= 34.2 Hz), 107.02 (t of q, J_{CF} = 266.5 Hz, J_{CCF} = 38.1 Hz), 37.36 (d), 30.92 (d), 22.36 (d), 22.11 (d), 13.74 (t); IR (neat) 3500 vw, 2965 s, 2938 s, 2880 m, 2870 m, 1765 vs, 1480-1465 w, 1412 w, 1390-1380 w, 1360 m, 1342 s, 1240-1200 vs, 1172 s, 1140 m, 1128 s, 1100 w, 1070 m, 1040-1030 w, 990 w, 930 m, 895 w, 840 vw, 757 w, 736 w, 720 m cm^{-1}; exact mass M_r calcd for $C_8H_{11}F_5O$ m/e (M + H, CI, CH_4 reagent gas) 219.0808, found 219.0804.

Anal. Calcd for $C_8H_{11}F_5O$: C, 44.04; H, 5.08. Found: C, 44.44; H, 5.14.

Acknowledgment. We are indebted to the National Science Foundation for a grant which supported this investigation, and to the Fairfield Chemical Company for a gift of pentafluoroethyl iodide. We thank D. Britton for his help in acquiring the X-ray crystallographic data on 3.

Supplementary Material Available: ORTEP drawing of 3, tables of atomic coordinates and thermal parameters of nonhydrogen atoms of 3, general temperature factor expressions, least-squares planes, torsional angles in degrees, and positional parameters (including hydrogens) and their standard deviations (9 pages). Ordering information is given on any current masthead page.

A Chiral Stationary Phase Derived from (*R*,*R*)-Tartramide with Broadened Scope of Application to the Liquid Chromatographic Resolution of Enantiomers

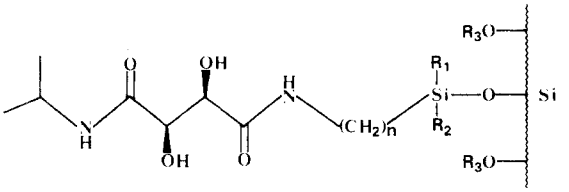
Yasuo Dobashi and Shoji Hara*

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Received October 29, 1986

An understanding of the retention process of solute enantiomers on a chiral stationary phase (CSP) would indicate the importance of eliminating the nonenantioselective, i.e., solute–silanol, interaction that occurs in this process. For clarification of this matter, a CSP in which a (*R*,*R*)-*N*,*N*′-dialkyltartramide derivative is linked to the silica gel surface via 11 methylene units and the remaining silanol groups are trimethylsilylated was synthesized. This CSP was found capable of chiral recognition of broad categories of enantiomers containing α- or β-hydroxy carbonyl, α-amino acid, β-amino alcohol, primary amine derivatives, barbiturates, glutarimide, α-hydroxy ketoximes, carbinols, 1,2-diols, and bi-β-naphthol. The driving force to bring about enantioselective association is ascribable to hydrogen bonding. The effects of a reduction in the number of remaining silanol groups on CSP and a long alkyl chain as a linkage of the tartramide moiety to CSP are discussed on the basis of retentivity of enantiomers.

The chiral-stationary-phase (CSP) method for the liquid chromatograhic resolution of enantiomers has gained general acceptance owing to its ease of operation and preparative-scale applications. However, among a number of CSPs developed to date, those with a general scope of application are few.[1-3] The present study describes a new type of CSP derived from (*R*,*R*)-tartramide (CSP 1) on which broad categories of enantiomers are readily resolved.



CSP 1, $R_1 = R_2 = CH_3$; $R_3 = Si(CH_3)_3$; $n = 11$

CSP 2, $R_1 = R_2 = CH_3$; $R_3 = H$; $n = 11$

CSP 3, $R_1 = OH$; $R_2 = O\text{-}\{Si\}$; $R_3 = H$; $n = 3$

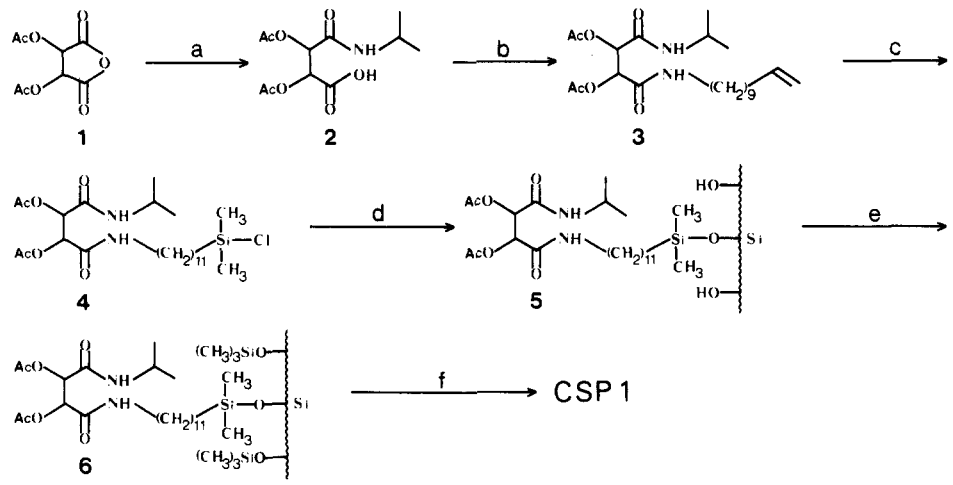
The performance of CSP is determined by the efficiency of the resulting column and scope and magnitude of chiral recognition. Of these two factors, the later depends primarily on the intrinsic ability of the resolving agent incorporated into CSP. We recently reported that (*R*,*R*)-*N*,*N*′-diisopropyltartramide (DIPTA)[4] functions as a broadly applicable chiral-mobile-phase additive (CMPA) in silica gel chromatography. This CMPA recognizes the molecular chirality of enantiomers through its dual hydrogen-bond association and is capable of resolving enantiomers containing α- or β-hydroxy carboxylic acid, β-hydroxy ketone, β-amino alcohol, α-amino acid, α-hydroxy ketoxime, 1,2-diol derivatives, and bi-β-naphthol. Successful resolution using (*R*,*R*)-DIPTA as a CMPA indicates that the tartramide derivative holds promise for being incorporated into CSP. CSPs are generally prepared by a surface modification of a porous silica gel with an appropriate resolving agent since the methods for this are well established[5] and, most importantly, a high efficiency of the resulting column is possible. At our initial stage of the developement of a CSP derived from tartramide, the tartramide derivative was linked to the silica gel surface via a propylene unit through reaction of the corresponding triethoxysilyl derivative with a silica gel (CSP 3).[6] Although a series of *N*-*tert*-butyl-β-hydroxy carboxamides were resolved well on this phase, its scope of application was not equal to that obtained by using (*R*,*R*)-DIPTA as a CMPA.

The unsatisfactory results of our initially designed CSP are ascribed to remaining silanol groups on CSP. The remaining silanol groups interact with the solute enantiomers by forming hydrogen bonds in competition with the chiral moiety of CSP. In such a case, the separation

(1) Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 3964.
(2) Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 352.
(3) Okamoto, Y.; Honda, S.; Okamoto, I.; Yuki, H.; Murata, S.; Noyori, R.; Takaya, H. *J. Am. Chem. Soc.* **1981**, *103*, 6971.
(4) Dobashi, Y.; Hara, S. *J. Am. Chem. Soc.* **1985**, *107*, 3406.
(5) Unger, K. K. *Porous Silica*; Elsevier: Amsterdam, 1979.
(6) Dobashi, Y.; Hara, S. *Tetrahedron Lett.* **1985**, *26*, 4217.

0022-3263/87/1952-2490$01.50/0 © 1987 American Chemical Society

Scheme I[a]



[a] (a) Isopropylamine; (b) di-*N*-succinimidyl oxalate, 10-undecenylamine; (c) dimethylchlorosilane, cat. H_2PtCl_6; (d) Nucleosil 100-5; (e) (trimethylsilyl)imidazole; (f) NH_3–MeOH.

factor (α),[7] indicating the magnitude of the observed enantioselection, is expressed by eq 1,

$$\alpha = (K_r[\mathrm{Ch}] + K[\mathrm{SiOH}])/(K_s[\mathrm{Ch}] + K[\mathrm{SiOH}]) \quad (1)^8$$

where Ch is a chiral moiety of CSP, SiOH is a remaining silanol group, K is an association constant between the solute enatiomer and silanol group assumed identical for both R and S enantiomers, and K_r and K_s are association constants between the chiral moiety and solute enantiomers. Equation 1 is based on a simplified model of the chromatographic process but provides an important principle for designing CSP: for enantioselectivity, due to association between the chiral moiety and the solute enantiomers, to be maximally obtained as enantioselection observed on CSP, interaction between the solute and silanol groups should be minimal.

On the basis of the above guiding principle, we designed CSP 1. In this phase, two different approaches to minimize the nonenantioselective interaction were followed. Use of a long alkyl chain consisting of 11 methylene units to link the chiral moiety to the silica gel surface should lessen accessibility of the solute to silanol groups. The number of remaining silanol groups on CSP is actually decreased by trimethylsilylation of the modified silica gel. In addition, the monochlorosilane derivative was used as a silylating reagent. This type of silane has high reactivity, permitting a sufficient degree of surface modification and, most importantly, there is no possibility of regenerating the silanol groups on the surface modified by such a reagent. The chiral recognition ability of (*R,R*)-tartramide should be fully available in this CSP system.

Results and Discussion

Our synthetic approach to CSP 1 is shown in Scheme I. Aminolysis of diacetyl anhydride **1** with isopropylamine in CH_2Cl_2 afforded half-amide **2**. This half-amide was condensed with 10-undecenylamine by using di-*N*-succinimidyl oxalate[9] in MeCN. The resulting diamide derivative **3** was then hydrosilylated with dimethylchlorosilane in the presence of a catalytic amount of chloroplatinic acid in $CHCl_3$. Following removal of the solvent and excess silane in vacuo, the monochlorosilane derivative **4** thus obtained was made to react directly with 5-μm porous silica gel in a mixture of benzene and pyridine (2:1 v/v). The modified silica gel **5** was found to contain 0.42 mmol/g of the tartramide moiety by elemental analysis of nitrogen. Further reaction of the material with (trimethylsilyl)imidazole in $CHCl_3$ at reflux increased the carbon content from 12.3% to 14.2%. Hydrolysis of the acetyl groups of the chiral gel **6** by 0.6 N NH_3 in MeOH afforded CSP 1. This material was slurry packed into a 0.1 (i.d.) × 50 cm stainless steel tube[10] by a conventional procedure.

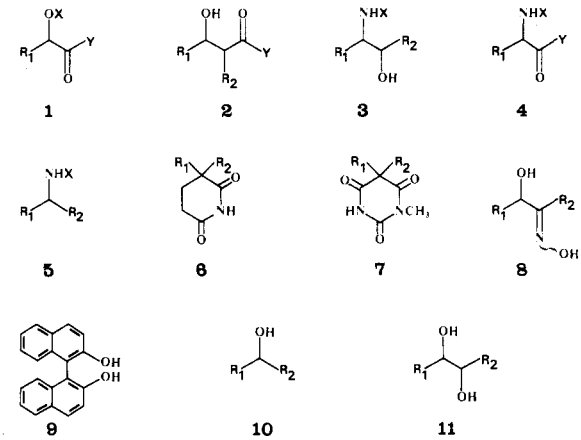


Figure 1. Members of categories of compounds whose enantiomers are resolvable on CSP 1.

With CSP 1, a greater scope and magnitude of enantioselection not possible with the initially designed CSP become realizable, and resolution of the broad categories of enantiomers listed in Figure 1 can be carried out. Table I gives chromatographic data on the resolution of these enantiomers. The separation factors observed here typically ranged from 1.1 to 1.8. These degrees of chiral recognition are not large but quite sufficient to insure satis-

(7) 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[8] of the lesser retained enantiomer and that of the more retained enantiomer.

(8) The capacity factor (k') is defined as $k' = pC_s/C_m$, where C_s and C_m are the concentration of the solute in a stationary and a mobile phase and p is the phase ratio. This parameter is calculated as follows: k' = (retention time − dead time)/(dead time). In the present study, K_r and K are defined as K_r = [Ch–Sr]/([Ch][Sr]) and K = [SiOH–Sr]/([SiOH][Sr]), where Ch–Sr is the associate consisting of the chiral moiety and enantiomer, and SiOH–Sr is that consisting of the silanol group and enantiomer. In each case, a 1:1 associate was considered. Since C_s is the sum of [Ch–Sr] and [SiOH–Sr], the capacity factor of a single enantiomer is represented as $k'r = p(K_r[\mathrm{Ch}] + K[\mathrm{SiOH}])$ and thus eq 1 should hold.

(9) Takeda, K.; Sawada, I.; Suzuki, A.; Ogura, H. *Tetrahedron Lett.* **1983**, *24*, 4451.

(10) Owing to the preliminary nature of this work, a microbore column technique was employed so as to minimize consumption of the chiral gel: Scott, R. P. W.; Kucera, P. *J. Chromatogr.* **1979**, *169*, 51.

Table I. Chromatographic Resolution of Enantiomers on CSP 1[a]

R_1	R_2	X	Y	rel confign	k'_1[8]	α[7]	R_s[11]	strong solvent in *n*-hexane (%, v/v)
			α-Hydroxy Carbonyl Derivatives **1**					
Bzl		CONHPh	OMe		4.64	1.15	1.85	Et_2O (10)
Me		CONHPh	OMe		3.69	1.15	1.99	Et_2O (10)
CH_2COOMe		CONHPh	OMe		7.40	1.18	2.70	Et_2O (10)
i-Pr		CONHPh	Oi-Pr		2.06	1.23	2.47	Et_2O (10)
Ph		CONHPh	Ph		5.52	1.14	1.92	Et_2O (10)
			β-Hydroxy Carbonyl Derivatives **2**					
Ph	Et		NH-*t*-Bu	threo	1.37	1.83	6.39	2-PrOH (2)
Ph	Me		NH-*t*-Bu	threo	1.54	1.77	6.78	2-PrOH (2)
Ph	Me		NH-*t*-Bu	erythro	3.35	1.11	1.36	2-PrOH (2)
Ph	*i*-Pr		NH-*t*-Bu	erythro	2.79	1.22	2.47	2-PrOH (2)
Ph	Me		OMe	threo	2.86	1.19	1.98	Et_2O (10)
Ph	Et		OMe	threo	2.97	1.20	2.32	Et_2O (10)
Ph	Et		OMe	erythro	1.72	1.00		Et_2O (10)
H	Ph		NH-*t*-Bu		2.49	1.43	5.03	2-PrOH (2)
H	*i*-Pr		NH-*t*-Bu		1.76	1.39	3.89	2-PrOH (2)
H	Et		NH-*t*-Bu		2.18	1.30	3.33	2-PrOH (2)
Ph	H		NH-*t*-Bu		2.90	1.32	3.61	2-PrOH (2)
i-Pr	H		NH-*t*-Bu		1.48	1.27	2.87	2-PrOH (2)
Et	H		NH-*t*-Bu		2.31	1.20	2.14	2-PrOH (2)
2-(1-hydroxybenzyl)-1-cyclohexanone				threo	2.14	1.17	1.58	Et_2O (10)
2-(1-hydroxybenzyl)-1-cyclohexanone				erythro	2.03	1.07	0.67	Et_2O (5)
			β-Amino Alcohol Derivatives **3**					
Ph	Ph	CONHPh		threo	6.22	1.16	1.89	$CHCl_3$ (80)
Ph	Ph	CONHPh		erythro	6.50	1.16	1.82	$CHCl_3$ (80)
Bzl	H	CONHPh			12.66	1.34	2.73	$CHCl_3$ (80)
			α-Amino Acid Derivatives **4**					
Ph		$COCH_3$	NH-*t*-Bu		2.50	1.22	2.20	2-PrOH (2)
i-Pr		CONHPh	OMe		3.18	1.15	1.88	THF (20)
i-Bu		CONHPh	OMe		4.75	1.20	2.72	THF (20)
Me		CONHPh	OMe		6.20	1.21	3.07	THF (20)
			Amine Derivatives **5**					
Ph	Me	CONHPh			4.46	1.14	1.65	$CHCl_3$ (50)
1,2,3,4-tetrahydro-1-naphthyl		CONHPh			3.53	1.12	1.31	$CHCl_3$ (50)
			Glutarimide **6**					
Ph	Et				5.65	1.25	3.02	2-PrOH (4)
			Barbiturates **7**					
Me	1-cyclohexenyl				5.08	1.11	1.56	2-PrOH (4)
Ph	Et				4.87	1.20	2.89	2-PrOH (4)
			α-Hydroxy Ketoximes **8**					
Ph	Ph			syn	18.03	1.12	1.98	$CHCl_3$ (50)
Ph	Ph			anti	12.37	1.13	1.80	$CHCl_3$ (50)
			Bi-β-naphthol **9**					
					9.17	1.15	2.52	CH_2Cl_2 (20)
			Carbinols **10**					
Ph	2-pyridyl				2.51	1.17	1.47	THF (5)
Ph	2-hydroxyphenyl				7.29	1.06	0.81	THF (5)
			1,2-Diols **11**					
9,10-dihydroxy-9,10-dimethylphenanthrene				trans	2.25	1.47	4.89	$CHCl_3$ (50)
9,10-dihydroxy-9,10-dihydrophenanthrene				trans	5.26	1.10	1.60	THF (20)
4,5-dihydroxy-4,5-dihydrobenzo[*a*]pyrene				trans	6.49	1.10	1.65	THF (20)
1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene				trans	5.73	1.06	0.93	THF (20)
1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene				cis	7.72	1.07	1.09	THF (10)

[a] See Figure 1 for the structures of the substituents, R_1, R_2, X, and Y.

factory resolution as evident from the R_s values[11] ranging from 1.5 to 6.8. In the present system, dual hydrogen-bonding between solute enantiomers and the tartramide moiety of CSP is assumed to be essential for the chiral recognition. Thus, enantiomers considered to intrinsically have functionality adaptable to such associations were directly resolvable on CSP 1. For example, β-hydroxy ketones, glutarimide, barbiturates, α-hydroxy ketoximes, bi-β-naphthol, carbinols, and 1,2-diols were resolved without any derivatization.

Benzoin oxime provides a pair of syn and anti diastereomers owing to differences in the geometry of hydroxyimino groups. In the resolution of these enantiomers

(11) This parameter was defined as R_s(resolution) = 2 × (distance of the two peak positions)/(sum of the band widths of the two peaks). If R_s value is more than 1.5, the complete base-line resolution of the enantiomers is achieved. Even in the separation with a R_s value of 1.0, the overlap between two peaks is only 2% of each.

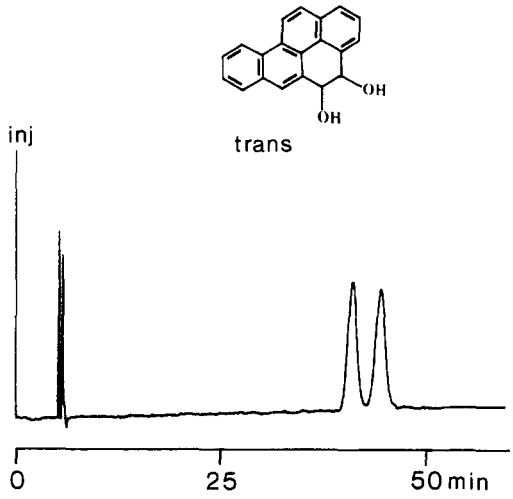
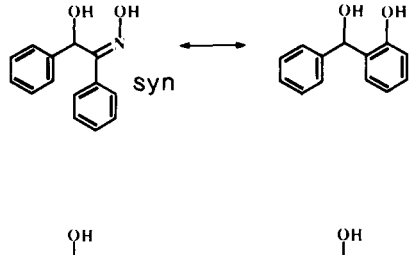


Figure 2. Optical resolution of *trans*-4,5-dihydroxy-4,5-dihydrobenzo[*a*]pyrene on CSP 1. The chromatographic conditions are as follows: column, 50 × 0.1 (i.d.) cm stainless steel tube packed with CSP 1; mobile phase solvent, 10% (v/v) tetrahydrofuran in *n*-hexane; column temperature, 20 °C; flow rate, 60 μL/min; detection, UV at 254 nm.

using (*R,R*)-DIPTA as a CMPA, only syn oxime was resolved. In contrast to this biassed enantioselection, both diastereomers were equally resolved into the corresponding antipodes on CSP 1. Considering the geometry of the hydroxyimino groups of these diastereomers, their bonding sites responsible for the dual hydrogen-bond associations with the tartramide moiety of CSP are assumed to be two hydroxy groups in a syn isomer, one hydroxy group at an asymmetric center, and a lone pair of nitrogen in an anti isomer. Similar association sites were observed in two kinds of carbinols. For example, hydrogen-bond sites of (2-hydroxyphenyl)phenylcarbinol and 2-pyridylphenylcarbinol are considered to correspond to those of *syn*- and *anti*-benzoin oxime, respectively, as illustrated below. As expected from such similarity of bonding sites, both carbinols were resolved on CSP 1.



Also in the resolution of 1,2-diol derivatives, a difference in the enantioselection was observed between the CSP and CMPA methods. Both cyclic and acyclic diols were members of enantiomers sufficiently resolvable by the CMPA method using DIPTA. Although acyclic diols such as *threo*-1,2-diphenyl-1,2-ethanediol provided only shoulder peaks on CSP 1 throughout the region examined, for cyclic diols, CSP 1 was highly capable of chiral recognition to an extent not possible by the CMPA method. For example, *trans*-9,10-dihydroxy-9,10-dimethylphenanthrene was resolved with a separation factor of 1.45 on CSP 1. This higher enantioselectivity for cyclic 1,2-diols made CSP 1 applicable to the resolution of biologically important dihydro diols of polycyclic aromatic hydrocarbons. Figure 2 shows the resolution of *trans*-4,5-dihydroxy-4,5-dihydrobenzo[*a*]pyrene as an example of this.

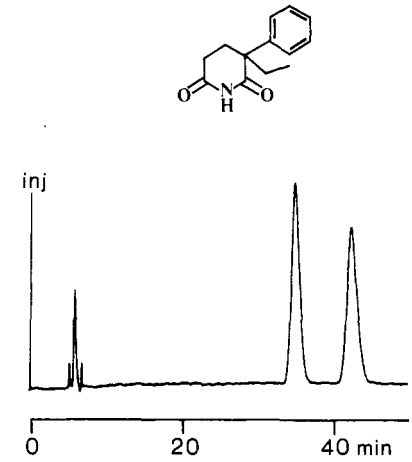


Figure 3. Optical resolution of glutethimide on CSP 1. The mobile-phase solvent is 4% (v/v) 2-propanol in *n*-hexane. Other chromatographic conditions are the same as those described in the legend of Figure 2.

Glutarimides and barbiturates are heterocycles of pharmacological interest and have imide functionality capable of forming multiple hydrogen bonds. A specially designed CSP has been recently developed by Feibush et al.[12] to achieve resolution of these heterocyclic drugs. In this case, enantioselection of derivatives is based on highly specific triple hydrogen bonding between imide functionality and complementary *N,N'*-2,6-pyridinediyl[(*S*)-2-phenylbutanamide]. Also in our system, these heterocycles were well-resolved. Figure 3 shows the resolution of glutethimide on CSP 1 as a typical example. Although hydrogen-bond association through the imide functionality is undoubtedly responsible for the enantioselection observed here, a careful examination of the Dreiding molecular model of tartramide led us to consider that the steric arrangement of the hydrogen-bond sites of this derivative was not suited to simultaneous triple hydrogen bonding with the imide functionality. The association mode in our resolution is probably more flexible dual hydrogen bonding.

Other classes of enantiomers were derivatized so that they would possess appropriate bonding sites. Such derivatizations involve O- or N-acylation, esterification, and conversion to amides, all these processes being easily carried out. β-Hydroxy carboxylic acids were resolved as either ester or amide derivatives. The higher degree of enantioselection was observed for the latter derivatives. Figure 4 shows the resolution of the *N-tert*-butylamide derivative of *threo*-(1-hydroxybenzyl)butyric acid as a typical example. With regard to β-hydroxy carbonyl derivatives possessing threo–erythro diastereomerism, because both α- and β-carbons are chiral centers, threo isomers gave larger separation factors than the corresponding erythro isomers regardless of the nature of the carbonyl component.

Appropriate derivatization makes possible resolution of an enantiomer essentially lacking dual hydrogen-bonding sites. For example, a monofunctional primary amine such as α-methylbenzylamine was converted to the urea derivative through reaction with phenyl isocyanate and then resolved successfully as shown in Figure 5. It should be noted that this derivatization provides not only an appropriate functionality adaptable to enantioselective association with the tartramide moiety but also a strong

(12) Feibush, B.; Figueroa, A.; Charles, R.; Onan, K. D.; Feibush, P.; Karger, B. L. *J. Am. Chem. Soc.* **1986**, *108*, 3310.

Table II. Retention Data for a Series of *N-tert*-Butyl-β-hydroxy Carboxamides on CSP 1, 2, and 3[a]

			CSP 1[13]			CSP 2[13]				CSP 3[b]		
R_1	R_2	rel config	k'_1	k'_2	α	k'_1	k'_2	α	$\Delta k_1'/\Delta k'_2$[c]	k'_1	k'_2	α
Ph	Et	threo	1.22	2.22	1.82	1.72	2.73	1.58	0.98	2.56	3.76	1.46
Ph	*i*-Pr	threo	1.27	1.86	1.46	1.90	2.51	1.32	0.97	2.73	3.40	1.25
Ph	Me	erythro	2.85	3.10	1.09	4.95	5.29	1.07	0.96	7.43[d]		1.00
Ph	*i*-Pr	erythro	2.57	3.05	1.19	3.06	3.51	1.15	1.07	4.51	4.92	1.09
H	Ph		2.04	2.84	1.39	3.76	4.75	1.26	0.90	5.05	6.06	1.20

[a] The eluent was 2% (v/v) 2-propanol in *n*-hexane. [b] Data from ref 6. [c] $\Delta k'_1 = k'_1$(CSP 2) − k'_1(CSP 1). $\Delta k'_2 = k'_2$(CSP 2) − k'_2(CSP 1). [d] The shoulder could be definitely detected.

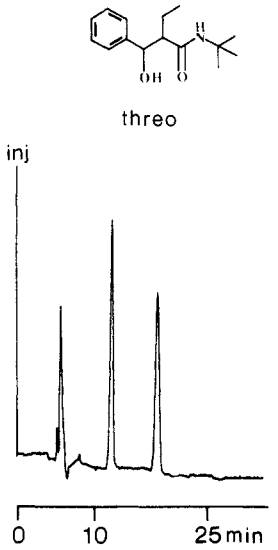


Figure 4. Optical resolution of *N-tert*-butylamide derivative of *threo*-2-(1-hydroxybenzyl)butyric acid on CSP 1. The mobile-phase solvent is 2% (v/v) 2-propanol in *n*-hexane. Other chromatographic conditions are the same as those described in the legend of Figure 2.

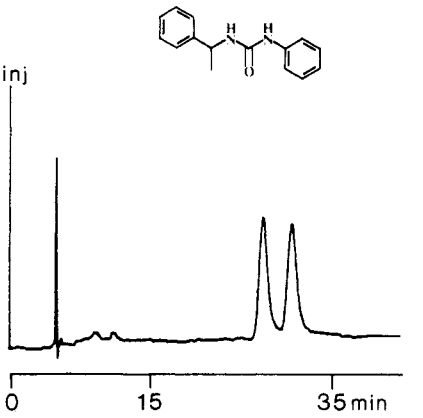


Figure 5. Optical resolution of the phenylcarbamoyl derivative of α-methylbenzylamine on CSP 1. The mobile-phase solvent is 50% (v/v) chloroform in *n*-hexane. Other chromatographic conditions are the same as those described in the legend of Figure 2.

absorbing chromophore to facilitate UV detection. In addition to the monofunctional primary amine, O-acylation of α-hydroxy ketones and carboxylates and N-acylation of α-amino acid esters and β-amino alcohols by phenyl isocyanate were found to be quite effective ways to achieve enantioselection of these derivatives. In the resolution of the urethane derivatives of α-hydroxy carbonyl compounds, the carbonyl components appear to be important in bringing about enantioselection of this type of derivatives, since the urethane derivatives of β-hydroxy ketones and monofunctional secondary alcohols could not be resolved on CSP 1 throughout the region examined.

Finally, we demonstrate that the improved performance of CSP 1 really stems from elimination of nonenantioselective interactions occurring in the retention process. Of the two different approaches employed to eliminate such interactions, trimethylsilylation of the modified gel **5** decreases the concentration of silanol groups of the surface. On the basis of eq 1, it is expected that the effect of this secondary modification will be observed as a decrease in the retentivity of a pair of enantiomers and as enhanced enantioselection. In such a case, since a decrease in silanol concentration has no effect on the association constants between an enantiomeric pair and chiral moiety of CSP, the loss in retentivity of a single enantiomer must be equal to that of the corresponding counterpart. For clarification of this matter, we compared the retention data obtained on CSP 1 with that on CSP 2.[13] CSP 2 was prepared by aminolysis of the modified gel **5** and thus contains the same concentration of the tartramide moiety as CSP 1 but has a higher concentration of silanol groups than CSP 1. Table II gives the retention data for a series of *N-tert*-butyl-β-hydroxy carboxamides using CSP 1 and CSP 2 under the same conditions. The higher degree of enantioselection is always observed on CSP 1. The capacity factors of a given enantiomeric pair decrease on changing CSP 2 to CSP 1. In addition, the loss in retentivity is the same for a pair of enantiomers as evident by the fact that $\Delta k'_1/\Delta k'_2$ are approximately unity in all cases. These results are consistent with the above expectation. Consequently, the higher performance of CSP 1 is ascribed to elimination of the interactions of silanol groups with the solute.

Another approach to elimination of solute–silanol interactions is use of a long alkyl chain to link the tartramide moiety to the silica surface. The effect of a long alkyl chain as such a linkage can be observed by comparing the enantioselection on CSP 2 and that on CSP 3, since the concentrations of the tartramide moiety and silanol groups of CSP 3 are comparable to those of CSP 2.[14] In this case, the observed effect is related to a change in the equilibrium constants responsible for retentivity of solute enantiomers. Table II also gives the retention data for *N-tert*-butyl-β-hydroxy carboxamides, obtained on CSP 3. In all cases, enhancement of enantioselection and decrease in retentivity were observed on changing CSP 3 to CSP 2. These results can be easily explained on the basis of a decrease

(13) CSP 1 and 2 used in the experiments of this section were prepared from modified gel **5** of the batch different from that used in the previous sections. This modified gel was found to contain 0.28 mmol/g of the tartramide moiety.

(14) CSP 3 contains 0.33 mmol/g of the tartramide moiety. This CSP was prepared by using the corresponding triethoxysilyl derivative. Since the triethoxysilane reacts with two silanol groups to form the bidentate junction with the silica gel surface, one ethoxy group of the silane will remain unreacted. However, this unstable silyl ether is assumed to be readily hydrolyzed to a silanol group. Consequently, this type of silylating reagent is considered to be equivalent to the corresponding monochlorosilane derivative with regard to the number of remaining silanol groups of the resulting CSP.

in association constant between the solute and silanol group. The long alkyl chain consisting of 11 methylene units is considered to shield the silanol groups from attack by solute enantiomers and thus decrease their association constants. This effect of the linkage is probably essential for improving the performance of CSP 2. Should the long alkyl chain have no effect on silanol–solute interactions, the enhancement of enantioselection would be ascribable to an increase in the ratio of association constants between the chiral moiety and an enantiomeric pair. In addition, since such enhancement is coupled with loss in retentivity, both association constants for a pair of enantiomers must decrease. It should be noted that a decrease in these constants has the effect of reducing the observed enantioselection, since the contribution of silanol–solute interactions to retentivity of solute enantiomers becomes greater. Thus, the ratio of these constants for a pair of enantiomers should considerably increase so as to offset unfavorable effects due to a decrease in the constants themselves. The ratio of these constants, i.e., the difference in the stability of diastereomeric associates, depends strongly on the steric environment of the association sites of the tartramide moiety of CSP. However, the tartramide moieties of CSP 2 and CSP 3 differ only in the substituent at the γ-position of the *n*-propylamide unit. Since the substituent at this position is sufficiently remote from the association sites of tartramide to have little effect on the steric environment of such sites, the capacity for chiral recognition of the chiral moiety of CSP 2 is considered not significantly superior to that of CSP 3. It is thus difficult to account for the improved performance for CSP 2 without considering the above effects of the long chain linkage.

In conclusion, a CSP designed so as to minimize nonenantioselective interaction in the reaction process of solute enantiomers has been shown in the present paper to have greater capacity for chiral recognition. Our results demonstrate that the performance of a given CSP is determined not only by the design of the resolving agent to be incorporated into CSP but also by that of the total system of CSP. Since the complete chemical modification of a silica gel surface is not possible, silanol groups capable of interacting with solute enantiomers should still remain in the present CSP. Thus, the enantioselectivity observed here does not corresponding exactly to differences in the stability of diastereomeric associates between solute enantiomers and the tartramide moiety, indicating the possibility of greater enantioselection by this type of CSP.

Experimental Section

Instruments. The liquid chromatogrphic system consisted of a Shimadzu LC-5A pump, a Rheodyne 7413 injector with a 0.5-μL loop, and a variable-wavelength UV detector, Jasco UVIDEC-100 equipped with a 0.3-μL cell. The detector was operated at 230 nm or 254 nm. The column was a 50 × 0.1 (i.d.) cm stainless steel tube packed with modified silica gel. The column temperatures were maintained constant by placing the columns in an air oven, Jasco TU-100. Chromatographic runs were made at a constant flow rate of 60 μL/min and constant temperature of 20 °C. ^{1}H NMR spectra were obtained on a Varian EM-390 spectrometer; chemical shifts are reported in parts per million (δ) relative to Me_4Si as the internal standard. IR spectra were obtained on a Hitachi 260-10 spectrometer. MS spectra were obtained with a Hitachi M-80 instrument. Chemical ionization MS spectra were measured by using isobutene as reagent gas. Optical rotations were determined with a Jasco DIP-360 polarimeter. Melting points were determined on a micro hot-plate melting point apparatus. All melting points were uncorrected. Microelemental analysis was conducted by the Microanalytical Center of this college.

Samples and Reagents. Tetrahydrofuran and diethyl ether were distilled from benzophenone ketyl; chloroform was distilled from diphosphorus pentoxide; 2-propanol, *n*-hexane, pyridine, acetonitrile, and dichloromethane were distilled from calcium hydride; benzene was distilled from sodium metal. Other solvents and reagents were of reagent grade purity. *trans*-4,5-Dihydroxy-4,5-dihydrobenzo[*a*]pyrene was kindly provided by Dr. A. Hiratsuka (this college). Glutethimide and barbiturates were kindly provided by Dr. T. Shibata (Daicel Chemical Industries, Ltd). The phenylcarbamoyl derivatives used in this study were prepared as follows: α-hydroxy carbonyl compounds were acylated with phenyl isocyanate in benzene at reflux. β-Amino alcohols and amines were made to react with 1.0 equiv of phenyl isocyanate in chloroform at 0 °C. For the β-amino alcohol, only *N*-acyl products were obtained. α-Amino acids were acylated with phenyl isocyanate by the Schotten–Baumann procedure. The resulting *N*-acyl amino acids were esterified with methanol containing a catalytic amount of *p*-toluenesulfonic acid at reflux. (2-Hydroxyphenyl)phenylcarbinol was prepared through the reaction of salicylaldehyde with phenylmagnesium bromide. 2-Pyridylphenylcarbinol was prepared by the sodium borohydride reduction of 2-benzoylpyridine. Other analytes were available from previous studies. All of these compounds are well-known and were identified by ^{1}H NMR, IR, and MS spectra.

Synthesis of CSP 1. 10-Undecenamide. To a vigorously stirred solution of 10-undecenyl chloride (27.1 g, 134 mmol, Tokyo Kasei) in 320 mL of benzene was introduced dry ammonia gas at 0 °C until acyl chloride could no longer be detected by TLC (Merck silica gel 60-F-254 plates, ethyl acetate–*n*-hexane (2:1 v/v)). After the mixture had been stirred at room temperature for 1 h, 500 mL of ethyl acetate and 200 mL of 0.06 N hydrochloric acid were added. The organic layer thus separated was washed with 2 N hydrochloric acid, water, saturated sodium bicarbonate, and brine successively and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford crystalline product. This was recrystallized from a mixture of chloroform and *n*-hexane to give 19.4 g (79 %) of the pure amide as colorless crystals: mp 88.5–89 °C; IR (KBr) 3350, 3190, 2920, 2850, 1660, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (br s, 12 H), 1.92–2.28 (m, 4 H), 4.87–5.07 (m, 2 H), 5.53 (br s, 2 H, exchangeable with D_2O), 5.57–6.03 (m, 2 H); MS (chemical ionization), calcd for $C_{11}H_{21}NO$ 183, found 184 (MH^+).

10-Undecenylamine. To a refluxing suspension of lithium aluminum hydride (9.97 g, 263 mmol) in 360 mL of diethyl ether was slowly added 10-undecenamide (19.4 g, 106 mmole) by a procedure[15] using a Soxhlet extractor. After a period of 38 h of extraction, the suspension was cooled to 0 °C followed by the dropwise addition of 100 mL of water. The white precipitate thus formed was separated by decantation and extracted several times with diethyl ether. The combined ether extract was evaporated and the residual pale yellow liquid was distilled under reduced pressure to afford 11.8 g (66 %) of the desired amine as a colorless liquid: bp 123–124 °C/21 mmHg; IR (neat) 3420, 3340, 2980, 2910, 1845, 1665, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (s, 2 H, exchangeable with D_2O), 1.29 (br s, 14 H), 1.93–2.17 (m, 2 H), 2.58–2.72 (m, 2 H), 4.83–5.08 (m, 2 H), 5.60–6.03 (m, 1 H); MS (chemical ionization), calcd for $C_{11}H_{23}N$ 169, found 170 (MH^+).

(*R*,*R*)-Diacetyltartaric Acid Anhydride (1).[16] To a mixture of finely powdered (*R*,*R*)-tartaric acid (5.48 g, 36.6 mmol) in 12 mL of acetic anhydride was added 0.2 mL of concentrated sulfuric acid with stirring at room temperature. Following the exothermic reaction, the solution was gently refluxed for 10 min and then cooled to 0 °C. The crystalline product thus formed was collected by filtration and washed with benzene. This crude product was stirred with 16 mL of diethyl ether at 0 °C for 10 min, filtered, washed with diethyl ether, and dried to afford 5.82 g (74%) of the anhydride: mp 135 °C; IR (KBr) 2940, 1900, 1825, 1763, 1380 cm^{-1}; NMR ($CDCl_3$) δ 2.22 (s, 6 H), 5.68 (s, 2 H). This material was immediately used in the next step.

(*R*,*R*)-*N*-Isopropyldiacetyltartaric Acid Monoamide (2). To a solution of (*R*,*R*)-diacetyltartaric acid anhydride (5.82 g, 26.9 mmol) in 30 mL of dichloromethane was added isopropylamine

(15) Wilson, C. V.; Stenberg, J. F. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol 4, p 564.
(16) Shriner, R. L.; Furrow, C. L., Jr. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol 4, p 242.

(3.45 g, 58.4 mmol) at 0 °C under an atmosphere of argon. After the solution had been stirred at this temperature for 20 min, the solvent was removed under reduced pressure. To the residual oil were added 400 mL of ethyl acetate and 50 mL of 5 N hydrochloric acid saturated with sodium chloride. The organic layer was washed three times with 30 mL of brine and dried over anhydrous sodium sulfate. The solvent was evaporated to afford the crude product. Recrystallization from a mixture of 2-propanol and *n*-hexane gave 6.49 g (88 %) of the pure half-amide as colorless crystals: mp 176.5–177 °C dec; IR (KBr) 3330, 2970, 1750, 1635, 1555 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d^6 (20:1 v/v)) δ 1.13 (d, 3 H, J = 6.6 Hz), 1.15 (d, 3 H, J = 6.0 Hz), 2.11 (s, 3 H), 2.17 (s, 3 H), 3.85–4.24 (m, 1 H), 5.59–5.68 (m, 2 H), 6.67 (br d, 1 H, J. = 7.5 Hz, exchangeable with D_2O), 10.12 (br s, 1 H, exchangable with D_2O); MS (chemical ionization), calcd for $C_{11}H_{17}O_7N$ 275, found 276 (MH^+); $[\alpha]^{28}_D$ −21.9° (*c* 1.26, ethanol).

(*R*,*R*)-*N*-(10-Undecenyl)-*N'*-isopropyldiacetyltartramide (3). A mixture of di-*N*-succinimidyl oxalate (1.15 g, 4.05 mmol, Chemiscience Ltd. Tokyo), the half-amide **2** (1.12 g, 4.07 mmol), and pyridine (322 mg, 4.07 mmol) in 50 mL of acetonitrile was stirred at room temperature for 12 h under an atmosphere of argon. The resulting almost clear solution was cooled to 0 °C followed by the addition of a mixture of 10-undecenylamine (678 mg, 4.01 mmol) and triethylamine (406 mg, 4.01 mmol) in 15 mL of acetonitrile. After the mixture was stirred at this temperature for 1.5 h, 700 mL of ethyl acetate and 100 mL of water were added. The layers were separated and the organic layer was washed with water, 1.5 N hydrochloric acid, saturated sodium bicarbonate, and brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using 30 g of silica gel and an acetone–*n*-hexane (1:4 v/v) mixture to yield 1.14 g (66%) of the pure diamide as a white solid: mp 148–149 °C; IR (KBr) 3280, 2980, 2930, 2860, 1755, 1650, 1545 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (d, 3 H, J = 6.0 Hz), 1.27 (br s, 14 H), 1.92–2.17 (m, 2 H), 2.14 (s, 6 H), 3.12–3.33 (m, 2 H), 3.83–4.22 (m, 1 H), 4.83–5.08 (m, 2 H), 5.55–6.03 (m, 3 H), 6.33–6.73 (br m, 2 H, exchangeable with D_2O); MS (electron impact), calcd for $C_{22}H_{38}O_6N_2$ 426, found 426 (M^+); $[\alpha]^{27}_D$ −13.43° (*c* 2.57, ethanol).

(*R*,*R*)-*N*-(11-(Chlorodimethylsilyl)undecyl)-*N'*-isopropyldiacetyltartramide (4). To a solution of the olefin **3** (877 mg, 2.06 mmol) in 8 mL of chloroform was added 0.1 mL of a 2-propanol solution of chloroplatinic acid (0.13 mol/L) at room temperature. After the mixture was stirred for 4 min, 3 mL of dimethylchlorosilane was added. The mixture was then heated to reflux for 30 min. The solvent and excess silane were removed in vacuo and the residue was coevaporated twice with chloroform to afford the desired silane as a slightly brownish gum. This material was used next stage without purification.

Modified Gel 5. A suspension of 2.0 g of porous silica (Nucleosil 100-5, 5 μm, 100 Å, Marcherey-Nagel, Düren) in 16 mL of benzene was concentrated to ca. 12 mL under an atmosphere of argon. To this azeotropically dried mixture was added a solution of the silane **4** in 6 mL of pyridine at room temperature. After the mixture was gently stirred for 24 h, the modified gel was collected by filtration and washed with chloroform, methanol, acetone, and *n*-hexane, successively: IR (KBr) 2930, 2850, 1760, 1655, 1550 cm^{-1}. Anal. Found: C, 12.33; N, 1.19.

Trimethylsilylated Gel 6. To a suspension of 540 mg of modified gel **5** in 18 mL of chloroform was added 2 mL of (trimethylsilyl)imidazole (Tokyo Kasei). After the mixture was refluxed for 12 h under an argon atmosphere, the silica gel was collected by filtration and washed as described above. Anal. Found: C, 14.24; N, 1.19.

Aminolysis of Modified Gel 6. To a suspension of 520 mg of modified gel **6** in 5 mL of methanol was added 10 mL of 0.6 N ammonia in methanol at 0 °C. After the mixture was gently stirred 5 h at the same temperature, the silica was collected by filtration and washed with methanol, acetone, and *n*-hexane: IR (KBr) 2920, 2850, 1650, 1540 cm^{-1}.

Acknowledgment. We thank Mr. Y. Shida and Ms. S. Kaneko for MS measurements and Mr. S. Suzuki for the elemental analyses.

Lanthanide Ion Assisted Electrochemically Initiated Aldol Condensations

Albert J. Fry,* Marko Susla, and Michael Weltz

Department of Chemistry, Wesleyan University, Middletown, Connecticut 06457

Received November 26, 1986

An electrochemical process for effecting directed aldol condensation is described. It is carried out under neutral conditions, can tolerate a wide variety of functional groups, is highly selective for aldehydes over ketones, requires only simple apparatus, and depends for its success upon the efficient mediating effect of trivalent lanthanide ions.

It is well established that electrochemical reduction of alkyl halides generates carbanions.[1] Inasmuch as this electrochemical route to carbanions offers in principle a number of potential advantages over conventional chemical methods (e.g., selectivity[1b] and the possibility of generating carbanions under neutral operating conditions), much useful chemistry would result if one could successfully trap such carbanions with electrophilic reagents. Several reports have described the successful addition of electrochemically generated stabilized carbanions, e.g., those from carbon tetrachloride, ethyl trichloroacetate, and benzylic halides, to a variety of carbonyl acceptors.[2] Attempts in this laboratory and others to effect intermolecular reaction between electrophiles and carbanions generated by the electrochemical reaction of simple alkyl halides have, however, met with little success, apparently because the highly reactive carbanions react with solvent or adventitious proton donors in the medium as fast or faster than they react with the electrophile.

We felt that a solution to this problem might be developed by effecting electrochemical reduction of the alkyl

(1) (a) Fry, A. J. *Synthetic Organic Electrochemistry*; Harper & Row: New York, 1972. (b) Fry, A. J.; Mitnick, M. A.; Reed, R. G. *J. Org. Chem.* **1970**, *35*, 1232.

(2) (a) Shono, T.; Kise, N.; Masuda, M.; Suzumoto, T. *J. Org. Chem.* **1985**, *50*, 2527. (b) Shono, T.; Kise, N.; Yamazaki, A.; Ohmizu, H. *Tetrahedron Lett.* **1982**, *23*, 1609. (c) Silvestri, G.; Gambino, S.; Filardo, G. G.; Gulotta, A. *Tetrahedron Lett.* **1984**, *25*, 4307. (d) Karrenbrock, F.; Schafer, H. J. *Tetrahedron Lett.* **1978**, *19*, 1521. (e) Steiniger, M.; Schafer, H. J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 79. (f) Gisselbrecht, J.-P.; Lund, H. *Acta Chem. Scand., Ser. B* **1985**, *39B*, 773, 823.

0022-3263/87/1952-2496$01.50/0 © 1987 American Chemical Society