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ANALYTICAL ENANTIOMER SEPARATION OF ALIPHATIC DIOLS AS BORONATES AND ACETALS BY COMPLEXATION GAS CHROMATOGRAPHY

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SUMMARY. *Cyclic boronates and acetals of mono- and dialkylsubstituted 1,2-, 2,3- 1,3- & 1,4-diols have been quantitatively separated into enantiomers by complexation gas chromatography utilizing optically active metal chelates. An efficient, precise & sensitive method for determining enantiomeric purities for volatile glycols is thus available.*

Optically active glycols are useful building blocks in chiral synthesis [1]. Optically enriched aliphatic diols may also occur as hydrolysis products of the biochemical transformation of racemic oxiranes by *epoxide hydratase* [2]. In connection with our ongoing studies on these subjects we required a sensitive & accurate method for determining enantiomeric compositions of simple diols with a precision of ± 0.5% over the total range of e.e. 0 - 100%.

Reliable *optical purity* determinations of glycols are precluded by the notorious sensitivity of their specific rotation to water impurities [1b]. Methods for determining *enantiomeric purities* of monosubstituted 1,2-diols include conversion with benzaldehyde into epimeric 2-phenyl-1,3-dioxolanes and subsequent ^{1}H-NMR analysis of the benzyl protons using an auxiliary chiral shift reagent [3] or reaction with *S*-2-propylcyclohexanone (which must be enantiomerically pure) to diastereomeric acetals followed by ^{13}C NMR or HPLC analysis [4]. These derivatizations give rise to the formation of a new chiral centre at the dioxocarbon atom producing additional stereoisomers.

Gas chromatography represents a powerful technique for the *direct* enantiomer analysis of chiral substrates which can be resolved with high resolution factors [5]. The enantiomer separation of *bis*-perfluoroacylated mono- and diaryl glycols has been achieved by gas chromatography on chiral polysiloxanes (*e.g., Chirasil-Val*) [6]. This approach has very recently been extended to aliphatic diols which were resolved as carbonates [7]. Separation factors, however, rarely exceed $\alpha = 1.03$.

The high propensity of *complexation gas chromatography* for the direct enantiomer separation of spiro, bi- and tricyclic acetals (*e.g.*, the pheromone constituents *exo*-brevicomin 1 or lineatin 2) [8] encouraged us to scrutinize simple diol acetals and heteroatom derivatives such as boronates toward their separation into enantiomers without resorting to diastereomer pre-formation.


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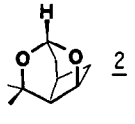
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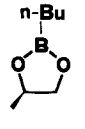
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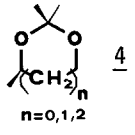
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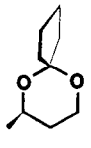
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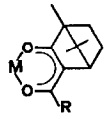
M = Ni/2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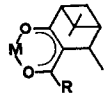
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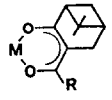
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R = $CF_2CF_2CF_3$

Thus, four mono-alkylsubstituted 1,2-diol *n*-butylboronates 3 were resolved on Ni(II)-*bis*-(3-heptafluorobutyryl-(*1R*)-camphorate) 6 [9] (TABLE 1) and 13 mono- and dialkylsubstituted 1,2-, 2,3-, 1,3- and 1,4-diol acetonides 4 were resolved on Ni(II)-*bis*-(3-heptafluorobutyryl-(*1R,2S*)-pinan-4-onate) 7 [10] or Ni(II)-*bis*-(3-heptafluorobutyryl-(*1R*)-nopinonate) 8 [11] (TABLE 2) by using deactivated glass capillary columns [9b] coated with the metal chelates in OV 101. The highest separation factor is $\alpha = 1.37$ for *erythro* 2 3-pentanediol acetonide and the lowest is $\alpha = 1.02$ for 2-methyl-1,2-butanediol acetonide. An aromatic diol acetal, *i.e.*, phenylglycol acetonide can also be resolved. 7 shows a higher degree of chiral recognition as compared to 8 which is devoid of the stereochemically fixed methyl group. Retention times on 8 are much shorter than on 7. 1,2-Diols may also be separated into enantiomers as boronates which are easily accessible. Spirocyclic diol acetals may also be resolved (TABLE III). Typical complexation gas chromatograms are shown in FIG. I & II.

There is a consistent relationship between the absolute configuration of the diols and the order of elution. Thus, the first eluting 1,2-diol *n*-boronate enantiomer has configuration *S* on 6 obtained from *1R*-camphor whereas the second eluting diol acetonide has configuration *S* on 7,8 derived from *1R,2S*-pinan-4-one and *1R*-nopinone, respectively, for all compounds investigated.

Previously, no racemization has been observed upon dioxolan formation [3]. This is confirmed for acetonide formation of enantiomerically pure *erythro* & *threo* 2,3-pentanediol as no trace of the antipode could be detected in the gas chromatogram (for circumstantial evidence cf. Ref. 13).

In principle, e.e. of chiral ketones may be determined *via* acetal formation using this method. Fortunately, many ketones can be directly resolved by complexation gas chromatograpy [14].

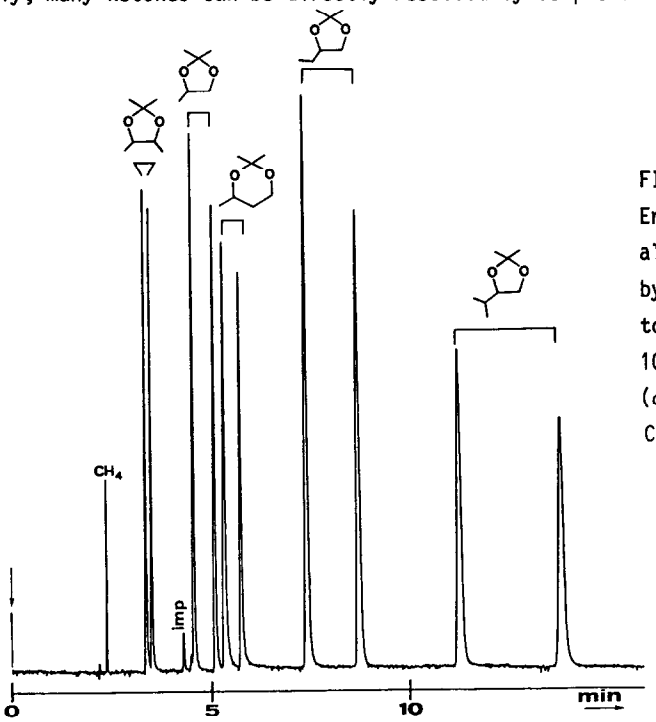

FIGURE I:
Enantiomer separation of aliphatic diol acetonides by complexation gas chromatography on 8 (0.17 *m* in OV 101) at 80°C (imp = acetone) (cf. TABLE II)
Carrier gas: N_2.

TABLE 1: Separation factors α of racemic 1,2-diol *n*-butylboronates 3 on Ni(II)-*bis*-(3-heptafluorobutyryl-(*1R*)-camphorate) 6 at 60°C.

Diol	α* on 6 #	absolute configuration of the first eluting enantiomer
1,2-Propanediol	1.07	*S*
1,2-Butanediol	1.07	*S*
3-Methyl-1,2-butanediol	1.07	*S*
1,2-Hexanediol	1.04 (90°C)	**

TABLE 2: Separation factors α of racemic 1,2-, 1,3- and 1,4-diol acetonides 4 on Ni(II)-*bis*-(3-heptafluorobutyryl-(*1R,2S*)-pinan-4-onate) 7 and Ni(II)-*bis*-(3-heptafluorobutyryl-(*1R*)-nopinonate) 8.

Diol	α* on 7 ## 100°C	α* on 8 ### 80°C	absolute configuration of the first eluting enantiomer
1,2-Propanediol	1.20	1.15	*R*
3-Chloro-1,2-propanediol	1.14	1.11	**
3-Bromo-1,2-propanediol	1.14	1.07	**
1,2-Butanediol	1.21	1.18	*R*
2-Methyl-1,2-butanediol	***	1.02	*R*
3-Methyl-1,2-butanediol	1.25	1.20	*R*
2,3-Butanediol (*threo*)	1.03	1.06	*2R,3R*
2,3-Pentanediol (*threo*)	1.18	1.08	*2R,3R*
2,3-Pentanediol (*erythro*)	1.37	1.12	*2R,3S*
1,3-Butanediol	1.09	1.07	*R*
1,3-Hexanediol	1.08	1.07	**
1,4-Pentanediol	1.15	1.17	**
Phenyl-1.2-ethanediol	1.09	1.07	*R*

TABLE 3: Separation factors α of racemic 1,3-butanediol acetals 5 on Ni(II)-*bis*-(3-heptafluorobutyryl-(*1R*)-nopinonate) 8 at 80°C.

Diol acetal	α* on 8 ###	absolute configuration of the first eluting enantiomer
1,3-Butanediol acetonide	1.07	*R*
1,3-Butanediol cyclopentanide	1.11	*R*
1,3-Butanediol cyclohexanide	1.05	*R*

* Retention time of the second *vs.* the first eluting enantiomer from methane peak

** not determined

*** not resolved

\# 37 m x 0.25 mm deactivated glass capillary coated with 0.125 *m* 6 in OV 101

50 m x 0.25 mm deactivated glass capillary coated with 0.07 *m* 7 in OV 101

40 m x 0.25 mm deactivated glass capillary coated with 0.17 *m* 8 in OV 101

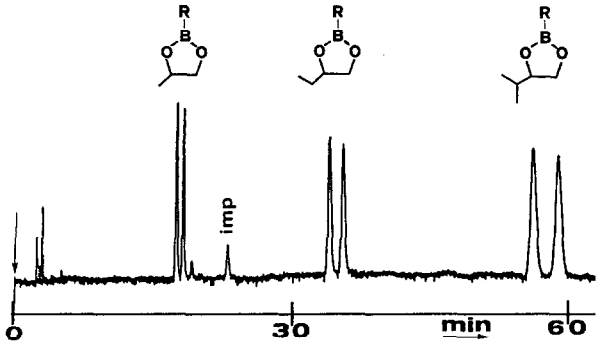

FIGURE II.
Enantiomer separation of aliphatic 1,2-diol *n*-butylboronates by complexation gas chromatography on 6 (0.125 *m* in OV 101) at 70°C (cf. TABLE 1)
Carrier gas: N_2.

Derivatization [12]

(a) Boronate: Dissolve 1 mg diol in 100 µl anhydrous DMSO or ether. Add *n*-butylboronic acid and allow to stand at 20°C for 10 min. Analyze solution or head-space.
(b) Acetonide: Dissolve 1 mg diol in 1 ml acetone, and add 1 mg TsOH. Allow to stand at 22°C for 20 min. Analyze head-space. Or: Cool solution in ice and add 1 ml *n*-hexane and 3 ml H_2O. Mix well, remove organic phase, dry over Na_2SO_4. Analyze solution.

Acknowledgments

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13 *S*-Propanediol has been prepared by LAH reduction (racemization?) of *S*-ethyl lactate (e.e. = 99.0±0.1% (B.Koppenhoefer et al., J.Chromatogr. 260 (1983) 63). Upon complexation gas chromatography e.e. of the diol boronate was measured e.e. = 98.2±0.5% (five measurements) and that of the acetonide was measured e.e. = 98.3±0.3% (eight measurements).

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