Contribution

Development of Highly Potent Chiral Discrimination Methods that Solve the Problems of Diastereomer Method

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The development of highly potent chiral discrimination methods that solve the problems of the diastereomer method is described. Explaining the significant results of separations of diastereomers having chiral centers separated by 13 – 27 bonds with reversed-phase HPLC was hitherto impossible. To attract more scientific interest toward the mechanism of the separation, the author proposes a hypothesis, Induced Chiral Fields, that the achiral reversed phases can provide chiral fields depending on the structures of the substrates.

1 Introduction

Since the discovery of enantiomerism by Pasteur in 1848,[1] discrimination of optical isomers has always been one of the major subjects in the fields of chemistry and biology because optical purities of substrates with asymmetries are critical for the evaluation of their biological activities.

In the existing methods for chiral discrimination, it has been recognized that the most reliable one is the diastereomer method. Until recently, however, the most widely used diastereomer method has a fatal problem in that it is impossible to discriminate the diastereomers having chiral centers separated by more than 4 bonds. The problem has been assumed to be intrinsic to the diastereomer method and has been very difficult to solve.

The following hypothesis has been proposed by the author as a solution to the problem: if diastereomers were provided with a helically chiral conformation by the chirality of the chiral labeling reagent, the other chiral center in the diastereomers would be involved in the helically chiral molecule (no longer the chiral center remote from the other chiral center) and, therefore, would be discriminated by some means (Fig. 1).[2-4]

A study to examine the validity of this hypothesis has been pursued. On the basis of the results obtained, a new hypothesis, "Induced Chiral Fields namely that the achiral reversed phase can provide chiral fields depending on the the structure of substrates," is proposed to explain the significant results of separation of the diastereomers derived from new chiral labeling reagents and optical isomers by reversed-phase HPLC, which was hitherto impossible.
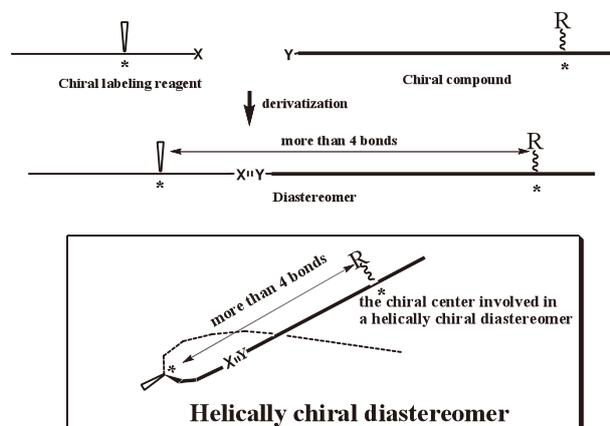

Fig 1. A solution of the problem of the diastereomer method by providing the diastereomer with a helically chiral conformation by the chirality of the labeling reagent.

2 Design of Fluorescent and Chiral Labeling Reagents That Provide Diastereomers with a Helically Chiral Conformation by the *Gauche* Effect and the Ability of such Reagents

2-(Anthracene-2,3-dicarboximido)propanol (**1**) and 1-(anthracene-2,3-dicarboximido)-2-propanol (**2**) and their *O*-triflates (**3**,**4**) were designed as fluorescent and chiral labeling reagents for chiral carboxylic acids (Fig. 2);[3,4] it was expected that the preferred conformation of their esters would be the helically chiral *gauche-trans* (*gt*) as the result of the *gauche* effect[5] between the oxygen atom of ester and the nitrogen atom of imido group and that the *gt* conformation could be further stabilized by CH-π interaction (Fig. 3).[6] The anthracenedicarboximido group is useful for both highly sensitive fluorometry and anisotropy for ^{1}H-NMR study (Fig. 2).

Chiral carboxylic acids can be labeled with reagent **1 - 4** to give diastereomers, for example **5** in Fig. 3. The preferred conformation of **5** will be *gt* among the three possible conformations due to the *gauche* effect between the ester oxygen atom and the imido nitrogen atom. The *gt* conformer is a helically chiral molecule. Thus, the diastereomer could be provided with a helical chiral conformation by the chirality of the labeling reagent, and the other chiral center in the diastereomer originated from the chiral carboxylic acid is the one involved in the helically chiral molecule (no longer the chirality remote from the other chiral center irrespective of the distance between the two chiral centers) and therefore could be discriminated by some means (Figs. 1 and 3).
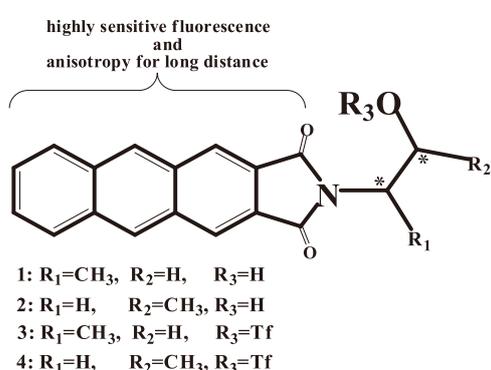
The enantiomers of anteiso fatty acids (C5 - C14) were separated by means of reversed-phase HPLC and were detected at the femto (10^{-15}) mole level by fluorometry. There is a rule in the elution order between (*R*)- and (*S*)-configuration of the branched methyl groups, namely, that the diastereomers of (*S*)-reagents with (*S*)-fatty acids having a chiral center at an even number carbon will elute faster than the diastereomers of (*S*)-reagents with (*R*)-fatty acids and that the elution order will change with those at an odd number carbon.[3,4]

However, the enantiomers of C15 anteiso fatty acid (12-methyltetradecanoic acid) could not be separated as the diastereomers of these reagents by HPLC. Therefore, the HPLC discrimination of higher anteiso fatty acids was not studied.

The chirality of hydroxyl carboxylic acids could also be discriminated by labeling with these reagents and using normal-phase HPLC. The labeling reaction of hydroxyl carboxylic acids with *O*-triflate reagents (**3**, **4**) can be performed in an SN2 manner using tetraethyl ammonium carbonate (TEAC) as the base in CH₃CN or DMF at room temperature without the formation of either intra- or intermolecular esters of substrates. It should be noted that the labeling with **4** proceeds with complete inversion of the stereochemistry of **4** (Fig. 3).

Esters and lactones are labeled with **3** or **4** in one pot, first by treatment of them with TEAC in MeOH and then by evaporation of MeOH followed by treatment with **3** or **4** in CH₃CN (or DMF). The diastereomers are next separated by means of normal-phase HPLC. For example, all four stereoisomers of beraprost sodium[7] and 3-hydroxy-4-methyloctanoic acid (Fig.4)[8] were separated by labeling with **4**.

1: R₁=CH₃, R₂=H, R₃=H
2: R₁=H, R₂=CH₃, R₃=H
3: R₁=CH₃, R₂=H, R₃=Tf
4: R₁=H, R₂=CH₃, R₃=Tf

Fig 2. Fluorescent and chiral labeling reagents that are expected to provide a helically chiral diastereomer by the chirality of labeling reagents and *gauche* effect between the oxygen atom and the nitrogen atom.

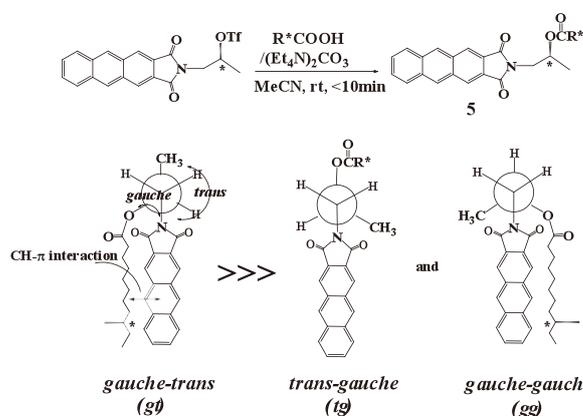**Fig 3.** Expected preferred *gauche-trans* conformation of the esters of the fluorescent and chiral labeling reagents, **1 - 4**.
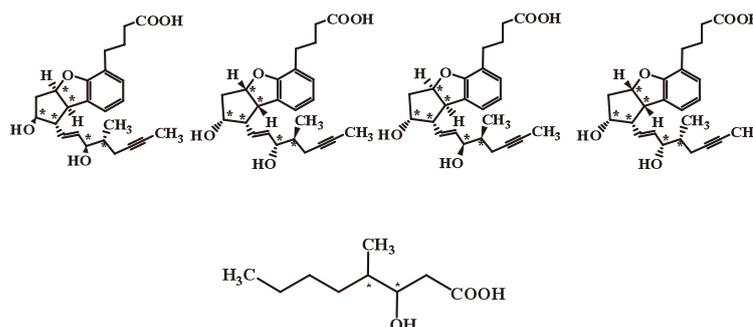

Fig 4. Structures of the four stereoisomers of beraprost and 3-hydroxy-4-methyloctanoic acid.
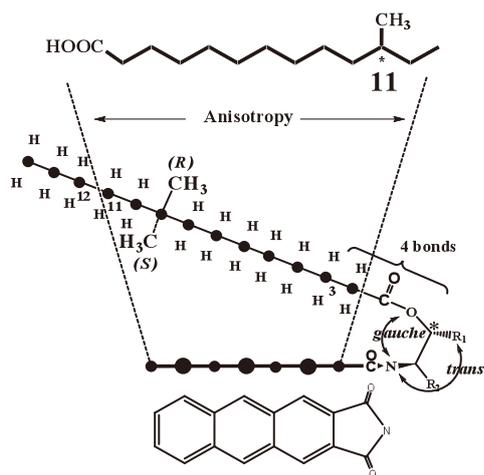
Fig 5. Side view of the *gauche-trans* conformer of the ester of a methyl branched long chain carboxylic acid derived with the fluorescent and chiral labeling reagents, **1 - 4**.
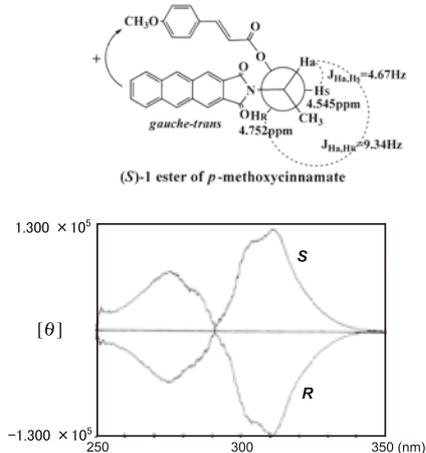

(S)-1 ester of *p*-methoxycinnamate

Fig 6. CD spectrum of (*S*)-2-(2,3-anthracenedicarboximido)propyl-*p*-methoxycinnamate and the vicinal coupling constants of protons of the aminoethanol moiety of the reagent.

Table 1. Population of *gt*, *tg*, and *gg* of *p*-methoxycynnamate of **1**.

	Population[a]
gt	77.5
tg	20.7
gg	1.8

R= CH₃O─⟨⟩─

a. Ref. 11
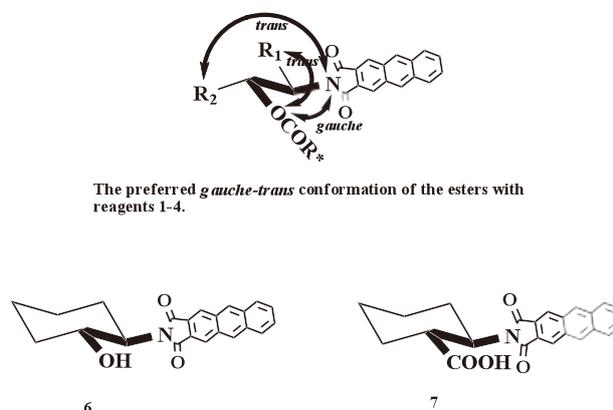

The preferred *gauche-trans* conformation of the esters with reagents 1-4.

Fig 7. The structures of cyclohexane reagents, **6** and **7** that have a fixed chiral *gauche* conformation.

On the other hand, by means of ¹H-NMR, the (*R*)- and (*S*)-stereochemistries of the branched methyl groups of methyl-branched carboxylic acids can be discriminated up to C11-methyl branching, which indicates that the anisotropy of the anthracene ring of these reagents can reach up to the C11-methyl group (Fig. 5).[3,4]

The conformational analysis of *p*-methoxycinnamate of **1** by both exciton CD and ¹H-NMR studies showed that the proportion of *gauche-trans:trans-gauche: gauche-gauche* conformations was *ca.* 77 : 21 : 2 (Fig. 6 and Table 1).[8-11] The results suggested that the chiral labeling reagent that provides the helically chiral *gauche* conformer in 100% will give better chiral discrimination.

3 Design of the Fluorescent and Chiral Labeling Reagents That Provide Diastereomers with a Single Helically Chiral *Gauche* Conformer and the Ability of such Reagents

The *gt* conformation of the diastereomers derived from reagents **1 - 4** by the *gauche* effect could be fixed by forming a ring as shown in Fig. 7. In this way, the fluorescent and chiral labeling reagents **6** for chiral carboxylic acid and **7** for chiral alcohol were prepared.[12,13] It should be noted that the *gauche* effect is not necessary for either **6** or **7** to provide helically chiral *gauche* diastereomers.

3-1 Reversed-phase HPLC discrimination of diastereomers derived from 6 and 7

Enantiomers of anteiso fatty acids (C7 - C29) were separated by C30 reversed-phase HPLC as the diastereomers labeled with **6**.[12,13] There is a rule regarding the elution order, namely, that the elution order of the fatty acids having a methyl group at C4 - C11 is the same as that of diastereomers with the reagents **1 - 4**, but the elution order will change at the fatty acid having a methyl group at C12.[13] A similar turning point in the elution order was observed at C10 with the diastereomers derived from
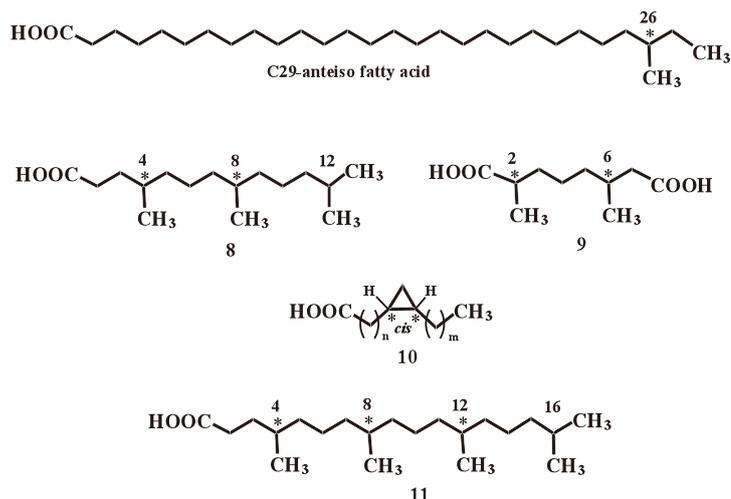
Fig 8. Structures of chiral carboxylic acids. All the stereoisomers of them except **11** can be separated by the present method.
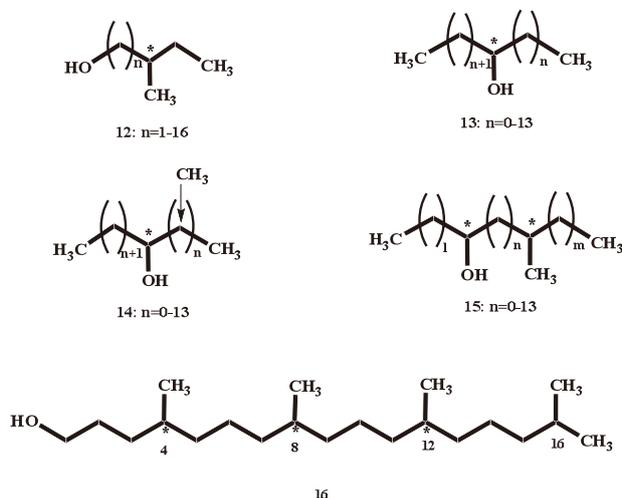

Fig 9. Structures of chiral alcohols. All the stereoisomers of them except **16** can be separated by the present method.
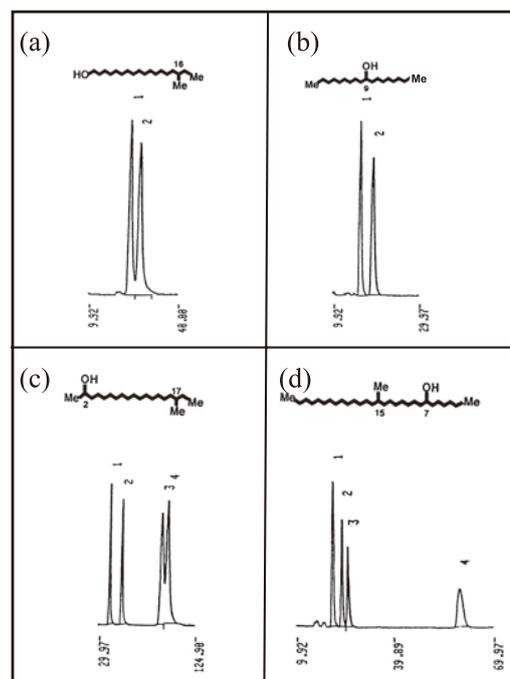

Fig 10. Representative HPLC chromatograms of (1*R*,2*R*)-2-(anthracene-2,3-dicarboximido)cyclohexane carboxylic acid derivatives of chiral alcohols.

(1*R*,2*R*)-naphtharene-2',3'-dicarboximidocyclohexanol, which is one benzene ring smaller than **6**, and methyl branched fatty acids.[14]

The change of the elution order indicated that the chiral discrimination mechanism will be different for the diastereomers having the branched methyl group over the anthracene ring and those having the branched methyl group beyond the anthracene ring.

It should be noted that ODS (C18) can separate the enantiomers up to C21 anteiso fatty acid (18-methylicosanoic acid) but not the enantiomers of higher anteiso fatty acids.[13] These results suggested that the chain length of the reversed phase played an important role in the discrimination. They also suggest that the methylene chains of the diastereomers and those of the reversed-phases did not bend and did fully interact with each other.

Reagent **6** can discriminate the four stereoisomers of 4,8,12-trimethyltridecanoic acid (**8**),[4] 2,6-dimethyloctane-1,8-dioic acid

(**9**),[16] and cyclopropanecarboxylic acid (**10**).[16] However, **6** can not completely discriminate all eight stereoisomers of 4,8,12,16-tetramethylheptadecanoic acid (**11**).[4] In this case as well, up to the C11-branched methyl group of fatty acid can be discriminated by means of ^{1}H-NMR as the diastereomers derived from **6**. The structures of C29-anteiso fatty acid and **8 - 11** are shown in Fig. 8.

Enantiomers of anteiso fatty alcohols (C5 - C19) (**12**) were separated by C30-reversed-phase HPLC as the diastereomers derived from **7**.[12-14] The enantiomers of chiral secondary alcohols up to C30 with methylene chains that are different by only one carbon at the asymmetric carbon (**13**),[17] secondary

alcohols with a branched methyl group on any carbon of the shorter methylene chain of **13** (**14**),[17] and all four stereoisomers of secondary alcohols with a branched methyl group (**15**)[18] could be discriminated by labeling with **7** and reversed-phase HPLC. However, **7** cannot completely discriminate all eight stereoisomers of 4,8,12,16-tetramethylheptadecanol (**16**). The structures of **12 - 16**, and their representative HPLC chromatograms are shown in Figs. 9 and 10.

3-2 ¹H-NMR chiral discrimination of secondary alcohols by 7

Mosher's methods[19] and Kusumi's new Mosher's method[20] are useful means for the determination of absolute configurations of chiral secondary alcohols.

The preferred conformations of the ester of **7** and secondary alcohol are the 1,3-*syn* relationship between the the oxygen atom of the carbonyl group and the α-hydrogen atom of the alcohol and the *s-trans* relationship between the oxygen atom of the carbonyl group and the α-hydrogen on the cyclohexane ring. Since one substituent of the secondary alcohol stays over the
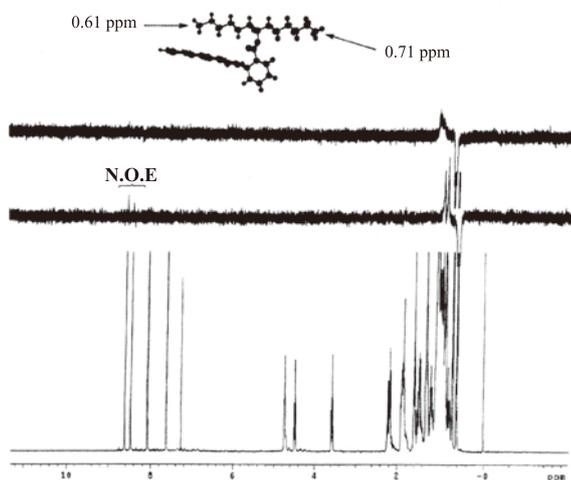
anthracene ring, as can be seen in Fig. 14, reagent **7** could act as a modified Mosher's reagent for ¹H-NMR study and could also be used for a longer distance than the preceding Mosher's reagents.

The ¹H-NMR spectra of the **7**-tridecanol ester of (1*R*, 2*R*)-**7** is shown in Fig.11. The signals of the terminal methyl groups appeared at different positions that were more shielded than those of 7-tridecanol. The results indicated that both methyl groups have a chance to come over the anthraceneimido group by rotation, however, N.O.E. was observed only between the more shielded methyl group and the protons of the anthracene ring.[17] Judging from the preferred conformation, one can assign the more shielded methyl signal to that of the pro-*S* methylene chain.

The ¹H-NMR spectra of the (*S*)-5-undecanol ester of (1*R*, 2*R*)-**7** (**17**) are shown in Fig. 12. The terminal methyl groups have different chemical shifts that are more shielded than those of (*S*)-5-undecanol.[17] Judging from the preferred conformation of **17**, one can assign the more shielded methyl signal to that of the C5-terminal. The assignment was confirmed by the study of the HOHAHA spectrum of **17** conducted by Bax and Davis.[21] Thus, the methyl signal at 0.52 ppm, which appeared faster than the other one by irradiation of the signal of alcohol methine proton at 4.75 ppm, was assigned to the methyl group of the shorter methylene chain.

The ¹H-NMR spectra of the (1*R*,2*R*)-**7** amide of (*R*)- and (*S*)-2-heptylamine (**18***R* and **18***S*) are shown in Fig. 13. In this case as well, the spectra showed that the preferred conformations of **18** are the 1,3-*syn* relation between the carbonyl oxygen and the methine hydrogen of the amine and the *s-trans* relation between the carbonyl oxygen and the α-hydrogen on the cyclohexane ring, which are similar to those of the **7**-esters of secondary alcohols. Thus, the absolute configuration of chiral amines can be determined by the ¹H-NMR of their **7**-amides.[21] Thus, **7** is a very useful reagent for chiral discrimination by ¹H-NMR.

3-3 Application of 7 to X-ray crystallography

One of the characteristics of the anthracenedicarboximino reagents is that they give crystalline derivatives that are suitable for X-ray studies. The X-ray structures of the (1*R*,2*R*)-**7** ester of (*S*)-11-docosanol (**19**)[17] and (1*R*,2*R*)-**7** amide of (*S*)-2-heptamine (**18***S*)[21] are shown in Figs. 14 and 15, respectively. In Fig. 14, the shorter methylene chain of **19** is laid over the anthracenedicarboximido group to show that the preferred conformation (the 1,3-*syn* relationship between the carbonyl
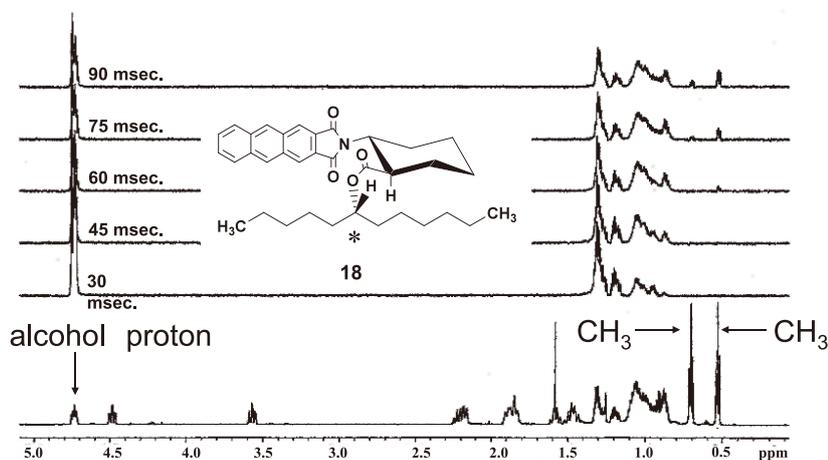

Fig 11. ¹H-NMR spectra of (*R*)-7-tridecanoyl (1*R*,2*R*)-2-(anthracene-2,3-dicarboximido)cyclohexane carboxylate and N.O.E between the protons of the terminal methyl group and those of anthracene ring.

Fig 12. HOHAHA spectrum of (*S*)-6-dodecanoyl (1*R*,2*R*)-2-(anthracene-2,3-dicarboximido)-cyclohexane carboxylate by irradiation of the alcohol proton.

oxygen and the α-hydrogen of the secondary alcohol and the *s-trans* relationship between the carbonyl oxygen and the α-hydrogen on the cyclohexane ring) continues to have a crystalline structure. On the other hand, in Fig. 15, the pentyl group of **18S** is laid over the anthracenecarboximido group
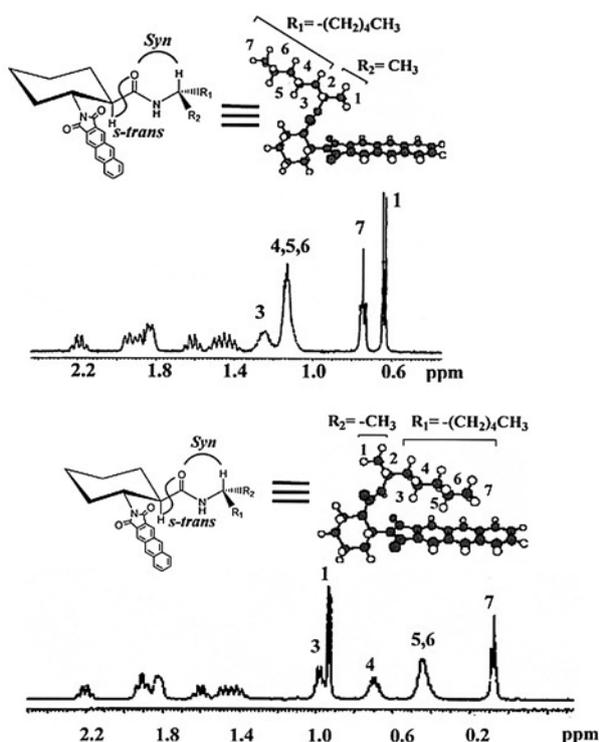
to show that the 1,3-*syn* conformation between the carbonyl oxygen and the α-hydrogen of amino group of **18S**, which is preferred in solution, continues to have a crystalline structure but the *s-trans* conformation between the carbonyl oxygen and the α-hydrogen on the cyclohexane ring was changed to *s-cis* in the crystalline structure due to the intra- and intermolecular CH-τ interactions between the pentyl methylene groups and the anthracenedicarboximido group that are necessary for crystallization. Thus, **7** is a useful reagent for determination of the absolute configuration of alcohols and amines by X-ray crystallography.

4 Design of Sugar Labeling Reagents

It is known that 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-gluopyranose (**20**) gives β-glycoside selectively by Lewis-acid catalyzed glycosidation of alcohols.[23]

In order to examine the effect of the polarity of the labeling reagents on the reversed-phase HPLC separation, we prepared 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(anthracene-2,3-dicarboximido)-β-D-glucopyranose (**21**), its *O*-benzoyl (**22**), and the *O*-methyl analog (**23**) as fluorescent and chiral labeling reagents (Fig. 16).[23]
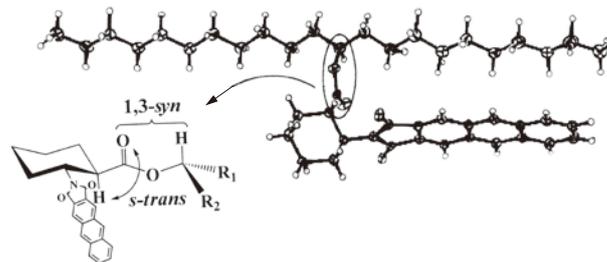

Fig 13. ¹H-NMR spectra of (*S*)-heptyl (1*R*,2*R*)-2-(anthracene-2,3-dicarboximido)cyclohexane carboxamide (**18S**) and its (*R*)-isomer (**18R**).

Fig 14. X-ray structure of (*R*)-11-docosanoyl (1*S*,2*S*)-2-(anthracene-2,3-dicarboximido)cyclohexane carboxylate (**18R**).
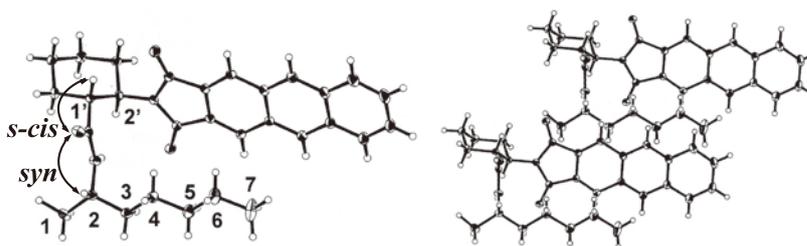

Fig 15. X-ray structure of (*S*)-heptyl (1*R*,2*R*)-2-anthracene-2,3-dicarboximido)cyclohexane carboxamide (**18S**).
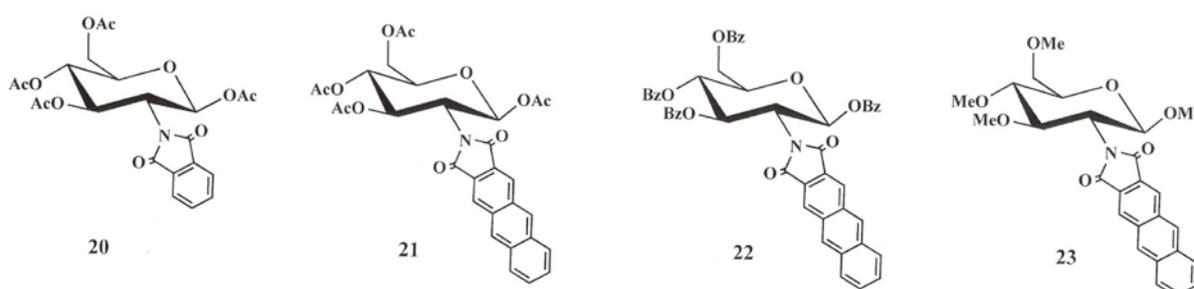

Fig 16. Structures of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (**20**) and sugar reagents, **21**, **22**, and **23**.
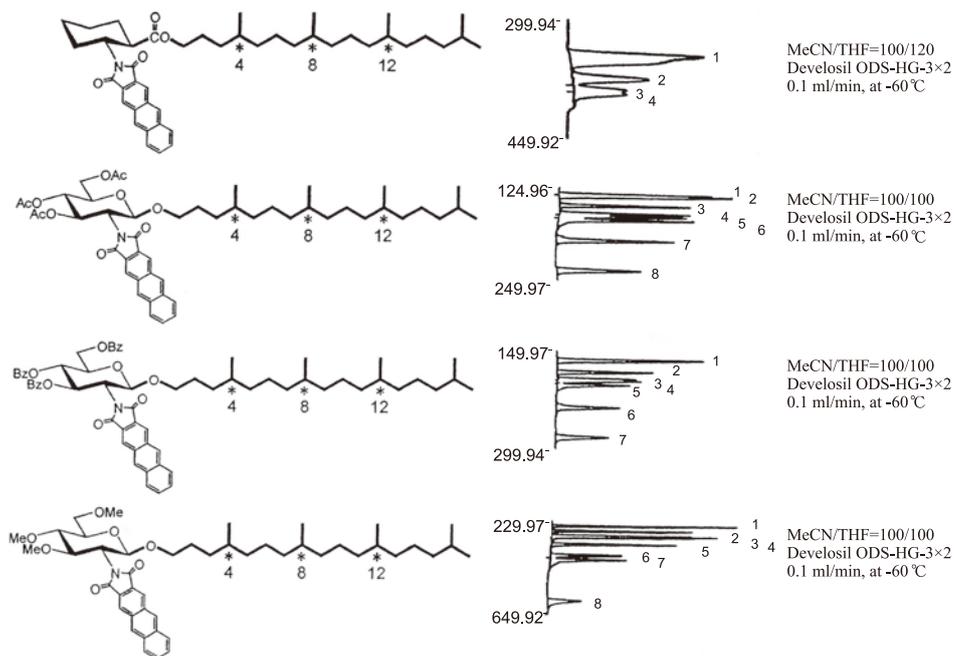
Fig 17. HPLC chromatograms of the diastereomers of 4,8,12,16-tetramethyl heptadecanol labeled with the cyclohexane reagent and sugar reagents.
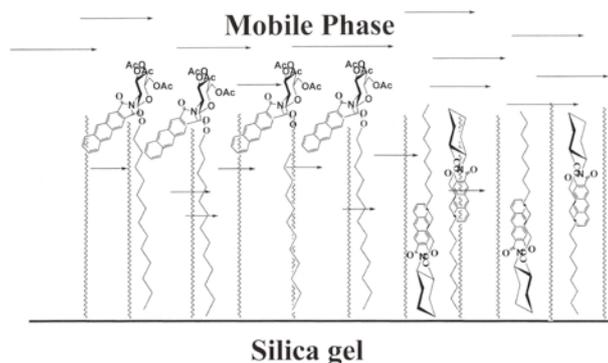

Fig 18. Difference of the mode of interaction with the reversed phase between the derivatives labeled with the nonpolar cyclohexane reagent and those labeled with polar sugar reagents.

Fig 19. HPLC chromatogram of stereoisomers of α-tocopherol labeled with 1,3,4,6-tetra-O-acetyl-2-anthracene-2',3'-dicarboximido-2-deoxy-β-D-glucopyranose.

The HPLC chromatograms of the 4,8,12,16-tetrametyl-heptadecanoyl glycosides of **21**, **22**, and **23**, together with that of the **16** ester of **7**, are shown in Fig. 17. The sugar regents **21** and **23** can discriminate all eight stereoisomers of **16**, but **7** cannot.

The most remarkable difference between **7** and the sugar reagents is their polarity. Thus, the difference in their ability for HPLC separation could be explained as follows.The non-polar diastereomers derived from **7** and **16** will interact with the methylene chains of the reversed phase in two ways, as shown in Fig. 18; one interaction is cyclohexane part of the molecule directed to the mobile phase, and the other interaction is the cyclohexane part directed to silica gel (upside down). The mechanism of chiral discrimination between the two ways will be different. Therefore, good separation of diastereomers cannot
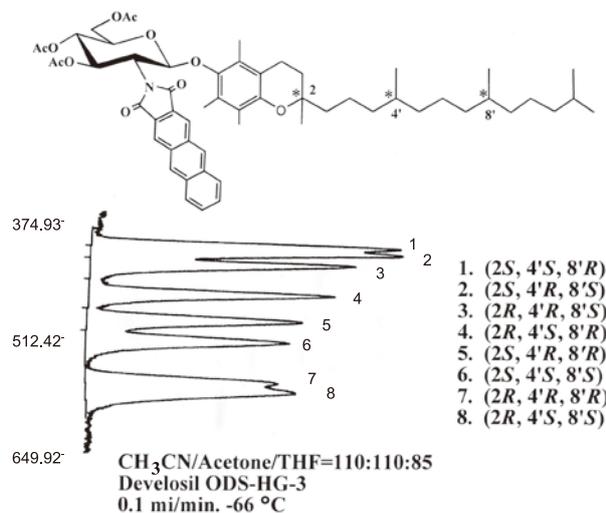
be attained. On the other hand, the polar diastereomers derived from sugar reagents and **16** will interact with the reversed phase mostly in a way in which the polar sugar part is directed to the mobile phase. Thus, the more orderly interaction of the polar diastereomer with the reversed phase will result in the separation of all eight diastereomers.

In addition, it should be noted that **21** can separate all eight stereoisomers of α-tocopherol (Fig. 19).[24] These results indicate that the reversed-phase column is a kind of chiral column.
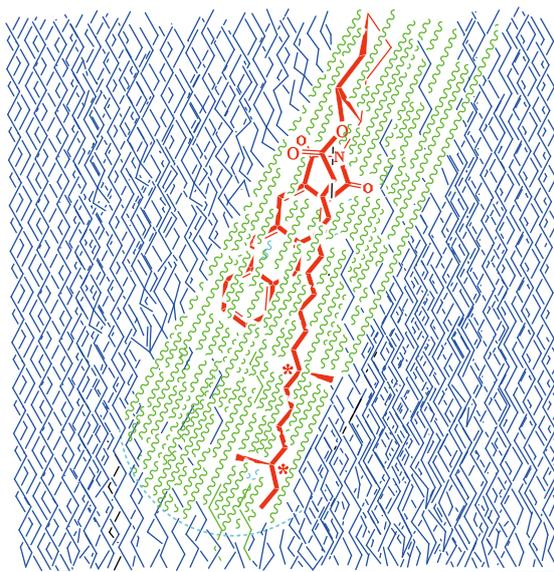
Fig 20. Induced Chiral Fields.

5 Proposal of Induced Chiral Fields

The separation of the diastereomers by reversed-phase HPLC can usually be explained by the differences of the three-dimensional shapes among diastereomers.

The separation of diastereomers up to C11 methyl branched anteiso-carboxylic acids could be understood to be in this category.

However, it is very difficult to identify the differences between the shapes of the diastereomers derived from **7** and those of the enantiomers of C29-anteiso fatty acid well enough to achieve separation by reversed-phase HPLC. Furthermore, the results described above suggest that the methylene chains of the diastereomer and those of the reversed-phase fully interact with each other. Taking these results into account and in order to attract the scientific interest toward the mechanism of the separation, I would like to propose here a hypothesis, "Induced Chiral Fields," to explain the results of separation of diastereomers by reversed-phase HPLC.

The hypothesis of Induced Chiral Fields proposes that the interaction of large helically chiral molecules having a long methylene chain, such as the diastereomer derived from **7** and C29-anteiso fatty acids, and an anthracenecarboximido group with the methylene chains of reversed-phase chirally bends or twists the methylene chains of the reversed-phase to create the appearance of new chiral fields. (Fig.20) The rate at which the diastereomers move from the chiral fields to the achiral methylene chains of the reversed-phase to create new Induced Chiral Fields is different in the (*R*)- and (*S*)-stereochemistry of the branched methyl groups in the diastereomers. Thus, the diastereomers are separated by reversed-phase HPLC.

Thus, the Induced Chiral Fields hypothesis proposes that the achiral reversed phase could be the chiral phase depending on the structure of the substrate.

6 Conclusion

Highly potent chiral discrimination methods for both ^{1}H-NMR and HPLC that have solved the problems assumed to be intrinsic to the diastereomer method were developed, and a hypothesis to explain the significant separation of diastereomers by reversed phase was proposed. I hope that the study presented in this paper is a contribution to the advance of chiral discrimination.

7 Acknowledgement

8 References

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Introduction of the author :

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Hiroshi Ohrui received his B.S. (1965) and Ph.D. degrees (1971) from The University of Tokyo. He worked for Ube Industries, Ltd. (1966). He joined the Laboratory of Dr. Umetaro Suzuki at the Institute for Physical and Chemical Research (RIKEN) in 1967. He worked at the Dr. J. J. Fox at Sloan-Kettering Institute for Cancer Research as a research associate (1972-1973), at the Dr. J. G. Moffatt at Syntex Research as a postdoctoral fellow (1973-1974). He was promoted to an associate professor at the Department of Food Chemistry, Faculty of Agriculture, Tohoku University in 1981, a visiting professor at the Technische Universität Darmstadt in 1991, a professor at the Graduate School of Life Sciences, Tohoku University in 1997. He has been a professor at the Yokohama College of Pharmacy since 2006. His awards include The Agricaltual Chemical Society of Japan Award for Young Scientists in 1974, Inoue Prize for Science in 2001, Japan Prize of Agricultural Science in 2004, and The Japan Society for Analytical Chemistry Award in 2004.
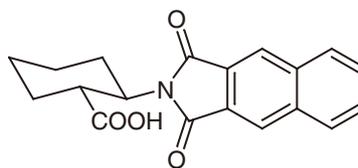[Specialties] Bioorganic, analytical chemistry.

TCI Related Compounds

Highly Potent Chiral Derivatizing Reagents

*see. Fig.7 cyclohexane reagents **6**, **7***
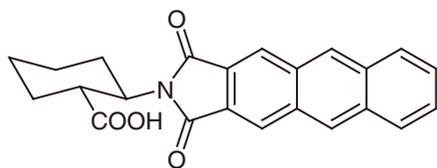
(1*R*,2*R*)- : A1657
(1*S*,2*S*)- : A1658

(1*R*,2*R*)- : N0713
(1*S*,2*S*)- : N0714

A1657	(1R,2R)-2-(Anthracene-2,3-dicarboximido)cyclohexanecarboxylic Acid	100mg
A1658	(1S,2S)-2-(Anthracene-2,3-dicarboximido)cyclohexanecarboxylic Acid	100mg
N0713	(1R,2R)-2-(Naphthalene-2,3-dicarboximido)cyclohexanecarboxylic Acid	100mg
N0714	(1S,2S)-2-(Naphthalene-2,3-dicarboximido)cyclohexanecarboxylic Acid	100mg