Extremely High Enantiomer Recognition in HPLC Separation of Racemic 2-(Benzylsulfinyl)benzamide Using Cellulose Tris(3,5-dichlorophenylcarbamate) as a Chiral Stationary Phase

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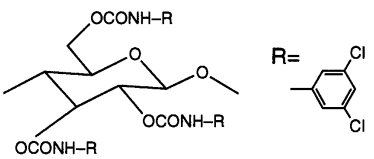
An extremely high enantioselectivity of cellulose tris(3,5-dichlorophenylcarbamate) was found when it was used as a chiral stationary phase (CSP) in high-performance liquid chromatography (HPLC). The enantioseparation factor (α = 112) reported in this system for 2-(benzylsulfinyl)benzamide seems to be the highest among many enantiomer-differentiating separations using polysaccharide derivatives as CSPs.

The high chiral recognition ability of cellulose tris(3,5-dichlorophenylcarbamate) (CDCPC) was previously observed in HPLC using *n*-hexane/2-propanol as a mobile phase.[1] However, CDCPC is soluble in *n*-hexane/2-propanol and due to this reason it was impossible to recommend this material as practically useful CSP for HPLC enantioseparations. In our recent study, it was shown that CDCPC is practically insoluble in methanol and water–methanol solutions and may be used as CSP in HPLC in combination with methanol and aqueous methanol as mobile phase. Previously observed high chiral recognition ability of CDCPC[1] was also confirmed using methanol and aqueous methanol as mobile phases.[2] The applicability of CDCPC for the HPLC enantioseparation of a wide range of chiral chemicals and pharmaceuticals was also shown.[3]



CDCPC

Further optimization of separation conditions using CDCPC as CSP in HPLC mode allowed to achieve high enantioseparation factors for some chiral sulfoxides. The enantioseparation factor observed in one of the cases seems to be among the highest ever observed in HPLC[4] with any kind of chiral stationary phase and several times higher compared to previously observed highest value for polysaccharide derivatives.[5] In addition, chiral sulfoxides represent a class of substances with high importance as bioactive compounds[6] and chiral auxiliaries in asymmetric reactions,[7] especially as very useful intermediates in the syntheses of optically active β-lactams[8] and 6-membered heterocyclic compounds.[9] Therefore, CSPs with high chiral recognition ability are of especial interest for HPLC enantioseparation of these compounds on a preparative scale.

CDCPC was prepared as described previously[1] by the reaction of microcrystalline cellulose (Avicel, Merck, Darmstadt, Germany) with an excess of 3,5-dichlorophenyl isocyanate in dry pyridine at ca. 100 °C overnight and isolated as a methanol insoluble fraction. The column packing material was prepared according to a common technique for polysaccharide-type CSPs[1] by coating CDCPC (dissolving 0.8 g in 10 mL tetrahydrofuran) onto the previously aminopropylsilanized macroporous silica (Daisogel SP-2000) (25% w/w). This material was packed using the conventional high-pressure slurry packing technique into a stainless-steel column of 25 cm × 0.46 cm size. The reference columns containing cellulose and amylose tris(3,5-dimethylphenylcarbamate)s were commercially available Chiralcel OD and Chiralpak AD, respectively, from Daicel Chemical Industries, Ltd. (Tokyo, Japan). For the chromatographic experiments, the following equipments were used: pump; JASCO PU 986, degasser; JASCO DC-980-50, UV detector; JASCO 875-UV, and polarimetric detector; JASCO OR-990. Structures of chiral sulfoxides used in this study are shown in Figure 1.

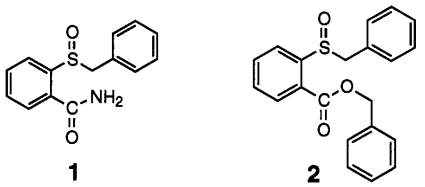


Figure 1. Structures of chiral sulfoxides studied. **1**: 2-(benzylsulfinyl)benzamide; **2**: 2-(benzylsufinyl)benzoic acid benzyl ester.

The chromatograms obtained using a CDCPC column and two commercial columns, Chiralcel OD and Chiralpak AD, which are known to exhibit high chiral recognition toward a wide range of racemates,[1] with pure methanol as the mobile phases is represented in Figure 2. As shown in this figure, in pure methanol, the enantiomers of compound **1** were resolved on all three columns, and the enantioselectivity of the separation was much higher with the CDCPC column (α = 8.5) compared to the Chiralcel OD (α = 2.0) and Chiralpak AD (α = 1.4) columns. The enantiomer elution order on the amylose derivative (Chiralpak AD) was opposite to that observed with both cellulose-based CSPs [(+)-**1** before (–)-**1**]. Previous studies indicated that CDCPC contains much higher amount of free carbamate moieties compared to other polysaccharide phenylcarbamates.[10] These groups may act as hydrogen-bonding sites between a CSP and a chiral analyte. Although the amount of free hydrogen-bonding sites is not the only difference between these three polysaccharide phenylcarbamates, the chromatograms shown in Figure 2 clearly indicate that these sites significantly contribute to the chiral recognition at least in the case of this particular group of chiral compounds. In order to compare the contributions of hydrogen bonding and hydrophobic interactions to the

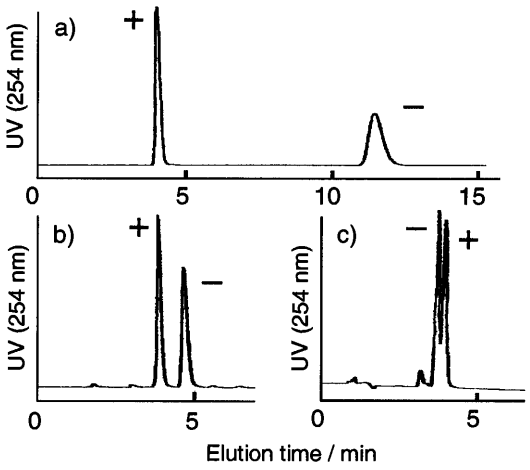


Figure 2. Enantioseparation of 2-(benzylsulfinyl)benzamide (**1**) on the column containing CDCPC (a) and commercial Chiralcel OD (b) and Chiralpak AD (c) using methanol as a mobile phase.

retention and chiral recognition, the structural analog (compound **2**) of compound **1** containing a benzyl ester group instead of an amide was studied. The retention of the first eluted enantiomer of this analyte was longer on CDCPC column compared to compound **1** but the enantioselectivity of the separation was much lower (Figure 3).[11] Thus, it seems that compound **1** contains the

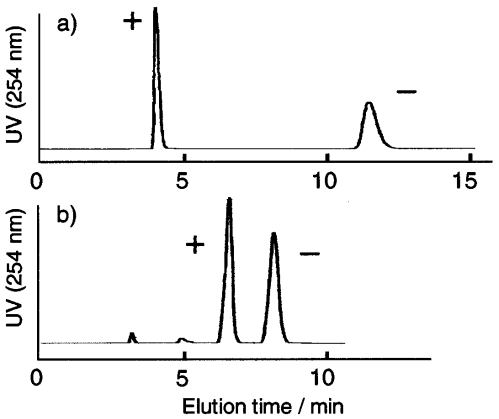


Figure 3. Enantioseparation of 2-(benzylsulfinyl)benzamide (**1**) (a) and 2-(benzylsulfinyl)benzoic acid benzyl ester (**2**) (b) on the column containing CDCPC using methanol as a mobile phase.

ideal combination of structural elements contributing to the chiral recognition. Ethanol and 2-propanol were also studied as the mobile phases in order to intensify the hydrogen-bonding interactions between the analytes and CSP at the expense of the hydrophobic forces. A further increase in the retention and enantioselectivity of separation was observed in the order: methanol < ethanol < 2-propanol, suggesting again that hydrogen-bonding is a dominant factor for chiral recognition (Figure 4). Thus, the value of the enantioselectivity (α = 112) shown in Figure 4c is several times higher than the previously observed best value of the polysaccharide-type CSPs.[5] Moreover, although a rather high enantioselectivity has been previously reported in very few HPLC enantioseparations using low-molecular weight[4a,b,d] or protein type[4c] CSPs, the present result observed with CDCPC seems to be among the highest value of enantioseparation factor

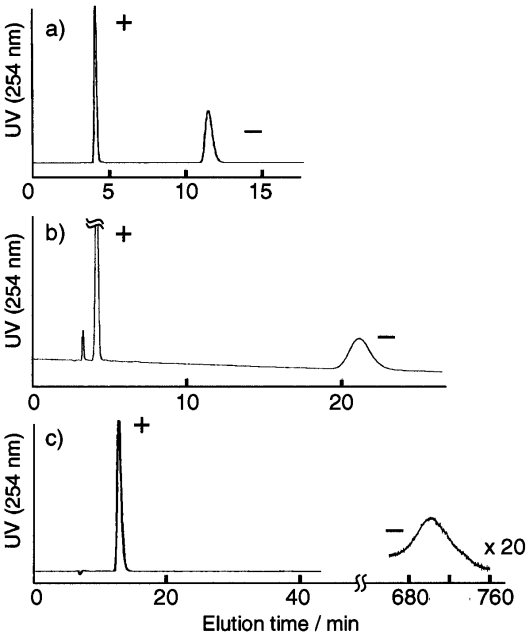


Figure 4. Enantioseparation of 2-(benzylsulfinyl)benzamide (**1**) on the column containing CDCPC using methanol (a), ethanol (b), and 2-propanol (c) as a mobile phase.

observed in HPLC.

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11 The α value for compound **2** was 1.43 on CDCPC column, which was higher than α = 1.12 on Chiralcel OD column with methanol as eluent.