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DIRECT RESOLUTION OF ENANTIOMERS BY LIQUID CHROMATOGRAPHY WITH THE NOVEL CHIRAL STATIONARY PHASE DERIVED FROM (R,R)-TARTRAMIDE

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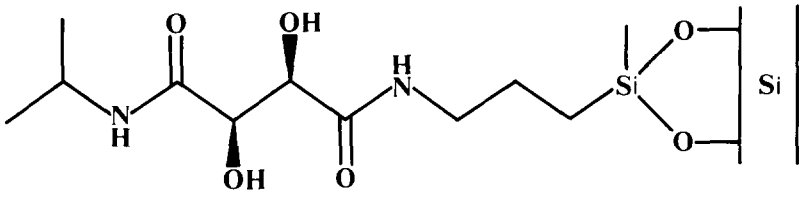
ABSTRACT: The synthesis of the novel chiral stationary phase (CSP) derived from (R,R)-tartramide and direct resolution of a series of β-hydroxycarboxylic acid derivatives on this CSP are described.

The recognition of molecular chiralities is a subject of great interest since the need to determine enantiomeric compositions and absolute configurations of enantiomers and prepare enantiomerically pure compounds has obviously become greater in many branches of chemistry. The application of liquid chromatographic techniques with the chiral stationary phase (CSP) is a most ingenious means for meeting these needs[1] and consequently, attempts to develop the CSP are worthwhile. We wish to communicate in this paper the first example of the CSP derived from (R,R)-tartramide and the direct resolution of β-hydroxycarboxylic acid derivatives on this CSP.

Our approach to chiral recognition is based on the use of hydrogen bonds as the driving force for molecular association to bring about enantioselectivity.[2] During a systematic investigation on this matter, the addition of (R,R)-diisopropyltartramide (DIPTA) to the nonaqueous mobile phase liquid was found to result in the chiral recognition of a broad range of enantiomers containing 1,2-diol, α-amino acid, β-amino alcohol, α- or β-hydroxycarboxylic acid, β-hydroxy ketone, α-hydroxy ketoxime derivatives and bi-β-naphthol.[3] This finding led us to design CSP 1 derived from tartramide.



CSP 1

The design of this CSP was based on the following considerations. In the above mentioned resolution using the chiral additive, (R,R)-DIPTA interacts with solute enantiomers by hydrogen bonds to form transient diastereomeric complexes. This process generated the observed enantioselections of the solutes. These diastereomeric complexes should differ from

each other in stability and distribution coefficients between the two phases of chromatography. The enantiomeric resolution on the CSP is based on differences in the stability of diastereomeric complexes between enantiomeric pairs and the chiral moiety of the CSP. That is, the chiral molecule analogous to DIPTA can be applied to the chiral moiety of the CSP on which the direct resolution of the enantiomers is readily effected.

Scheme 1 illustrates our approach to the synthesis of CSP 1. Aminolysis of diacetyl anhydride 1[4] with isopropylamine (CH_2Cl_2, 0 °C, 30 min) afforded a half amide 2. This half amide was condensed with N-hydroxy-5-norbornene-2,3-dicarboximide (DCC, THF, 0 °C, 5 hr) and the resulting activated ester 3 was subjected to aminolysis with γ-aminopropyltriethoxysilane in the presence of triethylamine (CH_2Cl_2, 0 °C, 3 hr). The reaction mixture was directly purified by silica gel chromatography (25% Me_2CO in n-hexane), affording pure silylating reagent 4[5] in a 78% yield from 2. Modified silica gel 5 was obtained on reaction of microporous silica gel (5 μm) with 4 (toluene, 100 °C, 36 hr). Removal of the acetyl groups of 5 (0.35N NH_3-MeOH, 0 °C, 8 hr) provided CSP 1. The ir spectral data of CSP 1 (KBr, 1540 cm^{-1}, 1650 cm^{-1}) indicated the complete removal of acetyl groups and a surface modification of the silica gel with tartramide derivative. From the elemental analysis of nitrogen (0.91%), it was estimated that CSP 1 contained 0.325 mmole/g of the chiral moiety.

Scheme 1

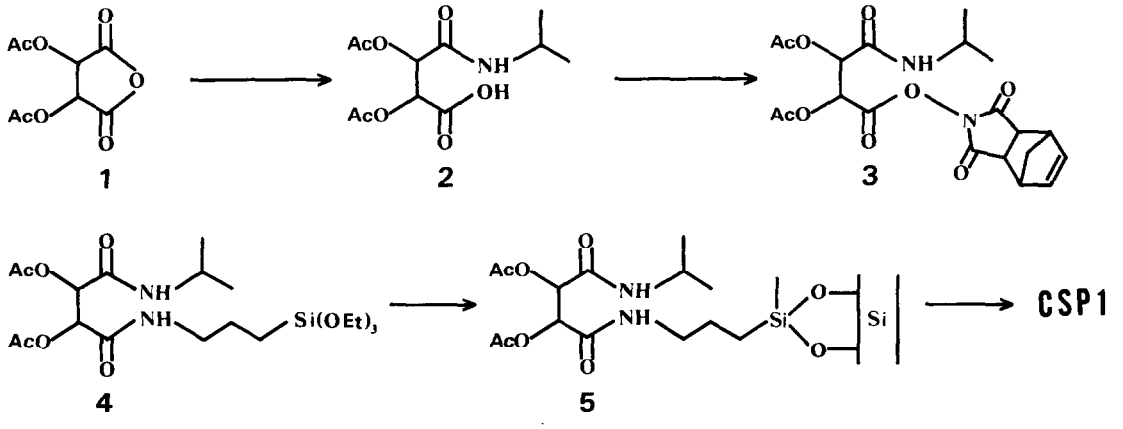
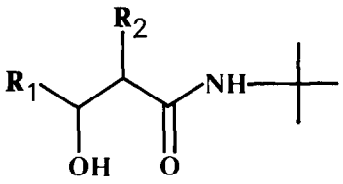


Table 1 gives the chromatographic data for the resolution on CSP 1 of a series of β-hydroxycarboxylic acids as tert-butylamide derivatives. Figure 1 shows the resolutions of compound 5 and 9 as typical examples. The baseline resolutions were obtained for almost all the enantiomers listed in Table 1 and are indicated as Rs values. The enantiomeric pairs interact with the tartramide moiety on the silica gel surface and thus come to differ from each other in retentivity. It should be mentioned that the enantiomers which form more stable complexes with chiral moiety of the CSP are retained to a greater extent than the corresponding antipodes. There is no doubt that intermolecular hydrogen bonds play a dominant role in the enantioselective process. This is supported by the fact that the aliphatic β-hydroxycarboxylic acids were resolved on CSP 1 to a considerable degree, since these

Table 1 Chiral Recognition of β-Hydroxycarboxylic Acid Derivatives on CSP 1[a]



compound	R_1	R_2	relative configuration	k'_1[b]	k'_2	α[c]	Rs[d]
1	Ph	H	-	6.51	7.40	1.14	1.64
2	iso-Pr	H	-	3.31	3.74	1.13	1.55
3	Et	H	-	5.82	6.32	1.09	1.13
4	H	Ph	-	5.05	6.06	1.20	2.75
5	H	iso-Pr	-	3.86	4.62	1.20	2.54
6	H	Et	-	5.60	6.42	1.14	1.83
7	Ph	Me	threo	3.25	4.46	1.37	4.00
8	Ph	Me	erythro	7.43		>1.00[e]	<0.30
9	Ph	Et	threo	2.56	3.76	1.46	5.00
10	Ph	Et	erythro	5.70	6.03	1.06	0.71
11	Ph	iso-Pr	threo	2.73	3.40	1.25	2.82
12	Ph	iso-Pr	erythro	4.51	4.92	1.09	1.17

a) The column was a 50 x 0.1 (i.d.) cm stainless steel tube packed with the modified silica gel. Chromatographic runs were performed at a constant flow rate of 60 μl/min, and constant temperature of 20 °C. The eluent was 2(v/v)% 2-propanol in n-hexane. The eluate was detected UV at 230 nm for entries 2, 3, 5, and 6 and at 254 nm for other entries. b) k'(capacity factor) = (retention time - dead time)/(dead time). k'_1: capacity factor of a lesser retained enantiomer. k'_2 : capacity factor of an enantiomer retained more. c) α(separation factor) = k'_2 /k'_1. d) Rs(resolution) = 2 x (distance of the two peak positions)/(sum of the bandwidths of the two peaks). e) The shoulder could be definitely detected.

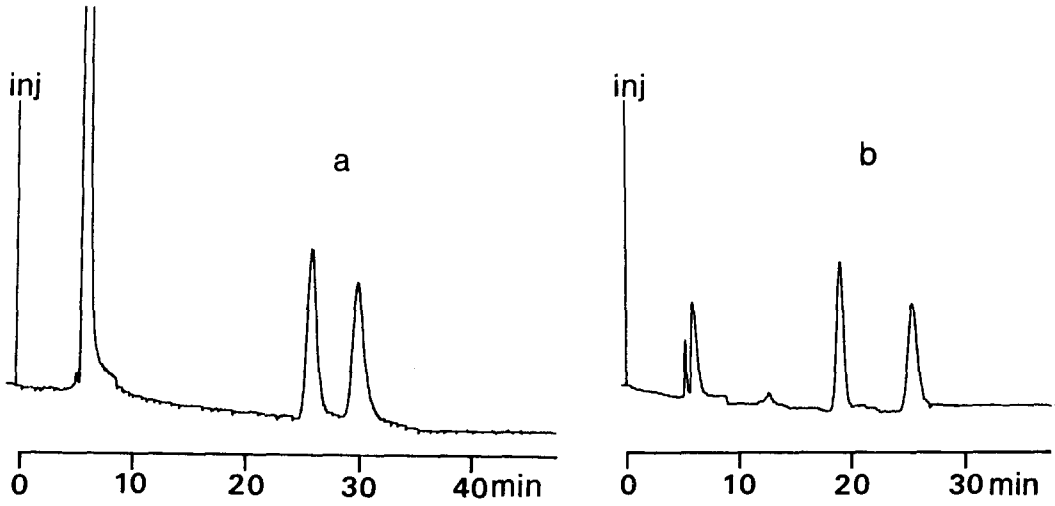


Figure 1. Direct resolutions of tert-butylamide derivatives of β-hydroxycarboxylic acids on CSP 1. Chromatographic conditions are described in the legend of Table 1. a) compound 5. b) compound 9.

derivatives can offer only sites for hydrogen bonding. The association mode responsible for the observed enantioselectivities is considered to be dual hydrogen bonds between solutes and the chiral moiety of the CSP through hydroxyl groups and amide units of the solutes. The separation factors indicate the degree of chiral recognition on CSP 1 and directly reflect differnces in the stability of the diastereomeric complexes of solute enantiomers and the chiral moiety of the CSP. In a series of β-hydroxycarboxylic acids with only one asymmetric center, an increase in the steric bulkiness of the substituent at asymmetric center enhanced the separation factor. This observation suggests that steric interactions between substituents at the asymmetric centers of the solutes and the chiral moiety of the CSP during their association contribute to generate the differences in the stability of the diastereomeric complexes. It was also recognized that β-hydroxycarboxylic acids with the asymmetric center at the α-position afforded greater separation factors than their isomers with the asymmetric center at the β-position. With regard to enantiomers possessing threo-erythro diastereoisomerism, a higher degree of chiral recognition was obtained for threo isomers. In addition to the enantiomers listed in Table 1, β-hydroxy ketone, α-hydroxy ketoxime, and α-amino acid derivatives were also resolvable on CSP 1. For example, threo-2-(1'-hydroxybenzyl)-1-cyclohexanone,[6-a] syn-benzoin oxime,[6-b] and N-acetyl phenylalanine tert-butylamide[6-c] were resolved with separation factors of 1.06, 1.07, and 1.10 respectively.

In conclusion, we have developed a general method for the surface modification of a silica gel with a tartramide derivative and demonstrated this derivative to function as a chiral moiety of the CSP on which various enantiomers can be resolved. Correlations between the absolute configurations of enantiomers and their elution orders along with additional applications of the CSP derived from tartramide will be reported subsequently.

References and Notes

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5. Data for 4: colorless solid; mp 152-153 °C; ^{1}HNMR($CDCl_3$,δ) 0.51-0.68(m, 2H), 1.09-1.29(m, 15H), 1.45-1.79(m, 2H), 2.14(s, 6H), 3.14-3.37(m, 2H), 3.81(q, J = 6.6Hz, 6H) + 3.69-4.21(m, 1H), 5.53-5.63(m, 2H), 6.08(brd, J = 8.3Hz, 1H), 6.48(brt, 1H); IR(KBr, cm^{-1}) 1550, 1650, 1658(shoulder), 1758, 3348; MS 478(M^+ for 4).

6. Chromatographic conditions were the same as those described in the legend of Table 1 except for the eluent and/or column temperature for a) and b). a) 1(v/v)% 2-propanol in n-hexane, 10 °C. b) 50(v/v)% dichloromethane in n-hexane.

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