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Substitution Criteria Based on Stereoisograms to Determine Prochirality and Pro-RS-Stereogenicity

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Abstract

In contrast to the mathematical formulation reported in Fujita, S. *Tetrahedron*, **2006**, *62*, 691–705, the terms *prochirality* and *pro-RS-stereogenicity* have been alternatively formulated by emphasizing relational terms which specify relationships between two objects (ligands etc.), i.e., *enantiotopic* and *RS-diastereotopic*. By developing the substitution criteria for enantiotopicity and for RS-diastereotopicity on the basis of stereoisograms, the relational terms are linked to the corresponding terms for specifying RS-stereoisomerism: i.e., enantiomeric relationships for chirality, RS-diastereomeric relationships for RS-stereogenicity, and holantimeric relationships for sclerality. Then, enantiotopic, RS-diastereotopic, and holantitopic relationships are employed to specify prochirality, pro-RS-stereogenicity, and prosclerality. The concept of prochirality characterized by the term *enantiotopic* gives a sound basis to the capability of deriving chiral compounds selectively from achiral precursors. On the other hand, the concept of pro-RS-stereogenicity characterized by the term *RS-diastereotopic* gives a sound basis to the capability of giving *pro-R/pro-S*-descriptors. The substitution criteria are correlated to the previous mathematical formulation through the membership criteria which are defined on the basis of coset representations. The difference between "stereoheterotopic" of conventional usage and *RS-stereoheterotopic* of the present approach is discussed in connection with the differences between "prostereoisomerism" and the present term *pro-RS-stereoisomerism* as well as between "diastereotopicity" and the present term *RS-diastereotopicity.* Addition criteria for prochirality and for pro-RS-stereogenicity are also developed to discuss two faces of a carbonyl ligand.

1 Introduction

The term "prochirality" proposed by Hanson [1] is yet used in different, sometimes contradictory ways, as pointed out by the IUPAC Recommendations 1996 on "Basic Terminology of Stereochemistry" [2] . This stems from the fact that conventional ways of terminology mix up two aspects of stereochemistry, i.e.,

(Aspect 1): the capability of giving *pro-R/pro-S*-descriptors and

(Aspect 2): the capability of deriving chiral compounds selectively from achiral precursors.

In fact, the term "prochirality" varies in its connotation about Aspects 1 and 2 by every articles [1, 3] , reviews [4, 5] , IUPAC Recommendations (1996) [2] , and textbooks [6, 7] . The differences due to the unfixed connotation are seemingly slight but conceptually essential so as to cause serious confusion, as analyzed in our previous paper entitled "Complete Settlement of Long-Standing Confusion on the Term 'Prochirality' in Stereochemistry. Proposal of Pro-RS-Stereogenicity and Integrated Treatment with Prochirality" [8, 9] .

Our recipe [8] for avoiding the confusion is that the term "prochiral" of conventional ambiguous usage should be replaced by the term *pro-RS-stereogenicity* (for Aspect 1) and the term *prochiral* (for Aspect 2) should be used only in a purely geometrical meaning. It follows that the usage of the terms "enantiotopic", "diastereotopic", and "stereoheterotopic" with reference to Aspect 1 should be altogether abandoned, because these terms have been widely employed to specify the "prochirality" of Aspect 1 *without a sound basis.* In particular, we have clarified that the term "enantiotopic" should be used in purely geometrical meanings in agreement with the original definitions by Mislow and Raban [10] , because the terms have encountered the "verbal transmutation" pointed out by Mislow [11] .

Shortly after the publication of the article [8] , we have heard of criticisms against its mathematical features. Although the original formulation adopted a diagrammatical approach using stereoisograms [8] , it was based on orbits (equivalence classes) according to our USCI (unit-subduced-cycle-index) approach [12] . Thus, the term *prochirality* was determined by means of the sphericity of an orbit (a homospheric orbit, an enantiospheric orbit, a hemispheric orbit) and the term *pro-RS-stereogenicity* was determined by means of the RS-tropicity of an orbit (an RS-homotropic orbit, an RS-enantiotropic orbit, an RS-hemitropic orbit). The formulation inevitably required a *paradigm shift from relationships to equivalence classes (orbits)* (cf. [13, Chapter 5]), where sphericity or RS-tropicity as an *attribute* of an orbit was used in place of topicity as a *relationship* among the members of the orbit [12] .

The paradigm shift from relationships to equivalence classes would be prerequisites for discussing such quantitative applications as chemical combinatorics [12 –16] . One who makes the necessary effort to understand the paradigm shift would be rewarded by the acquisition of powerful and quantitative methods for analyzing stereochemical phenomena without relying on terms of relationships. However, if one has been more intimately acquainted with the conventional terminology of relationships, he/she would have more difficulties to grasp the paradigm shift. Hence, if he/she intends to examine Aspects 1 and 2 qualitatively, the usage of such relational terms as *enantiotopic* after explicit definitions is rather suitable for such intention.

In the present paper, the relational terms *enantiotopic* and *RS-diastereotopic* are defined by means of the substitution criterion based on stereoisograms. By using the relational terms in place of attributive terms such as *enantiospheric* and *RS-enantiotropic*, we are able to redefine the formulation described in the previous article [8] . As a result, we obtain alternative definitions, which have such traditional formats that do not necessitate knowledge on mathematics (e.g., group theory). Thereby, the relational term *enantiotopic* specifies the concept of *prochirality* and the relational term *RS-diastereotopic* specifies the concept of *RS-stereogenicity.* The relational terms *enantiotopic* and *RS-diastereotopic* defined here are discussed in comparison with the relational terms *enantiotopic* and *diastereotopic* of conventional usage.

2 Stereoisograms and RS-Stereoisomerism

In an accompanying paper, we will discuss the versatility of stereoisograms which we have recently developed [17, 18] . To keep the present article self-contained, however, a minimum set of necessary terms should be briefly introduced here. Each stereoisogram is composed of the following three relationships:

symbol	relationship [19]	attribute
←◉→	enantiomeric	chiral
═◉═	(self-enantiomeric)	achiral
←○→	*RS*-diastereomeric	*RS*-stereogenic
═○═	(self-*RS*-diastereomeric)	*RS*-astereogenic
←●→	holantimeric	scleral
═●═	(self-holantimeric)	ascleral

The symbol ○ denotes an operation of causing a skeletal change but no change of ligand chirality; the symbol • denotes an operation of changing ligand chirality with no skeletal change; and their combination means the changing of a skeleton along with ligand chirality. The three relationships correspond to three pairs of attributes for characterizing a promolecule: chiral/achiral, *RS*-stereogenic/*RS*-astereogenic, and scleral/ascleral. As a result, there appear an enantiomeric pair (enantiomers) for chirality, an *RS*-diastereomeric pair (*RS*-diastereomers) for an *RS*-stereogenicity, and a holantimeric pair (holantimers) for a sclerality, which are collectively called *RS-stereoisomers*.

The three pairs (i.e., chiral/achiral, *RS*-stereogenic/*RS*-astereogenic, and scleral/ascleral) are combined to give eight cases, among which five combinations are effective to characterize a promolecule:

Type I — chiral/*RS*-stereogenic/ascleral $[-,-,a]$
Type II — chiral/*RS*-astereogenic/scleral $[-,a,-]$
Type III — chiral/*RS*-stereogenic/scleral $[-,-,-]$
Type IV — achiral/*RS*-astereogenic/ascleral $[a,a,a]$
Type V — achiral/*RS*-stereogenic/scleral $[a,-,-]$

where a combined symbol $[-,-,a]$, for example, represents a chiral, *RS*-stereogenic, and ascleral promolecule (Type I), and so on, because the symbol $-$ represents the absence of the prefix a, and the letter a represents the presence of the prefix a. The existence of five types for stereoisograms has been proved in general [20] .

By drawing stereoisograms, tetrahedral promolecules have been categorized into the five types, as summarized in Fig. 1 [17, 18] . It should be noted that an arbitrary enantiomer for each pair of enantiomers (Types I, II, and III) is depicted in Fig. 1. Two *RS*-diastereomers tied with an underbrace (Type III) are accompanied by their enantiomers, so that totally four *RS*-stereoisomers appear in a stereoisogram. In contrast, two *RS*-diastereomers tied with an underbrace for Type V are achiral, where they exhibit a pseudoasymmetric case.

One of the most important conclusions is that chirality and *RS*-stereogenicity are discriminated from each other without ambiguity by means of stereoisograms.

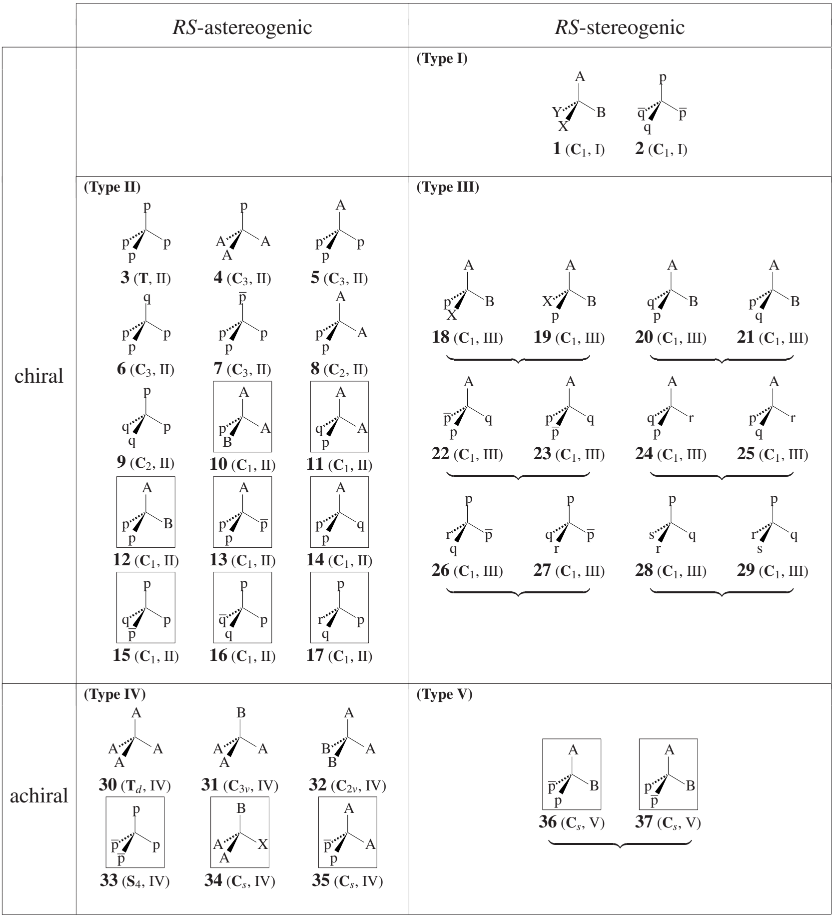

Figure 1: Point groups and *RS*-stereoisomeric types (Types I to V) for tetrahedral molecules. The symbols A, B, X, and Y represent atoms or achiral (pro)ligands. The symbols p, q, r, and s represents chiral (pro)ligands, while each symbol with an overbar represents the corresponding chiral (pro)ligand with the opposite chirality. Each promolecule surrounded by a box is a prochiral and/or pro-*RS*-stereogenic one.

1. Thus, *the chirality is distinctly specified in terms of enantiomeric relationships appearing in stereoisograms*:
    (a) Promolecules of Types I $[-,-,a]$, II $[-,a,-]$, and III $[-,-,-]$ are chiral. Each of them cannot be superposed to its mirror image (enantiomer). Note that all the symbols have the form $[-,*,*]$, which means chirality.
    (b) On the other hand, promolecules of Types IV $[a,a,a]$ and V $[a,-,-]$ are achiral. Each of them can be superposed to its mirror image. Note that all the symbols have the form $[a,*,*]$, which means achirality.
2. *The RS-stereogenicity is distinctly specified in terms of RS-diastereomeric relationships appearing also in stereoisograms*:
    (a) Promolecules of Type I $[-,-,a]$, Type III $[-,-,-]$, and Type V $[a,-,-]$ are *RS*-stereogenic, so that their configurations are characterized by *R*- or *S*-descriptors of the CIP-system. Note that all the symbols have the form $[*,-,*]$, which means *RS*-stereogenicity.
    (b) On the other hand, promolecules of Type II $[-,a,-]$ and Type IV $[a,a,a]$ are *RS*-*a*stereogenic, so that their configurations are not specified by the CIP-system. Note that all the symbols have the form $[*,a,*]$, which means *RS*-*a*stereogenicity.

The *RS*-stereoisomerism formulated by stereoisograms is an intermediate concept which is located between stereoisomerism and enantiomerism.

$$\begin{aligned} \text{stereoisomerism} &\supset \textit{RS}\text{-stereoisomerism} &(1)\\ &= \text{enantiomerism} + \textit{RS}\text{-diastereomerism} + \text{holantimerism} &(2)\\ &\leftrightarrow \text{chirality} + \textit{RS}\text{-stereogenicity} + \text{sclerality.} &(3)\end{aligned}$$

The enantiomerism shown in eq. 2 corresponds to the term *chirality* in a purely geometrical meaning (eq. 3), the *RS*-diastereomerism shown in eq. 2 corresponds to the term *RS-stereogenicity* (eq. 3), and the holantimerism shown in eq. 2 corresponds to the term *sclerality* (eq. 3). Hence, eq. 2 is concerned with attributes, where the relational terms are changed into the corresponding attributive terms by adding a suffix “ism” [21] .

3 Conventional Ways for Determining “Prochirality”

The clear discrimination between chirality and *RS*-stereogenicity, which has been described in the preceding section, provides us a succinct tool to comment on conventional ways for determining “prochirality” and “prostereogenicity” (or “prostereoisomerism”). This section is devoted to clarifying the scope and limitations of such conventional ways. To emphasize the present terminology, terms in agreement with it are printed in italics if necessary, while conventional terms not to be adopted here are shown by a pair of double quotation marks.

Enantiotopicity in a Geometrical Meaning Because the concept of *enantiotopicity* (as paired with “diastereotopicity”) has been widely used to discuss “prochirality” and “prostereogenicity”, its scope and limitations should first been demonstrated in the context of the present approach. To the best of our knowledge, there are four methods for specifying an *enantiotopic relationship* and related ones:

1. Substitution criterion [10]
2. Symmetry criterion [10]
3. Membership criterion (1) of mathematical basis [12, 22, 23]
4. Membership criterion (2) of intuitive approach [24, 25]

These criteria have aimed at the specification of an enantiotopic relationship as a geometrical property in a molecule so that the enantiotopic relationship thus determined is intended to predict Aspect 2. Although the two membership criteria combined with the concept of stereoisograms have been successfully extended to cover Aspect 1 along with Aspect 2 [8] , the direct application of the substitution criterion to Aspect 1 has caused some confusion, as pointed out in Ref. [26] . In view of the fact that the substitution criterion for Aspect 2 has been widely accepted by organic chemists because of its straightforwardness, it is important to investigate whether or not the substitution criterion can be extended to cover Aspect 1 in the light of the methodology underlying the successful extension of the membership criteria [8] .

Among the promolecules listed in Fig. 1, promolecules surrounded by a box should be examined. By following the substitution criterion of the original definition [10] , we obtain the following five cases (Items 1–5):

(Item 1): The enantiotopicity emerges in the two A’s of **34** (Type IV according to the present classification).

(Item 2): The enantiotopicity emerges in the following cases: any pair of p and $\overline{\mathrm{p}}$ selected from the set of $\{\mathrm{p}, \mathrm{p}, \overline{\mathrm{p}}, \overline{\mathrm{p}}\}$ of **33** and the pair of p and $\overline{\mathrm{p}}$ of **35** (Type IV according to the present classification).

Table 1: Terminologies for “Prochirality”

conventional terminologies		
term for specification	“prochiral”	“not prochiral”
enantiotopic (original) [10]	Items 1, 2, 3	Items 4, 5
“prochiral (original)” [1]	Items 1, 4, 5	Items 2, 3
“prochiral (Def. 1)”[6]	Items 1, 2, 3	Items 4, 5
“prochiral (Defs. 1 & 2)” [6]	Item 1	Items 2, 3, 4, 5
“prochiral (Def. $1'$)” [2]	Items 1, 2, 3, 4, 5	
“prochiral (Defs. $1'$ & 2)” [2, 6]	Items 1, 4, 5	Items 2, 3
the present terminology [8]		
term for specification	Aspect 1 (*pro-RS-stereogenic*)	Aspect 2 (*prochiral*)
prochiral	–	Items 1, 2, 3
pro-RS-stereogenic	Items 1, 4, 5	–

(Item 3): The enantiotopicity also emerges in the pair of p and $\overline{\mathrm{p}}$ of **36** and the pair of p and $\overline{\mathrm{p}}$ of **37** (Type V according to the present classification).

(Item 4): On the other hand, the “diastereotopicity” emerges in the following cases: the two A’s of **10**, the two A’s of **11**, the two p’s of **12**, the two p’s of **13**, the two p’s of **14**, the two p’s of **15**, the two p’s of **16**, and the two p’s of **17** (Type II according to the present classification).

(Item 5): The “diastereotopicity” emerges also in the two A’s of **35** (Type IV according to the present classification). Note that **35** exhibits enantiotopicity at the same time because of the presence of enantiotopic proligands p and $\overline{\mathrm{p}}$.

Prochirality for Aspect 2 Table 1 shows how Items 1–5 are treated by conventional terminologies for determining “prochirality” as well as by the present terminology.

When the term *prochiral* is used in agreement with Aspect 2 (i.e., when it is used in a purely geometrical meaning), the enantiotopicity described in Items 1, 2, and 3 is a proper criterion to detect *prochirality*, as shown in Table 1 (the first row denoted as “enantiotopicity (original)”).

“Prochirality” for Aspect 1 In contrast to the above-mentioned *prochirality* in a purely geometrical meaning, the original connotation of the term “prochirality” described by Hanson [1] has aimed at Aspect 1 (the 2nd row denoted as “prochiral (original)” in Table 1). Thus, Items 1, 4, and 5 are recognized to be “prochirality” of the original connotation (Aspect 1), while Items 2 and 3 are not “prochiral”. Obviously, the original connotation is inconsistent with the *prochirality* in a purely geometrical meaning (Aspect 2), because Items 1, 2 and 3 should be recognized to be *prochiral*, while Items 4 and 5 should be recognized not to be *prochiral*.

In oder to demonstrate this situation, it would be advisable to cite a comment from Ref. [26, page 3326] : "We thus recognize that 'elements of prochirality' suffer from the same lack of correspondence to local symmetry characteristics as 'elements of chirality'. This problem can be easily avoided if the usage of 'prochirality' with reference to prostereoisomerism is altogether abandoned, and such a course of action seems at least worthy of consideration." The present article is devoted to clarify further that the term "prostereoisomerism" used in this citation should be replaced by a more discriminating term *pro-RS-stereogenicity*.

Changing "Prochirality" for Aspect 1 into "Prostereogenicity" To avoid this type of confusion, the term "prostereogenicity" or "prostereoisomerism" has been used to determine Aspect 1, where the term "prostereogenicity" (or "prostereoisomerism") is regarded as a superior concept over the term *prochiral* for determining Aspect 2 [5] , i.e.,

$$\text{“prostereogenicity” (“prostereoisomerism”)} \supset \textit{prochiral}. \tag{4}$$

Obviously, this inclusion relationship does not always hold true, because only Item 1 satisfies eq. 4 as found by comparing the 1st row with the 2nd row of Table 1.

In order to reinforce the solution by eq. 4, the term "prostereogenicity" (or "prostereoisomerism") has been linked with the term "stereoheterotopicity", which was defined as follows on the analogy of the dichotomy concerning stereoisomers (i.e., stereoisomers = enantiomers + diastereomers):

$$\text{stereoheterotopic} = \text{enantiotopic} + \text{diastereotopic (others)}, \tag{5}$$

where the right-hand side indicates a dichotomy for intramolecular relationships [27, 28] . Then the "stereoheterotopicity" defined by eq. 5 has been regarded as a criterion for determining Aspect 1 (the 2nd row of Table 1).

Note that the enantiotopic pair of p and $\overline{\text{p}}$ of **35** (Type IV according to the present classification) is not specified by *pro-R*/*pro-S*-descriptors (Item 2) as well as that the enantiotopic pair of p and $\overline{\text{p}}$ of **36** or **37** (Type V according to the present classification) is not specified by *pro-R*/*pro-S*-descriptors (Item 3). Because the enantiotopicity is a kind of stereoheterotopicity according to eq. 5, Items 2 and 3 indicate that the stereoheterotopicity is by no means a criterion for determining Aspect 1. As a result, *pro-R*/*pro-S*-descriptors specify several cases among pairs of enantiotopic ligands (Item 1) and several cases among pairs of diastereotopic ligands (Items 4 and 5), whereas Items 2 and 3 (enantiotopic cases) as well as remaining diastereotopic cases are not specified by *pro-R/pro-S*-descriptors. Hence, there has been no single criterion for determining Aspect 1 (i.e., what *pro-R/pro-S*-descriptors specifies), so long as we remain within the conventional terminology and we follow eq. 5.

Consequently, the difficulty in discriminating between Aspect 1 and Aspect 2 could not be avoided, even if the term "prostereogenicity" (or "prostereoisomerism") is used in place of the term "prochirality" of the original connotation [1] (eq. 4) and even if the term "stereoheterotopic" is used in place of the set of terms "enantiotopic" and "diastereotopic" (eq. 5). In other words, so long as we rely on the conventional terminologies, we have been unable to find a more proper term to take the place of the term "prochirality" of the original connotation [1] .

Modification of "Prochirality" To avoid the difficulty described in the preceding paragraphs, the definition of the term "prochirality" has been modified in accord with eqs. 4 and 5 as follows:

> Def. 1 ("Prochirality" [6]) "A term referring to the existence of stereoheterotopic ligands or faces in a molecule, such that appropriate replacement of one such ligand or addition to one such face in an achiral precursor gives rise to chiral products. . . ."

Although Def. 1 contains the term "stereoheterotopic", the presence of the phrase "such that appropriate replacement of one such ligand or addition to one such face in an achiral precursor gives rise to chiral products" indicates that Item 4 (a chiral precursor) and Item 5 (an achiral precursor into an achiral product) are recognized not to be "prochiral (Def. 1)". Thereby, Items 1, 2, and 3 are recognized to be "prochiral (Def. 1)", while Items 4 and 5 are recognized not to be "prochiral (Def. 1)". This conclusion is the same as that of "enantiotopicity (original). Even if an enantiotopic relationship (in a purely geometrical meaning) is replaced by the relationship "stereoheterotopic" in Def. 1, the term "prochiral (Def. 1)" would give the same result as no such replacement (cf. the first row of Table 1).

The "prochiral (Def. 1)" is obviously inconsistent with the original connotation of the term "prochirality" described by Hanson [1] (the 2nd row of Table 1) even if eqs. 4 and 5 are taken into consideration. This is because that the decision is done under Def. 1 in which the *enantiotopicity* contained in the "stereoheterotopicity" is used in a purely geometrical meaning. Hence, the *enantiotopicity* has been modified as follows:

> Def. 2 ("Enantiotopic" ligands and faces [6]) "Homomorphic ligands in constitutionally equivalent locations that are related by a symmetry plane (or

> center or alternating axis of symmetry) but not by a (simple) symmetry axis. Replacement of one or the other enantiotopic ligand by a new ligand produces enantiomers. . . ."

The term "enantiotopic (Def. 2)" is not the same as the term *enantiotopic* in a purely geometrical meaning [10] . Item 1 is recognized to be "prochiral (Defs. 1 & 2)" on the same line as "prochiral (Def. 1). According to the presence of the term "homomorphic" in Def. 2, however, Items 2 and 3 are recognized not to be "prochiral (Defs. 1 & 2)", whereas they are "prochiral (Def. 1)" as shown in Table 1. Items 4 and 5 are recognized not to be "prochiral (Def. 1)" as well as not to be "prochiral (Defs. 1 & 2)", although their symmetrical characteristics are different.

Because the term "prochiral (Defs. 1 & 2)" covers Item 1 only among the items which the original connotation of the term "prochirality" described by Hanson [1] has intended to cover (the 2nd row of Table 1), one can say that the term "prochiral (Defs. 1 & 2)" is partially successful to abstract items for Aspect 2 (i.e., Item 1) from those for Aspect 1 (i.e., Items 1, 4, and 5). If we rename the term "prochirality (original)" as "prostereogenicity", and the term "prochiral (Defs. 1 & 2)" is regarded as a new "prochiral", the inclusion relationship (eq. 4) is seemingly satisfied. However, the other items for Aspect 2 (i.e., Items 2 and 3) are nullified by the term "prochiral (Defs. 1 & 2)", because the term *enantiotopic* in a purely geometrical meaning [10] is transmuted into Def. 2. Note that the term "enantiotopicity (Def. 2)" accepts Item 1 only and repels Items 2 and 3. This result is rather inconsistent to such an action that Def. 1 contains the phrase "appropriate replacement of one such ligand or addition to one such face in an achiral precursor gives rise to chiral products". This phrase is more suitable to the term "enantiotopicity (original)", which adopts Items 1, 2, and 3 because of its purely geometrical meaning.

Alternative Modification of "Prochirality" Suppose that Def. $1'$ is obtained from Def. 1 by deleting the phrase "appropriate replacement of one such ligand or addition to one such face in an achiral precursor gives rise to chiral products". The procedure based on Def. $1'$ ("prochiral (Def. $1'$)") is equivalent to that described in the IUPAC recommendations [2, 29] , where the concept "enantiotopic" contained in the term "stereoheterotopic" is regarded as being equivalent to the "enantiotopicity (original)" [10] . As a result, Items 2 and 3 along with Items 1, 4, and 5 are also regarded as "prochiral (Def. $1'$)".

By the combined use of Defs. $1'$ and 2, we can select Items 1, 4, and 5 to be "prochiral (Defs. $1'$ & 2)" so that Aspect 1 would be ascribed to the "stereoheterotopicity" (eq. 5) combined with "enantiotopicity (Def. 2)". Thereby, one may say that Items 1, 4, and 5 are characterized by *pro-R*/*pro-S*-descriptors (Aspect 1) because of "stereoheterotopicity" (eq. 5), while Items 2 and 3 are not characterized by *pro-R*/*pro-S*-descriptors (Aspect 1) because of being not "stereoheterotopic" (eq. 5).

No Plausible Solutions Within Conventional Terminologies As found in the complicated discussions described above, the conventional terminologies involve sources of confusion (Table 1). The term "prochirality (Def. 1)", if the *enantiotopicity* in a purely geometrical meaning is used in place of the "stereoheterotopicity", properly explain Aspect 2, i.e., the term *prochirality* in a purely geometrical meaning. However, it gives no sound basis to Aspect 1. On the other hand, the term "prochirality (Defs. 1 & 2)" partly explain Aspect 2 (only for Item 1) in a consistent fashion with Aspect 1. However, it gives no sound basis to the total features of Aspect 2.

A key of arriving at a plausible solution has been reported to develop a pair of terms, i.e., prochiral (for Aspect 2) and pro-RS-stereogenic (for Aspect 1), on the basis of a pair of terms for characterizing orbits in a molecule, i.e., enantiospheric and RS-enantiotropic [8] . The present article is devoted to obtain an alternative approach to the key on the basis of a pair of terms for intramolecular relationships, i.e., enantiotopic and RS-diastereotopic. This course is in a parallel way to the development of a pair of terms, i.e., chiral and RS-stereogenic, on the basis of a pair of terms for intermolecular relationships, i.e., enantiomeric and RS-diastereomeric.

4 Prochirality and Pro-RS-Stereogenicity

4.1 Sphericities and RS-Tropicities

In the present approach, we take account of five types of promolecules listed in Fig. 1. The categorization of the five types are based on chiral/achiral, RS-stereogenic/RS-astereogenic, and scleral/ascleral. The pair of terms *chiral/achiral* is correlated to the concept *prochirality*, while the pair of terms *RS-stereogenic/RS-astereogenic* is correlated to the concept *pro-RS-stereogenicity*. Obviously, achiral nature (for Types IV and V) is a necessary condition for exhibiting prochirality, while RS-*a*stereogenic nature (for Types II and IV) is a necessary condition for exhibiting pro-RS-stereogenicity.

1. *Prochirality* specifies Aspect 2, where achiral promolecules (Type IV and V) are converted into chiral promolecule (Type I, II, III). Among the promolecules listed in Fig. 1, we find at least the following three cases:
    (a) (Type IV into Type I): the two A's of **34** (cf. Item 1),
    (b) (Type IV into Type II): any pair of p and $\overline{\mathrm{p}}$ selected from the set of {p, p, $\overline{\mathrm{p}}$, $\overline{\mathrm{p}}$} of **33** (cf. Item 2), and the pair of p and $\overline{\mathrm{p}}$ of **35** (cf. Item 2),

   (c) (Type V into Type III): the pair of p and $\overline{\mathrm{p}}$ of **36** and the pair of p and $\overline{\mathrm{p}}$ of **37** (Item 3).

2. *Pro-RS-stereogenicity* specifies Aspect 1, where *RS*-astereogenic promolecules (Type II and IV) to *RS*-stereogenic (Type I, III, and V). Among the promolecules listed in Fig. 1, we find at least the following three cases:
   (a) (Type IV into Type I): the two A's of **34** (cf. Item 1),
   (b) (Type II into Type III): the two A's of **10**, the two A's of **11**, the two p's of **12**, the two p's of **13**, the two p's of **14**, the two p's of **15**, the two p's of **16**, and the two p's of **17** (cf. Item 4),
   (c) (Type IV into Type V): the two A's of **35** (cf. Item 5)

Logically speaking, there is a case of converting Type IV into Type III, which can be regarded as a combined case: Type IV → Type II → Type III or Type IV → Type V → Type III.

The original formulation [8] have been based on orbits (equivalence classes) according to Fujita's USCI (unit-subduced-cycle-index) approach [12] , where the pair of terms *chiral/achiral* and the pair of terms *RS-stereogenic/RS-astereogenic* as keys for defining *prochirality* and *pro-RS-stereogenicity*, respectively.

After defining the sphericity of an orbit (a homospheric orbit, an enantiospheric orbit, a hemispheric orbit), the term *enantiospheric* has been used to determine the term *prochirality* without deriving the topicity terms [12, 23] , as shown in Fig. 2 (the sphericity criterion). Even if the determination of prochirality is conducted through the term *enantiotopic* by either of the two membership criteria (cf. Refs. [12, 22, 23] or Refs. [24, 25]), the importance of the sphericity concept is common so as to introduce the term *enantiotopic*, as illustrated in the upper half part of Fig. 2. Note that the term *enantiospheric* is an attributive term characterizing the nature of an orbit at issue, while the term *enantiotopic* is a relational term characterizing a symmetrical relationship between two sites in a molecule.

On the same line as the sphericity concept introduces the attributive term *enantiospheric* to define prochirality, the *RS*-tropicity of an orbit (an *RS*-homotropic orbit, an *RS*-enantiotropic orbit, an *RS*-hemitropic orbit) can be used to determine *pro-RS-stereogenicity* through the attributive term *RS-enantiotropic*, as illustrated in the bottom half part of Fig. 2 (the *RS*-tropicity criterion) [8] .

By inspection of Fig. 2, we are aware of a parallelism between the upper half part and the bottom half one. Hence, on the same line as the sphericity concept [23, 12] is correlated to the other criteria for determining prochirality as shown in the upper half,

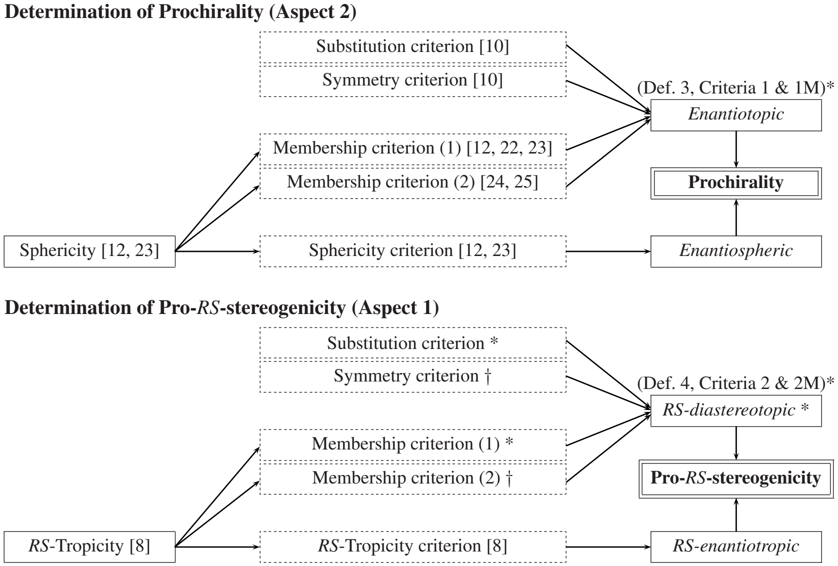

Figure 2: Various Methods for Determining Prochirality and Pro-RS-stereogenicity. The substitution criterion (Criterion 2) and the membership criterion (Criterion 2M) marked with an asterisk (*) is developed in the present work after the coinage of the term *RS-diastereotopic* by using stereoisograms. On the same line, the term *enantiotopic* is redefined by Def. 3 and Criteria 1 & 1M (marked with an asterisk) on the basis of stereoisograms. The methods marked with a dagger (†) will be reported in future reports.

the RS-tropicity concept [8] is capable of generating counterpart criteria for determining pro-RS-stereogenicity (i.e., the substitution criterion, the symmetry criterion, and the membership criteria). To accomplish such a new terminology, we shall coin a relational term *RS-diastereotopic*, which is correlated to the attributive term *RS-enantiotropic*, as described in the next subsection. Thereby, the pair of relational terms *enantiotopic/RS-diastereotopic* (Fig. 2) will be adopted in place of the conventional pair of relational terms "enantiotopic/diastereotopic".

4.2 Enantiotopicity and RS-Diastereotopicity

Because the direct use of the substitution criterion does not require the afore-mentioned paradigm shift from relationships to equivalence classes (orbits), it would be convenient if one intends to pursue qualitative applications only. Hence, the present paper is devoted to develop the substitution criterion for determining pro-RS-stereogenicity and to discuss the combined use of it with the substitution criterion for determining prochirality.

To discuss prochirality, we first define the term *enantiotopic* by using the substitution criterion, which is essentially equivalent to the original definition [10] .

> **Def. 3** (Enantiotopic relationship) Relationship between two ligands (or objects) in a molecule, where replacement of one or the other ligand (or object) by a new ligand (or a new object) produces either one of enantiomers.

This relationship is concerned with two members of an enantiospheric orbit in an original context [23, 12] . It should be noted that the enantiomers are distinctly specified by using a stereoisogram [17, 18] .

To discuss pro-RS-stereogenicity, on the other hand, we define the term *RS-diastereotopic* by using the substitution criterion as follows:

> **Def. 4** (RS-Diastereotopic relationship) Relationship between two ligands (or objects) in a molecule, where replacement of one or the other ligand (or object) by a new ligand (or a new object) produces either one of RS-diastereomers.

This relationship is concerned with two members of an RS-enantiotropic orbit in an original context [8] . It should be noted that the RS-diastereomers are distinctly specified by using a stereoisogram [17, 18] .

Logically speaking, there should exist an intramolecular relationship that corresponds to a holantimeric relationship. Hence we define the term *holantitopic* by using such a substitution criterion as defined in a similar way to Defs. 4 and 5. However, the term *holantitopic* is not so effective in comparison with the terms *enantiotopic* (Def. 3) and *RS-diastereotopic* (Def. 4).

To demonstrate Defs. 3 and 4 in a diagrammatical fashion, we examine a conversion of a Type IV stereoisogram (the left of Fig. 3) into a Type I stereoisogram (the right of Fig. 3), where the conversion comes from the substitution of deuterium. The left stereoisogram of Fig. 3 shows that ethanol (**38**) belongs to Type IV, i.e., achiral/RS-astereogenic/ascleral $[a, a, a]$. The right stereoisogram of Fig. 3 shows that S-1-D-ethanol (**39**) or R-1-D-ethanol ($\overline{\textbf{39}}$) belongs to Type I, i.e., chiral/RS-stereogenic/ascleral $[-, -, a]$.

1. By the comparison between the two stereoisograms, we find that the self-RS-diastereomeric relationship (═○═) in the horizontal direction of the left stereoisogram is converted into the RS-diastereomeric relationship (←○→) in the right stereoisogram. Let us focus our attention on the methylene hydrogens in ethanol (**38** or **38**′) and the set of {H, D} in S-1-D-ethanol (**39**) or R-1-D-ethanol ($\overline{\textbf{39}}'$). Thereby, the intermolecular conversion depicted in the horizontal direction of Fig. 3 can be interpreted as the RS-diastereotopic relationship between the two hydrogens on the methylene of ethanol (**38**) in agreement with Def. 4.

   Compare **38** with S-1-D-ethanol (**39**). This comparison is regarded as the procedure of the substitution criterion for determining pro-RS-descriptors. Thereby, the H_S of **38** is assigned to *pro-S*-configuration. Compare **38**′ with R-1-D-ethanol ($\overline{\textbf{39}}'$). Thereby, the H_R of **38**′ (or also the corresponding hydrogen in **38**) is assigned to *pro-R*-configuration.

2. On the other hand, the self-enantiomeric relationship (═●═) in the vertical direction of the left stereoisogram is converted into the enantiomeric relationship (←●→) in the right stereoisogram. Let us again focus our attention on the methylene hydrogens in ethanol (**38** or **38**″) and the set of {H, D} in S-1-D-ethanol (**39**) or R-1-D-ethanol ($\overline{\textbf{39}}$), where our attention is put in vertical direction. Thereby, the intermolecular conversion depicted in the vertical direction of Fig. 3 can be interpreted as the enantiotopic relationship between the two hydrogens on the methylene of ethanol (**38**) in agreement with Def. 3.

   Compare **38** with S-1-D-ethanol (**39**) and compare **38**″ with R-1-D-ethanol ($\overline{\textbf{39}}$). Each comparison is regarded as the procedure of the substitution criterion for determining prochirality. Thereby, the H_S of **38** assigned to *pro-S* and the H_R of **38**′ (or also the corresponding hydrogen in **38**) assigned to *pro-R* are determined to be enantiotopic so that ethanol has prochiral nature.

As found in Fig. 3, this example demonstrates the features of Item 1 described above, where the two hydrogens on the methylene of ethanol (**38**) is in an RS-diastereotopic relationship as well as in an enantiotopic relationship. The capability of giving *pro-R*/*pro-S*-descriptor (Aspect 1) for ethanol stems from the RS-diastereotopic relationship, while

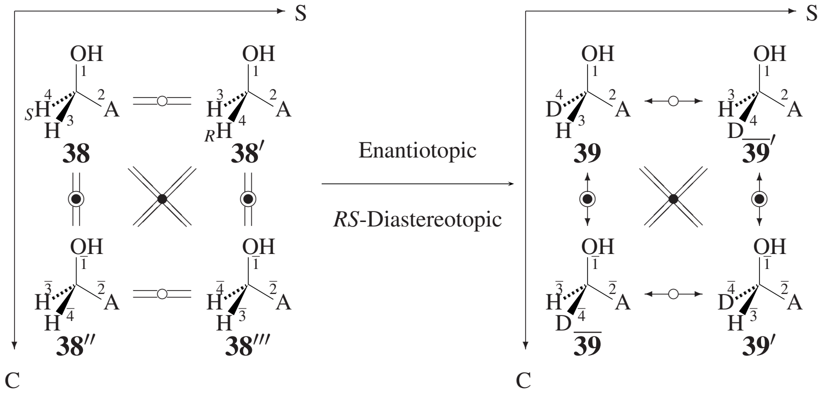

Figure 3: Conversion of a Type IV stereoisogram into a Type I stereoisogram, which denotes the enantiotopic and *RS*-diastereotopic relationship between the methylene hydrogens in ethanol, where A = CH_3.

the capability of participating in asymmetric synthesis (Aspect 2) for ethanol stems from the enantiotopic relationship. Although the discrimination between the two relationships is clear, it is not always clear which of the two relationships corresponds to prochirality or pro-*RS*-stereogenicity. Hence, we should examine a further example.

For this purpose, let us examine a conversion of a Type II stereoisogram (the left of Fig. 4) into a Type III stereoisogram (the right of Fig. 4). The left stereoisogram of Fig. 4 shows that *R*-glyceraldehyde (**40**) belongs to Type II, i.e., chiral/*RS*-astereogenic/scleral $[-, a, -]$, where we put p = CH(OH)CH=O-*R*. The right stereoisogram of Fig. 4 shows that **41** (or **42**) belongs to Type III, i.e., chiral/*RS*-stereogenic/scleral $[-, -, -]$.

1. Let us compare the two stereoisograms in Fig. 4. Then, we find that the self-*RS*-diastereomeric relationship (═○═) in the horizontal direction of the left stereoisogram is converted into the *RS*-diastereomeric relationship (←○→) in the right stereoisogram. By focusing our attention on the methylene hydrogens, we find that those in the glyceraldehyde (**40** or **40′**) are converted into the set of {H, D} in the *S*-derivative (**41**) or *R*-derivative (**42**). Thereby, the intermolecular conversion depicted in the horizontal direction of Fig. 4 can be interpreted as the *RS*-diastereotopic relationship between the two hydrogens on the methylene of the glyceraldehyde (**40**) in agreement with Def. 4. The *RS*-diastereotopic relationship indicates that the H_S of **40** is assigned to *pro-S*-configuration while the H_R of **40′** (or also the corresponding hydrogen in **38**) is assigned to *pro-R*-configuration.

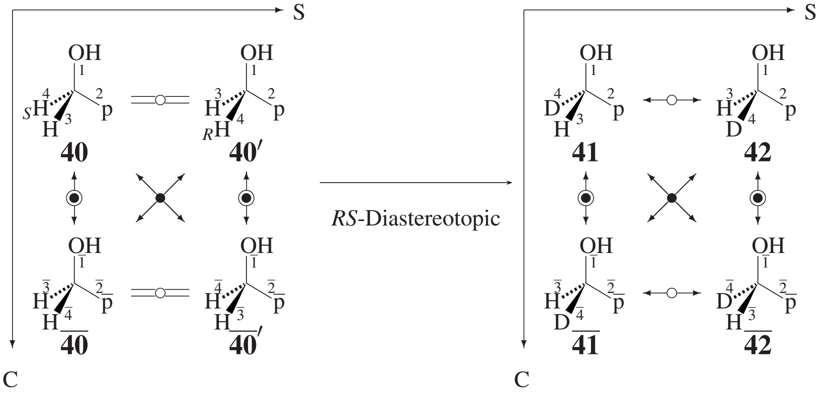

Figure 4: Conversion of a Type II stereoisogram into a Type III stereoisogram, which denotes the *RS*-diastereotopic relationship between the methylene hydrogens in *R*-glyceraldehyde, where p = CH(OH)CH=O-*R*.

2. On the other hand, the enantiomeric relationship (←◉→) in the vertical direction of the left stereoisogram of Fig. 4 means that **40** is already chiral and does not exhibit prochirality. Note that **40** and $\overline{\mathbf{40}}$ are enantiomeric, where p of **40** and $\overline{\mathrm{p}}$ of $\overline{\mathbf{40}}$ are not equivalent under the $\mathbf{T}$-symmetry. The two methylene hydrogens of **40** are not interchanged by any symmetry operations contained in the $\mathbf{T}_d$-symmetry of a tetrahedral skeleton.

The comparison of Fig. 3 with Fig. 4 clearly demonstrates that the capability of giving *pro-R*/*pro-S*-descriptors (Aspect 1) comes from pro-*RS*-stereogenicity linked with *RS*-diastereotopicity. In particular, Fig. 3 shows that the methylene hydrogens are in an *RS*-diastereotopic relationship and at the same time in an enantiotopic relationship. This fact is a source of confusion that the enantiotopic relationship has been erroneously ascribed to the capability of giving *pro-R*/*pro-S*-descriptors (Aspect 1), as exemplified in the comments on Defs. 1 and 2.

5 Substitution Criteria for Prochirality and for Pro-RS-Stereogenicity

5.1 Substitution Criteria Based on Stereoisograms

The idea described in Figs. 3 and 4 can be modified into a more intuitive format. In accord with Defs. 3 and 4, we obtain the *substitution criteria based on stereoisograms* as follows:

Criterion 1 (Substitution Criterion for Prochirality Through Enantiotopicity)
The substitution criterion after a rightward (or leftward) access to a stereoisogram indicates that, if two proligands to be tested are substituted to give enantiomers, they are *enantiotopic* so as to exhibit *prochiral* nature.

Criterion 2 (Substitution Criterion for Pro-RS-stereogenicity Through RS-Diastereotopicity)
On the other hand, the substitution criterion after a downward (or upward) access to a stereoisogram indicates that, if two proligands to be tested are substituted to give RS-diastereomers, they are *RS-diastereotopic* so as to exhibit *pro-RS-stereogenic* nature.

We select **38** from the left stereoisogram of Fig. 3, which is regarded as a starting promolecule. Thereby, Fig. 3 is modified into Fig. 5. By applying Criterion 1 rightward to the C-axis, Fig. 5 shows the enantiotopicity between H_α and H_β so that **38** exhibits prochirality. By applying Criterion 2 downward to the S-axis, Fig. 5 shows the RS-diastereotopicity between H_α and H_β so that **38** exhibits pro-RS-stereogenicity.

By selecting **40** from the left stereoisogram of Fig. 4 as a starting promolecule, Fig. 4 is modified into Fig. 6. By applying Criterion 2 downward, Fig. 6 shows the RS-diastereotopicity between H_α and H_β so that **40** exhibits RS-stereogenicity. On the other hand, Criterion 1 cannot be applied to the stereoisogram of Fig. 6, so that **40** does not exhibit prochirality. Note that **40** is not directly converted into $\overline{\mathbf{41}}$, because of the difference between p and $\overline{\mathrm{p}}$.

As a further example, Fig. 7 shows the application of Criterion 1 to a pseudoasymmetric promolecule (**36**). Thereby, the pair of p and $\overline{\mathrm{p}}$ is in an enantiotopic relationship so that **36** exhibits prochirality. Because **36** is already RS-stereogenic, Criterion 2 cannot be applied to **36**. Hence, **36** exhibits no pro-RS-stereogenicity.

The promolecules surrounded by a box (Fig. 1) are examined by means of the substitution criteria (Criterion 1 and Criterion 2) based on stereoisograms in similar ways to Figs. 5–7. The results are summarized in Table 2, which involves precursors and products for Criteria 1 and 2 as well as prochirality and pro-RS-stereogenicity specified.

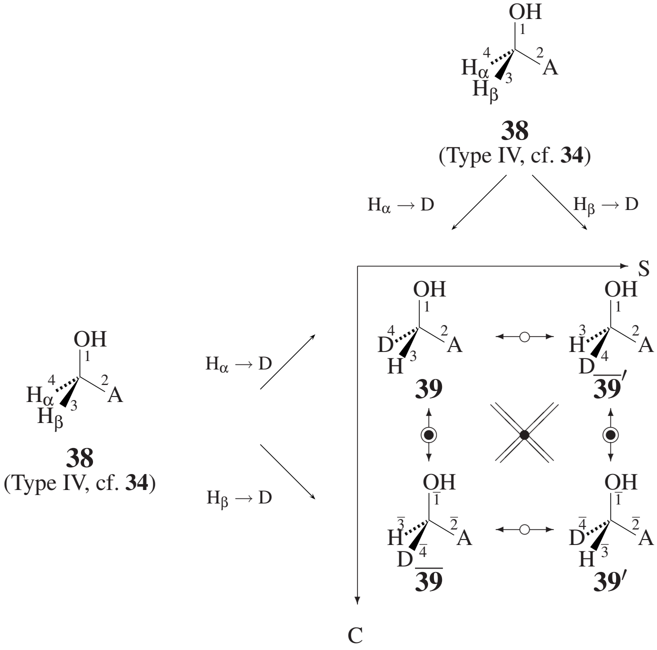

Figure 5: Conversion of **38** (Type IV $[a, a, a]$) into a pair of **39** and $\overline{\mathbf{39}}$ (Type I $[-, -, a]$), which shows the prochiral and pro-RS-stereogenic nature of the two hydrogens in **38**.

It would be worthwhile to mention that the term *holantitopic* is an exceptional case. For example, suppose that **1** is converted into **18** (or **19**), where we put Y $=$ COCH$_3$, for example. The conversion of the proligand Y (**1**) into the proligand p (**18**) implies that an inner enantiotopic relationship of Y (its two enantiotopic faces as a proligand in isolation) is considered to be an outer holantitopic relationship. This case can be directly discussed by focusing our attention to the inner enantiotopic relationship (in isolation), which can be regarded as an RS-diastereotopic in a molecule (cf. Fig. 9). At any rate, exceptional cases of this type are open to further investigations.

6 Membership Criteria for Prochirality and for Pro-RS-Stereogenicity

In the previous paper [8] , the sphericity criterion for prochirality and the RS-tropicity criterion for pro-RS-stereogenicity have been developed (cf. Fig. 2). These criteria should

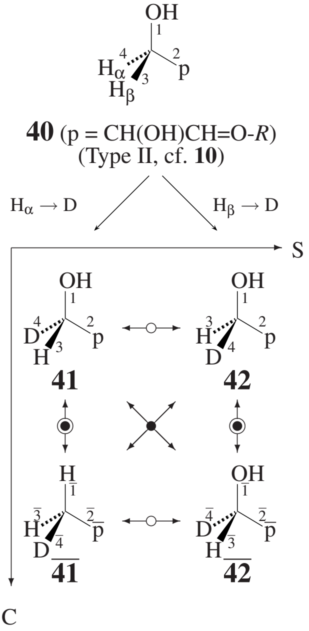

Figure 6: Conversion of **40** (Type II $[-, a, -]$) into a pair of **41** and **42** (Type III $[-, -, -]$), which shows the pro-RS-stereogenic nature of the two hydrogens in **40**.

be compared with the substitution criteria (Criteria 1 and 2) of the present article. As described in a previous paper [23] and a book [12] , the sphericities are related to topicity terms. In particular, an enantiospheric orbit corresponds to an enantiotopic relationship via a coset representation (CR). This correspondence is a basis of the membership criterion [22, 24] :

Criterion 1M (Membership Criterion for Prochirality via Enantiotopicity)

> Each member of one half of an enantiospheric orbit is determined to be *enantiotopic* to each member of the other half of the orbit. The orbit exhibits *prochiral* nature.

The symmetry criterion [10] and the substitution criterion [10] have been derived from the membership criterion [22, 24] .

On the same line, the RS-tropicities can be related to relational terms. Hence, the RS-tropicity criterion for pro-RS-stereogenicity can be used to develop the membership criterion for pro-RS-stereogenicity through the correspondence between RS-enantiotropic nature and an RS-diastereotopic relationship. That is to say:

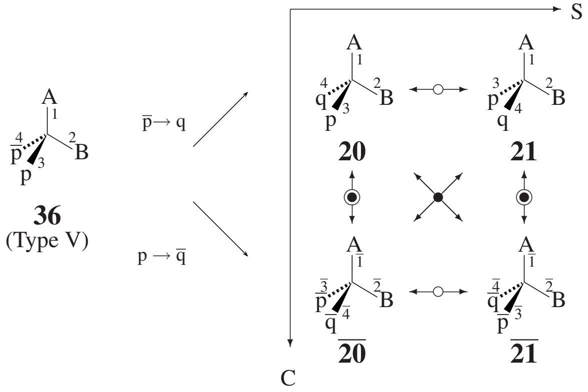

Figure 7: Conversion of **36** (Type V $[a, -, -]$) into a pair of **20** and $\overline{\mathbf{20}}$ (Type III $[-, -, -]$), which shows the prochiral nature of the p and $\overline{\text{p}}$ in **36**.

Criterion 2M (Membership Criterion for Pro-*RS*-stereogenicity via *RS*-Diastereotopicity)

Each member of one half of an *RS*-enantiotropic orbit is determined to be *RS-diastereotopic* to each member of the other half of the orbit. The orbit exhibits *pro-RS-stereogenic* nature.

By means of the membership criteria (Criteria 1M and 2M), let us reexamine the results (Table 2) derived by the substitution criteria (Criteria 1 and 2). The re-examination results are listed in Table 3.

The two A's of **10** construct an orbit governed by a coset representation (CR) which is characterized by a CR type $\frac{[-,a,-]}{[-,-,-]}$. The middle part $\frac{[a]}{[-]}$ of the CR type indicates that the orbit composed of the two A's is *RS*-enantiotropic so that the two A's are in an *RS*-diastereotopic relationship in terms of Criterion 2M. Because the two p's of **12** construct an orbit characterized by a CR type $\frac{[-,a,-]}{[-,-,-]}$, their *RS*-diastereotopic relationship is also determined by Criterion 2M. The other promolecules of Type II listed in Table 2 (**11** and **13**–**17**) have two-membered *RS*-enantiotropic orbits, whose members are also concluded to be in *RS*-diastereotopic relationships in terms of Criterion 2M.

The four-membered orbit $\{\text{p}, \text{p}, \overline{\text{p}}, \overline{\text{p}}\}$ appearing in **33** is characterized by a CR type $\frac{[a,a,a]}{[-,a,-]}$. The top part $\frac{[a]}{[-]}$ of the CR type indicates that the four-membered orbit is enantiospheric so that each pair of p and $\overline{\text{p}}$ is determined to be in an enantiotopic relationship in terms of Criterion 1M. The four-membered orbit exhibits *prochiral* nature.

The two A's of **34** construct an orbit governed by a coset representation (CR) which is characterized by a CR type $\frac{[a,a,a]}{[-,-,a]}$. The top part $\frac{[a]}{[-]}$ of the CR type indicates that the

Table 2: Substitution Criteria for Prochirality and Pro-RS-Stereogenicity of Tetrahedral Promolecules

substitution criteria		proligands	enantiotopic and/or RS-diastereotopic	prochiral and/or pro-RS-stereogenic	examples
precursor	product				
10	**18**, **19**	A_2	RS-diastereotopic	pro-RS-stereogenic	
11	**20**, **21**	A_2	RS-diastereotopic	pro-RS-stereogenic	
12	**20**, **21**	p_2	RS-diastereotopic	pro-RS-stereogenic	Fig. 6
13	**22**, **23**	p_2	RS-diastereotopic	pro-RS-stereogenic	
14	**24**, **25**	p_2	RS-diastereotopic	pro-RS-stereogenic	
15	**26**, **27**	p_2	RS-diastereotopic	pro-RS-stereogenic	
16	**26′**, **27′**	p_2	RS-diastereotopic	pro-RS-stereogenic	
17	**28**, **29**	p_2	RS-diastereotopic	pro-RS-stereogenic	
33	**15**	$(\mathrm{p}\overline{\mathrm{p}})_2$	enantiotopic	prochiral	
34	**1**	A_2	enantiotopic RS-diastereotopic	prochiral pro-RS-stereogenic	Fig. 5
35	**36**, **37**	A_2	RS-diastereotopic	pro-RS-stereogenic	
	11	p, $\overline{\mathrm{p}}$	enantiotopic	prochiral	
36	**20**, **21**	p, $\overline{\mathrm{p}}$	enantiotopic	prochiral	Fig. 7
37	**20**, **21**	p, $\overline{\mathrm{p}}$	enantiotopic	prochiral	

Table 3: Membership Criteria for Prochirality and Pro-RS-Stereogenicity of Tetrahedral Promolecules

precursor	orbit	CR type	sphericity and RS-tropicity	enantiotopicity and/or RS-diastereotopicity	prochirality and/or pro-RS-stereogenicity
10	A_2	$\frac{[-,a,-]}{[-,-,-]}$	hemispheric RS-enantiotropic	— RS-diastereotopic	— pro-RS-stereogenic
12	p_2	$\frac{[-,a,-]}{[-,-,-]}$	hemispheric RS-enantiotropic	— RS-diastereotopic	— pro-RS-stereogenic
33	$\mathrm{p}_2\overline{\mathrm{p}}_2$	$\frac{[a,a,a]}{[-,a,-]}$	enantiospheric RS-homotropic	enantiotopic —	prochiral —
34	A_2	$\frac{[a,a,a]}{[-,-,a]}$	enantiospheric RS-enantiotropic	enantiotopic RS-diastereotopic	prochiral pro-RS-stereogenic
35	A_2	$\frac{[a,a,a]}{[a,-,-]}$	homospheric RS-enantiotropic	— RS-diastereotopic	— pro-RS-stereogenic
	$\mathrm{p}\overline{\mathrm{p}}$	$\frac{[a,a,a]}{[-,a,-]}$	enantiospheric RS-homotropic	enantiotopic —	prochiral —
36	$\mathrm{p}\overline{\mathrm{p}}$	$\frac{[a,-,-]}{[-,-,-]}$	enantiospheric RS-hemitropic	enantiotopic —	prochiral —
37	$\mathrm{p}\overline{\mathrm{p}}$	$\frac{[a,-,-]}{[-,-,-]}$	enantiospheric RS-hemitropic	enantiotopic —	prochiral —

two-membered orbit is enantiospheric so that the two members A's are determined to be in an enantiotopic relationship in terms of Criterion 1M. At the same time, the middle part $\frac{[a]}{[-]}$ of the CR type indicates that the orbit is RS-enantiotropic so that the two A's are in an RS-diastereotopic relationship in terms of Criterion 2M. Hence, the two-membered orbit of A's in **34** exhibits prochiral and pro-RS-stereogenic characters.

The promolecule **35** has two kinds of orbits, i.e., a two-membered orbit of A_2 characterized by $\frac{[a,a,a]}{[a,-,-]}$ and a two-membered orbit $\{\mathrm{p}, \overline{\mathrm{p}}\}$ characterized by $\frac{[a,a,a]}{[-,a,-]}$. The former orbit of A's is RS-enantiotropic so that the two A's are in an RS-diastereotopic relationship, exhibiting pro-RS-stereogenic nature. The latter orbit $\{\mathrm{p}, \overline{\mathrm{p}}\}$ is enantiospheric so that the two members are in an enantiotopic relationship. The orbit exhibits prochiral nature.

The two-membered orbit $\{\mathrm{p}, \overline{\mathrm{p}}\}$ appearing in **36** (or **37**) is characterized by a CR type $\frac{[a,-,-]}{[-,-,-]}$. The top part $\frac{[a]}{[-]}$ of the CR type indicates that the two-membered orbit is enantiospheric so that the pair of p and $\overline{\mathrm{p}}$ is determined to be in an enantiotopic relationship in terms of Criterion 1M. Hence, the two-membered orbit exhibits *prochiral* nature.

The results obtained by the substitution criteria (Table 2) are identical with those obtained by the membership criteria (Table 3). However, they are different in their methodologies. The substitution criteria require two stereoisograms, i.e., one for a precursor (the left of Fig. 3) and the other for a product (the right of Fig. 3). In contrast, the membership criteria require only one stereoisogram for a precursor, because the sphericity and RS-tropicity criteria for deriving the membership criteria require only one stereoisogram for a precursor, as discussed in the previous article [8] . The latter fact implies that prochirality and pro-RS-stereogenicity are attributes of a promolecule through its stereoisogram.

7 Addition Criteria for Prochirality and for Pro-RS-Stereogenicity

The two faces of an aldehyde **43** are non-equivalent under chiral conditions to be capable of giving either one of enantiomers predominantly. Let us consider a hypothetical deuterium addition to the carbonyl group of **43** (Fig. 8). On the same line as the substitution criterion described for Fig. 5, we consider the downward access to the RS-diastereomeric relationship (←○→) of the S-axis. It follows that the two faces at issue are concluded to be RS-diastereotopic. On the other hand, the rightward access to the enantiomeric relationship (←◉→) of the C-axis shows that the two faces at issue are concluded to be enantiotopic at the same time.

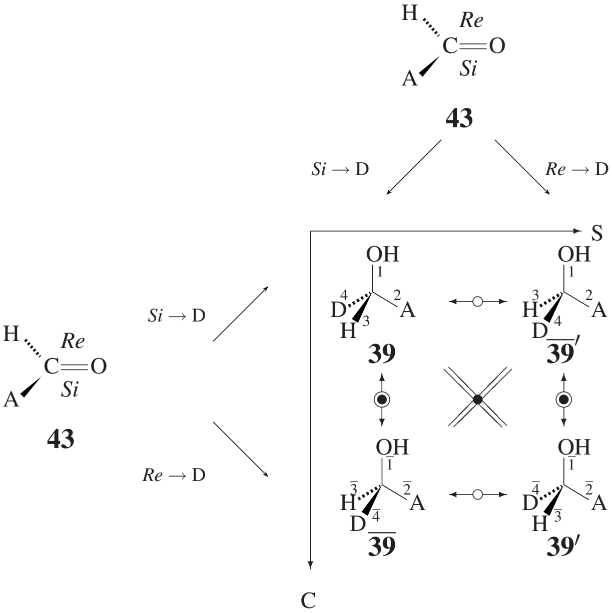

Figure 8: Conversion of **43** (Type IV $[a, a, a]$) into a pair of **39** and $\overline{\mathbf{39}}$ (Type I $[-, -, a]$), which shows the prochiral and pro-RS-stereogenic nature of the two faces in **43**.

The two faces of another aldehyde **44** are non-equivalent under achiral and chiral conditions to give either one of RS-diastereomers predominantly. Let us consider a hypothetical deuterium addition to the carbonyl group of **44** (Fig. 9). On the same line as the substitution criterion described for Fig. 6, we consider the downward access to the RS-diastereomeric relationship (←○→) of the S-axis. It follows that the two faces at issue are concluded to be RS-diastereotopic. On the other hand, the rightward access to the enantiomeric relationship (←◉→) of the C-axis is not permitted because $\overline{\mathrm{p}}$ is contained in $\overline{\mathbf{44}}$ in place of p contained in **44**.

Consequently, Fig. 8 and Fig. 9 show that the presence of an RS-diastereotopic relationship assures the capability of giving *Re*/*Si*-descriptors. Although Fig. 8 contains the enantiotopic relationship along with the RS-diastereotopic relationship, it is more plausible to adopt the RS-diastereotopic relationship for determining the capability of giving *Re*/*Si*-descriptors.

A view from the upper side of the aldehyde (**43**) with the priority “OH > A > H”, the upper-side face is determined to be *Re*. The priority of “face (D) > OH > A > H” gives an identical specification (*Re*), if the face attacked by D is regarded as a hypothetical

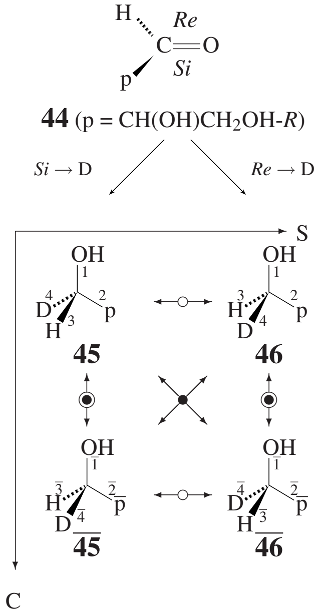

Figure 9: Conversion of **44** (Type II $[-, a, -]$) into a pair of **45** and **46** (Type III $[-, -, -]$), which shows the pro-RS-stereogenic nature of the two faces in **44**.

proligand. The attack of deuterium from the *Re*-face produces **39′** (the same as **39**) of R-configuration because of the priority "OH $>$ A $>$ D $>$ H".

It should be noted that an *Re*-descriptor for a precursor does not always correspond to an R-descriptor for a product. For example, suppose that the priority "face (H) $>$ OH $>$ A $>$ D" for another precursor ADC=O specifies *Re* in the addition of hydrogen (hydride). Then the priority for a product ("OH $>$ A $>$ D $>$ H") specifies an S-configuration. The present approach does not refer to which R or S (or *Re* or *Si*) is selected; but it is concerned with the capability of giving RS-descriptors or *Re*/*Si*-descriptors (Aspect 1).

8 Discussions

8.1 Stereoheterotopic vs. RS-Stereoheterotopic

In the present approach, too, the term *stereoheterotopic* is used in the same meaning as the conventional usage. However the term *stereoheterotopic* is redefined in connection with the present term *RS-stereoheterotopic*, which is newly coined to refer to a set of the three relationships collectively, i.e., enantiotopic (Def. 3), RS-diastereotopic (Def. 4), and holantitopic. On the analogy of eqs. 1 and 2, the present approach is based on the following inclusion relationship:

$$\begin{aligned}\text{stereoheterotopic} \quad &\supset \quad RS\text{-stereoheterotopic} && (6)\\ &= \quad \text{enantiotopic} + RS\text{-diastereotopic} + \text{holantitopic} && (7)\\ &\leftrightarrow \quad \text{prochiral} + \text{pro-}RS\text{-stereogenic} + \text{proscleral} && (8)\end{aligned}$$

where the term *holantitopic* (and *proscleral*) is not so effective because of being not so fully investigated. The inclusion relationship (eq. 6) can be alternatively represented by a dichotomy:

$$\text{stereoheterotopic} = RS\text{-stereoheterotopic} + \text{others}, \tag{9}$$

which is an analogy to the conventional dichotomy (eq. 5).

In summary, we obtain Fig. 10 to demonstrate the difference between the conventional terminologies and the present one. Obviously, eq. 9 contains the term *RS-stereoheterotopic* in place of the term *enantiotopic* contained in eq. 5. Moreover, the term *RS-stereoheterotopic* connotes the term *enantiotopic*, as shown in eq. 7. It follows that the term *RS-stereoheterotopic* is regarded as representing an intermediate concept between “stereoheterotopic” and “enantiotopic”.

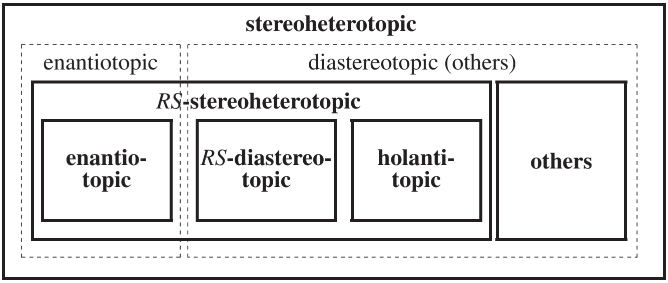

Figure 10: Conventional terminology vs. the present terminology for topicities. A broken-lined box represents a term of the conventional terminology, while a solid-lined box represents a term of the present terminology.

8.2 Diastereotopicity/Prostereoisomerism vs. RS-Diastereotopicity/Pro-RS-stereoisomerism

The stereochemical convention has treated stereoheterotopic and enantiotopic in terms of eq. 5. This means that the term "diastereotopic" corresponds to the residual part of stereoheterotopicity minus enantiotopicity. Hence, the connotation of the term "diastereotopic" has not been fully specified. Moreover, the term "enantiotopic" has suffered from such a verbal transmutation as found in Def. 2.

In contrast, the present approach takes account of the term *RS-stereoheterotopic*, which is defined strictly in terms of stereoisograms. Moreover, the term *RS-diastereotopic* along with the term *enantiotopic* is defined strictly in terms of stereoisograms. Thereby, the term *RS-diastereotopic* is linked with Aspect 1 in a rigorous fashion.

The stereochemical convention has treated prostereoisomerism and prochirality in terms of eq. 4. The concept of "prostereoisomerism" contained in eq. 4 has not been defined strictly. In fact, the term "prostereoisomerism" has been used in place of the term "prochirality", only because the term "prochirality" turned out to be unsuitable and caused serious confusion.

8.3 Comments on Items 1–5

Merits of the Present Terminology Once we adopt Def. 3 for enantiotopic relationships, Items 1–3 described above can be treated properly in terms of *prochirality*, as shown in the bottom part of Table 1. The *prochirality* defined in a purely geometrical meaning is revitalized by the present formulation based on stereoisograms so as to treat Aspect 2.

Once we adopt Def. 4 for RS-diastereotopic relationships, Items 4 and 5 as well as Item 1 can be treated properly in terms of *pro-RS-stereogenicity*, as shown in the bottom part of Table 1. The term *pro-RS-stereogenicity* is also defined on the basis of stereoisograms so as to provide us with a new methodology for manipulating Aspect 1.

Table 2 combined with Fig. 1 indicates all cases of tetrahedral promolecules which exhibit *prochirality* and/or *pro-RS-stereogenicity*. The present concept *pro-RS-stereogenicity* is narrower than the conventional concept *prostereogenicity* but provides us with a more powerful method for comprehending stereochemistry. Thus, the present concept *pro-RS-stereogenicity* is capable of handling all of the features which the conventional concept *prostereogenicity* has intended to cover.

Conventional Terminologies to be Abandoned It is to be noted that Item 1 belongs to Aspect 1 as well as to Aspect 2. This situation is symbolically represented as follows:

$$\text{Aspect 1} \cap \text{Aspect 2} = \{\text{Items 1, 4, 5}\} \cap \{\text{Items 1, 2, 3}\} = \{\text{Item 1}\}. \qquad (10)$$

It follows that we obtain Aspect 1 $\supset$ {Item 1}. However, the conventional terminologies seem to have adopted an erroneous presumption Aspect 2 = {Item 1} because Item 1 has been emphasized as a main subject to be discussed for Aspect 2. As a result, the inclusion relationship Aspect 1 $\supset$ ({Item 1} =) Aspect 2 has been erroneously adopted in place of eq. 10. Hence, we can safely say that this misunderstanding has caused the confusion on "prochirality".

Among the conventional terminologies listed in Table 1, the "prochirality (Def. 1 & 2)" has been mainly used in biochemistry (as well as chemistry), because Item 1 has been a main subject to be discussed in most cases. The previous decisions of "prochirality" on Item 1 in terms of the "prochirality (Def. 1 & 2)" are not changed even if we adopt the present terms *prochirality* and *pro-RS-stereogenicity.*

However, the "prochirality (Def. 1 & 2)" has conceptual drawbacks as discussed in the preceding sections (Table 1). It is worthwhile to add comments on it.

1. If we adopt the "prochirality (Def. 1 & 2)" (covering Item 1) as well as the "prochirality (original)" after renamed as "prostereogenicity" (covering Items 1, 4, and 5), the inclusion relationship (eq. 4) is seemingly satisfied. The inclusion relationship (eq. 4) implies another inclusion relationship, i.e., Aspect 1 $\supset$ Aspect 2, where an erroneous presumption Aspect 2 = {Item 1} is adopted in place of eq. 10. The inclusion relationship (Aspect 1 $\supset$ Aspect 2) does not hold true because Aspect 2 involves Items 2 and 3 along with Item 1. Hence, eq. 4 should be abandoned.

2. The "prochirality (Def. 1 & 2)" refers to the case of Items 2 and 3 (prochiral in a geometrical meaning) and the case of Items 4 and 5 ("prochiral (original)") as being not "prochiral (Def. 1 & 2)", although the two cases have no common symmetrical characteristics. Thus they are accidentally categorized into a single class by the transmuted definition of "enantiotopicity" (Def. 2). For the present interpretation, see eq. 10.

Consequently, it is strongly advisable to abandon the usage of the "prochirality (Def. 1 & 2)". The adoption of this course would not depend on whether or not one has mathematical skills necessary for full understanding the previous formulation [8] . By the present formulation, the terms *enantiotopicity* (Def. 3) and *RS-diastereotopicity* (Def. 4) are introduced diagrammatically by using stereoisograms. Thereby, the present terminology (Table 1) provides us with a succinct tool for treating Aspects 1 and 2 properly.

9 Conclusion

In a previous paper [8] , prochirality and pro-RS-stereogenicity have been defined by combining the sphericity concept and the RS-tropicity concept, where attributive terms of orbits (homospheric, enantiospheric, and hemispheric; as well as RS-homotropic, RS-enantiotropic, and RS-hemitropic) have been employed. In contrast, the present paper has emphasized relational terms which specify relationships between two objects (ligands etc.). Thus, enantiotopic relationships, RS-diastereotopic relationships, and holantitopic relationships are employed to specify prochirality, pro-RS-stereogenicity, and prosclerality. By developing the substitution criterion for enantiotopicity and the substitution criterion for RS-diastereotopicity on the basis of stereoisograms, the relational terms are linked to the corresponding terms for specifying RS-stereoisomerism: i.e., enantiomeric relationships for chirality, RS-diastereomeric relationships for RS-stereogenicity, and holantimeric relationships for sclerality. The membership criteria for enantiotopicity and for RS-diastereotopicity are also developed to correlate the present substitution criteria to the previous methods [8] . Then, the difference between "stereoheterotopic" of conventional usage and *RS-stereoheterotopic* of the present approach is discussed in connection with the difference between "prostereoisomerism" and the present term *pro-RS-stereoisomerism* as well as between "diastereotopicity" and the present term *RS-diastereotopicity.* The addition criteria for prochirality and for pro-RS-stereogenicity are also developed to discuss two faces of a carbonyl ligand.

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[9] The assignments of configurations shown in Fig. 1 of our previous article [8] should be corrected for **2** (or **4**) and $\overline{\mathbf{2}}$ (or $\overline{\mathbf{4}}$). The configuration at the 3-carbon of **2** (or **4**) should be read as R, while the configuration at the 3-carbon of $\overline{\mathbf{2}}$ (or $\overline{\mathbf{4}}$) should be read as S. In spite of these corrections, the discussions in the text of the previous paper [8] hold true.

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[19] Conventionally, the term *achiral* (an attributive term) has been used in place of a newly coined term *self-enantiomeric* (a relational term), although the term *achiral* should be paired with the attributive term *chiral*. Note that an expression “a chiral compound” is permitted if the compound is given; and, on the same line, an expression “an achiral compound” is permitted if the compound is given. In contrast, an expression “an enantiomeric compound” is permitted only if a pair of two compounds having opposite configurations are given; and, as a result, there is no relational term for denoting an achiral compound. The coinage of the term *self-enantiomeric* as a relational term provides us with consistent terminology for discriminating between relational terms and attributive terms [30] .

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[21] Strictly speaking, if the term *enantiomerism* is paired with the term *self-enantiomerism*, it has the same meaning as the attributive term *chirality* paired

with the term *achirality*. The term *handedness* is also used as a rather attributive term which is derived from rather relational terms *right-handed* and *left-handed*. In this case, it is difficult to find a term corresponding to the term *achirality*. We may coin *both-handedness* as such an attributive term.

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[29] The third definition of the term *prochiral* by the IUPAC recommendations (1996) [2] states: “The term prochiral also applies to a tetrahedral atom of an achiral or chiral molecule which is bonded to two stereoheterotopic groups.” The term *enantiotopic* is defined by the IUPAC recommendations (1996) as follows [2] : “Constitutionally identical atoms or groups in molecules which are related by symmetry elements of the second kind only (mirror plane, inversion centre or rotation-reflection axis). . . .” This definition is identical with the enantiotopicity in a purely geometrical meaning.

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