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Resolution of Chiral [2.2]Paracyclophanes by Enantioselective Gas Chromatography

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Abstract: [2.2]Paracyclophanes possessing a substituent on the aromatic ring are dissymmetric compounds due to the restricted rotation of the benzene rings. For interconversion of enantiomers temperatures above 200 °C are necessary. We have succeeded in resolving the enantiomers of some mono-substituted [2.2]paracyclophanes by enantioselective gas chromatography using 2,3-di-O-methylated β-cyclodextrins with bulky O-(1,1,2-trimethylpropyl)-dimethylsilyl or O-*t*.butyl-dimethylsilyl substituents in the 6-position of the glucose units as chiral stationary phases.

INTRODUCTION

Compared to the importance of stereogenic centres in structural and synthetic chemistry the potential of planar chirality has so far remained largely unexplored. The reasons for this neglection are manifold, one important drawback being the previously rather limited availability of optically active planar chiral compounds. This situation has changed, however, during the last few years, since the most important planar chiral systems, chiral metallocenes and cyclophanes, are now available in sufficient amounts and in large structural variety. Regardless of the possible uses of these compounds, e. g. in stereoselective synthesis, a reliable and fast analytical method to determine their enantiomeric purity is a *conditio sine qua non* for further applications. Having shown that various [2.2]paracyclophanes can be separated by high performance liquid chromatography on tris(3,5-dimethylphenylcarbamates) of cellulose and amylose[1] we now describe the resolution of these compounds by capillary gas chromatography on modified cyclodextrins.

EXPERIMENTAL

Heptakis(2,3-di-O-methyl-6-O-dimethylthexylsilyl)-β-cyclodextrin

To a solution of 120 mg (83 μmol) of heptakis(2,3-di-O-methyl)-β-cyclodextrin[2] in 10 ml of dry tetrahydrofuran at 0 °C and under N_2 200 mg (8.7 mmol) sodium hydride and after 10 min dropwise 1 g (5.81 mmol) of dimethylthexylsilyl chloride were added and the mixture allowed to warm up to room temperature under stirring. After periods of 24 h, 48 h and 96 h portions of 100 mg of sodium hydride and 0.35 g of dimethylthexylsilyl chloride were added. After 120 h the excess of sodium hydride was destroyed with methanol and the solvent was removed *in vacuo*. The residue was dissolved in chloroform, washed with sat. NaCl solution, dried over $MgSO_4$ and the solvent evaporated. The product was purified by flash chromatography over silica (eluent petroleum ether/ethyl acetate gradient 7:1 to 2:1) to give 61.5 mg (33 %) of crystalline material.

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 0.06, 0.07 (2s, 6H, $(CH_3)_2Si$), 0.83 (2s, 6H, $(CH_3)_2C(iBu)Si$), 0.87, 0.88 (2d, 6H, $(CH_3)_2CH$-), 1.61 (cm, 1H, $(CH_3)_2CH$-), 3.03 (dd, 1H, **H**-2, $^3J_{1,2}$ = 3.56 Hz), 3.50 (s, 3H, OCH_3), 3.53 (dd, 1H, **H**-3, $^3J_{2,3}$ = 9.67 Hz), 3.59-3.65 (m, 2H, **H**-5, **H**-6b), 3.66 (s, 3H, OCH_3), 3.73 (dd, 1H, **H**-4), 4.12 (dd, 1H, **H**-6a, $^2J_{6a,b}$ = 11.7 Hz), 5.19 (d, 1H, **H**-1)

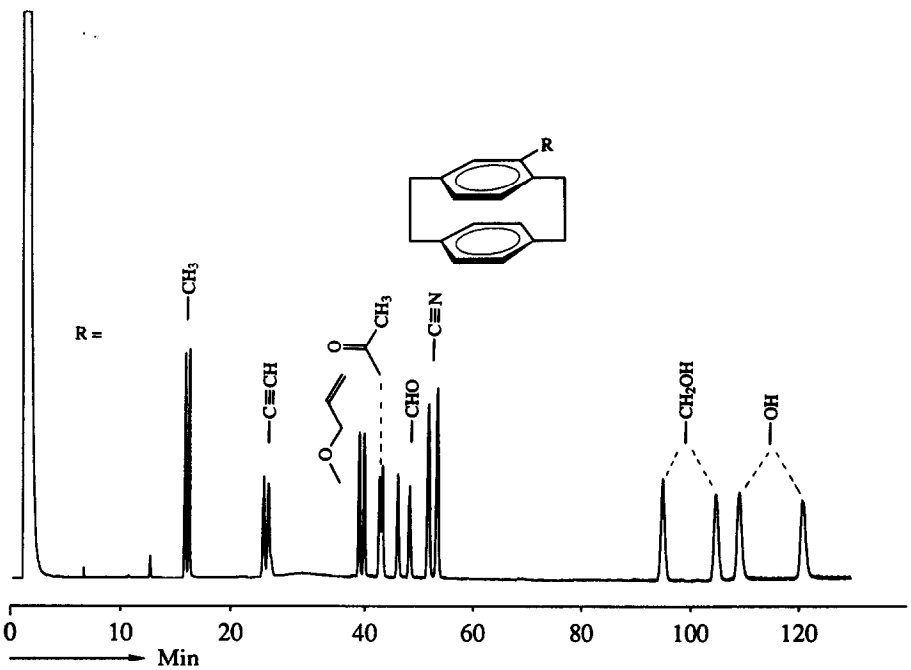

Figure 1: Gas chromatographic enantiomer separation of 4-substituted [2.2]paracyclophanes. 25 m fused silica capillary with heptakis(2,3-di-O-methyl-6-O-dimethylthexylsilyl)-β-cyclodextrin, 50% in polysiloxane OV 1701 (w/w). Column temperature 160 °C, carrier gas H_2 at 0.5 bar inlet pressure.

Gas chromatography

Fused silica capillary columns were prepared as described in a previous publication[4].

RESULTS AND DISCUSSION

O-Alkylated or -acylated cyclodextrins have shown astonishing selectivity towards a wide range of molecules with stereogenic centres[3]. In addition, many examples of the separation of compounds with axial and planar chirality are documented (allenes[4], atropisomeric biphenyls[5], cycloalkylidene derivatives[6], tricarbonyl-iron(0) complexes[7]). [2.2]Paracyclophanes with substituents on the aromatic system owe their dissymmetry to the restricted rotation of the arene rings (conformational chirality). While [2.2]paracyclophanes are configurationally stable up to at least 200 °C[8], homologues bridged by 3 and more methylene units on each side become more and more configurationally labile[9]. As shown in Figure 1 and Table 1 [2.2]paracyclophanes with a variety of substituents in position 4 could be resolved by gas chromatography using fused silica capillary columns with heptakis(2,3-di-O-methyl-6-O-dimethylthexylsilyl)-β-cyclodextrin (thexyl = 1,1,2-trimethylpropyl) as a chiral stationary phase. These separations are quite unexpected, because the discriminating properties of cyclodextrins are commonly attributed to the formation of diastereomeric inclusion complexes (host-guest interactions). In the case of the very rigid [2.2]paracyclophanes is it hardly conceivable that an inclusion complex is formed unless a dramatic conformational change of the macrocyclic host system takes place. The selectivity factors (α-values, Table 1) are dependent on the type of substituent R in the 4-position.

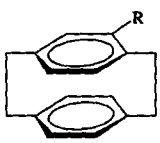

Table 1: Separation factors (α) and elution temperature for the enantiomers of 4-substituted [2.2]paracyclophanes on a 10 m fused silica capillary column with heptakis(2,3-di-O-methyl-6-O-dimethylthexylsilyl)-β-cyclodextrin (50% in poly-siloxane OV 1701)

R =	temp. [°C]	α-value
CH_3	130	1.049
C≡CH	130	1.039
Cl	135	1.024
CHO	135	1.081
CN	140	1.020
$COCH_3$	140	1.045
$OCH_2CH{=}CH_2$	150	1.032

	temp. [°C]	α-value
$OCH_2CH_2CH_3$	150	1.059
OCH_3	140	1.039
OH	170	1.090
CH_2OH	180	1.075
CH_2Br	150	1.063
$CH(OH)CH_3$	140	1.146
		1.036

No separation was observed for R = $CH{=}CH_2$, Br, COOMe and COOEt. In case of a 2-hydroxypropyl substituent the presence of the stereogenic center gives rise to two pairs of enantiomers, which are both completely resolved. Very similar separations were achieved with heptakis(6-O-*t*.butyldimethylsilyl-2,3-di-O-methyl)-β-cyclodextrin as a chiral stationary phase. This cyclodextrin derivative was described by Mosandl et al.[10] as very useful for the investigation of chiral flavour compounds and constituents of

essential oils. The great versatility of this cyclodextrin derivative in gas chromatographic enantiomer separation is surprising. Previous investigations[11] indicated a gain in selectivity when small substituents were attached to the 6-position of the glucose moieties. Bulky (e.g. benzyl) or polar (e.g. acetyl) substituents at the narrow opening of the cyclodextrin macrocycle were associated with a drastic loss in enantioselectivity[12]. The unexpectedly high enantioselectivity of cyclodextrin derivatives silylated in 6-position may be related to a conformational change induced by the silyl groups and to the formation of diastereomeric complexes with a substrate molecule approaching the macrocycle from the wider entrance[13].

Acknowledgements

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