New Chiral Polysiloxane Derived from (*R*,*R*)-Tartramide for Enantiomer Resolution by Capillary Gas Chromatography

Yasuo Dobashi,[2] Kouji Nakamura,*[,1] Takafumi Saeki,[1] Masaaki Matsuo,[1] Shoji Hara,[2] and Akira Dobashi[2]

Analytical Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., 16-89, Kashima 3-chome, Yodogawa-ku, Osaka 532, Japan, and Tokyo College of Pharmacy 1432-1, Horinouchi, Hachioji, Tokyo 192-03, Japan

Received June 20, 1990

The synthesis was conducted of a polysiloxane in which the (*R*,*R*)-tartramide derivative as a chiral selector was attached to the polysiloxane backbone via 11 methylene units. Capillary gas chromatography using this polysiloxane as a chiral stationary phase was found to be capable of recognizing the molecular chirality of broad categories of volatile enantiomers containing 1,2-diols, 1-methoxy-2-alkanols, dialkyl tartrates, methyloximes of 2-hydroxy ketones, *N*,*N*′-bis(perfluoroacyl)-1,2- and -1,3-diamines, *N*-alkylamides of 2- and 3-halo carboxylic acids, and *N*-alkylamides of 2- and 3-hydroxy carboxylic acids. The mode of complexation responsible for the observed enantioselection was ascribed to dual hydrogen bonding between the (*R*,*R*)-tartramide moiety of the polysiloxane and solute enantiomers to be resolved. Dual hydrogen bonding between (*R*,*R*)-tartramide and some enantiomers is discussed on the basis of the differences in ^{1}H NMR chemical shifts observed for the enantiomeric pair in a $CDCl_3$ solution containing (*R*,*R*)-*N*,*N*′-diisopropyltartramide.

Introduction

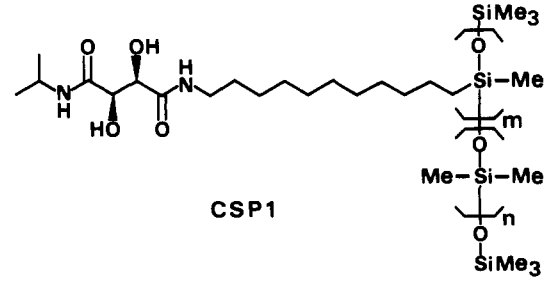
As a part of our program for the design and synthesis of chiral selectors capable of forming transient diastereomers differing in stability with target enantiomers, examination was made of (*R*,*R*)-*N*,*N*′-dialkyltartramides as such selectors that function mainly through dual hydrogen bonding.[3] The following combinations of complementary bonding sites lead to the formation of dual hydrogen bonds, where A and D denote an acceptor and a donor in

hydrogen bonding. Three types of dual hydrogen bond sites (acceptor–acceptor, donor–donor, and acceptor–donor) are possible for many categories of enantiomers, although the steric environment surrounding a set of bonding sites is a variable.

In our previous study, the chiral recognition of various types of enantiomers possessing at least two sites for hydrogen bonding was found to be possible by liquid chromatography using a chiral stationary phase (CSP) derived from the (*R*,*R*)-*N*,*N*′-dialkyltartramide[3b,4] Such enantiomers contained *O*-phenylcarbamoyl 2-hydroxy carbonyl derivatives (esters and ketones), 3-hydroxy carbonyl derivatives (esters, ketones, and *N*-alkylamides), *N*-phenylcarbamoyl derivatives of primary amines, amino esters, and 2-amino alcohols, glutarimides, barbiturates, 2-hydroxy ketoximes, 1,1′-bi-2-naphthol, [(2-hydroxyphenyl)phenyl]carbinol, (2-pyridylphenyl)carbinol, and 1,2-diols.

Chiral recognition on a CSP is based on stability differences in transient diastereomers between the chiral selector of the CSP and solute enantiomers via intermolecular force. It thus follows that the (*R*,*R*)-*N*,*N*′-dialkyltartramide forms energetically different diastereomers with these categories of enantiomers most likely through dual hydrogen bonding. It is important to note that the tartramide derivative provides dual hydrogen bond sites complementary to those of the versatile enantiomers listed previously. One factor responsible for this flexibility of the tartramide molecule for dual hydrogen bond formation may possibly be conformational change involving the formation and/or scission of intramolecular hydrogen bond(s) at the time of complexation. Such conformational reorganization is regarded as "induced fit" in a small molecular system.

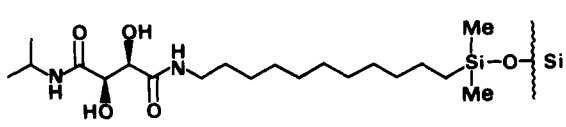
Efforts are presently being made to verify this hypothesis through determination of the structure of the complex giving rise to observed enantioselection and also develop new systems for chiral recognition incorporating the (*R*,*R*)-*N*,*N*′-dialkyltartramide as a chiral selector. For the latter purpose, examination was made of the enantioselectivity of (*R*,*R*)-*N*,*N*′-dialkyltartramide in a gas chromatographic system using a capillary column. Capillary gas chromatography using a CSP is highly effective and sensitive for determining enantiomer excess. Recently, we designed and synthesized CSP 1 in which the (*R*,*R*)-tartramide moiety was attached to polysiloxane as the matrix through a long alkyl chain comprised of 11 methylene units. Enantiomer resolution of underivatized 1,2-diols by capillary gas chromatography using CSP 1 was shown to be an outstanding application of this phase.[5] In this paper, the synthetic details of CSP 1 and extended applications to gas chromatographic resolution of enantiomers are presented.



CSP1

Prior to our work, many kinds of CSPs for gas chromatography were already developed.[6] Some of them are

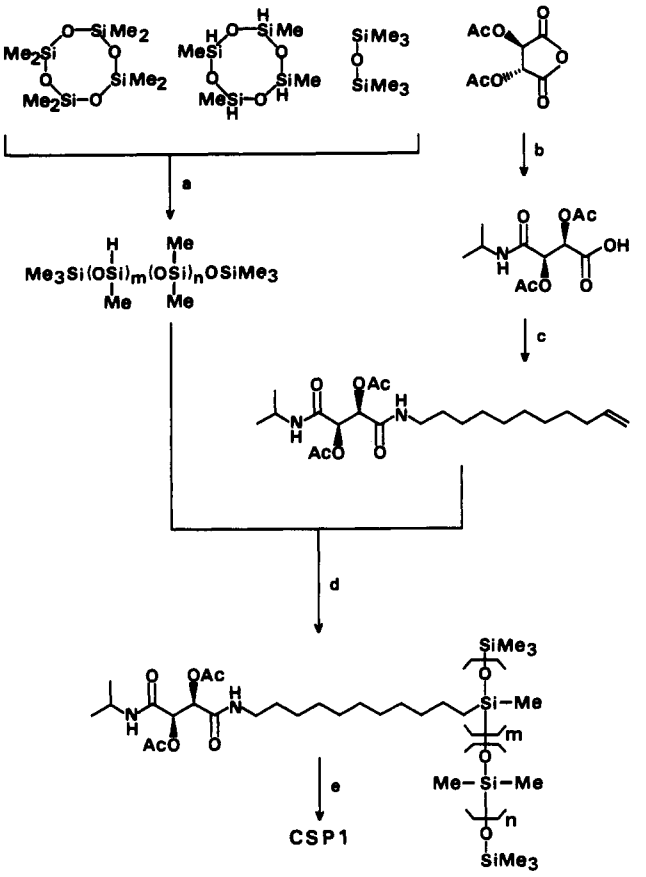
(1) Tanabe Seiyaku Co., Ltd.
(2) Tokyo College of Pharmacy.
(3) (a) Dobashi, Y.; Hara, S. *J. Am. Chem. Soc.* **1985**, *107*, 3406. (b) Dobashi, Y.; Hara, S. *J. Org. Chem.* **1987**, *52*, 2490.
(4) The structure of a silica-based CSP used in ref 3b is as follows:



(5) (a) Nakamura, K.; Saeki, T.; Matsuo, M.; Hara, S.; Dobashi, Y. *Anal. Chem.* **1990**, *62*, 539. For the prototype of CSP 1, see: (b) Nakamura, K.; Hara, S.; Dobashi, Y. *Anal. Chem.* **1989**, *61*, 2121.

0022-3263/91/1956-3299$02.50/0

Scheme I[a]



[a] Key: (a) cat. CF_3SO_3H; (b) $(CH_3)_2CHNH_2$; (c) *N*-(ethoxycarbonyl)-2-ethoxy-1,2-dihydroquinoline, 10-undecenylamine; (d) cat. H_2PtCl_6; (e) NH_3.

of practical use. There are, however, no CSPs capable of resolving all volatile enantiomers of interest in many branches of chemistry. Therefore, it should be still worthwhile to expand and extend the scope of gas chromatographic chiral recognition through development of a new type of CSP.

Results and Discussion

Synthesis and Characterization of CSP 1. Our synthetic route for preparing CSP 1 is shown in Scheme I. The polysiloxane structure as the backbone of the CSP was prepared by the acid-catalyzed ring-opening copolymerization of octamethylcyclotetrasiloxane, 1,3,5,7-tetramethylcyclotetrasiloxane, and hexamethyldisiloxane.[7] The polyhydromethylsiloxane thus obtained was found to contain dimethylsiloxane and hydromethylsiloxane units

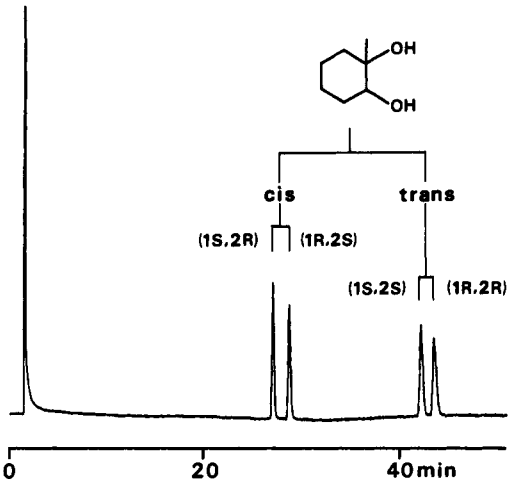


Figure 1. Resolution of the four stereoisomers of 1-methyl-1,2-cyclohexanediol on CSP 1: column temperature, 85 °C isothermal; carrier gas, 0.9 kg/cm² He.

in a ratio of 10:1, on the basis of relative signal intensities of corresponding protons in the ^1H NMR spectrum of the material. Analysis using gel permeation chromatography (GPC) indicated the average molecular weight of this polymer to be ca. 5×10^4.

Synthesis of the tartramide unit to be incorporated into the polysiloxane was a straightforward process consisting of aminolysis of diacetyltartaric anhydride by isopropylamine and subsequent condensation of the resulting half-amide with 10-undecenylamine using *N*-(ethoxycarbonyl)-2-ethoxy-1,2-dihydroquinoline.[8] The hydrosilylation reaction of the alkenyl derivative of diacetyltartramide with the previous polyhydromethylsiloxane catalyzed by chloroplatinic acid produced a linkage between the chiral selector and siloxane matrix. GPC of the crude product to remove small molecular weight material such as the catalyst and excess alkenyl derivative afforded pure diacetyl CSP 1. Strong absorptions observed at 1760, 1650, 1540 cm^{-1} in IR spectrum of this polymer indicated a incorporation of the tartramide unit into the matrix. CSP 1 was obtained as a slightly brownish gum by ammonolysis of the diacetyl polymer. The complete removal of acetyl groups was confirmed by the IR spectrum of CSP 1. This CSP was found to contain 0.68 mmol/g of the tartramide moiety based on the elemental analysis of nitrogen.

Gas Chromatographic Resolution of Enantiomers Using CSP 1. The chiral recognition of a broad range of enantiomers was successfully conducted on CSP 1. In Table I are given gas chromatographic data for the resolution of these enantiomers. The degree of chiral recognition is indicated by the separation factor.[9] This parameter reflects the ratio of association constants between the (*R*,*R*)-tartramide moiety and a pair of solute enantiomers. Separation factors for the enantiomeric pair in this study ranged from 1.01 to 1.10. Rs values[10] indicate the degree of peak separation. Complete base line separation is possible at an Rs value of more than 1.5. Even in separation at a value of 1.0, overlap between two peaks

(6) For reviews of gas chromatographic chiral recognition, see: (a) Schurig, V. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, p 59. (b) Koppenhoefer, B.; Bayer, E. In "The Science of Chromatography"; Bruner, F., Ed.; Elsevier: Amsterdam, 1985; Vol. 32, p 59; *J. Chromatogr. Libr.* **1985**, *32*, 1. (c) Gil-Av, E. In "The Science of Chromatography"; Bruner, F., Ed.; Elsevier: Amsterdam, 1985; Vol. 32, p 111; *J. Chromatogr. Libr.* **1985**, *32*, 111. (d) Koenig, W. A. "The Practice of Enantiomer Separation by Capillary Gas Chromatography"; Huethig: Heidelberg, 1987. For recent works, see: (e) Nowotny, H.-P.; Schmalzing, D.; Wistuba, D. Schurig, V. *J. High Resolut. Chromatogr.* **1989**, *12*, 383. (f) Koenig, W. A.; Krebber, R. *J. High Resolut. Chromatogr.* **1989**, *12*, 641. (g) Watabe, K.; Charles, R.; Gil-Av, E. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 192. (h) Schurig, V.; Ossig, J.; Link, R. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 194. (i) Schurig, V.; Nowotny, H.-P.; Schmalzing, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 736. (j) Armstrong, D. W.; Li. W.; Chang, C.-D.; Pitha, J. *Anal. Chem.* **1990**, *62*, 914.

(7) Bradshaw, J. S.; Aggarwal, S. K.; Rouse, C. A.; Tarbet, B. J.; Markides, K. E.; Lee, M. L. *J. Chromatogr.* **1987**, *405*, 169.

(8) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651.

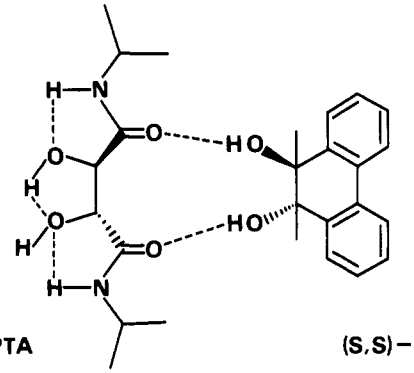
(9) The separation factor (α) is defined by the following equation: $\alpha = k'_2/k'_1$, where k'_1 and k'_2 are the capacity factor (see the following text) of the lesser retained enantiomer and that of the more retained enantiomer, respectively. The capacity factor (k') is defined by the following equation: k' = (retention time–dead time)/(dead time).

(10) This parameter is defined as Rs (resolution) = 2 × (distance of two peak positions)/(sum of the band widths of the two peaks at their bases).

is only 2% of each. In our system, chiral recognition with a separation factor of only 1.02 can be detected as peak separation with Rs of approximately 1.0.

Structurally diverse 1,2-diols are included in the scope of chiral recognition on CSP 1. CSP 1 was highly sensitive to differences in the stereochemistry of two carbons bearing hydroxyls of 1,2-diols. For example, all stereoisomers of 1-methyl-1,2-cyclohexanediol were resolved, thus giving the four distinct peaks shown in Figure 1.

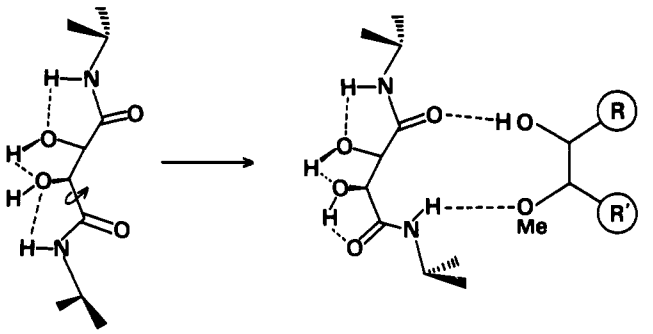
In the previous study using (R,R)-N,N'-diisopropyltartramide (DIPTA) as a chiral mobile-phase additive in silica gel liquid chromatography,[3a] the gauche relationship between two hydroxyls was found to be required for 1,2-diols to bring about enantioselectivity in the complexation with (R,R)-DIPTA. Recognition of the molecular chirality of 1,2-diols by (R,R)-DIPTA may thus possibly be based on dual hydrogen bonding between gauche hydroxyls of 1,2-diols and (R,R)-DIPTA, although the bonding site in (R,R)-DIPTA was obscure. Recently, dual hydrogen bonding of 1,2-diol and (R,R)-tartramide derivatives was actually observed in an X-ray crystal structure of a complex consisting of (R,R)-DIPTA and (S,S)-9,10-dimethyl-9,10-dihydrophenanthrene-9,10-diol (DIMPDOL).[11] (S,S)-DIMPDOL interacts more strongly with CSP derived from the (R,R)-DIPTA analogue than its enantiomer,[3b,4] thus showing the complex of (S,S)-DIMPDOL and (R,R)-DIPTA to be more stable than the corresponding diastereomer. The results of an ^1H NMR study were also compatible with the S,S selectivity of (R,R)-DIPTA toward DIMPDOL through dual hydrogen bonds with two hydroxyls of DIMPDOL.[11] The structure equivalent to this complex is the following:



In the crystal structure, the relationship between two hydroxyls of (S,S)-DIMPDOL, that between two hydroxyls of (R,R)-DIPTA, and that between two amide units of (R,R)-DIPTA was of the gauche, gauche, and anti type, respectively. An intramolecular hydrogen bond between two hydroxyls of (R,R)-DIPTA in the figure could not actually be observed in the crystal structure, but is assumed to be formed in solution. The gauche relationship between two hydroxyls of (R,R)-DIPTA makes intramolecular hydrogen bonding possible. Most importantly, such bond formation should be energetically favored. The previous mode of dual hydrogen bonding is considered the probable cause of the enantioselection of 1,2-diols by (R,R)-tartramide in solution, and this would also apply to the present gas chromatographic system.

Enantiomers of a series of dialkyl tartrates were well-resolved on CSP 1. These derivatives are closely related to 1,2-diols. Accordingly, the mode of dual hydrogen bonding observed in the DIMPDOL–DIPTA system may also be responsible for the enantioselection of dialkyl tartrates. The ^1H NMR study conducted here indicated the hydroxyls of dialkyl tartrates to participate in the formation of transient diastereomers with (R,R)-DIPTA. Resonance for the two hydroxyl protons in 0.03 M $CDCl_3$ solution of racemic dibenzyl tartrate (DBnT)[12] at 27 °C appeared at δ 3.158 as a doublet (J = 7.5 Hz). The addition of (R,R)-DIPTA to the solution caused a shift difference in the resonance for the two hydroxy protons of DBnT (a doublet (J = 7.5 Hz) at δ 3.436 for (S,S)-DBnT, a doublet (J = 7.5 Hz) at δ 3.396 for (R,R)-DBnT, 0.10 M in (R,R)-DIPTA). There is a possibility that the ester functionality of the tartrates may be essential to enantioselective complexation with (R,R)-tartramide owing to its hydrogen bond ability. However, the role of the ester functionality in the complexation could not be determined in this study.

In addition to that of 1,2-diols, enantioselection of the monomethyl ethers of these derivatives was also possible on CSP 1. Dual hydrogen bonds involving methoxyls as acceptors were possibly operative as the mode of complexation responsible for the enantioselection of these 1-methoxy-2-alkanols. Support for this possibility is provided by the fact that monofunctional secondary alcohols such as 2-butanol and 2-hexanol could not be resolved into enantiomers on CSP 1 throughout the region examined. To form dual hydrogen bonds with 1-methoxy-2-alkanols, two bonding sites of (R,R)-tartramide should involve at least one hydrogen bond donor. Such bonding sites of (R,R)-tartramide can be made through minor modification of the conformer in the complex with (S,S)-DIMPDOL, as follows:



Other dual hydrogen bond sites complementary to those of 1-methoxy-2-alkanols are possible in (R,R)-tartramide molecule. However, the conformer of the (R,R)-tartramide equivalent to that shown in the figure was noted in the X-ray crystal structure of self-associated (R,R)-DIPTA.[13] Difference in the mode of dual hydrogen bonding was reflected in enantioselection on CSP 1. For example, CSP 1 was insensitive to the chirality of *trans*-1,2-cyclopentanediol, while enantiomers of the monomethyl ether of this diol could be resolved with a separation factor of 1.051 on CSP 1.

Other classes of enantiomers were derivatized so as to possess the proper functionality to bring about the enantioselective hydrogen bonding with the present chiral selector. The derivatization also ensured the volatility of solute enantiomers required for gas chromatography. Such achiral derivatization effecting the chiral recognition is summarized as follows.

(11) Dobashi, Y.; Hara, S.; Iitaka, Y. *J. Org. Chem.* 1988, *53*, 3894.

(12) Enantiomers of dibenzyl tartrate were resolved on CSP derived from the (R,R)-tartramide[4] with a separation factor of 1.5 when 10% (v/v) 2-propanol in *n*-hexane was used as the mobile-phase solvent at 20 °C. The most retained enantiomer of dibenzyl tartrate showed a capacity factor of 5.26 and the S,S configuration.

(13) Dobashi, Y.; Dobashi, A.; Hara, S.; Iitaka, Y. Manuscript in preparation.

Table I. Gas Chromatographic Resolution of Enantiomers on CSP 1

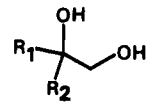
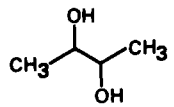
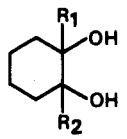
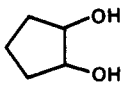
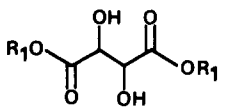
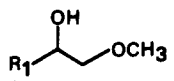
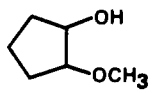
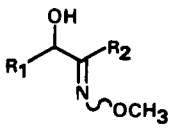
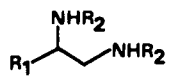
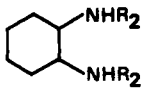
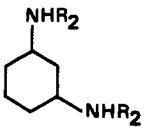
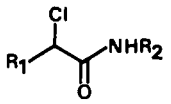
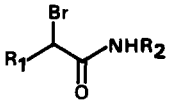
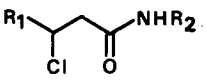
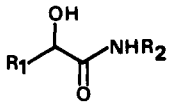
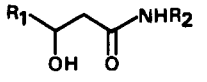
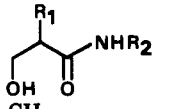
R_1	R_2	rel config	k'_1[a]	α[a]	Rs[b]	most retained enantiomer	column temp (°C)
			1,2-Diols				
							
CH_3	H		8.00	1.084	1.73	*R*	65
C_2H_5	H		13.10	1.039	1.72	*R*	70
$(CH_3)_2CH$	H		21.03	1.031	1.63	*R*	70
$(CH_3)_3C$	H		27.28	1.047	2.40		70
C_2H_5	CH_3		12.76	1.019	0.90		70
$(CH_3)_2CH$	CH_3		22.36	1.039	1.75		70
$(CH_3)_3C$	CH_3		30.32	1.000			70
C_3H_7	H		27.99	1.029	1.05		70
$(CH_3)_2CHCH_2$	H		44.12	1.016	0.76		70
$(CH_3)_3CCH_2$	H		51.80	1.030	1.24		70
C_3H_7	CH_3		26.26	1.028	1.17		70
$(CH_3)_2CHCH_2$	CH_3		36.72	1.032	1.71		70
$(CH_3)_3CCH_2$	CH_3		53.45	1.022	1.01		70
		threo	7.32	1.053	1.25	2*R*,3*R*	65
							
H	H	trans	31.56	1.073	3.73	1*R*,2*R*	85
CH_3	H	cis	18.49	1.064	3.45	1*R*,2*S*	85
CH_3	H	trans	29.47	1.034	1.91	1*R*,2*R*	85
CH_3	CH_3	trans	16.81	1.051	2.75	1*R*,2*R*	85
		trans	18.37	1.000			90
			Dialkyl Tartrates				
							
CH_3			13.15	1.040	1.82	*S*,*S*	120
C_2H_5			22.44	1.038	1.78	*S*,*S*	120
$(CH_3)_2CH$			25.54	1.034	1.88	*S*,*S*	120
			Methoxy Alcohols				
							
CH_3			1.84	1.043	1.12	*R*	35
C_2H_5			4.34	1.044	1.59	*R*	35
		trans	12.55	1.051	2.21		55
			Methyloximes of 2-Hydroxy Ketones				
							
CH_3	CH_3	syn	5.87	1.026	1.18		50
CH_3	CH_3	anti	9.31	1.000			50
C_2H_5	C_2H_5	syn	16.40	1.027	1.52		50
C_2H_5	C_2H_5	anti	25.94	1.000			50
C_3H_7	C_3H_7	syn	62.12	1.026	1.62		50
C_3H_7	C_3H_7	anti	98.86	1.000			50
			N,*N*′-Bis(perfluoroacyl) Diamines				
							
CH_3	CF_3CO		12.72	1.028	1.39		140
CH_3	C_2F_5CO		9.25	1.033	1.51		140
CH_3	C_3F_7CO		11.81	1.031	1.45		140

Table I (Continued)

R_1	R_2	rel config	k'_1[a]	α[a]	Rs[b]	most retained enantiomer	column temp (°C)
	CF_3CO	trans	21.94	1.079	4.49	1*S*,2*S*	150
	C_2F_5CO	trans	16.21	1.090	4.72	1*S*,2*S*	150
	C_3H_7CO	trans	19.54	1.098	5.19	1*S*,2*S*	150
	CF_3CO	trans	24.75	1.014	0.82		150
	C_2F_5CO	trans	13.19	1.015	0.81		150
	C_3F_7CO	trans	16.97	1.012	0.65		150
		N-Alkyl-2-halo Carboxamides					
							
CH_3	CH_3		9.73	1.036	1.08	*R*	55
CH_3	$(CH_3)_2CH$		10.18	1.019	0.90	*R*	55
CH_3	$(CH_3)_3C$		8.27	1.015	0.82	*R*	55
C_2H_5	CH_3		18.75	1.034	1.54		55
C_2H_5	$(CH_3)_2CH$		20.08	1.020	1.15		55
C_2H_5	$(CH_3)_3C$		16.42	1.015	0.93		55
							
CH_3	CH_3		7.71	1.023	1.26	*R*	80
C_2H_5	CH_3		13.08	1.022	1.32	*R*	80
$(CH_3)_2CH$	CH_3		16.91	1.022	1.33	*R*	80
C_3H_7	CH_3		24.85	1.023	1.48	*R*	80
		N-Alkyl-3-halo Carboxamides					
							
CH_3	CH_3		32.98	1.021	1.29		80
CH_3	$(CH_3)_2CH$		30.60	1.025	1.50		80
CH_3	$(CH_3)_3C$		21.07	1.026	1.63		80
		N-Alkyl-2-hydroxy Carboxamides					
							
CH_3	$(CH_3)_2CH$		14.83	1.026	0.91	*R*	110
CH_3	CH_3		14.88	1.028	1.10	*R*	110
C_2H_5	CH_3		22.68	1.032	1.28	*R*	110
$(CH_3)_2CH$	CH_3		26.59	1.036	1.67	*R*	110
C_3H_7	CH_3		40.89	1.031	1.33		110
		N-Alkyl-3-hydroxy Carboxamides					
							
CH_3	CH_3		20.17	1.021	0.98	*R*	115
CH_3	$(CH_3)_2CH$		19.12	1.029	1.40	*R*	115
CH_3	$(CH_3)_3C$		13.91	1.031	1.40	*R*	115
C_2H_5	$(CH_3)_3C$		21.05	1.035	1.82		115
$(CH_3)_2CH$	$(CH_3)_3C$		25.87	1.039	2.19		115
							
CH_3	$(CH_3)_3C$		14.90	1.043	2.01	*R*	115
C_2H_5	$(CH_3)_3C$		23.64	1.059	2.73		115
$(CH_3)_2CH$	$(CH_3)_3C$		29.05	1.072	3.57		115

[a] See ref 9. [b] See ref 10.

2-Hydroxy ketones were converted to methyloximes, giving syn and anti diastereomers, of which only the enantiomers of *syn*-oximes could be resolved.

For the derivatization of enantiomeric 1,2-diamines, perfluoroacylation was conducted. The enantiomers of *trans*-1,3-diaminocyclohexane were also resolvable on CSP 1 following the perfluoroacylation, though the extent of enantioselection was modest.

For their chiral recognition on CSP 1, 2- and 3-halo carboxylic acids as well as 2- and 3-hydroxy carboxylic acids were converted to the corresponding *N*-alkylamides. Increase in the steric bulkiness of *N*-alkyl substituents enhanced the enantioselection of the 3-halo carboxamides on CSP 1, while the reverse effect was noted for the *N*-alkyl substituents of 2-halo carboxamide. The same tendency was also observed for the enantiomer resolution of the corresponding hydroxy carboxamides.

All the above derivatized enantiomers possess at least two hydrogen bond sites: a hydroxyl and methoxyl pair in *syn*-methyloximes of 2-hydroxy ketones, two amide units in *N,N'*-diacyldiamines, a halogen and amide unit pair of halo carboxamides, and a hydroxyl and amide unit pair of hydroxy carboxamides. Each pair of hydrogen bond sites can be orientated in the same direction within reasonable conformational change. The chiral recognition of these derivatives may thus be assumed to be based on dual hydrogen bonding with the (*R,R*)-tartramide.

Of the enantiomers derivatized to render them sensitive to CSP 1, complexation between a *N-tert*-butylamide derivative of 3-hydroxy carboxylic acid and (*R,R*)-DIPTA was investigated by using ^{1}H NMR spectroscopy. The enantiomers of *N-tert*-butyl-2-hydroxy-3-phenylpropanamide (TBHP) were resolved with a separation factor of 1.20 by liquid chromatography using a CSP derived from (*R,R*)-DIPTA analogue.[3b,4] (*S*)-TBHP exhibited greater retentivity on this CSP, consequently giving rise to a more stable diastereomer with the (*R,R*)-tartramide. The same sense of enantioselectivity toward *N-tert*-butyl-3-hydroxybutanamide was observed in the present gas chromatographic system, although the absolute configuration of this carboxamide was denoted as *R* in adherence to the priority rule.[14]

The resonance of the hydroxy proton and that of the amide proton in 0.08 M $CDCl_3$ solution at 27 °C were observed at δ 4.343 as a doublet (J = 3.0 Hz) and at δ 5.485 as a relatively broad singlet, respectively. These signals shifted downfield and split into a pair of doublets at δ 4.732 and 4.781 and a pair of singlets at δ 5.863 and 5.961 with essentially the same intensity when the solution was 0.18 M (*R,R*)-DIPTA. The coupling constants of these doublets did not change significantly. Both a doublet and singlet appearing downfield relative to their counterparts were assigned to the corresponding resonance of (*S*)-TBHP on the basis of the correlation of the relative intensity of the signals with the enantiomeric composition of TBHP.

The downfield shift noted for hydroxyl and amide protons of TBHP following the addition of (*R,R*)-DIPTA reflected hydrogen bonding of (*R,R*)-DIPTA with hydroxyls and/or amide units of TBHP, although it was difficult to determine whether these bonding sites function as acceptors or receptors. The shift differences observed for both protons of the hydroxyls and amide units of TBHP enantiomers strongly indicated these groups to be involved simultaneously in the formation of transient diastereomers with (*R,R*)-DIPTA. Thus, dual hydrogen bonding of (*R,R*)-tartramide with the hydroxyls and amide units of 3-hydroxy carboxamides appears quite likely to be the mode of enantioselective complexation.

In conclusion, we have developed a new polysiloxane derived from the (*R,R*)-tartramide as a CSP for capillary gas chromatography. The present gas chromatographic system proved to have a wide range of application to enantiomer resolution. Several categories of enantiomers resolvable on CSP 1 were beyond the limits of the CSP derived from the (*R,R*)-tartramide in liquid chromatography.[3b] The enantioselection in this system thus provides more detailed information on the structures of enantiomers capable of undergoing enantioselective hydrogen bonding with (*R,R*)-tartramides. One factor making possible the high performance of CSP 1 may be the use of a nonpolar long alkyl chain as a spacer between the chiral selector and polysiloxane backbone. This approach is relatively common in design for achieving higher enantioselectivity on silica-based CSPs in normal-phase liquid chromatography.[3b,15] Clarification of the effects of spacer length on enantioselectivity in a gas chromatographic system and the mechanism of molecular recognition based on complexation with (*R,R*)-tartramide is presently being pursued.

Experimental Section

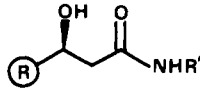
General Procedures. Melting points were determined on a micro hot plate melting point apparatus and are uncorrected. NMR spectra were measured on a Brucker AM-500 or JEOL FX-100 spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane. As the internal standard, tetramethylsilane or residual solvent was used. ^{1}H NMR spectra were evaluated as first-order spectra. The abbreviations br, s, d, t, q and qn refer to broad, singlet, doublet, triplet, quartet, and quintet, respectively. IR spectra were obtained on a Hitachi 260-30 or Perkin-Elmer FTIR 1710 spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter. Microelemental analysis was conducted by the Microanalytical Center of Tokyo College of Pharmacy. Thermogravimetric analysis was conducted using a Shimadzu TGA-50 instrument under an atmosphere of nitrogen.

Gas chromatography was conducted with a Shimadzu GC-14A equipped with a split injector and flame ionization detector. Helium was used as the carrier gas. The inlet pressure of the capillary column was 0.9 kg/cm^2, and the split ratio was 1:60. The temperature of the injection port was maintained at 200 °C. Chromatographic signals were recorded and processed by a Shimadzu C-R4AX data processor. Preparative high-performance liquid chromatography (HPLC) was carried out with use of the column of a 115 × 22 (i.d.) mm glass tube packed with ca. 30 g of 10-μm irregularly shaped silica gel (Kusano CIG column Kusano Kagakukikai CO., Tokyo). GPC was performed by HPLC techniques using a Shodex GPC-A-80M column. Molecular weight of the polymers was estimated from a calibration curve obtained with polystyrene standards of different molecular weight (6200, 18 600, 42 200, 77 500).

Materials. Solvents for chromatography and extraction were reagent grade and used as received. Chloroform was distilled from diphosphorus pentoxide; tetrahydrofuran was distilled from benzophenone ketyl; dichloromethane and 2-propanol were distilled from calcium hydride.

Polyhydromethylsiloxane.[7] To a stirred mixture of octamethylcyclotetrasiloxane (1.0 mL, 3.223 mmol), 1,3,5,7-tetramethylcyclotetrasiloxane (0.12 mL, 0.474 mmol), and hexa-

(14) The absolute configuration of the enantiomers of *N*-alkyl-3-hydroxy carboxamides forming the more stable transient diastereomer with (*R,R*)-tartramide is the following:



(15) (a) Pirkle, W. H.; Hyun, M. H.; *J. Org. Chem.* **1984**, *49*, 3043. (b) Pirkle, W. H.; Pochapsky, T. C.; Mahler, G. S.; Corey, D. E.; Reno, D. S.; Alessi, D. M. *J. Org. Chem.* **1986**, *51*, 4991. (c) Feibush, B.; Figueroa, A.; Charles, R.; Onan, K. D.; Feibush, P.; Karger, B. L. *J. Am. Chem. Soc.* **1986**, *108*, 3310.

methyldisiloxane (0.003 mL, 0.014 mmol) was added trifluoromethanesulfonic acid (0.005 mL, 0.057 mmol) at room temperature under an atmosphere of argon. The reaction was continued for 18 h and then quenched by the addition of hexamethyldisilazane (0.005 mL, 0.024 mmol). The resulting mixture was diluted with *n*-pentane (10 mL). To the stirred solution was added dropwise methanol (10 mL). The lower layer thus separated was partitioned four times between *n*-pentane (10 mL) and methanol (10 mL) as described previously, and the solvent was evaporated. The desired polymer (1.0 g) was obtained as a colorless viscous oil: IR (thin film) 2970, 2160 (SiH), 1410, 1260 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.059 (s), 0.083 (s), 0.145 (d, J = 1.5 Hz, CH_3SiH), 4.682 (q, J = 1.5 Hz, CH_3SiH). The ratios of intensity of the methyl signals appearing at δ 0.059, 0.083, and 0.145 were 94:31:6.5, respectively. The ratio of the total intensity of these methyl signals to that of SiH signals was 67:1.

(*R,R*)-*N*-Isopropyldiacetyltartaric Acid Monoamide. This compound was prepared by aminolysis of (*R,R*)-diacetyltartaric anhydride[16] with isopropylamine according to the method described in our previous work:[3b] mp 176–177 °C dec; $[\alpha]^{26}_D$ = –22.0° (*c* 2.27, ethanol); IR (KBr) 3338 (NH), 2977, 2952 (OH), 1760 and 1747 (shoulder) (acetyl and carboxyl C=O), 1641 (amide C=O), 1562 (amide) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$–Me_2SO-d_6 (10:1 v/v) δ 1.143 and 1.163 (d each, 6 H in total, J = 6.6 Hz each, $CH(CH_3)_2$), 2.125 (s, 3 H, CH_3CO), 2.179 (s, 3 H, CH_3CO), 4.063 (d septet, 1 H, J = 8.0, 6.6 Hz, $CH(CH_3)_2$), 5.609 (d, 1 H, J = 2.7 Hz, CH_3COOCH), 5.682 (d, 1 H, J = 2.7 Hz, CH_3COOCH), 6.602 (br d, 1 H, J = 8.0 Hz, NH), 11.516 (br s, 1 H, OH); ^{13}C NMR (25 MHz, $CDCl_3$–Me_2SO-d_6 (10:1 v/v) δ 20.37, 20.71, 22.32, 22.46, 41.52, 71.49, 72.17, 164.85, 168.26, 169.00, 169.33. Anal. Calcd for $C_{11}H_{17}O_7N$: C, 48.00; H, 6.22; N, 5.09. Found: C, 48.13; H, 6.23; N, 4.99.

(*R,R*)-*N*-(10-Undecenyl)-*N'*-isopropyldiacetyltartramide.[17] To a mixture of the finely powdered (*R,R*)-*N*-isopropyldiacetyltartaric acid monoamide (475.2 mg, 1.726 mmol) and *N*-(ethoxycarbonyl)-2-ethoxy-1,2-dihydroquinoline[8] (432.9 mg, 1.751 mmol) was added tetrahydrofuran (10 mL) at room temperature under an atmosphere of argon. Stirring was continued at this temperature for 50 min. The solution was then cooled in an ice bath followed by the addition of 10-undecenylamine[3b] (283.8 mg, 1.676 mmol) in tetrahydrofuran (5.4 mL) over 5 min. The solution was stirred for 25 min and allowed to warm to room temperature. After the solution had been stirred at this temperature for 30 min, ethyl acetate (50 mL) and 1 N hydrochloric acid (10 ml) were added. The organic layer thus separated was washed with 1 N hydrochloric acid (10 mL × 2), saturated aqueous sodium bicarbonate (10 ml), water (10 mL), and brine (10 mL × 2) successively and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by preparative HPLC with 30% (v/v) acetone in *n*-hexane as the eluent. The pure diamide (469.3 mg, 67% based on the half-amide) was obtained as a white solid: mp 150–151 °C; $[\alpha]^{28}_D$ = –12.9° (*c* 2.14, ethanol); IR (KBr) 3285 (NH), 3079, 2977, 2929, 2856, 1758 (acetyl C=O), 1653 (amide C=O), 1550 (amide) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.145 and 1.162 (d each, 6 H in total, J = 6.6 Hz each, $CH(CH_3)_2$), 1.274 (br s, $W_{1/2}$ = 9.1 Hz, 10 H, $(CH_2)_2(CH_2)_5(CH_2)_2$),[18] 1.396 (br qn, 2 H, J = 7.0 Hz, $CH_2CH_2CH{=}CH_2$),[19] 1.489 (br qn, 2 H, J = 7.0 Hz, $NHCH_2CH_2$), 2.036 (q with further coupling, 2 H, J = 7.1 Hz, $CH_2CH_2CH{=}CH_2$),[20] 2.159 and 2.161 (s each, 6 H in total, CH_3CO × 2), 3.195 (ddt, 1 H, J = 13.2, 6.7, 6.7 Hz, NHC(*H*)H), 3.285 (ddt, 1 H, J = 13.2, 6.7, 6.7 Hz, NHC(H)*H*), 4.046 (d septet, 1 H, J = 7.9, 6.6 Hz, $CH(CH_3)_2$), 4.929 (ddt, 1 H, J = 10.2, 2.1, 1.1 Hz, CH=C(*H*)H), 4.990 (ddt, 1 H, J = 17.0, 2.1, 1.5 Hz, CH=C(H)*H*), 5.544 (d, 1 H, J = 3.8 Hz, CH_3COOCH), 5.583 (d, 1 H, J = 3.8 Hz, CH_3COOCH), 5.808 (ddt, 1 H, J = 17.0, 10.2, 6.7 Hz, $CH{=}CH_2$), 5.943 (br d, 1 H, J = 7.9 Hz, NHCH), 6.156 (br t, 1 H, J = 6.7 Hz, $NHCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.57, 20.60, 22.29, 22.44, 26.77, 28.86, 29.04, 29.19, 29.32, 29.36, 29.41, 33.73, 39.58, 41.65, 72.40, 114.10, 139.12, 165.16, 165.97, 169.16, 169.17. Anal. Calcd for $C_{22}H_{38}O_6N_2$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.80; H, 8.99; N, 6.52.

Diacetyl CSP 1. To a solution of (*R,R*)-*N*-(10-undecenyl)-*N'*-isopropyldiacetyltartramide (340 mg, 0.80 mmol) and polyhydromethylpolysiloxane (370 mg) in chloroform (15 mL) was added 0.1 M chloroplatinic acid in 2-propanol (0.1 mL) at room temperature under an atmosphere of argon. After the mixture had been stirred for 15 h at 80 °C, the solvent was removed under reduced pressure. The residue was subjected to GPC with tetrahydrofuran as the eluent, yielding a gumlike material (480 mg): IR (thin film) 3280 (NH), 2960, 2930, 1760 and 1750 (shoulder) (acetyl C=O), 1650 (amide C=O), 1540 (amide), 1260 cm^{-1}.

CSP 1. To a solution of (*R,R*)-diacetyl polymer (280 mg) in a mixture of chloroform and methanol (1:1 (v/v), 20 mL) was added 28% (v/v) aqueous ammonia (1.0 mL) at room temperature. After the mixture had been stirred at this temperature for 1.5 h, the volatiles were removed under reduced pressure to give CSP 1 (200 mg) as a gumlike material. Thermal stability was assessed by thermogravimetric analysis. CSP 1 exhibited no loss of weight up to 240 °C: IR (thin film) 3400 and 3300 (OH and NH), 2960, 2920, 1650 (shoulder) and 1630 (amide C=O), 1540 (amide), 1260 cm^{-1}. Anal. Found: C, 38.86; H 8.36; N, 1.89.

Column Preparation. A fused-silica capillary tube (25 m × 0.25 mm i.d.) was washed with dichloromethane, dried by passage of helium gas, and coated with a 0.3% (w/v) solution of CSP 1 in dichloromethane by the static method.[21] The resulting column was conditioned by passage of helium gas while the temperature was gradually raised to 150 °C.

Acknowledgment. We gratefully acknowledge Dr. H. Fujioka (Faculty of Pharmaceutical Sciences, Osaka University) for helpful discussion on the preparation of (1*R*,2*R*)- and (1*R*,2*S*)-1-methyl-1,2-cyclohexanediol. We thank Mr. N. Sato (this college) for his technical assistance. We also thank Mrs. T. Sakuma (this college) for NMR measurements and Mr. H. Fukaya (this college) for the elemental analyses. This research was partly supported by grants from the Ministry of Education of Japan (Grant-in-Aid No. 02771667 and No. 02771687).

(16) Shriner, R. L.; Furrow, C. L., Jr. *Organic Synthesis*; Wiley: New York, 1963; Collect. Vol. 4, p 242.

(17) In our previous study,[3b] this compound was prepared using di-*N*-succinimidyl oxalate and characterized insufficiently.

(18) A shoulder peak was observed at δ 1.287.

(19) The assignment was based on the results of decoupling experiments.

(20) The dd-coupling pattern (J = 1.1, 1.5 Hz) was observed for the outer two peaks of the quartet.

(21) Grob, K. "Making and manipulating capillary columns for gas chromatography"; Huethig: Heidelberg, 1986.