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Note

Resolution of chiral sulfur compounds on a cellulose-based high-performance liquid chromatographic chiral stationary phase

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Chiral sulfur compounds have received considerable attention in recent years because of their applications in synthetic organic chemistry. The structural versatility of sulfoximines, for example, allows a variety of synthetic transformations to be made by altering the nitrogen substituent[1]. Because of their synthetic utility, the resolution of optically active sulfur compounds without derivatization is of analytical and preparative interest.

A number of recently developed high-performance liquid chromatographic (HPLC) chiral stationary phases (CSPs) have been applied to the direct resolution of chiral sulfur compounds and to the determination of the enantiomeric purity of these compounds. Pirkle and co-workers[2–4] separated chiral sulfoxides by using a CSP composed of (*R*)-N-(3,5-dinitrobenzoyl)phenylglycine. Allenmark and Bomgren[5] also resolved chiral sulfoxides and an enantiomeric sulfoximine on a CSP based on bovine serum albumin–agarose bound to silica gel. Ichida *et al.*[6] recently reported the resolution of a series of chiral sulfoxides on CSPs consisting of various polysaccharide derivatives, particularly cellulose derivatives, adsorbed on macroporous silica gel.

This paper reports the applicability of one of the CSPs developed by Ichida *et al.*[6], a trisphenylcarbamate derivative of a cellulose-based CSP, to the resolution of several classes of chiral sulfur compounds —sulfoximines, sulfinamides and sulfilimines (Fig. 1). The effects on retention and stereoselectivity that are due to structural differences within and between these series of compounds indicate that hydrogen bonding and polar interaction between the solute and CSP play a role in the chiral recognition process.

EXPERIMENTAL

Apparatus

The chromatography was performed with a Spectra-Physics (Santa Clara, CA,

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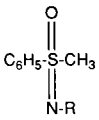

Compound	R
1a	H
1b	CH_3
1c	COC_6H_5

Compound	R_1	R_2
2a	p-CH_3-C_6H_4	CH_3
2b	C_6H_5	2-Pyridyl

Compound	R_1	R_2
3a	C_6H_5	COC_6H_5
3b	C_6H_5	$SO_2C_6H_4$-CH_3-p
3c	n-C_4H_9	$SO_2C_6H_4$-CH_3-p

Fig. 1. Structures of the compounds used in this study: sulfoximines (1a–c); sulfinamides (2a, b); sulfilimines (3a–c).

U.S.A.) Model 3500 liquid chromatograph, a Waters Assoc. (Milford, MA, U.S.A.) Model 450 variable-wavelength detector set at 254 nm, a Varian (Palo Alto, CA, U.S.A.) Model 2080 column oven, a Spectra-Physics Model 4050 data interface and a Spectra-Physics Model 4050 printer/plotter. The prepacked column used with this system was a stainless-steel Daicel "Chiralcel" OC column (25 cm × 4.6 mm I.D.) with a packing of "chiral gel" modified with cellulose carbamate (Daicel Chemical Industries, New York, NY, U.S.A.).

Materials

The sulfur compounds were prepared in our laboratory as described previously[1]. HPLC-grade methanol, 1-propanol, 2-propanol and acetonitrile were purchased from Burdick & Jackson Labs. (Muskegon, MI, U.S.A.), and absolute ethanol was purchased from Publicker (Philadelphia, PA, U.S.A.). HPLC-grade hexane and spectroscopic grade *tert.*-butanol were purchased from Fisher Scientific (Pittsburgh, PA, U.S.A.).

Sample preparation

A 1-mg portion of each chiral sulfur compound was dissolved in 10 ml of mobile phase.

Chromatographic conditions

The mobile phase consisted of hexane modified with an alcohol or with an alcohol plus acetonitrile. A flow-rate of 1 ml/min was maintained throughout the study, and a temperature of 20°C was used unless otherwise indicated.

RESULTS AND DISCUSSION

The CSP used in this study is a cellulose trisphenylcarbamate (Fig. 2) coated

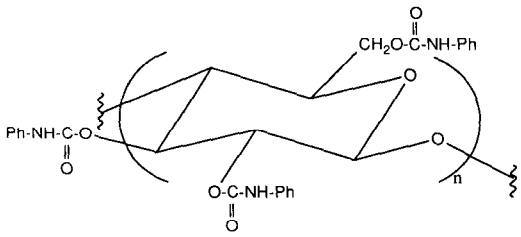

Fig. 2. Structure of the CSP used in this study. Ph = Phenyl.

on a macroporous silanized silica gel (approximately 20–23%, w/w)[6]. In the initial report of this CSP, Ichida *et al.*[6] attributed the formation of the solute–CSP complex to hydrogen bond formation between the urethane groups of the CSP and hydroxyl and/or amino groups in the solutes studied. Except for compounds 1a and 2a, the solutes used in this study do not contain hydrogen atoms which can participate as hydrogen bond donors. However, all the compounds used in this study have sites for hydrogen bond acceptance.

The results for the chromatography of the three classes of solutes used in this study are presented in Table I. It is noteworthy that for the series of sulfoximines (1a–c), sulfinamides (2a, b) and sulfilimines (3a–c), the structure of the substituent on the nitrogen atom appears to have a great effect on retention (k') and stereoselectivity (α).

For the sulfoximines, the replacement of the imine hydrogen by a methyl group (from 1a to 1b) reduced the retention of the first eluted enantiomer (k'_1) from 25.72 to 7.99 and increased the stereoselectivity (α) from 1.21 to 1.43. The change to a benzoyl substituent (from 1a to 1c) had the opposite effect —it increased k'_1 from 25.72 to 42.58 and decreased α from 1.21 to 1.06.

For the sulfilimines studied, the replacement of a benzoyl moiety by a *p*-tolylsulfonyl group (from 3a to 3b) increased k'_1 (from 7.13 to 19.60) and decreased α (from 1.27 to 1.10). The substitution of a pyridine moiety for a methyl group in the sulfinamide series (2a and 2b) increased the retention of 2b to such an extent that no chromatographic peaks were obtained.

TABLE I

RESOLUTION OF COMPOUNDS USED IN THIS STUDY

k'_1 = Capacity factor of the first eluted enantiomer; 1-propanol is the mobile phase modifier.

Compound	α	k'_1	*1-Propanol (%)*
1a	1.21	25.72	5.00
b	1.43	7.99	5.00
c	1.06	42.58	5.00
2a	1.15	1.19	25.00
b*			25.00
3a	1.27	7.13	25.00
b	1.10	19.60	25.00
c	1.15	10.78	25.00

* No peak obtained.

Although the retention and resolution of a solute represent the total of all the interactions between the solute, the mobile phase and the stationary phase, the results do allow some speculation about the mechanism of interaction between the solute and the CSP. The results suggest a chiral recognition model in which the diastereomeric solute–CSP complexes are formed through hydrogen bonding and polar interactions between the solute and the carbamate moiety of the CSP. The relative stabilities of these complexes and the stereoselectivity of each compound, which depends on these stabilities, are functions of the steric fit of the solute and the CSP.

In the case of the sulfoximine solutes, the strongest hydrogen bond is formed between the nitrogen moiety of the solute and the hydrogen atom on the carbamate nitrogen. For compound 1a, additional hydrogen bonding interactions are possible between the imine hydrogen and the carbamate carbonyl moiety, which may explain the increased retention of this compound compared with that of compound 1b. In addition, the solute–CSP complex based on the carbamate hydrogen–sulfoximine (CONH $\cdots$ N=S) interaction may favor retention of one enantiomer, whereas the solute-CSP complex based on the imine hydrogen–carbamate carbonyl (S=N–H $\cdot\cdot$ O=C) interaction may favor retention of the other enantiomer. Such a situation would explain the lower stereoselectivity of compound 1a compared with that of compound 1b, for which there is no competing interaction.

An additional possible site for hydrogen bonding is also present in compound 1c. In this case, the interaction is between the carbonyl carbon of the benzoyl group of the solute and the carbamate hydrogen. This interaction should result in increased retention and decreased stereoselectivity compared with the corresponding values for compound 1a. The magnitude of the actual changes in retention and stereoselectivity, however, suggest the existence of additional interactions with the CSP. A possibility is a polar interaction between the amide dipole of compound 1c and the corresponding dipole of the carbamate moiety of the CSP. A similar retention model based on dipole–dipole interactions between a carbamate-containing solute and an amide-containing CSP was recently reported[7].

The same relationships exist for the other series of solutes used in this study. The sulfinamides have two possible hydrogen bonding sites: the sulfinamide oxygen and the sulfinamide hydrogen; however, compound 2b contains a third site involving the pyridine moiety. The sulfilimines do not contain an oxygen on the chiral sulfur, and hydrogen bonding interactions most likely involve the imine nitrogen. For the

TABLE II

EFFECT OF ADDED POLAR MODIFIER ON CAPACITY FACTOR AND STEREOSELECTIVITY OF COMPOUND 1b

Mobile phase: 1.33 *M* modifier in hexane; k'_1 = capacity factor of the first eluted enantiomer.

Modifier	k'_1	α
Methanol	5.37	1.32
Ethanol	5.33	1.32
1-Propanol	4.36	1.37
2-Propanol	5.70	1.35
tert.-Butanol	12.41	1.17

TABLE III

EFFECT OF TEMPERATURE ON CAPACITY FACTOR AND STEREOSELECTIVITY

Mobile phase: hexane–1-propanol–acetonitrile (95:5:1); k'_1 = capacity factor of the first eluted enantiomer.

Temperature (°C)	*Compound 1a*		*Compound 1b*	
	k'_1	α	k'_1	α
15	15.52	1.30	3.81	1.53
20	10.85	1.29	3.00	1.49
25	10.85	1.29	2.96	1.48

series of sulfilimines, retention is lower and stereoselectivity is higher for compounds containing a benzoyl substituent, compared to the corresponding values for compounds containing a *p*-toluenesulfonyl moiety. These differences may be due to the higher polarity of the latter.

We also investigated the effect of the structure and properties of the polar modifier on retention and stereoselectivity (Table II). For compound 1b, the use of the various modifiers in the series methanol, ethanol, 1- and 2-propanol had little effect on k' and α. The increase in k' and the decrease in α with *tert.*-butanol as the modifier are probably due to the increased viscosity of the mobile phase; the chromatographic peaks were broad with a significant amount of tailing.

The effect of temperature on k' and α was also investigated for compounds 1a and 1b. The results (Table III) indicate that, over the temperature range studied, increased temperature has a slight effect on k' and little effect on α.

CONCLUSION

The commercially available series of cellulose-based CSPs are important additions to the chromatographer's arsenal. However, their optimum use requires an understanding of the corresponding chiral recognition mechanisms. Our investigation has just begun to address some of the problems involved in the application of these CSPs. Until additional enantiomers, including the members of a more extensive homologous series, are resolved, any definitive discussion of the mechanism of retention and stereoselectivity is impossible. Further studies are in progress.

REFERENCES

1 C. R. Johnson, *Aldrichimica Acta*, 18 (1985) 3.
2 W. H. Pirkle, J. M. Finn, J. L. Schreiner and B. C. Hamper, *J. Am. Chem. Soc.*, 103 (1981) 3964.
3 W. H. Pirkle, J. M. Finn, B. C. Hamper, J. Schreiner and J. R. Pribish, in E. L. Eliel and S. Otsuka (Editors), *ACS Symposium Series, No. 185, Asymmetric Reactions and Processes in Chemistry*, American Chemical Society, Washington, DC, 1982, pp. 245–260.
4 W. H. Pirkle, M. H. Hyun and B. Bank, *J. Chromatogr.*, 316 (1984) 585.
5 S. Allenmark and B. Bomgren, *J. Chromatogr.*, 252 (1982) 297.
6 A. Ichida, T. Shibata, I. Okamoto, Y. Yuki, H. Namikoshi and Y. Toga, *Chromatographia*, 19 (1984) 280.
7 T. D. Doyle, W. M. Adams, F. S. Fry, Jr. and I. W. Wainer, *J. Liq. Chromatogr.*, 9 (1986) 455.