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Stereoisograms for Specifying Chirality and *RS*-Stereogenicity. A Versatile Tool for Avoiding the Apparent Inconsistency Between Geometrical Features and *RS*-Nomenclature in Stereochemistry

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Abstract

The versatility of stereoisograms has been discussed in order to comprehend terms related to stereoisomerism. Each stereoisogram characterizes three kinds of relationships (an enantiomeric, an *RS*-diastereomeric, and a holantimeric relationship), which collectively formulate *RS*-stereoisomerism. In contrast to the inclusion relationship of conventional usage, i.e.,

stereoisomerism $\supset$ enantiomerism,

the *RS*-stereoisomerism is an intermediate concept which is located between the stereoisomerism and the enantiomerism so as to give a revised inclusion relationship

as follows:

$$\begin{aligned} \text{stereoisomerism} &\supset \textit{RS}\text{-stereoisomerism} \\ &= \text{enantiomerism} + \textit{RS}\text{-diastereomerism} + \text{holantimerism} \end{aligned}$$

Among the three relationships, the enantiomeric relationship is related to chirality. In addition, the *RS*-diastereomeric relationship is related to *RS*-stereogenicity, which is concluded to determine the capability of giving *RS*-descriptors of the CIP system. *RS*-stereogenic promolecules are categorized into Type I (chiral/*RS*-stereogenic/ascleral), Type III (chiral/*RS*-stereogenic/scleral), and Type V (achiral/-*RS*-stereogenic/scleral) by means of stereoisograms. On the other hand, *RS*-*a*stereogenic promolecules are categorized into Type II (chiral/*RS*-astereogenic/scleral) and Type IV (achiral/*RS*-astereogenic/ascleral). The differences between conventional concepts and the present ones (e.g., stereoisomers vs. *RS*-stereoisomers and diastereomeric relationships vs. *RS*-diastereomeric ones) have been discussed by clarifying implications of stereochemical conventions. Combined use of two or more stereoisograms is discussed to examine compounds having multiple *RS*-stereogenic centers.

1 Introduction

1.1 Backgrounds

Throughout any phases of stereochemistry, there are several sets of related topics which provide students and researchers with barriers to access to comprehension of stereochemistry. One of such sets is a set of *chirality* and *stereogenicity*. The IUPAC Recommendations (1996) [1] define these terms as follows:

1. (Def. 1) The term *chirality* [1, page 2203] is defined as "The geometric property of a rigid object (or spatial arrangement of points or atoms) of being non-superposable on its mirror image; such an object has no symmetry elements of the second kind (a mirror plane, $\sigma = S_1$, a centre of inversion, $i = S_2$, a rotation-reflection axis, S_{2n}. If the object is superposable on its mirror image the object is described as being achiral. See also handedness, superposability."

2. (Def. 2) The term *stereogenic unit* (stereogen/stereoelement) [1, page 2219] is defined as "A grouping within a molecular entity that may be considered a focus of stereoisomerism. At least one of these must be present in every enantiomer (though the presence of stereogenic units does not conversely require the corresponding chemical species to be chiral). Three basic types are recognized for molecular entities involving atoms having not more than four substituents:

(a) A grouping of atoms consisting of a central atom and distinguishable ligands, such that interchange of any two of the substituents leads to a stereoisomer. An asymmetric atom (chirality centre) is the traditional example of this stereogenic unit.

(b) A chain of four non-coplanar atoms (or rigid groups) in a stable conformation, such that an imaginary or real (restricted) rotation (with a change of sign of the torsion angle) about the central bond leads to a stereoisomer.

(c) A grouping of atoms consisting of a double bond with substituents which give rise to cis-trans isomerism."

According to Def. 2, the term *stereogenic unit* is related to the concept of *enantiomer* (a pairwise relationship between two chiral compounds). In addition, Def. 2 refers to an asymmetric atom as a chiral center. However, it is not clear to students and researchers how the term *stereogenic unit* is related to the term *chiral*, especially in the case (a) of Def. 2.

The term *stereogenic unit* was used to settle confusion brought about in practical applications of the CIP-system (Cahn-Ingold-Prelog-system) so that the descriptive basis of the CIP-system was shifted from "chirality" [2] to "stereogenicity" [3] . Note that the paper of the original proposal [2] was entitled as "Specification of Molecular Chirality", which did not contain the term *stereogenic unit*.

(Def. 3) The CIP-system [3, page 569] indicates three types of tetrahedral stereogenic units of the CIP system, i.e., the chirality center, the chirality plane, and the chirality axis. The CIP-system also refers to analogous pseudoasymmetric stereogenic units, i.e., the pseudoasymmetric center, the pseudoasymmetric plane, and the pseudoasymmetric axis.

Because a chirality center is related to a chiral compound and a pseudoasymmetric center is related to an achiral compound, the stereogenic units (i.e., the chirality center and the pseudoasymmetric center) can be recognized to specify chirality/achirality on one hand. However, Defs. 2 and 3 are silent about units other than such stereogenic units on the other hand. Hence, thoughtful students and researchers are puzzled over how such *a*stereogenic or non-stereogenic units are related to chirality/achirality.

1.2 The Absence of the Term "Astereogenic"

The aforementioned discussions reveal that the term *astereogenic* (or non-stereogenic) has been absent in contrast to the presence of the term *stereogenic* so that the pair of the terms *stereogenic/astereogenic* has not been a matter of discussion. This fact is rather

strange because the pair of terms *chirality/achirality* has been a basis of stereochemistry. Note that Def. 1 defines the pair of the terms *chiral* and *achiral* on the basis of "mirror-image" operations. Hence, it is a wonder that, although Def. 2(a) contains the expression "interchange of any two of the substituents leads to a stereoisomer", the "interchange" operation is not used to define the pair of the terms *stereogenic* and *astereogenic*. As a result, students and researchers would face some difficulties in the proper usage of the "mirror-image" operations and the "interchange" operation.

By judging from the terminology described in Defs. 1 and 2, the IUPAC Recommendations (1996) [1] have avoided a direct and general definition of the pair of the terms *stereogenic* and *astereogenic*, where several kinds of *stereogenic units* are listed instead. Because two or more kinds of stereogenic units (e.g., Defs. 2(a)–(c)) are present, possible attempts to define generally the pair of the terms *stereogenic* and *astereogenic* would have probably proved futile. We can safely say that the definition of the term *stereogenic unit* has been adopted as the second best by the IUPAC Recommendations (1996) in place of the definition of the pair of the terms *stereogenic* and *astereogenic*. As a result, the IUPAC Recommendations (1996) turn out not to aim at strict characterization of complicated relationship between chirality and stereogenicity. Although the concept of *stereogenic* itself (not paired with *astereogenic*) is regarded as connoting the concept of *chiral* (paired with *achiral*) (cf. Def. 2(a)), the relationship between stereogenicity and *a*chirality is not fully demonstrated. This fact has not been pointed out explicitly, but seems to have caused a sense of frustration, as described in recent papers under such titles as "Stereochemical Terminology and Its Discontents" [4] and "Infelicitous Stereochemical Nomenclature" [5] .

1.3 Aims and Scope

One of the aims of the present paper is to introduce a new idea for separating the concept of *RS*-stereogenicity from the connotations of the conventional term "stereogenic units". Thereby, a pair of terms *RS-stereogenic/RS-astereogenic* can be treated directly and generally on the same line as the pair of the terms *chiral/achiral*. Although the new idea has been originally developed in terms of mathematical stereochemistry [6 –8] , a non-mathematical version has been available now [9, 10] so as to assist efforts of students and researchers for comprehending stereochemistry. The present paper is devoted to provide a teaching or self-teaching guide to the non-mathematical version without keeping mathematical strictness excessively. In particular, we shall clarify the versatility of *stereoisograms*, whose gist can be intuitively grasped by students and researchers with a minimum set of mathematical knowledge.

2 Stereoisograms

2.1 Promolecular Models

For the sake of simplicity, the present paper puts a focus on tetrahedral molecules. Although our discussion is, thereby, restricted within stereogenic units described by Def. 2(a), its generality is by no means restricted. The terms *chiral*, *achiral* and *chirality* are used under Def. 1. The term *enantiomeric* is used to refer to a pairwise relationship between chiral three-dimensional objects (molecules, ligands, etc.) which are mirror-images of each other and non-superposable. The term *enantiomorphic* is not used here to designate a pair of chiral ligands because molecules and ligands in isolation can be commonly treated as 3D-objects by using the term *enantiomeric*.

Let us first consider the configuration of a glyceraldehyde, which is represented by a Fischer-like projection (**1**). The molecule (**1**) is also represented by a stereo-model having wedges and boldfaced broken lines (**2**). When we put A = OH, B = CHO, X = CH_2OH, and Y = H, we obtain an abstract expression (**3**), which is here called a *promolecule*. The abstract 3D-objects A, B, X, and Y are called *proligands*, where they are structureless but have chirality or achirality.

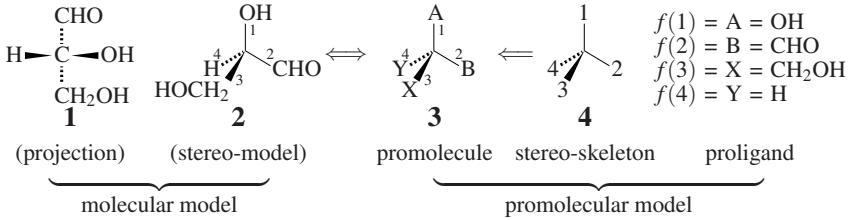

Figure 1: Promolecule composed of a stereo-skeleton and proligands for modelling a molecule.

Because the term *chirality* is restricted to specify a rigid object (Def. 1), chirality for multiple conformational changes around bonds has been discussed in the form of a fixed conformer with the highest attainable symmetry according to stereochemical conventions. The coinage of the terms *promolecule* and *proligand* [11, 12] enables us to discuss molecular symmetries strictly, without disturbance due to such conformational changes in a distinct way apart from the conventional fixation of conformation. For example, pentaerythritol ($C(CH_2OH)_4$) belongs to the point group $\mathbf{D}_{2d}$ at a highest-attainable symmetry, while tetramethylmethane ($C(CH_3)_4$) belongs to the point group $\mathbf{T}_d$ at a highest-attainable symmetry. We would be forced to discuss them separately if we do not coin the terms *promolecule* and *proligand*. After the coinage of the terms, they

can be discussed by using a common promolecule (CX_4) belonging to the point group $\mathbf{T}_d$. In spite of the difference in their point-group symmetries, the achiral nature of pentaerythritol ($C(CH_2OH)_4$) and that of tetramethylmethane ($C(CH_3)_4$) are retained in the promolecule (CX_4) of $\mathbf{T}_d$-symmetry. It should be emphasized again that the concepts of *promolecule* and *proligand* enable us to discuss chirality by regarding a promolecule as being a rigid object (cf. Def. 1) in place of a fixed conformer having such multiple conformational changes.

The promolecule (**3**) is alternatively constructed by the substitution of a stereo-skeleton (**4**) with four positions numbered from 1 to 4, where the proligands A, B, X, and Y are placed on the positions 1–4, as shown by $f(1)$ to $f(4)$. The symbol $f(i)$ ($i = 1$ to 4) represents an operation (a function) which puts a proligand on the position i without altering the chirality of the proligand.

2.2 Drawing of Stereoisograms

2.2.1 Symmetrical Behavior of a Tetrahedral Stereo-Skeleton

Let us next consider the symmetrical behavior of the stereo-skeleton (**4**). As shown in Fig. 2, the reflection of the stereo-skeleton (**4**) with respect to the mirror plane containing the plane spanned by 1–C–2 produces its mirror image (**6**), where the chirality of each position is altered as shown by numbering with an overbar ($\overline{1}$–$\overline{4}$). The reflection is represented by the symbol $\overline{(1)(2)(3\ 4)}$, in which position 1 and position 2 is fixed but its chirality is changed into the corresponding opposite one, while positions 3 and 4 are interchanged with each other and the chirality of each position is altered [13] . The term *stereo-skeleton* is used to emphasize the alternation of the local chirality of each position. Because the relationship between **4** and **6** is recognized to be enantiomeric, the axis designated by the letter C is called a *chiral/achirality axis* or shortly a *C-axis*.

On the other hand, let us consider an operation represented by the symbol $(1)(2)(3\ 4)$, which has the same permutation as the reflection $\overline{(1)(2)(3\ 4)}$ but does not exhibit the alternation of the chirality of each position. This operation converts the stereo-skeleton (**4**) into **5**. To designate the relationship between **4** and **5**, the term *RS-diastereomeric* is coined [9, 10] . The nature capable of exhibiting *RS*-diastereomeric relationships is called *RS-stereogenicity*. The axis designated by the letter S is called an *RS-stereogenicity/RS-astereogenicity* axis or shortly an *S-axis*.

When we apply the reflection operation $\overline{(1)(2)(3\ 4)}$ to **5**, we obtain its enantiomeric skeleton **7**. The same skeleton is obtained by applying the operation $(1)(2)(3\ 4)$ to **6**. We coin the term *holantimeric* in order to designate the relationship between the stereo-skeleton **7** and the original one **4** [9, 10] . The conversion of **4** into **7** is represented by

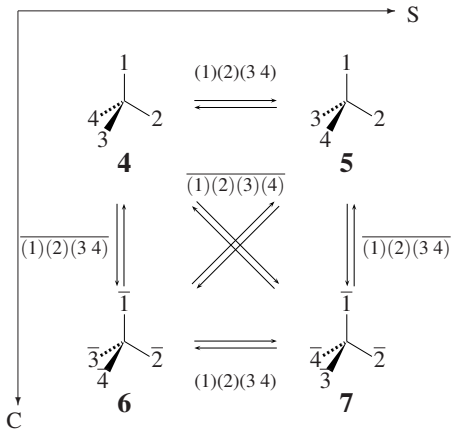

Figure 2: Tetrahedral stereo-skeleton for drawing stereoisograms.

the symbol $\overline{(1)(2)(3)(4)}$, which means that each position is fixed but the chirality of each position is altered. The nature capable of exhibiting holantimeric relationships is called *sclerality*, which is accompanied with terms *scleral* and *ascleral*.

When we presume the priority among the four positions to be $1 > 2 > 3 > 4$ in a similar way to the CIP nomenclature, the configuration of **4** is R, while that of **5** is S. To give the CIP nomenclature a consistency, we can select a rule for the $\overline{1} > \overline{2} > \overline{3} > \overline{4} >$ by starting from the priority $1 > 2 > 3 > 4$ in most cases. Thereby, the configuration of **6** is S, while that of **7** is R. For an exceptional case, see Exercise 2 shown below [14] .

The crux of the present approach is to discriminate between **5** and **6**. The CIP nomenclature is based on the two modes of numbering (**4** and **5**) regardless of alternation of ligand chirality. In contrast, the present approach takes account of the alternation of ligand chirality by considering **6** as a mirror-image stereo-skeleton of **4**.

2.2.2 Stereoisograms Based on a Tetrahedral Stereo-Skeleton

In a similar way to the derivation of **3** from the stereo-skeleton (**4**), we apply $f(1) = \mathrm{A}$ (= OH), $f(2) = \mathrm{B}$ (= CHO), $f(3) = \mathrm{X}$ (= CH_2OH), and $f(4) = \mathrm{Y}$ (= H) to each stereo-skeleton shown in Fig. 2. The symbol $f(\bar{i})$ represents an operation which puts such a promolecule with altering its chirality into an opposite one. Because the proligands A, B, X, and Y are achiral, we find that their (hypothetical) enantiomeric proligands (i.e., their mirror images) are superposable to the original ones [15] , i.e., $\overline{\mathrm{A}} = \mathrm{A}$, $\overline{\mathrm{B}} = \mathrm{B}$, $\overline{\mathrm{X}} = \mathrm{X}$, and $\overline{\mathrm{Y}} = \mathrm{Y}$. Thereby, we obtain Fig. 3, where we add vertical double-headed arrows with the

symbol ◉ because each of the vertical pairs (**3**/$\overline{\mathbf{3}}$ (left) or $\overline{\mathbf{3}}$/**3** (right)) is recognized to represent an enantiomeric relationship; horizontal double-headed arrows with the symbol ○ because each of the horizontal pairs (**3**/$\overline{\mathbf{3}}$ (top) or $\overline{\mathbf{3}}$/**3** (bottom)) is recognized to be in an *RS*-diastereomeric relationship; and diagonal equality symbols with the symbol • because each of the diagonal pairs (**3**/**3** or $\overline{\mathbf{3}}$/$\overline{\mathbf{3}}$) is recognized to be identical with each other. The resulting diagram is called a *stereoisogram*, which is categorized into Type I, as will be discussed later. A simplified stereoisogram, in which the promolecule (**3**) is represented by a boldfaced letter **A**, is also used to show essential features of Type I. It follows that the promolecule (**3**) represented by **A** is chiral, *RS*-stereogenic, and ascleral so as to be represented by the symbol $[-, -, a]$, where the symbol $-$ represents the absence of the prefix *a* and the letter *a* represents the presence of the prefix *a*.

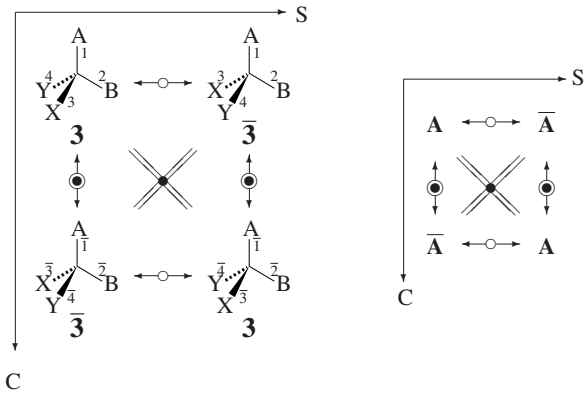

Figure 3: Stereoisogram for characterizing the promolecule **3** (left) and a simplified stereoisogram of of Type I (right). The chiral, *RS*-stereogenic, and ascleral nature is represented by the symbol $[-, -, a]$.

Suppose that we apply $f(1) = \mathrm{A}$, $f(2) = \mathrm{B}$, $f(3) = \mathrm{p}$, and $f(4) = \mathrm{p}$ to each stereoskeleton shown in Fig. 2, where the proligand A and B are achiral and the proligand p is chiral. Note that the enantiomeric ligand to p is represented by $\overline{\mathrm{p}}$. Thereby, we obtain Fig. 4, where we add vertical double-headed arrows with the symbol ◉ because each of the vertical pairs (**8**/$\overline{\mathbf{8}}$) is recognized to be enantiomeric to each other; horizontal equality symbols with the symbol ○ because each of the horizontal pairs (**8**/**8** and $\overline{\mathbf{8}}$/$\overline{\mathbf{8}}$) is recognized to be identical with each other; diagonal double-headed arrows with the symbol • because each of the diagonal pairs (**8**/$\overline{\mathbf{8}}$) is recognized to be holantimeric to each other. The resulting diagram is a stereoisogram of Type II, as will be discussed later collectively. It follows that the promolecule (**8**) is chiral, *RS*-astereogenic, and scleral so

as to be represented by the symbol $[-, a, -]$.

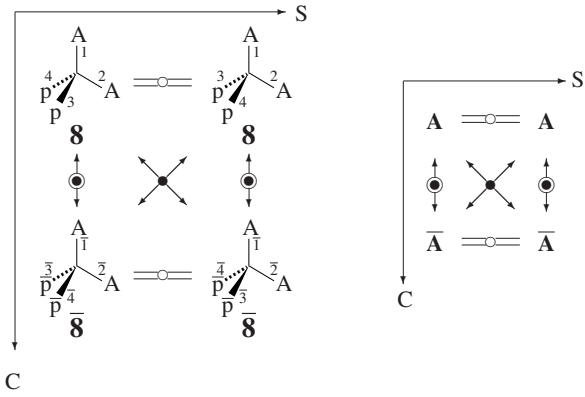

Figure 4: Stereoisogram for characterizing the promolecule **8** (left) and a simplified stereoisogram of of Type II (right). The chiral, *RS*-astereogenic, and scleral nature is represented by the symbol $[-, a, -]$.

2.2.3 Stereoisograms of Five Types

The three pairs of characterizing the symmetrical behavior of a promolecule (i.e., chiral/achiral, *RS*-stereogenic/*RS*-astereogenic, and scleral/ascleral) are combined to give eight cases, among which five combinations, i.e., $[-, -, a]$ (Type I), $[-, a, -]$ (Type II), $[-, -, -]$ (Type III), $[a, a, a]$ (Type IV), and $[a, -, -]$ (Type V), are effective to characterize the promolecule. Because the symbol $-$ represents the absence of the prefix a, and the letter a represents the presence of the prefix a, the combined symbol $[-, -, a]$ represents a chiral, *RS*-stereogenic, and ascleral promolecule (Type I), and so on. The remaining three combinations ($[a, a, -]$, $[-, a, a]$, and $[a, -, a]$) vanish into the $[a, a, a]$ case (Type IV). The existence of five types for stereoisograms has been proved in general [8] .

The possible five types of stereoisograms are listed in Fig. 5, where the boldfaced letters **A** and $\overline{\mathbf{A}}$ (or **B** and $\overline{\mathbf{B}}$) represent a pair of enantiomers. Each double-headed arrow indicates difference between relevant promolecules, while each equality symbol indicates that relevant promolecules are identical with each other. The symbols ◉ , ○ , • are respectively concerned with chirality/achirality, *RS*-stereogenicity/*RS*-astereogenicity, and sclerality/asclerality. By combining these symbols, we use the following combined symbols for representing relationships which are contained in stereoisograms:

symbol	relationship [16]	attribute [16]
	enantiomeric	chiral
	(self-enantiomeric)	achiral
	*RS*-diastereomeric	*RS*-stereogenic
	(self-*RS*-diastereomeric)	*RS*-astereogenic
	holantimeric	scleral
	(self-holantimeric)	ascleral

It should be noted that the symbol ( ) represents a "self-enantiomeric" relationship, which is designated only as being achiral in stereochemical convention. The symbol () explicitly indicates our practice of deciding the achirality on the basis of the definition of the term *enantiomer* in the IUPAC Recommendations (1996) [1, page 2207] : "One of a pair of molecular entities which are mirror images of each other and non-superposable." For example, a hypothetical enantiomeric relationship between a molecular entity A_2BX and its mirror image $\overline{A}_2\overline{BX}$ can be logically renamed a self-enantiomeric relationship because we presume $\overline{A}_2\overline{BX} = A_2BX$ when A, B, and X are achiral [15] . In a similar way, the symbol () represents a "self-*RS*-diastereomeric" relationship, which is designated as being *RS*-astereogenic if we emphasize the symmetrical nature of a relevant promolecule in the present terminology. A similar situation holds true for the symbol ().

As found easily in Fig. 5, a stereoisogram of Type I contains two promolecules (**A** and $\overline{\mathbf{A}}$) of an enantiomeric pair; a stereoisogram of Type II contains two promolecules (**A** and $\overline{\mathbf{A}}$) of an enantiomeric pair; a stereoisogram of Type III contains two *RS*-diastereomers, each of which is composed of two enantiomers (**A**/$\overline{\mathbf{A}}$ or **B**/$\overline{\mathbf{B}}$); a stereoisogram of Type IV contains one achiral promolecule (**A**); and a stereoisogram of Type V contains two achiral *RS*-diastereomers (**A** and **B**). Although the Type I stereoisogram and the Type II stereoisogram are akin to each other, they are different in holantimeric relationships (i.e.,  vs. ). This difference determines the capability of giving *RS*-descriptors of the CIP system, as will be discussed later.

When we take account of achiral proligands (A, B, X, and Y) and pairs of chiral proligands (p/$\overline{\text{p}}$, q/$\overline{\text{q}}$, r/$\overline{\text{r}}$, and s/$\overline{\text{s}}$), we can select a set of four proligands from them and put the set on the four positions of the stereo-skeleton shown in Fig. 2. Thereby, we obtain a promolecule which exhibits either one of the stereoisograms of five types shown in Fig. 5. Representative promolecules are itemized with respect to *RS*-stereoisomeric types (Type I to Type V) and collected in Fig. 6, where their point groups are designated.

It should be added that each promolecule of Type I, which corresponds to a *single* Type I stereoisogram, represents a pair of enantiomers (e.g., **9** and $\overline{\mathbf{9}}$); each promolecule of Type II, which corresponds to a *single* Type II stereoisogram, represents a pair of enan-

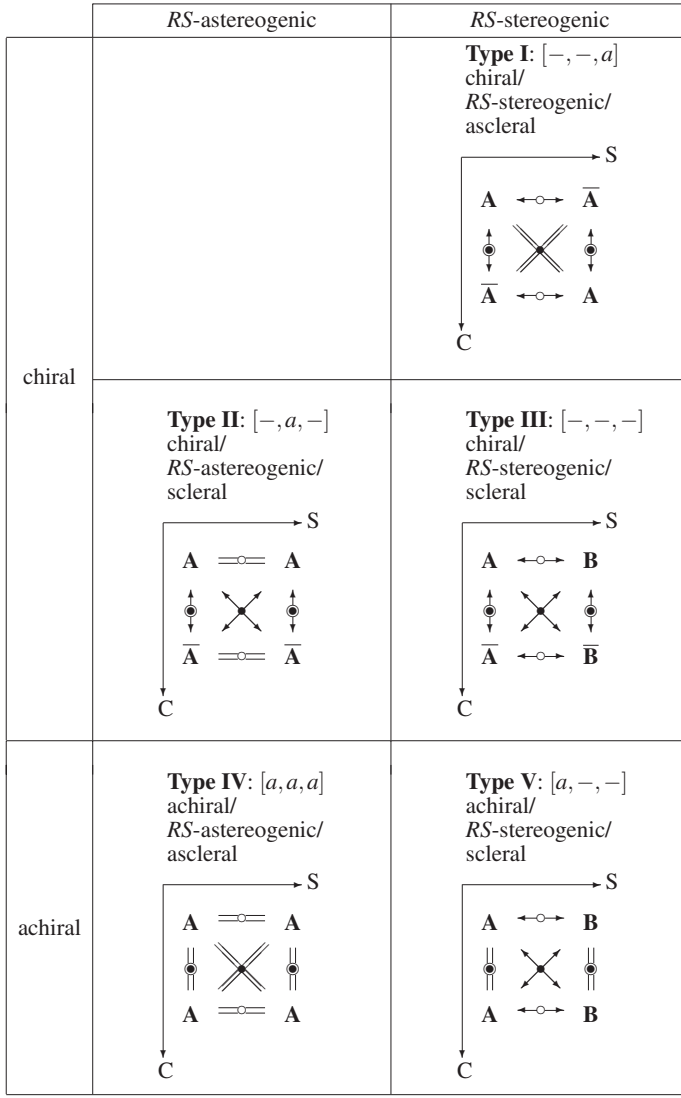

Figure 5: Stereoisograms of five types [10] . The symbols **A** and $\overline{\mathbf{A}}$ (or **B** and $\overline{\mathbf{B}}$) represent a pair of enantiomers.

tiomers (e.g., **11** and $\overline{\mathbf{11}}$); a set of two Type III promolecules linked with an underbrace, which corresponds to a *single* Type III stereoisogram, represents two *RS*-diastereomers, where each of the *RS*-diastereomers is accompanied by its relevant enantiomer (e.g., **26**/$\overline{\mathbf{26}}$ and **27**/$\overline{\mathbf{27}}$); each promolecule of Type IV, which corresponds to a *single* Type IV stereoisogram, represents an achiral promolecule (e.g., **38**); and finally each pair of Type V promolecules linked with an underbrace, which corresponds to a *single* Type V stereoisogram, represents two *RS*-diastereomers (e.g., **44** and **45**). Although this explanation of Fig. 6 does not contains holantimeric relationships, reference to Fig. 5 would fill such implicated information.

Note that each stereoisogram is not changed in its connotation even if anyone of the four promolecules contained in it is selected as a representative. This means that an arbitrary promolecule in the stereoisogram can be selected as a representative. We tentatively selected such a representative in the manner that its proligand set satisfies highest priority in a lexicographical order of proligands (A > B > p > $\overline{\text{p}}$> $\cdots$ > X > Y). When there exist equivalent promolecules such as A_2B_2, A_2X_2, etc., we depict the youngest promolecule (e.g., A_2B_2) in a lexicographical order of proligands. In addition, if such a representative promolecule is chiral, either one enantiomer is depicted for the sake of page-saving.

3 Stereoisograms for the *RS*-Nomenclature

3.1 *RS*-Stereogenicity

By developing *stereoisograms* as a versatile tool, the concept of *RS*-stereogenicity turns out to be more distinctive than the stereogenicity of conventional usage. *RS*-Stereogenic promolecules are categorized into Types I $[-,-,a]$, III $[-,-,-]$, and V $[a,-,-]$ in the present methodology. Compare this with the fact that these three types are all stereogenic so as not to be discriminated in terms of stereochemical convention.

The *RS*-stereogenicity corresponds to the capability of giving an *RS*-descriptor according to the CIP system. Although the concrete rules for giving *RS*-descriptors are not the subject of the present article, stereoisograms serve as a versatile tool for testifying the capability of giving *RS*-descriptors.

1. Each promolecule of Type I $[-,-,a]$ is paired with its non-superposable mirror-image, where the relevant promolecules are enantiomeric and *RS*-diastereomeric, as found in a stereoisogram of Type I. The *RS*-diastereomeric relationship corresponds to the capability of characterizing *R*- and *S*-configurations. Because the enantiomeric relationship is superposed with the *RS*-diastereomeric relationship,

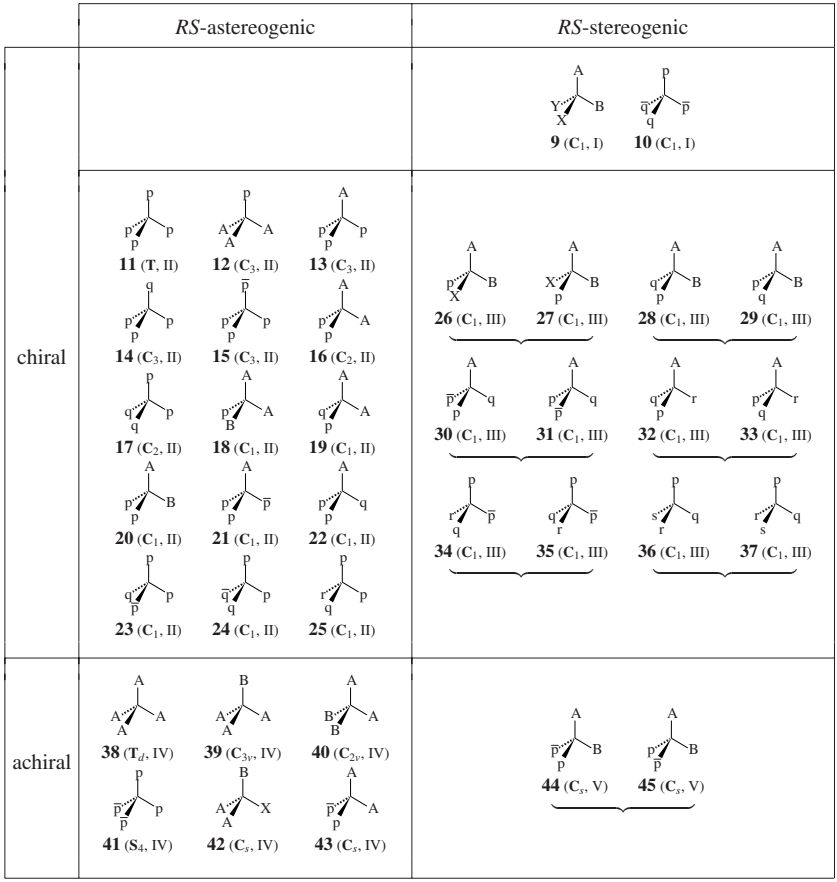

Figure 6: Point groups and *RS*-stereoisomeric types (Types I to V) for tetrahedral molecules. The symbols A, B, X, and Y represent atoms or achiral (pro)ligands. The symbols p, q, r, and s represents chiral (pro)ligands, while each symbol with an overbar represents the corresponding chiral (pro)ligand with the opposite chirality.

one may say that the enantiomeric relationship is the basis of the capability of characterizing *R*- and *S*-configurations. However, the selection of the *RS*-diastereomeric relationship for the *RS*-nomenclature is more reasonable because of the consistency among Types I, III, and V.

2. Each promolecule of Type III $[-,-,-]$ is paired with its *RS*-diastereomer, as linked with an underbrace in the Type III part of Fig. 6. For example, the promolecule (**26**) is paired with its *RS*-diastereomeric promolecule (**27**), where they appear in a stereoisogram of Type III shown in Fig. 3. Moreover, their enantiomers ($\overline{\mathbf{26}}$ and $\overline{\mathbf{27}}$) appear in the same stereoisogram. The *RS*-diastereomeric relationship between **26** and **27** (or between $\overline{\mathbf{26}}$ and $\overline{\mathbf{27}}$) gives a sound basis to the capability of characterizing *R*- and *S*-configurations. Although the corresponding enantiomeric relationship between **26** and $\overline{\mathbf{26}}$ (or between **27** and $\overline{\mathbf{27}}$) may be used for the *RS*-assignment, this assignment procedure would be inconsistent with that of Type V described below. See also Exercise 2 shown below.

3. Each promolecule of Type V $[a,-,-]$ is paired with its *RS*-diastereomer, as linked with an underbrace in the Type V part of Fig. 6. For example, the promolecule (**44**) is paired with its *RS*-diastereomeric promolecule (**45**), where they appear in a stereoisogram of Type V shown in Fig. 3. The *RS*-diastereomeric relationship between **44** and **45** gives a sound basis to the capability of characterizing *R*- and *S*-configurations. Obviously, this case represents pseudoasymmetric promolecules, which are both achiral. To integrate the three types (Types I, III, and V) into a consistent system, we should consider that *RS*-descriptors (*rs*-descriptors in Type V) are determined on the basis of *RS*-stereogenicity.

We now conclude that the capability of giving *RS*-descriptors by the CIP system does not stem from chirality but relies on *RS*-stereogenicity, which is conceptually separated from the conventional concept *stereogenic unit* (Def. 1). It should be emphasized that the *RS*-descriptors derived from *RS*-stereogenicity can be correlated to chirality/achirality through stereoisograms of Type I, III, and V, where the three categories (Types I, III, and V) distinctly demonstrate how the *RS*-descriptors are correlated to chirality/achirality.

The following exercises are devoted to special cases related to pseudoasymmetry, which have once been discussed by Mislow [4] and have been recently discussed by using stereoisograms [10] .

Exercise 1. Draw the stereoisogram of the pair of **44** and **45** (Type V). Then, assign an *R*- or *S*-descriptor to each of the four promolecules involved in the stereoisogram, where the priority of the proligands is tentatively postulated to be $\mathrm{p} > \overline{\mathrm{p}} > \mathrm{B} > \mathrm{A}$. Note that **44** (or **45**) is superposable to its mirror image $\overline{\mathbf{44}}$ (or $\overline{\mathbf{45}}$).

Exercise 2. Draw the stereoisogram of the pair of **30** and **31** (Type III). Then, assign an *R*- or *S*-descriptor to each of the four promolecules involved in the stereoisogram, where the priority of the proligands is tentatively postulated to be $p > \overline{p} > q > A$ (and $p > \overline{p} > \overline{q} > A$).

Exercise 3. Draw the stereoisogram of **10** (Type I). Then, assign an *R*- or *S*-descriptor to each of the four promolecules involved in the stereoisogram, where the priority of the proligands is tentatively postulated to be $p > \overline{p} > q > \overline{q}$. Note that **10** and its mirror image $\overline{\mathbf{10}}$ is enantiomeric and *RS*-diastereomeric.

Exercise 4. Discuss *RS*-stereogenicity and chirality by comparing the stereoisograms of Exercises 1 to 3 in combination with the resulting *RS*-descriptors. Then, discuss the effect of the term "reflection-invariant" which has been described in Ref. [3] .

In addition to the result of Exercise 2 (Type III), the examination of Type II $[-, a, -]$ cases demonstrates why the present term *RS-stereogenicity* should be separated from the term *stereogenicity* of conventional usage. For example, the central atom of the promolecule **8** (Fig. 4) is not a stereogenic unit if it is examined by itself by using Def. 2(a). This decision, however, silent on the existence of its enantiomeric promolecule $\overline{\mathbf{8}}$, which cannot be generated from **8** by the interchange operation described in Def. 2(a). The existence of the corresponding enantiomer $\overline{\mathbf{8}}$ (though **8** is not a stereogenic unit) is inconsistent with the expression "At least one of these must be present in every enantiomer . . ." in Def. 2. This inconsistency is because the relationship between chirality (enantiomerism) and stereogenicity is not fully demonstrated within Def. 2.

In contrast, the promolecule **8** is categorized into Type II $[-, a, -]$ after drawing the stereoisogram shown in Fig. 4, by which the relationship between chirality and *RS*-stereogenicity is characterized without ambiguity. The *RS-a*stereogenic nature of **8** is clearly shown by the stereoisogram (Fig. 4) along with the presence of its enantiomer $\overline{\mathbf{8}}$ (i.e., the chiral nature).

3.2 Comparison with Stereochemical Conventions

It is worthwhile to compare the concepts described in the present paper with related concepts used conventionally in stereochemistry. The comparison would reveal that the present concepts are substantial revisions of the conventional concepts.

3.2.1 *RS*-Diastereomeric Relationships vs. Diastereomeric Relationships

Let us first discuss the difference between *RS*-diastereomeric relationships and diastereomeric relationships of conventional usage.

Diastereomeric relationships (or diastereomers) of conventional usage have been defined as stereoisomeric relationships (or stereoisomers) other than enantiomeric relationships (or enantiomers). Thus, the IUPAC Recommendations (1996) [1, page 2205] define as follows:

> (Def. 4) The term *diastereoisomerism* (or *diastereomerism*) is defined as "Stereoisomerism other than enantiomerism. Diastereoisomers (or diastereomers) are stereoisomers not related as mirror images. Diastereoisomers are characterized by differences in physical properties, and by some differences in chemical behaviour towards achiral as well as chiral regents."

Thus, there emerges a dichotomy between enantiomers and diastereomers.

By virtue of stereoisograms, especially of Type-III stereoisograms, we are able to recognize three relationships, i.e., enantiomeric relationships ( ), *RS*-stereoisomeric relationships ( ), and holantimeric relationships ( ). By examining Def. 4, we find that the diastereomeric relationships of conventional usage (Def. 4) connote *RS*-diastereomeric relationships, holantimeric relationships, and others (not enantiomeric relationships), as illustrated in Fig. 7.

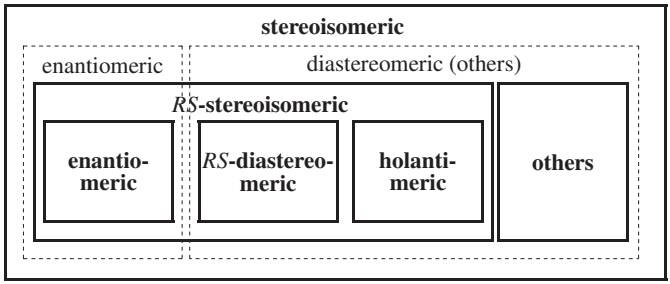

Figure 7: Conventional terminology vs. the present terminology for stereoisomerism. A broken-lined box represents a term of the conventional terminology, while a solid-lined box represents a term of the present terminology.

3.2.2 Stereoisomerism vs. *RS*-Stereoisomerism

We have coined the term *RS-stereoisomeric* [7] to refer collectively to the three relationships (i.e., enantiomeric relationships ( ), *RS*-diastereomeric relationships ( ), and holantimeric relationships ( )). The resulting concept *RS-stereoisomerism* should be compared with the conventional concept *stereoisomerism* so as to provide a perspective brought about by the use of stereoisograms.

As illustrated by broken-lined boxes in Fig. 7, the conventional dichotomy between enantiomers and diastereomers (Def. 4) is schematically represented as follows:

$$\text{stereoisomerism} \quad = \quad \text{enantiomerism} + \text{diastereomerism (others)}. \tag{1}$$

Even by obeying this scheme, the concept of chirality is linked with enantiomerism without ambiguity according to Def. 1. However, the concept of stereogenicity is not fully characterized because the concept is concerned with enantiomerism and diastereomerism, as found in Def. 2 for the term *stereogenic unit*.

In contrast, we have revised the above scheme by virtue of stereoisograms, so as to obtain a new scheme as follows:

$$\text{stereoisomerism} \quad = \quad RS\text{-stereoisomerism} + \text{others} \tag{2}$$

$$RS\text{-stereoisomerism} \quad = \quad \text{enantiomerism} + RS\text{-diastereomerism} + \text{holantimerism}. \tag{3}$$

Difference of these equations from eq. 1 is illustrated by solid-lined boxes in Fig. 7. Thereby, stereoisomers are first divided into *RS*-stereoisomers and other stereoisomers in contrast to the conventional dichotomy between enantiomers and diastereomers. Then, the *RS*-stereoisomers are conceptually divided into enantiomers, *RS*-diastereomers, and holantimers by using stereoisograms [17, 18] . Of course, such enantiomers, *RS*-diastereomers, and holantimers can overlap one another as found in Fig. 5 [19] . As a result, chirality is linked with enantiomerism; *RS*-stereogenicity is linked with *RS*-diastereomerism; and sclerality is linked with holantimerism.

It should be noted that the term *stereoisomerism* is decided distinctly to give an equivalent graph (a single constitutional isomer), and the term *enantiomerism* is decided distinctly to give a pair of mirror-image objects. However, the term *diastereomerism* is a residual part obtained by the stereoisomerism minus the enantiomerism. If we take account of whether or not there are operations to decide equivalence classes, the conventional dichotomy (eq. 1) means the following inclusion relationship:

$$\text{stereoisomerism} \supset \text{enantiomerism}, \tag{4}$$

where the term *diastereomerism* is defined subsidiarily (Def. 4).

On the other hand, the present approach shows that the term *RS-stereoisomerism* (cf. eqs. 2 and 3) is decided distinctly by means of stereoisograms. This provides us with a

revised inclusion relationship as follows:

$$\text{stereoisomerism} \supset \textit{RS}\text{-stereoisomerism} \quad (5)$$

$$= \text{enantiomerism} + \textit{RS}\text{-diastereomerism} + \text{holantimerism}. \quad (6)$$

The inclusion relationship (eq. 5) indicates that the remaining part (i.e. the "others" shown in eq. 2) should be studied separately [20 –24] . As for tetrahedral promolecules, eq. 2 is reduced into a special case: stereoisomerism = *RS*-stereoisomerism because of the absence of "others".

3.2.3 Implications of Stereochemical Conventions

The concept of *RS*-stereoisomerism based on stereoisograms is effective to reveal implications which are concealed in the conventional dichotomy between enantiomers and diastereomers. The conventional procedure presumes that a pair of stereoisomers is selected on the basis of the concept of *stereogenic unit* (Def. 2). This selection implies that *a*stereogenic (or non-stereogenic) cases are omitted so as not to be examined further. The two stereoisomers of the pair are compared as shown in Fig. 8.

Although the conventional procedure does not specify which of the three relationships ( ,  , and ) works in its decisions, we can find that such decisions are unconsciously based on the three relationships as follows:

1. Let us first examine Case (a) for Type I shown in Fig. 8. The conventional procedure recognizes the enantiomeric relationship between **3** (at the rightmost column) and $\overline{\mathbf{3}}$ (at the third column) as an implicit prerequisite, as linked by an underbrace. According to the conventional procedure (cf. Def. 2(a)), an interchange operation () on **3** at the leftmost column generates **46** (at the second column), which is recognized as being identical with $\overline{\mathbf{3}}$ (at the third column). Hence, **3** is a stereogenic unit so that the stereoisomeric relationship between **3** and **46** is concluded to be an enantiomeric one. In order to regard **46** as being identical with $\overline{\mathbf{3}}$, however, the numbering 1–4 of the substitution positions should be changed into $\overline{1}$–$\overline{4}$ (as found in $\overline{\mathbf{3}}$) in the light of the present approach. This implies an operation  which results in the replacement of A = $\overline{\text{A}}$, B = $\overline{\text{B}}$, X = $\overline{\text{X}}$, and Y = $\overline{\text{Y}}$. Thus, we can say that the operation is unconsciously applied in the conventional procedure for determining the enantiomeric relationship for Type I. By means of stereoisograms, we find that the determination of the enantiomeric relationship () is equivalent to a combined operation of and in the case of Type I. When the conventional procedure is applied, on the other hand, the effect of the self-holantimeric relationship () is ignored without any reliable interpretation so that is

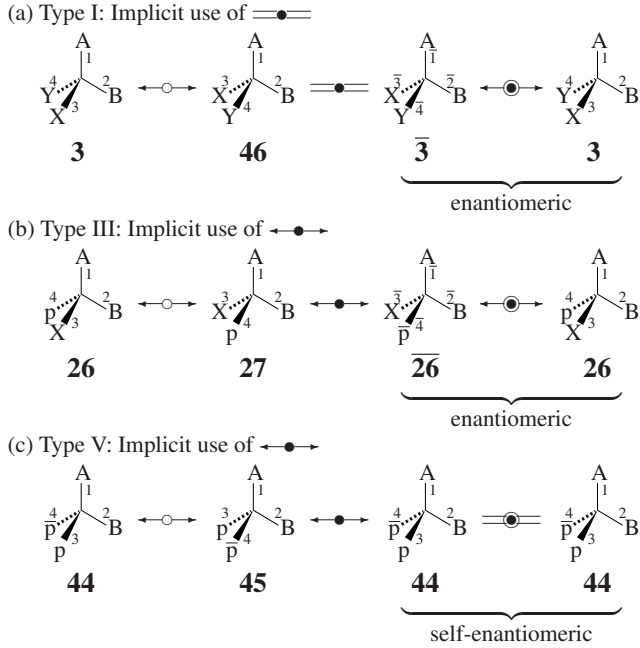

Figure 8: Relationships used for specification of stereoisomerism in conventional stereochemistry. These relationships are used after two relevant compounds are recognized to be stereoisomeric.

equalized to ←○→ as a matter of course. Note that the symbol ←○→ is used to represent an interchange operation in the conventional procedure (cf. Def. 2(a)), although the same symbol represents an *RS*-diastereomeric relationship in the present approach.

2. To test Case (b) for Type III (Fig. 8), the conventional procedure also presumes the enantiomeric relationship between **26** (at the rightmost column) and $\overline{\mathbf{26}}$ (at the third column) as an implicit prerequisite, as linked by an underbrace. The pair **26** (at the leftmost column) and **27** (at the second column), which are generated by an interchange operation (←○→) according to the conventional procedure (cf. Def. 2), is stereoisomeric, but not enantiomeric because the latter **27** (at the second column) is different from $\overline{\mathbf{26}}$ (at the third column). Hence, the pair **26** (at the leftmost column) and **27** (at the second column) is concluded to be diastereomeric because of the dichotomy between enantiomers and diastereomers. In the light of the present approach, the relationship between **26** (at the leftmost column) and **27**

(at the second column) is determined to be *RS*-diastereomeric (←○→). Moreover, the difference between **27** (at the second column) and $\overline{\mathbf{26}}$ (at the third column) is determined to be a holantimeric relationship (←●→), though the conventional procedure takes little account of this relationship.

3. Case (c) for Type V (Fig. 8) is tested by staring from the self-enantiomerism (achirality) of **44**, which is explicitly illustrated the third and fourth formulas linked with a underbrace. The pair **44** (at the leftmost column) and **45** (at the second column), which are generated by an interchange operation (←○→) according to the conventional procedure (cf. Def. 2), is stereoisomeric, but not enantiomeric because the latter **45** (at the second column) is different from $\overline{\mathbf{44}}$ (at the third column). Then, the pair of **44** and **45** is determined to be diastereomeric (*RS*-diastereomeric ←○→ by the present approach).

Obviously, Fig. 8 shows that the conventional procedure of deciding enantiomeric and diastereomeric relationships unconsciously uses holantimeric or self-holantimeric relationships. The unconsciousness of the usage in the conventional procedure has concealed the important feature that an enantiomeric relationship (←◉→) and an *RS*-diastereomeric relationship (←○→) overlap each other in the case of Type I. As a result, the *RS*-diastereomeric relationship (←○→) for Type I (e.g., the one between **3** at the leftmost column and **46** at the second column) has been ignored so that the interchange operation (e.g., the one from **3** at the leftmost column and **46** at the second column) has been stressed instead, as found in Def. 2(a). It follows that, in the conventional procedure, the interchange operation turns out to give enantiomeric relationships (←◉→) in the case of Type I as well as diastereomeric relationships (←○→) in the case of Types III and V. In other words, the interchange operation suffers from an unconscious shift of viewpoints according to the types of every pairs of compounds to be examined. Students and researchers would be forced to take some aimless training to get skillful at the shift of viewpoints without realizing the unconsciousness use of holantimeric (←●→) or self-holantimeric relationships (═●═).

Such an unconscious shift of viewpoints, in contrast, can be avoided by introducing stereoisograms described in the present article. In the present approach, for example, we consider the compound **3** at first without pairing it with $\overline{\mathbf{3}}$. The stereoisogram of the compound **3** generates its enantiomer ($\overline{\mathbf{3}}$) and other *RS*-stereoisomers in a logical fashion, where the three relationships (i.e., enantiomeric, *RS*-diastereomeric, and holantimeric ones) are examined spontaneously. Moreover, the resulting stereoisogram can be categorized into either one of the five types shown in Figs. 5 and 6. What students and researchers should do is to put the formula **3** on the upperleft or the upperright site of

the stereo-skeleton shown in Fig. 2 or to search the corresponding promolecule from the list shown in Fig. 6.

4 Combined Use of Two or More Stereoisograms

4.1 Local Chirality and Local *RS*-Stereogenicity

The present approach is capable of treating two or more carbon centers to be examined. Each of them is considered separately in terms of a promolecule. Strictly speaking, such a promolecule represents the local chirality, the local *RS*-stereogenicity, and the local sclerality around the carbon center relevant to the promolecule.

Let us consider a compound with three tetrahedral carbons, each of which is regarded as a center for characterizing a configuration, as shown in **47**, **47′**, and **47″** (Fig. 9). Because they represent the same compound, we call the compound under the name **47**. They produce distinct promolecules represented by **48**, **49**, and **50**, which are recognized to be Type III promolecules. Note that **48** corresponds to **26** (or **27**), **49** corresponds to **28** (or **29**), and **50** corresponds to **26** (or **27**).

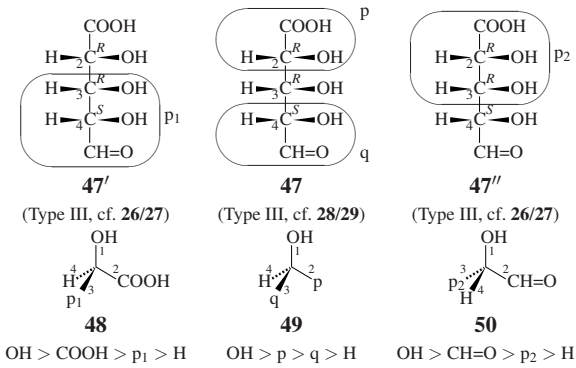

Figure 9: Combined Use of Two or More Promolecules of Type III

By starting from the promolecules (**48**, **49**, and **50**), we obtain three stereoisograms of Type III, where the right column of each stereoisogram represent the same pair of enantiomers (**47** and its enantiomer $\overline{\mathbf{47}}$).

It should be noted that the present concept of *proligand* is consistent with the concept of *hierarchical digraph* for the revised CIP-system [3] . Hence, we can use stereoisograms to testify the capability of giving *RS*-descriptors. Moreover, a stereoisogram can serve

as a direct device for determining an *R*- or *S*-descriptor if the numbering of positions of the stereo-skeleton is given in agreement with the priority of (pro)ligands, as found in the promolecules **48**, **49**, and **50**. For example, the priority shown by OH > COOH > p_1 > H can be used to assign the *R*-configuration of the 2-carbon center in **48**.

4.2 Pseudoasymmetric cases

To exemplify a procedure for characterizing pseudoasymmetric cases, let us examine a 2,3,4-trihydroxyglutaric acid shown in Fig. 10. One achiral acid (**51**) corresponds to a promolecule **53**, which is concluded to belong to Type V by referring to **44**/**45** shown in Fig. 6. If the promolecule (**53**) is tentatively assigned to one promolecule **44**, its *RS*-diastereomer is assigned to the other promolecule **45**. The achiral acid **51** and its *RS*-diastereomer are correlated to the Type V stereoisogram (Fig. 5) through the pair of *RS*-diastereomers (**44**/**45**).

The 2,3,4-trihydroxyglutaric acid (**51**) is achiral in its global symmetry. We presume that the global *RS*-stereogenicity is determined in the same stereoisogram which determines global chirality. The CIP-priority OH > p_2 > $\overline{p}_2$ > H for the corresponding promolecule **53** is used to assign the *r*-configuration to the 3-carbon center of **51**.

The 2,3,4-trihydroxyglutaric acid is regarded as being represented by **51′**, if the carbon with locant number 2 is taken into consideration. The corresponding promolecule **52** is found to belong to Type III by referring to **26**/**27** shown in Fig. 6. If the promolecule (**52**) is tentatively assigned to one promolecule **27**, its *RS*-diastereomeric promolecule is assigned to the other promolecule **26**. The formula **51′** and its *RS*-diastereomer are correlated to the Type III stereoisogram (Fig. 5) through the pair of *RS*-diastereomers (**27**/**26**).

The 2,3,4-trihydroxyglutaric acid is regarded as being represented by **51″**, if the carbon with locant number 4 is taken into consideration. The corresponding promolecule **54** is found to belong to Type III by referring to **26**/**27** shown in Fig. 6. On the same line as **51′**, the formula **51″** and its *RS*-diastereomer are correlated to the Type III stereoisogram (Fig. 5) through the pair of *RS*-diastereomers (**27**/**26**).

4.3 *RS*-Astereogenic Cases

To exemplify a procedure for characterizing a Type II case related to the pseudoasymmetric cases (Fig. 10), let us examine an enantiomer (**55**) of chiral 2,3,4-trihydroxyglutaric acids, which corresponds to a promolecule **57**. This promolecule is concluded to belong to Type II (chiral, *RS*-astereogenic, and scleral) by referring to **20** shown in Fig. 6.

Because the 2,3,4-trihydroxyglutaric acid (**55**) is chiral in its global symmetry, we

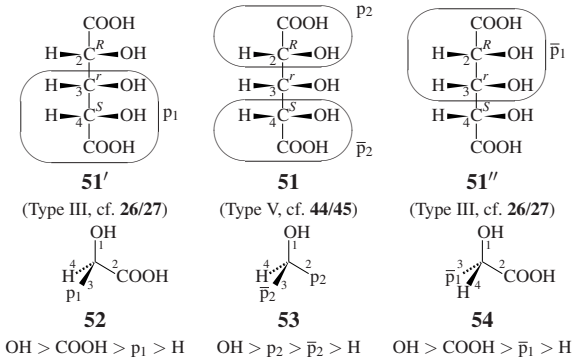

Figure 10: Combined Use of Two or More Promolecules of Type V and Type III

presume that the global *RS*-stereogenicity is determined in the same stereoisogram which determines global chirality.

The chiral 2,3,4-trihydroxyglutaric acid is regarded as being represented by **55′**, if the carbon with locant number 2 is taken into consideration. The corresponding promolecule **56** is found to belong to Type III by referring to **26**/**27** shown in Fig. 6.

If the promolecule (**56**) is tentatively assigned to one promolecule **27**, its *RS*-diastereomeric promolecule is assigned to the other promolecule **26**. The formula **55′** and its *RS*-diastereomer are correlated to the Type III stereoisogram (Fig. 5) through the pair of *RS*-diastereomers (**27**/**26**).

The 2,3,4-trihydroxyglutaric acid is regarded as being represented by **55″**, if the carbon with locant number 4 is taken into consideration. The corresponding promolecule **58** is found to belong to Type III by referring to **26**/**27** shown in Fig. 6.

2,4-Dihydroxyglutaric acid (**59**) shown in Fig. 12 corresponds to a promolecule **61**, which is concluded to belong to Type IV by referring to **43** (Fig. 6).

The 2,4-dihydroxyglutaric acid is regarded as being represented by **59′**, if the carbon with locant number 2 is taken into consideration. The corresponding promolecule **60** is found to belong to Type III by referring to **26**/**27** shown in Fig. 6. If the promolecule (**60**) is tentatively assigned to one promolecule **27**, its *RS*-diastereomeric promolecule is assigned to the other promolecule **26**. The formula **59′** and its *RS*-diastereomer are correlated to the Type III stereoisogram (Fig. 5) through the pair of *RS*-diastereomers (**27**/**26**).

The 2,4-dihydroxyglutaric acid is regarded as being represented by **59″**, if the carbon with locant number 4 is taken into consideration. The corresponding promolecule **62** is

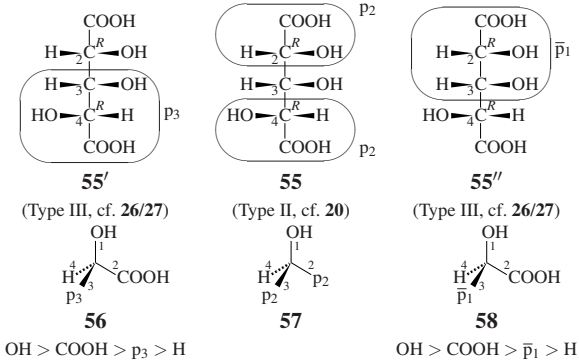

Figure 11: Combined Use of Two or More Promolecules of Type II and Type III

found to belong to Type III by referring to **26**/**27** shown in Fig. 6. On the same line as **59′**, the formula **59″** and its *RS*-diastereomer are correlated to the Type III stereoisogram (Fig. 5) through the pair of *RS*-diastereomers (**27**/**26**).

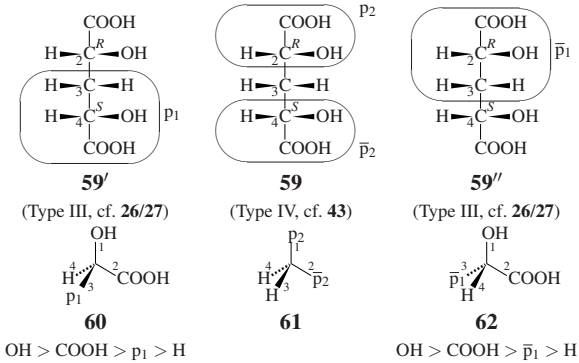

Figure 12: Combined Use of Two or More Promolecules of Type IV and Type III

5 Conclusion

The use of stereoisograms [9, 10] is discussed in order to treat terms related to stereoisomerism (particularly, *chirality* and *stereogenicity*) in introductory courses of stereochem-

istry. Each stereoisogram characterizes three kinds of relationships (an enantiomeric, an *RS*-diastereomeric, and a holantimeric relationship), which distinctly formulate *RS*-stereoisomerism. The *RS*-stereoisomerism is an intermediate concept which is located between stereoisomerism and enantiomerism:

$$\begin{aligned} \text{stereoisomerism} &\supset \textit{RS}\text{-stereoisomerism} \\ &= \text{enantiomerism} + \textit{RS}\text{-diastereomerism} + \text{holantimerism}. \end{aligned}$$

Among the three relationships, the enantiomeric relationship is related to chirality; and the *RS*-diastereomeric relationship is related to *RS*-stereogenicity. One of the merits of using stereoisograms is to demonstrate that the *RS*-stereogenicity is concluded to determine the capability of giving *RS*-descriptors of the CIP system. Thereby, *RS*-stereogenic promolecules are categorized into Type I (chiral/*RS*-stereogenic/ascleral), Type III (chiral/*RS*-stereogenic/scleral), and Type V (achiral/*RS*-stereogenic/scleral). They are able to be characterized by *RS*-descriptors. On the other hand, *RS*-*a*stereogenic promolecules are are categorized into Type II (chiral/*RS*-astereogenic/scleral) and Type IV (achiral/*RS*-astereogenic/ascleral), which are unable to be characterized by *RS*-descriptors.

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[13] There are 4! (= 24) ways of numbering for the four positions of the stereo-skeleton. We can use either one of the 24 ways of numbering without losing generality.

[14] The exceptional case was once been referred to by the term "reflection-variant" [3] .

[15] The present article aims at focusing a new light on implicit and intuitive steps of perceiving stereoisomers. Even when we discuss an achiral 3D-object (a molecule, a ligand, a promolecule, a proligand or others), we first regard its mirror image as a hypothetical enantiomer. If the hypothetical enantiomer is identical with (superposable to) the original object, they are regarded as being "self-enantiomeric" so that they are recognized to be achiral. In other words, the present approach means that the mirror image of a 3D-object **A** is first represented by $\overline{\mathbf{A}}$, whether the **A** is achiral or chiral. Then, the **A** is achiral if $\mathbf{A} = \overline{\mathbf{A}}$, while the **A** is chiral if $\mathbf{A} \neq \overline{\mathbf{A}}$. In contrast, the conventional way of perception implies that the mirror image of an achiral 3D-object **A** is **A** itself, while the mirror image of a chiral 3D-object **B** is its enantiomer $\overline{\mathbf{B}}$. The conventional way means that the "mirror-image" operation acts on achiral 3D-objects and chiral 3D-objects differently. Throughout the present article, even when we say that the mirror image of an achiral 3D-object **A** is **A** itself, we postulate the relationship $\mathbf{A} = \overline{\mathbf{A}}$.

[16] In the conventional stereochemistry, such a term *enantiomeric* is used to specify a relationship between two 3D-objects (e.g., **3** and $\overline{\mathbf{3}}$). In contrast, the present approach presumes that a 3D-object (e.g., **3**) has attributes shown in such a stereoisogram as Fig. 3 (i.e., chiral, *RS*-stereogenic, and ascleral). Terms for relationships can be correlated to these attributes. Thus, the chiral nature of **3** corresponds to the presence of its enantiomer, the *RS*-stereogenic nature corresponds to the presence of its *RS*-diastereomer; and the ascleral nature corresponds to the absence of its holantimer (or to a self-holantimeric relationship). Moreover, the stereoisogram (Fig. 3) exhibits the nature of Type I, which is totally ascribed to the 3D-object (**3**).

[17] It is worthwhile to point out some difficulty stemmed from the use of terms concerning *relationships*. The word "conceptually" is added to avoid the difficulty. Even if we use the term "enantiomers", for example, we should realize that we refer only to enantiomeric relationships, but not to specific objects, where the plural form "enantiomers" implies "an enantiomeric relationship". Note that the singular form

"enantiomer" can be used only when its counterpart is specified. It follows that, strictly speaking, the sentences in this paragraph should be read as an abbreviated expression of the following sentences: "Thereby, stereoisomeric relationships are first divided into *RS*-stereoisomeric relationships and other stereoisomeric relationships in contrast to the conventional dichotomy between enantiomeric relationships and diastereomeric relationships. Then, the *RS*-stereoisomeric relationships are divided into enantiomeric relationships, *RS*-diastereomeric relationships, and holantimeric relationships by using stereoisograms. Of course, such enantiomeric, *RS*-diastereomeric, and holantimeric relationships can be overlap one another as found in Fig. 5".

[18] If we emphasize equivalence classes (not such relationships), an alternative figure other than Fig. 7 should be drawn according to a scheme due to equivalence classes, e.g.,

stereoisomers =
a set of *RS*-stereoisomers + another set of *RS*-stereoisomers +
a further set of *RS*-stereoisomers + $\cdots$,

where each of the sets (quadruplets) may be selected from Type I to Type IV. For example, stereoisomers relevant to **20**, **44**, and **45** listed in Fig. 6 can be divided into equivalence classes in a scheme:

a set of Type II (**20** and its enantiomer) +
a set of Type V (**44** and **45**: both self-enantiomeric) + $\cdots$,

where each set is an equivalence class characterized by one of the stereoisograms shown in Fig. 5. Thus, the discussion based on equivalence classes under *RS*-stereoisomeric groups (with such stereoisograms as an intuitive tool) is quite different from the conventional stereochemistry, which is incapable of such categorization as shown in the scheme.

Fujita's USCI (unit-subduced-cycle-index) approach [12] and the concept of mandala [25, 26] employ another type of equivalence classes which is based on point groups in place of *RS*-stereoisomeric groups. Thereby, the stereoisomers described above (**20**, **44**, and **45**) can be divided into equivalence classes in another scheme:

a set of enantiomers (**20** and its enantiomer) +
a one-membered set of an achiral compound (**44**) +
a one-membered set of an achiral compound (**45**) + $\cdots$,

where each set is an equivalence class characterized by a point group (i.e., $\mathbf{T}_d$). Note that each achiral compound is regarded as a self-enantiomeric pair, which can

construct an equivalence class on the same line as an enantiomeric pair (such as a set of enantiomers (**20** and its enantiomer)).

According to the conventional stereochemistry based on relationships, the relationship between **20** (chiral) and **44** (achiral) as well as between **20** (chiral) and **45** (achiral) is diastereomeric; and the relationship between **44** (achiral) and **45** (achiral) is also diastereomeric. Obviously, the former diastereomeric relationship is different from the latter diastereomeric one. It should be added here that, strictly speaking, the conventional definition "diastereomers are stereoisomers other than enantiomers" cannot characterize the relationship between **44** (achiral) and **45** (achiral). Let us compare between **44** and **45**. We find that they are stereoisomeric. However, **44** (or **45**) has no enantiomer so that their relationship cannot be specified as being diastereomeric by the conventional definition "diastereomers are stereoisomers other than enantiomers". To avoid this difficulty, we should presume that the term "enantiomers" in this definition implicitly connotes "self-enantiomers".

[19] Such stereoisograms as shown Fig. 5 can be alternatively interpreted from this viewpoint. As found in Fig. 5, enantiomers (**A** and $\overline{\mathbf{A}}$) overlap *RS*-diastereomers (**A** and $\overline{\mathbf{A}}$) in the case of Type I; enantiomers (**A** and $\overline{\mathbf{A}}$) overlap holantimers (**A** and $\overline{\mathbf{A}}$) in the case of Type II; and *RS*-diastereomers (**A** and **B**) overlap holantimers (**A** and **B**) in the case of Type V.

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