

Optical resolution of racemic compounds on chiral stationary phases of modified cellulose

YOSHITAKA FUKUI*

Fine Cellulose Production Department, Aboshi Plant, Daicel Chemical Industries, Ltd., 1239 Shinzaike, Aboshiku, Himeji 671-12 (Japan)

and

AKITO ICHIDA, TOHRU SHIBATA and KYOZO MORI

Research Centre, Daicel Chemical Industries, Ltd., 1239 Shinzaike, Aboshiku, Himeji 671-12 (Japan)

ABSTRACT

Several alcohols having chiral centres on the chain linking phenyl and hydroxyl groups were chromatographed on a chiral stationary phase, based on cellulose tris-(3,5-dimethylphenylcarbamate) (Chiralcel-OD; OD-CSP). The mobile phases used were polar and non-polar solvents consisting of *n*-hexane and acetonitrile containing 2-propanol or benzene as modifier. The solutes containing hydroxyl groups were not eluted with non-polar eluents, and enantiomeric separation was less effective with eluents containing benzene. The enantiomeric elution order was not affected by changes in eluent polarity. The results suggest that the hydroxyl group was adsorbed on OD-CSP non-stereoselectively and that the phenyl group plays an essential part in the chiral recognition of solutes by OD-CSP. With both polar and non-polar eluents the solutes are oriented toward OD-CSP in a similar conformation.

INTRODUCTION

The use of chiral stationary phases (CSPs) for the separation of enantiomers has attained increasing prominence in the past decade, but the chiral recognition mechanism on a CSP has not been clarified in most instances. The chiral separation mechanism on a polymer-type CSP is more complex than that on a monomeric type. Recently, Shibata and co-workers^{1,2} and Wainer and co-workers^{3,4} suggested that the enantioselectivity on cellulose derivatives is based on attractive interactions between the solute and the CSP, such as dipole stacking, hydrogen bonding and π - π association. Therefore, expecting that the solute-CSP interactions could be controlled by a change in eluent polarity, we examined the chromatographic resolution of solutes containing a hydroxyl group and a phenyl group.

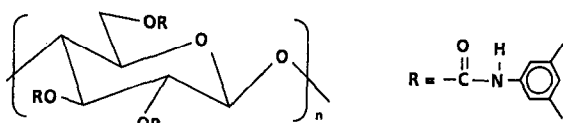


Fig. 1. Structure of the Chiralcel-OD chiral stationary phase.

EXPERIMENTAL

Chromatography was performed with a Shimadzu (Kyoto, Japan) LC-6A pump, a Shimadzu SPD-6A variable-wavelength spectrometric detector and a JASCO polarimetric detector. The CSP used for this study was cellulose tris(3,5-dimethylphenylcarbamate) (Fig. 1) adsorbed on macroporous silica gel (Chiralcel-OD; OD-CSP) and packed in a stainless-steel column (25 × 0.46 cm I.D.).

4-Phenyl-2-butanol, 1-phenyl-2-propanol, 2-phenyl-1-propanol, 3-phenyl-1-propanol, 1-phenoxy-2-propanol, 1-phenylethanol and (3-methylbutyl)benzene were purchased from Tokyo Kasei (Tokyo, Japan) and 3-phenyl-1-butanol and 3-cyclohexyl-1-propanol from Aldrich (Milwaukee, WI, U.S.A.). The methyl ethers of 4-phenyl-2-butanol, 4-cyclohexyl-2-butanol, the methyl ether of 3-phenyl-1-butanol and 3-cyclohexyl-1-butanol were derived from the respective parent alcohols. Acetonitrile (HPLC grade), *n*-hexane, 2-propanol and benzene were purchased from Wako (Osaka, Japan).

The solutes were dissolved in the respective eluents at concentrations of 0.136 mol/l. Mobile phases were prepared so that the total concentration of modifiers was 1.3 and 2.6 *M* in hexane or acetonitrile, respectively. The flow-rate was set at 0.5 ml/min and the temperature was kept at 25°C. The effluent was monitored with UV and polarimetric detectors.

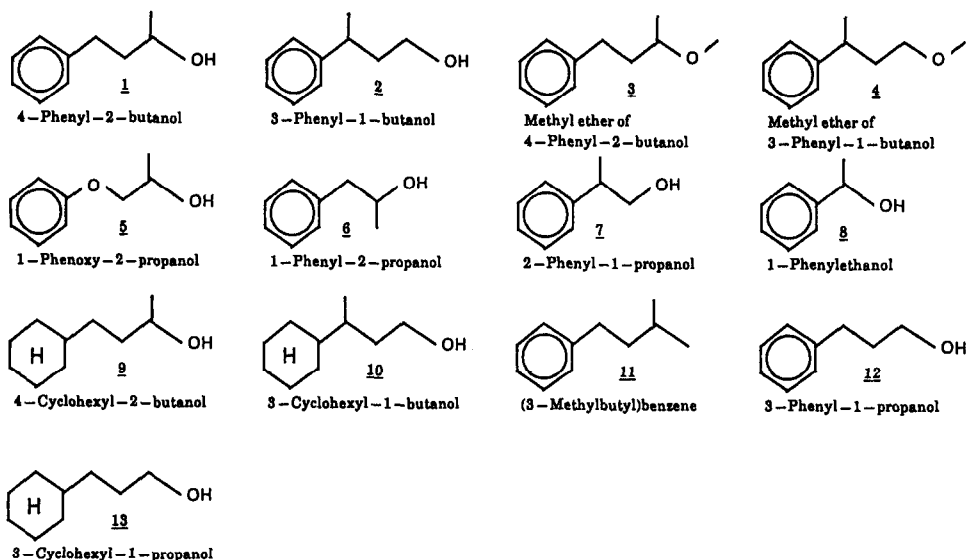


Fig. 2. The structure of the solutes used in this study.

TABLE I
 CHROMATOGRAPHIC RESULTS OBTAINED WITH OD-CSP AND MOBILE PHASE CONSISTING OF 2-PROPANOL OR BENZENE MODIFIER IN
 HEXANE

k' = Capacity factor of first-eluted enantiomer; α = stereoselectivity; E.O. = enantiomeric elution order.

Solute	1.3 M 2-propanol in hexane			2.6 M 2-propanol in hexane			1.3 M benzene in hexane			1.3 M 2-propanol and 1.3 M benzene in hexane		
	k'	α	E.O.	k'	α	E.O.	k'	α	E.O.	k'	α	E.O.
1	1.81	1.62	-, +	1.05	1.59	-, +				0.90	1.36	-, +
2	1.62	1.19	-, +	0.90	1.18	-, +				0.88	1.15	-, +
3	0.53	2.85	-, +	0.48	2.94	-, +	1.01	1.88	-, +	0.39	1.75	-, +
4	0.43	1.43	-, +	0.39	1.44	-, +	0.70	1.59	-, +	0.34	1.27	-, +
5	2.33	2.57	-, +	1.26	2.58	-, +				1.07	2.37	-, +
6	1.12	1.12	+, -	0.68	1.10	+, -				0.67	1.04	+, -
7	1.34	1.00	+, -	0.76	1.00	+, -				0.65	1.00	+, -
8	1.37	1.27	+, -	0.86	1.14	+, -				0.85	1.14	+, -
9	0.58	1.00	-	0.54	1.00	-				-	-	-
10	0.43	1.00	-	-	-	-				-	-	-
11	0.29	-	-	0.31	-	-	0.33	-	-	0.23	-	-
12	2.19	-	-	1.35	-	-				1.21	-	-
13	0.42	-	-	-	-	-				-	-	-

RESULTS AND DISCUSSION

The structures of the solutes used to investigate the interactions with OD-CSP are shown in Fig. 2. They have polar and non-polar groups and a chiral centre on the chain linking the two functional groups. The pairs **1** and **2**, **3** and **4**, **6** and **7** or **9** and **10** have different distances between these functional groups. The chromatographic results with hexane or modifier-containing hexane and with acetonitrile or modifier-containing acetonitrile as eluents are given in Tables I and II, respectively. The percentage change in retention and stereoselectivity for each solute with hexane-modifier mixtures and acetonitrile-modifier mixtures are presented in Table III and IV, respectively.

Compounds **1**, **2**, **5**, **6**, **7**, **8** and **12** were not eluted by 1.3 *M* benzene in hexane but they were eluted by 1.3 *M* 2-propanol in hexane.

Methyl ethers **3** and **4** and the hydrocarbon **11** were eluted with 1.3 *M* benzene in hexane. On the basis of these results, we suggest that the hydroxyl group of the solutes is mainly responsible for interactions with OD-CSP in a totally non-polar mobile phase. However, when the mobile phase already contained considerable amounts of a polar solvent (*e.g.*, 1.3 *M* 2-propanol in hexane and 100% acetonitrile), the k' values of the solutes decreased on addition of benzene and also on addition of 2-propanol (Tables III and IV).

The chromatographic behaviour of several solutes structurally analogous to the above was also examined, namely **11**, which has no hydroxyl group, and **9** and **13**, which have no phenyl ring. With the non-polar eluent, the k' values of **9** and **13** are slightly greater than that of **11**, but they were smaller than that of **1** (Table I). From these results it is concluded that both the hydroxyl and the phenyl group of **1** contribute to the adsorption on OD-CSP. The large k' value of **1** seems to be due to

TABLE II

CHROMATOGRAPHIC RESULTS OBTAINED WITH OD-CSP AND MOBILE PHASE CONSISTING OF ACETONITRILE OR ACETONITRILE WITH 2-PROPANOL OR BENZENE MODIFIER

k' , α and E.O. as in Table I.

Solute <i>N</i>	Acetonitrile			1.3 <i>M</i> 2-propanol in acetonitrile			1.3 <i>M</i> benzene in acetonitrile		
	k'	α	E.O.	k'	α	E.O.	k'	α	E.O.
1	0.63	1.08	-, +	0.52	1.08	-, +	0.49	1.00	-, +
2	0.61	1.00	-, +	0.51	1.00	-, +	0.49	1.00	-, +
3	0.52	2.03	-, +	0.46	1.85	-, +	0.33	S.P. ^a	Unknown
4		Unknown			Unknown			Unknown	
5	0.55	1.59	-, +	0.45	1.57	-, +	0.40	1.34	-, +
6	0.49	1.00	+, -	0.41	1.00	+, -	0.38	1.00	Unknown
7	0.46	1.00	Unknown	0.39	1.00	+, -	0.38	1.00	Unknown
8	0.46	1.20	+, -	0.39	1.19	+, -	0.31	1.00	+, -
9		Unknown		-	-	-	-	-	-
10		Unknown		-	-	-	-	-	-
11	0.47	-	-	0.45	-	-	0.38	-	-
12	0.66	-	-	0.54	-	-	0.50	-	-
13	0.38	-	-	0.36	-	-	-	-	-

^a Shoulder peak.

TABLE III

PERCENTAGE CHANGE IN RETENTION AND STEREOSELECTIVITY WHEN 2-PROPANOL OR BENZENE IS ADDED TO THE ELUENT 1.3 M 2-PROPANOL IN HEXANE

% k' and % α are values relative to those for 1.3 M 2-propanol in hexane as eluent in Table I being assigned values of 100%.

Solute	1.3 M 2-propanol in hexane		2.6 M 2-propanol in hexane		1.3 M isopropanol + 1.3 M benzene in hexane	
	% k'	% α	% k'	% α	% k'	% α
1	100	100	58	95	50	58
2	100	100	56	95	54	79
3	100	100	91	105	74	41
4	100	100	91	102	79	63
5	100	100	54	101	46	87
6	100	100	61	83	60	33
7	100	—	57	—	48	—
8	100	100	63	52	62	52
12	100	—	62	—	54	—

chelate formation between the hydroxyl group, the phenyl group of **1** and the xyllyl urethane group of cellulose tris(3,5-dimethylphenylcarbamate). The enantiomeric elution order of **1–8** remained constant regardless of the solvent polarity. In each pair of solutes, **1** and **2**, **3** and **4**, and **6** and **7**, the α value of the former is always larger than that of the latter component, regardless of solvent polarity. These two results suggest that the adsorptivity of solutes on OD-CSP are changed by the eluent polarity but the stereochemical features of the complex formed when the solutes are adsorbed on OD-CSP are not essentially affected by the eluent polarity.

Compounds **1**, **3** and **5** have similar distances between the phenyl and hydroxyl or methoxy groups. The k' and α values of these solutes are different, but their enantiomeric elution order is the same. On the other hand, compounds **6** and **8** have

TABLE IV

PERCENTAGE CHANGE IN RETENTION AND STEREOSELECTIVITY WHEN 2-PROPANOL OR BENZENE IS ADDED TO THE ACETONITRILE ELUENT

% k' and % α are values relative to those for acetonitrile as eluent in Table II being assigned values of 100%.

Solute	Acetonitrile		1.3 M 2-propanol in acetonitrile		1.3 M benzene in acetonitrile	
	% k'	% α	% k'	% α	% k'	% α
1	100	100	82	100	78	0
2	100	—	84	—	79	—
3	100	100	88	83	63	0
5	100	100	81	97	73	58
6	100	—	84	—	78	—
7	100	—	85	—	83	—
8	100	100	85	95	67	0
12	100	—	82	—	76	—

distances different from that of **1** between these groups and the enantiomeric elution order is also different from that of **1**. Both the k' and α values for **1**, **8** and **6** with non-polar eluents decrease in that order (Tables I and II). This suggests that a certain conformational flexibility and/or distance between these two functional groups is required for these compounds to fit well on the chiral recognition site of OD-CSP. The α values of solutes **1**–**7** were greatly decreased by the addition of benzene to the mobile phase, whereas the decrease caused by the addition of 2-propanol was much less (Tables III and IV). While solutes containing a benzene ring (**1** and **2**) were well resolved on OD-CSP, the corresponding saturated compounds **9** and **10** were not. These results indicate that the phenyl group of the solutes plays an important role in chiral recognition, presumably by π – π association with the xylyl group of cellulose tris(3,5-dimethylphenylcarbamate).

CONCLUSIONS

In the case of the solutes examined, the hydroxyl group causes strong adsorption on OD-CSP, but a major part of the adsorptive interaction seems to be non-stereoselective. The interaction between OD-CSP and the phenyl groups of the solutes plays an essential part in chiral recognition by OD-CSP.

With these alcohols, which contain phenyl groups, the stereochemical association feature which may be formed between the solutes and OD-CSP seems to be unchanged over a wide range of solvent polarities. In solutes whose chiral centre is on the chain linking the phenyl and the hydroxyl groups, a suitable distance between the phenyl and hydroxyl groups and/or flexibility are necessary for a good fit to the chiral recognition site of OD-CSP.

ACKNOWLEDGEMENTS

The authors acknowledge the kind help of Dr. Miyoshi and Mr. Yaso in the synthesis of the compounds.

REFERENCES

- 1 K. Torii, M. Yoshikane and T. Shibata, presented at the 32nd Meeting of the Research Group on Automatic Liquid Chromatography, Kyoto, January 1989.
- 2 I. W. Wainer, R. M. Stiffin and T. Shibata, *J. Chromatogr.*, 411 (1987) 139.
- 3 M. H. Gaffney, R. M. Stiffin and I. W. Wainer, *Chromatographia*, 27 (1987) 15.
- 4 I. W. Wainer, M. C. Alembik and E. Smith, *J. Chromatogr.*, 388 (1987) 65.