possible that the iron center present in the enzyme decreases B to 18.8 G.

Conclusions

The effect of a chiral carbon center in rendering adjacent methylene protons inequivalent is well-known for nitroxides, but few examples have been reported in other radical systems. The effect has now also been observed in the spectrum of the tyrosyl radical. One would anticipate that examples of this phenomenon should be apparent in the ESR spectra of many other radicals, in particular those from other amino acids and their derivatives. For example, sulfinyl radicals derived from several thiols[30,31] show inequivalent methylene protons.[32] Presumably ESR spectra of radicals from tyrosyl esters and peptides[2] show behavior similar to that found for tyrosyl, i.e., reflecting the effects of the chiral center and restricted rotation.

Acknowledgment. This work was supported by NIH Grant GM-29035. We thank Drs. P. Smith and K. K. Karkustis (Duke University) for carrying out preliminary ESR experiments on the flow oxidation of tyrosine and Dr. V. Fischer for helpful comments regarding the conformational analysis.

(30) J. C. Kertesz, W. Wolf, and H. Hayase, *J. Magn. Reson.*, **10**, 22-23 (1973).

(31) J. C. Kertesz and W. Wolf, *Intra-Sci. Chem. Rep.*, **5**, 371-374 (1971).

(32) B. C. Gilbert, H. A. H. Laue, R. O. C. Norman, and R. C. Sealy, *J. Chem. Soc., Perkin Trans. 2*, 892-900 (1975).

Extended Scope of Chiral Recognition Applying Hydrogen Bond Associations in Nonaqueous Media: (*R*,*R*)-*N*,*N*′-Diisopropyltartramide (DIPTA) as a Widely Applicable Resolving Agent

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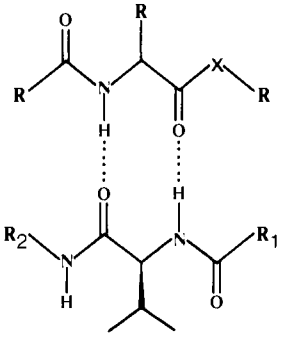
Abstract: The addition of (*R*,*R*)-*N*,*N*′-diisopropyltartramide (DIPTA) to the nonaqueous mobile-phase liquid of a silica gel column made possible the chiral recognition of a wide range of enantiomers containing α- or β-hydroxycarboxylic acid, β-hydroxy ketone, β-amino alcohol, α-amino acid, α-hydroxy ketoxime, 1,2-diol derivatives, and bi-β-naphthol. The enantioselections observed here were based on diastereomeric associations between the chiral additive and enantiomer to be resolved in the column. These associations were ascribed to the hydrogen bonds of the additive with the enantiomer. The steric environment of chiral centers and hydrogen bond sites of the solute enantiomers were found to influence the degree of enantioselectivity. For acyclic 1,2-diols, the dependence of the separation factors on the steric environment of the hydrogen bond sites is discussed on the basis of preferential conformations.

Recent investigations on chiral recognition by chromatography clearly demonstrate this technique to hold promise for the expeditious determination of optical purity, prediction of absolute configuration, and preparative-scale resolution of enantiomers.[1] We recently reported that enantiomers of α-amino acid derivatives (I) could be readily resolved on a silica gel surface by using the L-valine derivative IIa[2] as a chiral additive to a nonaqueous mobile-phase liquid as well as on chiral silica gel surface IIb[3] to which L-valine diamide was covalently bound. In such a case, the diastereomeric associations responsible for the observed enantioselectivities were attributed to dual NH···O=C hydrogen bonds of the resolving agents with solutes. Our observations proved that the association mode applying dual hydrogen bonds as the maximum number of bonding interactions can elicit a considerable degree of enantioselectivity, but the application of these systems to chiral recognition is limited to the α-amino acid family.



(I) X=O,NH

(II-a) R_1=CH_3, R_2=tert-Bu

(II-b) R_1=H, R_2=$(CH_2)_3Si$

However, functionalities which can serve as hydrogen bond sites are fairly common among many kinds of enantiomers of interest in the fields of synthetic and biological chemistry. Therefore, attempts to extend the scope of application of such association mode to chiral recognition through development of other types of resolving agents are deemed worthwhile. In this paper, it is shown that the scope of chiral recognition through the application of hydrogen bond associations in nonaqueous media can be extended to a wide range of enantiomers by using (*R*,*R*)-*N*,*N*′-di-

(1) Schurig, V. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983, Vol. 1, p 59. Pirkle, W. H.; Finn, J. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983, Vol. 1, p 87 and reference cited therein.

(2) Dobashi, A.; Hara, S. *Tetrahedron Lett.* **1983**, *24*, 1509. Dobashi, A.; Hara, S. *J. Chromatogr.* **1983**, *267*, 11. Dobashi, A.; Hara, S. *Anal. Chem.* **1983**, *55*, 1805.

(3) Hara, S.; Dobashi, A. *J. Chromatog.* **1979**, *186*, 543. Dobashi, A.; Oka, K.; Hara, S. *J. Am. Chem. Soc.* **1980**, *102*, 7122.

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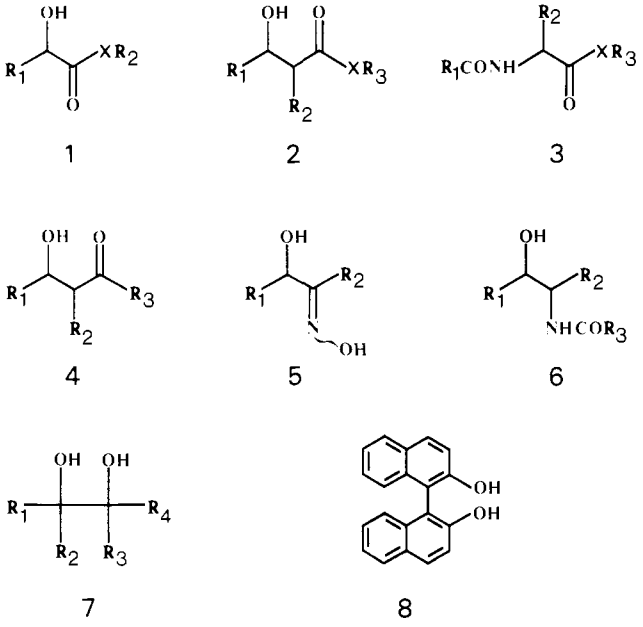
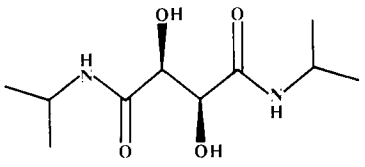


Figure 1.

isopropyltartramide (DIPTA) (III) as the resolving agent.[4]

In principle, enantiomer A, capable of associating with enantiomer B, may be capable of recognition of the molecular chirality of B and vice versa. This concept can be extended in scope. If



(III)

enantiomer A is able to associate with enantiomers B, C, and D, enantiomer A may recognize the molecular chiralities of each of these. However, the degree of chiral recognition depends on the association mode determined by the functionalities of these enantiomers. The results of our studies on the chiral recognition of α-amino acid derivatives provide a key for designing appropriate resolving agents. That is, an enantiomer possessing two hydrogen bond sites close to its asymmetric center may be resolved by association with an appropriate resolving agent through dual hydrogen bonds. The resolving agent must be able to adapt itself to the dual hydrogen bonds with the enantiomer to be resolved. *N,N'*-Dialkyltartramides have two different hydrogen bond sites at their asymmetric centers, i.e., hydroxyl groups and amide units. The hydrogen bonds through amide units are strong, but their directions are relatively restricted due to planarities of these units. The hydrogen bonds through hydroxyl groups have a greater scope of direction owing to the free rotations about the C–O single bond. Thus, the derivatives have both strong and flexible hydrogen bond sites. Also the two hydroxyl groups and two amide units of the derivatives are stereochemically equivalent due to *C*2 symmetry, and consequently, the derivatives can easily adapt themselves to dual hydrogen bonds with different enantiomers and thus function as resolving agents. The addition of (*R,R*)-DIPTA[5] to the nonaqueous mobile phase of chloroform and *n*-hexane in silica gel chromatography resulted in the chiral recognition of a wide range of enantiomers listed in Figure 1. Table I gives the chromatographic data for the chiral recognition of these enantiomers. Prior to our investigation, Bowman et al.[6] reported that certain enantiomeric pairs such as camphoric acid and *threo*-1,2-diphenyl-1,2-ethanediol were partially resolved by partitioning them between (*R,R*)-dialkyl tartrate (diisopropyl or diisoamyl ester) and the aqueous phase. More recently, Prelog et al.[7] reported a significant degree of chiral recognition of the salts of α-amino acid and β-amino alcohol with hexafluorophosphoric acid to be possible by liquid–liquid partition chromatography in which the mobile and stationary phases were 1,2-dichloroethane containing (*R,R*)-di-5-nonyl tartrate and the aqueous phase containing sodium hexafluorophosphate, respectively. In our system, (*R,R*)-dialkyl tartrates such as dimethyl and diisopropyl esters were also found to function as resolving agents for 1,2-diol and α-hydroxycarboxylic acid esters.[8] However, the ability of dialkyl tartrate as a resolving agent was apparently inferior to that of *N,N'*-dialkyltartramide with respect to the degree and the scope of chiral recognition.

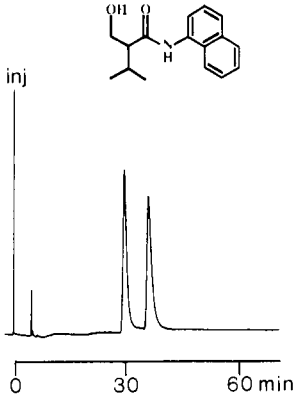


Figure 2. Chromatographic resolution of racemic *N*-α-naphthyl-2-(hydroxymethyl)-3-methylbutyramide. The chromatographic conditions and data are described in Table I and its legend.

Results and Discussion

(*R,R*)-DIPTA associates with enantiomeric pairs in the column to form transient diastereomeric complexes. As a result, the pairs come to differ in their retentivities. The separation factors indicate the degree of chiral recognition brought about by (*R,R*)-DIPTA and were found to depend on the steric environment of the asymmetric centers and hydrogen bond sites of enantiomers. The enantiomers of α- or β-hydroxycarboxylic acid and α-amino acid were resolved as either amide or ester derivatives. An increase in bulkiness of the substituents at the asymmetric centers of the derivatives caused the separation factors to become greater, and the effect of the bulkiness of the *N*- and *O*-alkyl groups on the separation factors was found to be as follows: (1) An increase in bulkiness of *N*-alkyl groups of *N*-alkyl-β-hydroxycarboxamides enlarged the separation factors. The bulkiness of the *N*- and *O*-alkyl groups of *N*-acyl-α-amino acid esters and amides had a similar effect. (2) An increase in the bulkiness of the *N*-alkyl groups of *N*-alkyl-α-hydroxycarboxamides reduced the separation factors, and a similar effect was also noted for *N*-alkyl groups of *N*-dialkyl-β-hydroxycarboxamides. To achieve their resolutions, aliphatic β-hydroxycarboxylic acids were derivatized to α-naphthylamides. The naphthyl ring has considerable steric bulkiness and functions as a strongly absorbing chromophore for UV detection. Figure 2 shows the resolution of the α-naphthylamide of 2-(hydroxymethyl)-3-methylbutanoic acid as a typical example. β-Hydroxycarboxylic acids with their asymmetric centers at the α position usually afforded greater separation factors than when

(4) The preliminary results have been published: Dobashi, Y.; Dobashi, A.; Hara, S. *Tetrahedron Lett.* **1984**, *25*, 329.

(5) The other *N,N'*-dialkyltartramide such as diethyl-, diisobutyl-, and dicyclohexylamide can be used as chiral additive in liquid–solid chromatography. However, they were inferior to DIPTA with regard to the solubility to the solvent mixture of chloroform and *n*-hexane.

(6) Bowman, N. S.; McCloud, G. T.; Schweitzer, G. K. *J. Am. Chem. Soc.* **1968**, *90*, 3848.

(7) Prelog, V.; Stojanac, Ž.; Kovačević, K. *Helv. Chim. Acta* **1982**, *65*, 377. Prelog, V.; Mutak, S.; Kovačević, K. *Helv. Chim. Acta* **1983**, *66*, 2279.

(8) For example, dibenzyl tartrate was resolved with a α value of 1.04 by using the mixture of chloroform and *n*-hexane (chloroform/*n*-hexane = 1:2 (v/v)) containing 0.4 mol % (*R,R*)-dimethyl tartrate as the chiral eluent. The details will be published elsewhere.

Table I. Chiral Recognition of Enantiomers by Using (*R,R*)-DIPTA as the Chiral Additive in Liquid–Solid Chromatography[a]

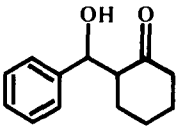
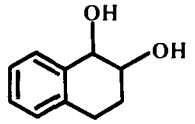
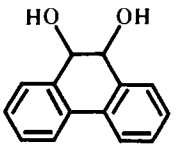
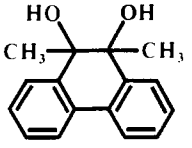
entry	R_1	R_2	R_3	R_4	X	rel config	k'_1[b]	k'_2	α[c]	R_s[d]
					α-Hydroxycarboxylic Acid Derivatives **1**					
1	Ph	Me			NH		11.40	12.80	1.12	2.15
2	Ph	Et			NH		6.50	7.02	1.08	1.01
3	Ph	*i*-Pr			NH		2.20	2.20	1.00	
4	Bzl	Me			NH		11.94	12.56	1.05	0.51[e]
5	Bzl	Et			NH		5.40	5.46	1.01	0.30
6	Bzl	Me			O		3.70	3.88	1.05	1.02
7	dibenzyl tartrate						1.84	2.65	1.44	5.87
					β-Hydroxycarboxylic Acid Derivatives **2**					
8	Ph	H	Et		NH		7.49	8.24	1.10	1.00
9	Ph	H	*i*-Pr		NH		3.74	4.10	1.10	1.30
10	Ph	H	*t*-Bu		NH		1.74	2.00	1.15	2.55
11	Ph	H	Me		NMe		1.84	1.94	1.05	0.90
12	H	Ph	Me		NH		7.98	8.91	1.11	1.56
13	H	Ph	Et		NH		4.11	4.64	1.13	2.62
14	H	Ph	*i*-Pr		NH		2.21	2.51	1.14	2.40
15	H	Ph	*t*-Bu		NH		1.07	1.28	1.20	3.00
16	H	Ph	Me		NMe		1.88	1.99	1.06	1.17
17	H	Ph	Et		NEt		1.00	1.00	1.00	
18	Me	H	α-napht[f]		NH		10.39	10.86	1.04	0.61[e]
19	Et	H	α-napht		NH		4.19	4.69	1.12	1.45
20	*i*-Pr	H	α-napht		NH		1.96	2.28	1.17	2.20
21	H	Me	α-napht		NH		11.47	12.71	1.11	1.43
22	H	Et	α-napht		NH		8.38	9.89	1.18	2.64
23	H	*i*-Pr	α-napht		NH		4.92	6.21	1.26	3.23
					α-Amino Acid Derivatives **3**					
24	*p*-NPh[g]	Me	*i*-Pr		O		8.16	9.17	1.12	2.04
25	*p*-NPh	*i*-Pr	*i*-Pr		O		2.17	2.33	1.08	1.13
26	*p*-NPh	*i*-Bu	*i*-Pr		O		3.76	4.11	1.09	1.52
27	*p*-NPh	Bzl	*i*-Pr		O		2.85	2.97	1.04	0.89
28	Ph	*i*-Bu	Me		O		2.55	2.70	1.06	0.97
29	Ph	*i*-Bu	Et		O		1.59	1.75	1.10	1.30
30	Ph	*i*-Bu	*i*-Pr		O		1.11	1.25	1.13	1.81
31	Ph	*i*-Bu	Et		NH		2.01	2.17	1.08	0.58[e]
32	Ph	*i*-Bu	*i*-Pr		NH		0.80	0.87	1.09	0.92
33	Me	Bzl	*t*-Bu		NH		2.27	2.90	1.28	3.91
34	Me	Ph	*t*-Bu		NH		2.14	2.53	1.19	2.67
					β-Hydroxy Ketones **4**					
35	Ph	H	Ph				2.61	2.74	1.05	1.18
36						erythro	2.35	2.49	1.06	1.20
37						threo	3.16	3.33	1.05	1.00
					α-Hydroxy Ketoximes **5**					
38	Ph	Ph				syn	2.22	2.62	1.18	3.16
39	Ph	Ph				anti	3.32	3.32	1.00	
40	Me	Ph				syn	4.60	5.18	1.13	3.26
41	Me	Ph				anti	7.82	7.82	1.00	
					β-Amino Alcohol Derivatives **6**					
42	Ph	Ph	Ph			erythro	0.96	1.05	1.09	1.18
43	Ph	Ph	Ph			threo	0.80	0.87	1.08	1.13
44	Ph	H	Ph				4.42	4.77	1.08	1.08
45	H	Ph	Ph				7.40	7.80	1.05	0.70[e]
46	H	Bz	Ph				6.43	6.84	1.06	1.10
					1,2-Diols **7**					
47	Ph	H	Ph	H		threo	2.39	2.67	1.12	2.41
48	Ph	H	*i*-Pr	H		threo	2.43	2.69	1.11	1.92
49	Ph	H	Me	H		threo	6.39	6.89	1.07	1.18
50	Ph	H	Me	H		erythro	7.33	7.55	1.03	0.50
51	Ph	H	*i*-Pr	H		erythro	1.77	1.77	1.00	
52	Ph	H	H	H			13.77	14.39	1.05	0.62[e]
53	Bzl	H	H	H			12.65	13.05	1.03	0.41[e]
54	Ph	Me	H	H			7.07	7.32	1.04	0.58[e]
55	Ph	H	Me	Me			2.39	2.51	1.05	1.10
56						cis	7.77	7.94	1.02	0.52
57						trans	14.89	15.17	1.02	0.40

Table I (*Continued*)

entry	R_1	R_2	R_3	R_4	X	rel config	k'_1 [b]	k'_2	α [c]	R_S [d]
58						trans	4.61	4.93	1.07	1.39
59						trans	2.88	3.08	1.07	1.18
					Bi-β-naphthol 8					
60							9.06	9.80	1.08	2.00

[a] A mixture of chloroform and *n*-hexane (chloroform/*n*-hexane = 14:3 (v/v)) containing 0.718 mol % (*R,R*)-DIPTA was used as the chiral eluent for entries 1-5, 8-23, 31-34, 38-46, and 47-59. The mixture of chloroform and *n*-hexane (chloroform/*n*-hexane = 3:8 (v/v)) containing 0.035 mol % (*R,R*)-DIPTA was used as the chiral eluent for entries 6, 24-30, 35-37, and 60. The solvent mixture of chloroform and *n*-hexane (chloroform/*n*-hexane = 4:5 (v/v)) containing 0.196 mol % of (*R,R*)-DIPTA was used as the chiral eluent for entry 7. The chiral eluent was kept at 30 °C for entries 1-5, 7-23, 31-34, 38-46, and 47-59. All other eluents were maintained at 20 °C. The order of emergence of some enantiomeric pairs was determined by coinjection with a single enantiomer. The lesser retained enantiomers were as follows: L isomer for entries 1, 2, and 7, D isomer for entries 28, 29, and 30, *S,S* isomer for entry 47, and *S* isomer for entries 52 and 60. [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] R_S (resolution) = 2(distance of the two peak positions)/(sum of bandwidths of the two peaks). [e] The peak tailing reduced the R_S value. [f] α-Naphthyl group. [g] *p*-Nitrophenyl group.

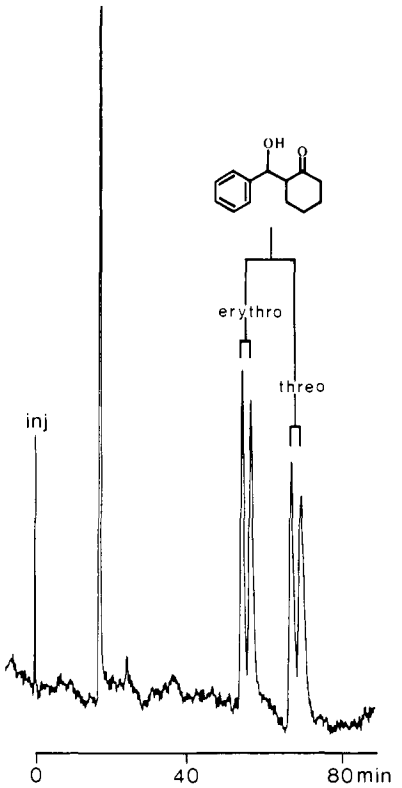


Figure 3. Chromatographic resolution of four stereoisomers of aldol adducts prepared from cyclohexanone and benzaldehyde. The chromatographic conditions and data are presented in Table I and its legend.

the asymmetric centers were at the β position. (*R,R*)-DIPTA recognizes the molecular chiralities not only of β-hydroxycarboxylic acids but those of β-hydroxy ketones, i.e., aldols as well. The aldol condensation is one of the most important tools for C–C bond formations. Recently, considerable attention by organic chemists has been directed to stereoselective aldol reactions in which C–C bond formation can be performed in stereochemically controlled fashion[9] and much effort is being made to develop these

(9) Heathcock, C. H. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111. Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Top. Stereochem.* **1982**, *13*,1 and reference cited therein.

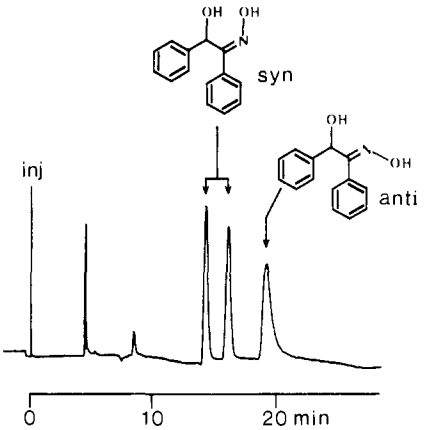


Figure 4. Chromatographic resolution of diastereomeric mixture of benzoin oximes. The chromatographic conditions and data are provided in Table I and its legend.

reactions. To evaluate the stereoselectivity of an aldol reaction, its stereochemical outcome must be ascertained. The ordinary aldol reaction of benzaldehyde with cyclohexanone provides four stereoisomers. In our system, all these were resolved to give the four distinct peaks shown in Figure 3. This is the first example of the resolution of aldol adducts based on hydrogen bond associations.

The oximation of an α-hydroxy ketone such as benzoin provides α-hydroxy ketoximes possessing syn-anti diastereoisomerism. These derivatives each have three kinds of hydrogen bond sites: a hydroxyl group at the asymmetric carbon, a hydroxyl group at the nitrogen, and a lone pair of nitrogen. The relative arrangements of these hydrogen bond sites in two isomeric oximes significantly differ from each other due to differences in the geometry of the hydroximino groups. In the syn isomer, two hydroxyl groups are on the same side of the C–N double bond, but in the anti isomer, the hydroxyl group at the asymmetric carbon and lone pair of nitrogen are on the same side of the C–N double bond. Of two diastereomeric oximes derived from benzoin, only the syn isomer was resolved into the corresponding antipodes. Consequently, three peaks depicted in Figure 4 were obtained. The same situation was encountered in the resolution of oximes derived from 2-hydroxy-1-phenyl-1-propanone. These results indicate that only association of (*R,R*)-DIPTA with the syn isomer can bring about enantioselection. Considering the arrangement of the hy-

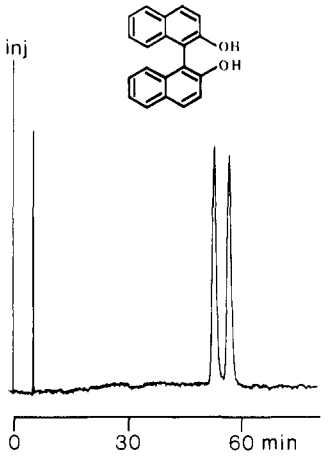
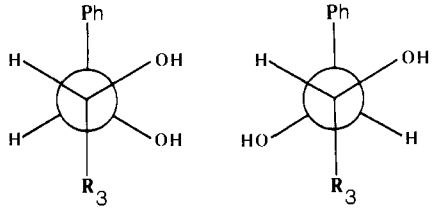


Figure 5. Chromatographic chiral recognition of bi-β-naphthol. The chromatographic conditions and data are described in Table I and its legend.

drogen bond sites in the syn isomer, it may be assumed that the isomer provides both of its hydroxyl groups to the chiral additive so that diastereomeric complexes consisting of intermolecular dual hydrogen bonds are formed.

(*R*,*R*)-DIPTA also recognizes the molecular chiralities of β-amino alcohol and 1,2-diol derivatives. In the resolution of a series of enantiomeric pairs of acyclic 1,2-diols, the separation factors for these derivatives was found to remarkably depend on the steric environments of two carbons each possessing a hydroxyl group. The acyclic 1,2-diols, whose carbons both bearing the hydroxyl groups are chiral centers, provide threo and erythro diastereomers. The threo isomers afforded greater separation factors than the corresponding erythro isomers. In the threo family of 2-alkyl-1-phenyl-1,2-ethanediol, an increase in the bulkiness of the alkyl substituent resulted in greater separation factors. But in the erythro family, the substituent bulkiness had the reverse effect on the separation factors. Variation in the separation factors due to increased bulkiness of alkyl substitutents is related to the preferential conformations of these derivatives. Increased bulkiness of substituents causes the threo derivatives to adopt the gauche conformation (I) with regard to the two hydroxyl groups, whereas the erythro derivatives adopt the anti conformation (II), as illustrated below.[10] That is, 1,2-diols which afford a higher degree



(I) (II)

of chiral recognition correspond to those preferring to exist as a gauche conformer which can take advantage of two hydroxyl groups as bonding sites for the dual hydrogen bonds with the chiral additive. Association of (*R*,*R*)-DIPTA with acyclic 1,2-diols through dual hydrogen bonds may thus be essential to the enantioselection of these derivatives.

Molecular associations based on interaction through two hydroxyl groups can be also applied to the chiral recognition of atropisomers. Figure 5 shows the resolution of bi-β-naphthol as such an example. The direct resolution of bi-β-naphthol has already been carried out successfully by other approaches in which the π–π interaction was incorporated into the diastereomeric complexation.[11] Although the degree of chiral recognition of this derivative in the present system is undoubtedly modest compared to those previously reported, our observation that a sufficient degree of enantioselectivity for the bi-β-naphthol can be obtained through the hydrogen bond association with (*R*,*R*)-DIPTA seems to be of interest since this indicates that our approach may be applicable to the resolution of bi-β-naphthol analogues and related atropisomers, such as biphenyl derivatives, possessing the substituents which prevent the π–π interaction.

Our results demonstrate that (*R*,*R*)-DIPTA associates with a wide range of enantiomers to make their chiral recognition possible. For chromatographic detection purposes, all enantiomers resolved by (*R*,*R*)-DIPTA have aryl substituents. Although there is still the possibility that these groups interact with hydroxyl groups and/or amide units of the chiral additive, the intermolecular hydrogen bonds of the chiral additives with enantiomers to be resolved undoubtedly play the principal role in chiral recognition in the present system. It should be mentioned that the association equilibrium between the chiral additive and enantiomers in the column is the determining factor for the retentivities of enantiomeric pairs in the chromatographic process, and thus factors influencing this equilibrium affect the degree of chiral recognition. For example, the presence of a large excess of a chiral additive causes the equilibrium to shift to the association side. Indeed, chiral recognition was found greater at higher chiral additive concentration. An increase in the polarity of the medium weakens the hydrogen bond between the chiral additive and enantiomeric pair, so that the equilibrium shifts to the dissociation side. Thus, the addition of a protic solvent such as an alcohol and/or an increase in the ratio of chloroform to *n*-hexane attenuates the degree of chiral recognition.

In conclusion, it should be noted that application of hydrogen bond associations in the liquid phase to chiral recognition has been extended through use of (*R*,*R*)-DIPTA as a resolving agent. Our findings also suggest that the chiral stationary phase derived from tartramide may have potential for recognizing the molecular chirality of a wide range of enantiomers. Although the degree of enantioselection of solutes due to association with (*R*,*R*)-DIPTA is somewhat modest, the high efficiency of the HPLC technique readily offsets this disadvantage and renders the resulting resolution satisfactory. Since correlation between the elution order of enantiomeric pairs and their absolute configurations has not yet been completely established, it is premature to rationalize the chiral recognition in the present system. This problem as well as that of extended application of this system is the objectives of our future investigations.

Experimental Section

General Procedure. The liquid chromatographic 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 254 nm. The column temperatures were maintained constant by being placed in an air oven, Jasco TU-100. The column (50 × 0.1 (i.d.) cm)[12] was slurry-packed by the usual technique with silica gel (Nucleosil 100-5 (5 μm), Marchery-Nagel, Düren). Chromatographic runs were made at a constant flow rate of 60 μL/min except entries 36 and 37, at which the flow rate was 20 μL/min.

Samples and Reagents. All solvents for the chromatography were of reagent grade. Chloroform was distilled prior to use.

(*R*,*R*)-DIPTA was prepared by treating (*R*,*R*)-dimethyl tartrate (purchased from Tokyo Kasei, Tokyo) with isopropylamine in methanol. Recrystallization from chloroform–ethyl acetate gave a pure product: mp 190–190.5 °C; $[\alpha]_D$ +119.5 (*c* 0.1, ethanol).

Mandelic acid and β-phenyllactic acid were purchased from Tokyo Kasei and Sigma (St. Louis, MO), respectively. These acids were esterified with methanol and then treated with an appropriate alkylamine in methanol to give *N*-alkylcarboxamides.

Tropic acid was purchased from Tokyo Kasei. The other β-hydroxycarboxylic acids were prepared according to literature procedures.[13]

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These acids were converted to *O*-acetyl derivatives (acetyl chloride) and then treated with thionyl chloride. The resulting acid chlorides were subjected to aminolysis with appropriate amine. Hydrolysis (sodium hydroxide–methanol) of the products gave the N-substituted β-hydroxycarboxamides.

β-Amino alcohols prepared by reduction of the corresponding amino acid ethyl ester,[14] hydroxynitrile,[15] or hydroxy ketoxime[16] were acylated with benzoyl chloride. Hydrolysis (sodium hydroxide–methanol) of the *O,N*-dibenzoyl products gave *N*-benzoyl-β-amino alcohols.

Benzoin was purchased from Tokyo Kasei. 2-Hydroxy-1-phenyl-1-propanone were prepared by the procedure given in the literature.[17] α-Hydroxy ketone was treated with hydroxylamine to give a diastereomeric mixture of α-hydroxy ketoximes, which were separated into two isomers by preparative silica gel column.

α-Amino acid derivatives,[18] β-hydroxy ketones,[19] and 1.2-diols[20] were prepared according to literature procedures.

All derivatives were identified by their ^{1}H NMR, IR, and MS spectra. Bi-β-naphthol was kindly supplied by Dr. Takaya and Prof. Nohira.

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Electron-Transfer Reactions Associated with Host–Guest Complexation. Oxidation of Ferrocenecarboxylic Acid in the Presence of β-Cyclodextrin

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Abstract: The oxidation of ferrocenecarboxylic acid in the presence of β-cyclodextrin (β-CD) has been investigated by cyclic voltammetry in pH 9.2 aqueous solution in which the ferrocene is present as the anion, FCA^-. Binding of FCA^- by β-CD is indicated by changes in the UV–vis absorption spectrum and the appearance of induced circular dichroism. The latter data also show that FCA^- is complexed by β-CD in a configuration with the Cp–Fe–Cp axis parallel to the axis of the β-CD cavity. In slow scan rate cyclic voltammetry, β-CD causes a decrease in the peak current and a positive shift in the peak potential for FCA^- oxidation. Each of these effects was quantitatively evaluated, giving a formation constant for FCA^-–β-CD of 2200 M^{-1} at 20 °C and $\Delta H = -2.8$ kcal/mol, $\Delta S = 5$ cal/(K·mol). No binding of the oxidized form of FCA^- by β-CD could be detected. Fast scan rate studies revealed that the inclusion complex is oxidized via a CE scheme in which the complex first dissociates to FCA^- and β-CD followed by oxidation of the free FCA^-. Quantitative evaluation of the data gave 2.1×10^4 s^{-1} for the dissociation rate constant, and variable temperature studies yielded an activation enthalpy for dissociation of 15 kcal/mol. Significantly, no direct oxidation of FCA^-–β-CD at the electrode could be detected. Possible explanations are discussed, and the significance of the present results to earlier electrochemical synthetic studies with cyclodextrins is highlighted.

The cyclodextrins (CDs) are among the most important and widely studied examples of host molecules which are capable of forming inclusion complexes with a variety of guests by incorporating them within the relatively nonpolar cavity of these cyclic oligosaccharides.[2] The CDs have very interesting catalytic properties, and they have been used as models of hydrolytic enzymes. Previous studies have not emphasized the effect of CDs on the oxidation–reduction reactions of guest molecules, but there has been an increasing interest in their use as modifiers of organic electrode reactions.[3] It has been found that CDs, either added to solution or bound to the electrode surface, can cause substantial beneficial changes in the selectivity of electroorganic synthesis. A commonly proposed mechanism for this improved selectivity involves electron transfer to/from the electrode from/to the guest molecule in the inclusion complex forming a reactive intermediate (e.g., an anion radical) which is held within the CD cavity. The reactivity of this intermediate will differ from that of the uncomplexed intermediate leading to the change in selectivity which is observed in the presence of the CD.

Almost nothing is known about the details of electron-transfer reactions of guest molecules in the presence of hosts such as CDs so we set out to investigate a suitable model system, ferrocenecarboxylic acid (FCAH) and β-cyclodextrin (β-CD), the CD containing seven glucose units in its cyclic structure. Ferrocenes exhibit simple electrochemical behavior which is favorable to this study. Oxidation to the ferricinium ion is reversible and uncomplicated by associated chemical reactions. Addition of the carboxylic acid function gives excellent solubility in water, and other ferrocenes are known to be good guest compounds for CDs.[4] The formation constant of the ferrocene–β-CD complex has been determined by polarography.[4b] In the present study, the FCAH/β-CD system in pH 9.2 aqueous buffer has been inves-

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