

The above-prepared material (0.1 g) and 4-dimethylaminopyridine (1.7 mg, 0.01 mmol) were dissolved in dry dichloromethane (3.5 mL) under an atmosphere of nitrogen. After the addition of triethylamine (0.09 mL, 0.63 mmol), butyric anhydride (0.1 mL, 0.56 mmol) was added. The mixture was stirred under reflux. After 2 d, another portion of triethylamine (0.09 mL) and butyric anhydride (0.1 mL) was added, and the mixture was heated at reflux for 8 d. The excess amount of reagent and other volatiles were removed under a stream of nitrogen, and the product was taken up in diethyl ether. The organic layer was washed with water, diluted $NaHCO_3$ solution, water, diluted NaH_2PO_4 solution, and lastly water. After drying with Na_2SO_4 and removal of the solvent, the raw product was chromatographed over silica (toluene/ethyl acetate, 9:1) to obtain **1** (0.3 g, 35%). MS (ESI): m/z = 1570 $[M + 2H]^{2+}$ (main species, $C_{169}H_{306}O_{50}$). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.81–0.94 (78 H, CH_3, a-f-m), 1.11–1.38 (68 H, CH_2, b-c-g-h), 1.39–1.65 (52 H, CH_2, d-i-n), 2.17–2.30 (CH_2, o, 18 H), 2.91–4.22 (73 H, CH_2, e-l, H^2, H^4, H^5, H^{6a}, H^{6b}), 4.52–5.75 (17 H, $H^{4''}$, H^1, H^3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 13.4–22.5 (C^a, C^f, C^m), 28.1–36.4 (C^b, C^c, C^d, C^g, C^h, C^i, C^n), 62.8–82.2 (C^e, C^l, C^2, C^3, C^4, C^5, C^6), 96.1–103.5 (C^1) 128.2 (C^o), 172.1–172.8 (C=O) ppm.

Supporting Information (see footnote on the first page of this article): Further details (materials and general methods) of synthetic procedures and selected enantioseparation/enantiodiscrimination.

Acknowledgments

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