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A new scheme for investigating geometric and stereoisomeric features in stereochemistry

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ABSTRACT

The concept of *RS*-stereoisomers is proposed as an intermediate concept between enantiomers and stereoisomers. Stereoisograms developed for examining relationships between *RS*-stereoisomers contain three kinds of relationships (enantiomeric, *RS*-diastereomeric, and holantimeric relationships). Because these relationships correspond to three attributes (chirality, *RS*-stereogenicity, and sclerality), a quadruplet of *RS*-stereoisomers can be regarded as an equivalence class. The intermediacy of such *RS*-stereoisomeric relationships provides a paradigm shift from the conventional terminology of stereochemistry to a new terminology based on the concept of *RS*-stereoisomers. In addition, the recognition of a quadruplet of *RS*-stereoisomers as an equivalence class provides another paradigm shift on the basis of such equivalence classes. For example, the basis of the Cahn–Ingold–Prelog system for generating *RS*-descriptors is changed from the stereogenicity of conventional stereochemistry to the *RS*-stereogenicity specified by stereoisograms.

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1. Introduction

In standard systems of studying stereochemistry, stereoisomeric relationships (stereoisomers) are divided into enantiomeric relationships (enantiomers) and 'others', as found typically in flowchart determination of isomeric relationships.[1] The 'others' at issue are usually referred to as diastereomeric relationships (diastereomers), where there have appeared various expressions, e.g., "Diastereoisomerism is stereoisomerism other than enantiomerism.",[2] "Diastereoisomers are stereoisomers that are not enantiomers.",[3] "Diastereomers (or diastereoisomers) are stereoisomers (i.e., isomers of identical constitution but differing in three-dimensional architecture) that do not bear a mirror-image relation to each other."[4] As found in reviews[5,6] and most textbooks on stereochemistry,[7–9] the conventional stereochemistry heavily depends on the dichotomy between enantiomers and diastereomers as one of the most fundamental principles, as shown by broken-lined boxes in Figure 1.

On the other hand, the Cahn–Ingold–Prelog (CIP) system for generating *RS*-descriptors has been familiar to organic chemists as a standard and reliable method for differentiating stereoisomers, where it was originally regarded as specifying molecular chirality, as shown apparently in the title of its proposal.[10] After practical applications of wide variety, the CIP system has been revised so as to specify stereogenicity,[11] where the term 'stereogenic element or unit' was used by following McCasland[12] to designate an element or unit, which produces stereoisomers by ligand permutation (cf. footnote 24 of Ref. 11 and footnote 24 of Ref. 13).

According to the conventional stereochemistry, ligand permutations may produce both enantiomers (such as CABXY, where A, B,

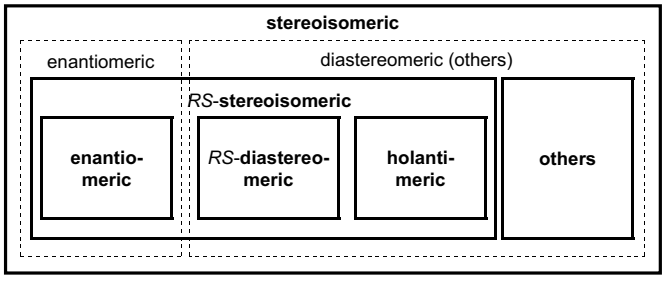

Figure 1. A paradigm shift for dichotomies due to relationships in the terminology of stereochemistry.

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X, and Y represent achiral ligands) and diastereomers (such as CABp$\overline{p}$, where p and $\overline{p}$ represent a pair of enantiomeric ligands) so that the term stereogenicity can be used to designate enantiomeric relationships and diastereomeric relationships. The two cases (CABXY and CABp$\overline{p}$) can be specified by *RS*-descriptors of the CIP system. In contrast, ligand permutations applied to an olefinic molecule ABC=CXY produce diastereomers, which exhibit stereogenicity but cannot be specified by *RS*-descriptors. This means that the term stereogenicity cannot fully explain the capability of giving *RS*-descriptors. As a result, there exist at least three stereogenic cases: i.e.,

(1) two stereogenic cases producing diastereomers, which are (a) capable (e.g., CABp$\overline{p}$) and (b) incapable (e.g., ABC=CXY) of giving *RS*-descriptors in addition to
(2) a stereogenic case producing enantiomers such as CABXY, which are capable of being specified by *RS*-descriptors.

Obviously, item (1) contradicts the broken-lined dichotomy shown in Figure 1; or at least, we can safely say that the broken-lined dichotomy shown in Figure 1 is over-simplified. So long as the broken-lined dichotomy shown in Figure 1 is postulated, item (2) implies that the *RS*-descriptors of the CIP system are seemingly so impure that they specify two conceptually different targets, i.e., enantiomers and diastereomers. If we do not accept this implication of item (2), we are forced to encounter a fundamental question: What do *RS*-descriptors specify? Enantiomers, diastereomers, or others?

To answer this question, the above-mentioned statement according to the conventional stereochemistry, 'ligand permutations may produce both enantiomers (e.g., CABXY) and diastereomers (e.g., CABp$\overline{p}$)', should be reexamined carefully by taking reflection operations into consideration. Obviously, such enantiomers (e.g., CABXY) as produced by ligand permutations (without reflections) are conceptually different from such enantiomers (e.g., CABXY) as produced by reflections, because they are produced in different ways. The two concepts of enantiomers are distinct on a conceptual level, even though the former enantiomers are later equalized to the latter by ligand reflection operations. In the conventional stereochemistry, however, the former are unconsciously hidden behind the latter by means of the broken-lined dichotomy shown in Figure 1. Worse, the dichotomy brings out a misleading postulation that permutation operations and reflection operations are mixed up in the examination of CABXY within the scope of the conventional stereochemistry. It should be noted that, even though results produced by permutations can be equalized to results produced by reflections in terms of appropriate procedures, the permutations as operations cannot be by any means equalized to the reflections. Still worse, permutations confused with reflections in the conventional stereochemistry misleadingly link stereogenicity (cf. item (2) described above) with chirality, because ligand permutations on CABXY produce its enantiomer, which is chiral. As a result, the term 'chirality centers' has been traditionally used in place of the term 'stereogenic centers'.[11]

Over-simplified features of the conventional dichotomy (illustrated by broken-lined boxes in Fig. 1) can be remedied by the concept of *RS-stereoisomers* specified by stereoisograms,[14] in which a quadruplet of promolecules is correlated by means of three kinds of relationships, i.e., enantiomeric, *RS*-diastereomeric, and holantimeric relationships. Thereby, such a quadruplet of promolecules is characterized to be one of the five types (Types I–V) in terms of the corresponding three attributes, i.e., chirality (the same as the traditional term), *RS*-stereogenicity, and sclerality. A group-theoretical treatment of stereoisograms has shown that there exist only five types of stereoisograms or *RS*-stereoisomers.[15] The capability of giving *RS*-descriptors has been ascribed to *RS*-stereogenicity (not chirality nor stereogenicity).[14] In addition, the capability of giving *pro-R*/*pro-S*-descriptors has been ascribed to *pro-RS*-stereogenicity (not prochirality nor prostereogenicity).[16,17] Stereoisograms of Types I–V have been applied to various type of compounds[18–21] as well as to the problems of pseudoasymmetry[22] and prochirality.[16,23] Incomplete differentiation between chirality and stereogenicity has been mainly ascribed to over-simplified features of the conventional dichotomy between enantiomers and diastereomers.[17,24] The concepts of *RS*-stereoisomers and stereoisograms show that the conventional paradigm based on the dichotomy between enantiomers and others (diastereomers) has been shifted to a new paradigm based on the dichotomy between *RS*-stereoisomers and others, as shown by the straight-lined boxes of Figure 1.[17,24]

The studies described in the preceding paragraphs have aimed at qualitative targets on the basis of 'relationships' between stereoisomers, so that the methodology based on relationships has been sufficiently effective to such qualitative applications. In order to go further to such quantitative applications as combinatorial enumerations of stereoisomers, another viewpoint of 'equivalence classes' should be applied to stereoisomers. We will here discuss conventions in the terminology of stereochemistry so that we will reveal several implications concealed in stereochemistry. By using stereoisograms from a viewpoint of equivalence classes, we will discuss how different the newly developed *RS*-stereogenicity is from chirality as well as from stereogenicity. Thereby, we will show that a paradigm shift from enantiomers to *RS*-stereoisomers is inevitable to give a more systematic format to the basic terminology of stereochemistry.

2. A new viewpoint to the terminology of stereochemistry

2.1. Enantiomeric pairs as equivalence classes

An enantiomeric relationship specifies two molecules, which are equivalent (superposable) to each other on the action of a reflection operator. The resulting two molecules construct *an equivalence class*, i.e., a pair of enantiomers. In contrast, when used according to the broken-lined boxes of Figure 1, a diastereomeric relationship does not specify any equivalence between molecules, where such a diastereomeric relationship can only characterize distinction between two or more molecules. In other words, the two or more molecules correlated by the diastereomeric relationship are incapable of constructing an equivalence class, so long as we rely on the classical dichotomy between enantiomers and diastereomers (illustrated by the broken-lined boxes of Fig. 1). Instead, a stereoisomeric relationship can specify a set of equivalent molecules, which is here called *a multiplet of stereoisomers* as a kind of equivalence class.

The discussion of the preceding paragraph reveals at least two features implied by stereochemical conventions:

(1) Enantiomeric relationships and stereoisomeric relationships serve as the respective criteria for categorizing molecules into equivalence classes.
(2) In contrast, diastereomeric relationships are unable to generate equivalence classes.

This situation is illustrated in Figure 2a. Thus, one or more pairs (equivalence classes) of enantiomers construct a multiplet (an equivalence class) of stereoisomers.

It is to be noted that an achiral molecule is regarded as a self-enantiomeric pair or a self-enantiomer in Figure 2a, where an enantiomeric relationship is extended to specify such an achiral molecule in terms of a self-enantiomeric relationship. As a result of the viewpoint shown in Figure 2a, a diastereomeric relationship

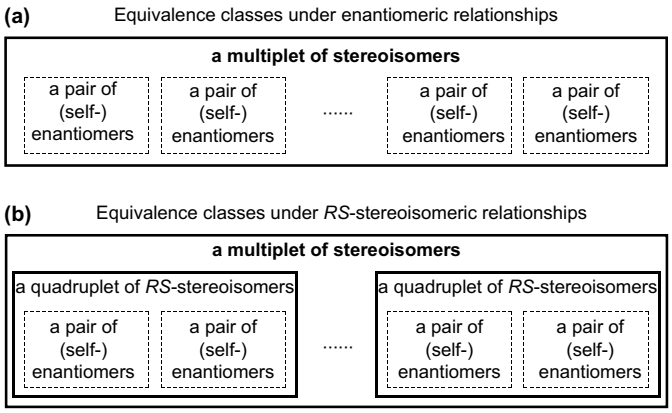

Figure 2. A paradigm shift for equivalence classes. (a) Equivalence classes under enantiomeric relationship in the conventions of stereochemistry and (b) equivalence classes under *RS*-stereoisomeric relationships in the present approach.

turns out to describe a relationship between an enantiomeric pair and another enantiomeric pair. Then, such enantiomeric relationships and such diastereomeric relationships are summed up to construct stereoisomeric relationships.

Keeping the above-mentioned discussion in mind, we compare Figure 1 (the broken-lined boxes) with Figure 2a. Thereby, we find that Figure 2a apparently contains no diastereomers, which are in turn involved in Figure 1 (the broken-lined boxes). This shows the unbalanced nature of the conventional dichotomy implied by the broken-lined boxes of Figure 1. Such an unbalanced feature appears also in the straight-lined boxes of Figure 1, so long as we stick to the methodology based on relationships. This point will be discussed later in this article.

A relationship, which is capable of generating equivalence classes can be correlated to an attribute, which is ascribed to each member of an equivalence class. An enantiomeric relationship can be correlated to *chirality*/*achirality* as attributes, which can be ascribed to each member of an enantiomeric pair or to each molecule superposable to its mirror image. A stereoisomeric relationship can be correlated to *stereoisomerism* (not to stereogenicity) as an attribute, which can be ascribed to each member of a multiplet of stereoisomers.

The term 'stereoisomerism' is used to emphasize nature generating an equivalence class (called *a multiplet of stereoisomers* in the present article). Hence, when two or more molecules of a set (i.e., a multiplet of stereoisomers) are converted to a single graph (a single constitutional isomer), the molecules of the set are defined as 'exhibiting stereoisomerism' or as 'being stereoisomerous'. Although this definition is essentially equivalent to that of the IUPAC 1996 Recommendations,[2] the present term 'stereoisomerism' is intended to indicate an attribute of a multiplet (an equivalence class) of stereoisomers or of its member molecule in terms of the expression 'exhibiting stereoisomerism'. The usage of stereoisomerism in place of the expression 'exhibiting stereoisomerism' would provide no confusion. Thus, a 'stereoisomerous' molecule is capable of generating a full set (multiplet) of stereoisomers, whereas the term 'stereoisomeric' is differently used to characterize relationships between stereoisomers. When the molecule of a one-membered set is converted to a single graph (a single constitutional isomer), the molecule is defined as 'exhibiting non-stereoisomerism' or as 'being non-stereoisomerous'.

On the other hand, the term 'stereogenicity' is used to specify a molecule having a 3D structure without considering the corresponding graph. When two molecules of a set are converted into each other by ligand permutations, the two molecules of the set are defined as exhibiting stereogenicity. When a molecule of a set is converted into itself by ligand permutations, the molecule is defined as exhibiting non-stereogenicity.

It should be noted that stereoisomerism (stereoisomerous nature) is defined by convertibility into a graph. Because stereogenicity is defined by ligand permutations, it is related to diastereomeric relationships, not directly to stereoisomeric relationships (and stereoisomerism). An explanation of how stereoisomerism and stereogenicity are different requires a more general discussion on the relation between graphs and 3D structures, which is open to future investigation. But the standpoint of the present article can be summarized as follows:

Relationship	Attribute for the corresponding equivalence classes	
Stereoisomeric	Stereoisomerism	(Stereoisomerous, non-stereoisomerous)
Enantiomeric	Chirality	(Chiral, achiral)
Diastereomeric	Stereogenicity	(Stereogenic, non-stereogenic)

In order to illustrate equivalence classes due to enantiomeric and stereoisomeric relationships, Figure 3a shows equivalence classes of stereoisomeric 2,3,4-trihydroxyglutaric acids. To simplify our discussions, the CH(OH)COOH ligands of opposite configurations are denoted by the symbols p and $\overline{\text{p}}$ so as to focus our attention on the C-3 carbon of each molecule. An achiral molecule **1** (ribaric acid) constructs a one-membered equivalence class on the action of a reflection operator. Another achiral molecule **2** (xylaric acid) also constructs a one-membered equivalence class. The two molecules are typical examples of the so-called pseudoasymmetric cases. In contrast, two chiral molecules **3** and $\overline{\mathbf{3}}$ construct a two-membered equivalence class, i.e., a pair of enantiomers $\mathbf{3}/\overline{\mathbf{3}}$. Finally, the three equivalence classes, each of which is surrounded with a broken-lined box, i.e., **1**, **2**, and $\mathbf{3}/\overline{\mathbf{3}}$, coalesce so as to construct a one-membered equivalence class (a multiplet of stereoisomers) under a stereoisomeric relationship.

It should be emphasized again that conventions of stereochemistry have heavily relied on the dichotomy shown by the broken-lined boxes of Figure 1, as found by a glimpse of the above cited references or additional references on a flow-chart approach.[1,5,25,26] Comparison of Figure 1 (broken-lined boxes) with Figure 2a and a close observation of Figure 3a indicate that the dichotomy shown in Figure 1 (broken-lined boxes) suffers from unconscious emphasis on chiral molecules at the expense of achiral molecules. Moreover, two chiral molecules of each enantiomeric pair are emphasized as being *different* from each other according to Figure 1 (broken-lined boxes) so that the connotation of the prefix 'iso' (Greek *isos*=equal) of the term 'isomer' seems to be overlooked. These unconscious emphases can be avoided by introducing the concept of *equivalence classes*, as found in Figure 2a. Even by the introduction of Figure 2a, however, there remain several difficulties, which will be discussed in the following subsection.

2.2. What do *RS*-descriptors specify?

2.2.1. Diastereomeric relationships (un-)specified by RS-descriptors

Let us examine relationships between equivalence classes appearing in Figure 3a, which shows a degenerate case called 'pseudoasymmetry' traditionally. The relationship between the two achiral molecules (**1** and **2**) is diastereomeric. The relationship between an achiral molecule **1** (or **2**) and the pair $\mathbf{3}/\overline{\mathbf{3}}$ is also recognized to be diastereomeric. However, the two diastereomeric relationships are different from the capability of being named by the CIP system. Thus, the former diastereomeric relationship serves as a key for applying the CIP system, so that the C-3 of the achiral molecule **1** is designated as having *r*-configuration by considering a priority sequence $\text{OH} > \text{p} > \overline{\text{p}} > \text{H}$. The same sequence is employed to conclude that the C-3 of the other molecule **2** has

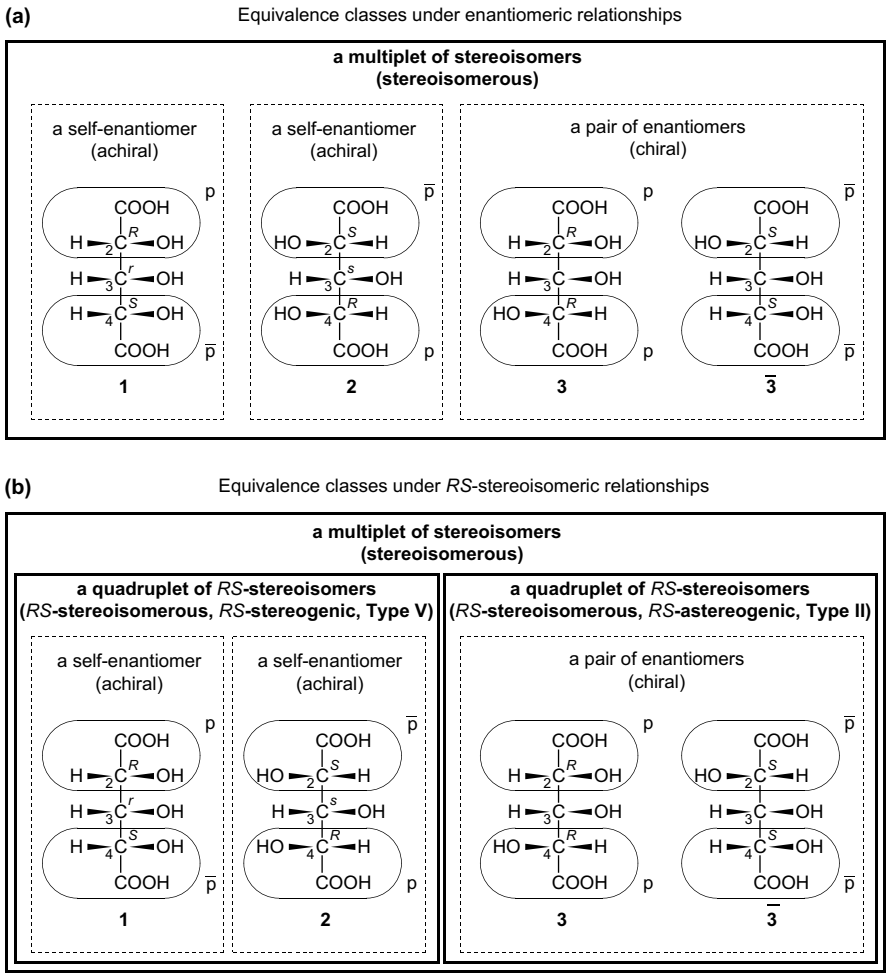

Figure 3. Equivalence classes of stereoisomeric 2,3,4-trihydroxyglutaric acids. (a) Under the action of enantiomeric relationships, equivalence classes are generated by enantiomeric and stereoisomeric relationships. (b) Under the action of *RS*-stereoisomeric relationships, equivalence classes are generated by enantiomeric, *RS*-stereoisomeric, and stereoisomeric relationships.

s-configuration. On the other hand, the latter diastereomeric relationship between **1** (or **2**) and the pair **3**/$\overline{\mathbf{3}}$ is by no means characterized by the CIP system when the C-3 of each molecule is watched.

As an example of non-degenerate case, let us next examine Figure 4a, which lists 2,3,4-trihydroxyglutaric acid monomethyl esters. In order that we focus our attention on the C-3 carbon of each molecule for the sake of simplicity, the CH(OH)COOH ligands of opposite configurations are denoted by the symbols p and $\overline{\text{p}}$ and the CH(OH)COOCH$_3$ ligands of opposite configurations are denoted by the symbols q and $\overline{\text{q}}$.

When enantiomeric relationships are applied to a multiplet of stereoisomers of 2,3,4-trihydroxyglutaric acid monoesters, there emerge four pairs of enantiomers, i.e., **4**/$\overline{\mathbf{4}}$, **5**/$\overline{\mathbf{5}}$, **6**/$\overline{\mathbf{6}}$, and **7**/$\overline{\mathbf{7}}$, as surrounded by each broken-lined box in Figure 4a. Hence there appear 6 (=3+2+1) diastereomeric relationships between these four pairs. It is a next task to clarify, which of the 6 possibilities are characterized by the CIP system.

Because the four ligands of **4** are aligned to give a priority sequence OH > q > $\overline{\text{p}}$ > H, the configuration of the C-3 of **4** is characterized by an *R*-descriptor according to the CIP system. If we employ the same priority sequence (OH > q > $\overline{\text{p}}$ > H) according to the CIP system, the corresponding *S*-descriptor is given to the C-3 of **5**. As a result, we should consider two enantiomeric pairs (**4**/$\overline{\mathbf{4}}$ and **5**/$\overline{\mathbf{5}}$) in a pairwise fashion at the same time in order to discuss the CIP system. More precisely speaking, a set of diastereomers **4** and **5** should be pairwise ascribed to a pair of *R*- and *S*-descriptors by employing the priority sequence (OH > q > $\overline{\text{p}}$ > H), while another set of diastereomers $\overline{\mathbf{4}}$ and $\overline{\mathbf{5}}$ should be pairwise ascribed to another pair of *R*- and *S*-descriptors by employing the other priority sequence (OH > $\overline{\text{q}}$ > p > H). Because of the difference in employed priority sequences, such a pairwise assignment of *R*- and *S*-descriptors is not applied to a diastereomeric relationship between **4** and $\overline{\mathbf{5}}$ or between $\overline{\mathbf{4}}$ and **5**.

On the same line, we should join **6**/$\overline{\mathbf{6}}$ and **7**/$\overline{\mathbf{7}}$(OH > q > p > H or OH > $\overline{\text{q}}$ > $\overline{\text{p}}$ > H) in order to discuss the CIP system. It follows that we should select the two diastereomeric relationships among the six possibilities, i.e., the diastereomeric relationship concerned with a set of [**4**/$\overline{\mathbf{4}}$, **5**/$\overline{\mathbf{5}}$] and the other diastereomeric relationship concerned with a set of [**6**/$\overline{\mathbf{6}}$, **7**/$\overline{\mathbf{7}}$]. The remaining four diastereomeric relationships are not specified by the CIP system when each C-3 is watched.

2.2.2. Enantiomeric relationships (un-)specified by RS-descriptors

Let us examine monomethyl esters (**8** and $\overline{\mathbf{8}}$) of 3-hydroxyglutaric acid, which are in an enantiomeric relationship as shown in Figure 5a. The pair of **8** and $\overline{\mathbf{8}}$ constructs a two-membered equivalence class, which is generated on the action of the enantiomeric relationship (a broken-lined box) as well as the action of the corresponding stereoisomeric relationship (a straight-lined box). When the CH$_2$COOH ligand and the CH$_2$COOCH$_3$ ligand (both achiral in isolation) are denoted by the symbols X and Y, a priority sequence OH>Y>X>H is applied to the C-3 centers of **8** and $\overline{\mathbf{8}}$ so

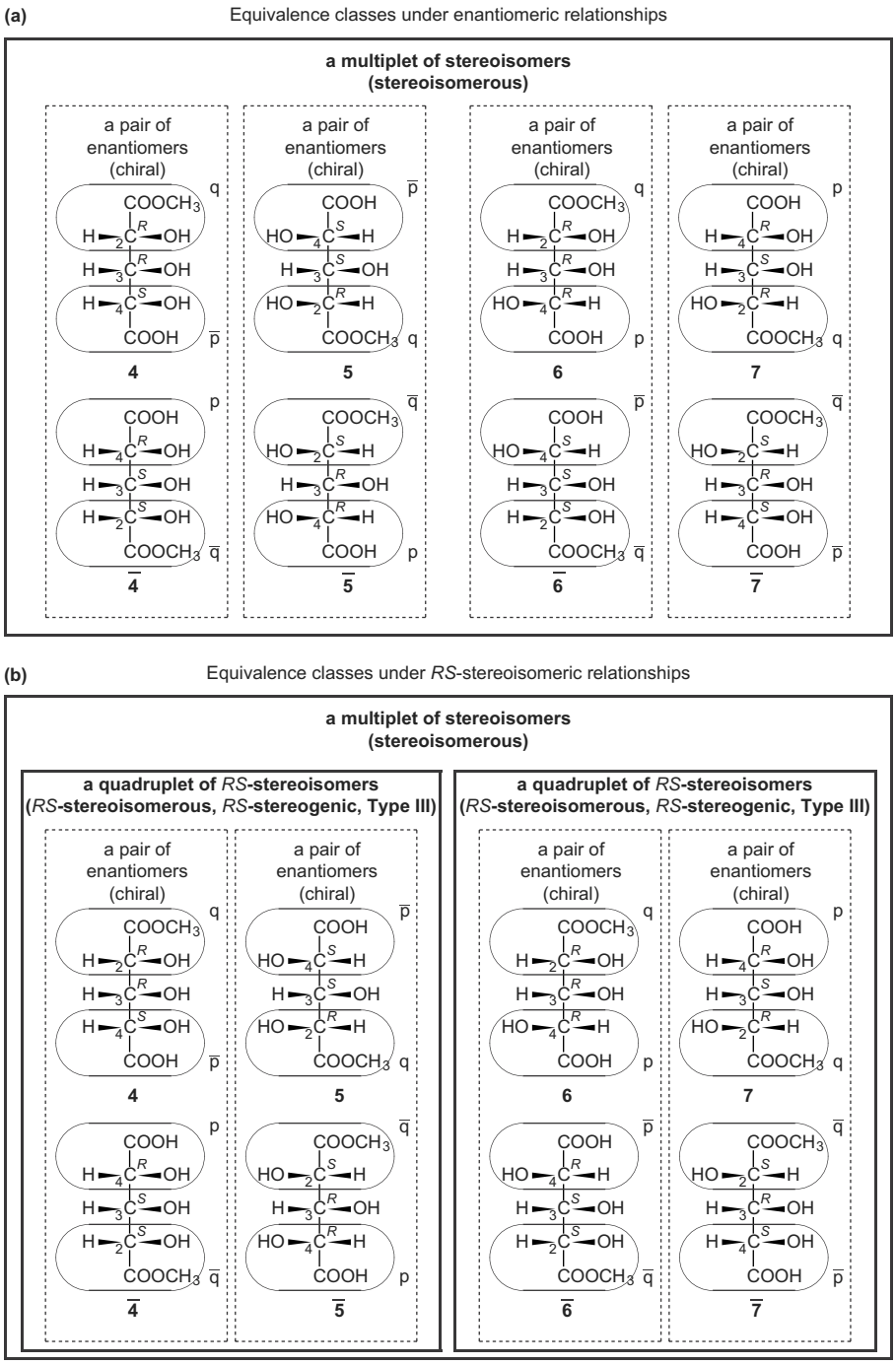

Figure 4. Equivalence classes of stereoisomeric monomethyl esters of 2,3,4-trihydroxyglutaric acids. (a) Under the action of enantiomeric relationships, equivalence classes to be considered are generated by enantiomeric and stereoisomeric relationships. (b) Under the action of *RS*-stereoisomeric relationships, equivalence classes are generated by enantiomeric, *RS*-stereoisomeric, and stereoisomeric relationships.

that their configurations are characterized by *R*- and *S*-descriptors, respectively. On the other hand, the enantiomeric pair of **3** and $\overline{\mathbf{3}}$ shown in Figure 3a cannot be characterized by *RS*-descriptors. It follows that the two enantiomeric relationships (**3**/$\overline{\mathbf{3}}$ and **8**/$\overline{\mathbf{8}}$) are different in the capability of generating *RS*-descriptors. The comparison between the two cases shows that there are two kinds of enantiomeric relationships, which can be or cannot be specified by the CIP system. Note that we pay attention to each C-3 atom.

2.2.3. *Fully degenerate cases*

An extreme case in which enantiomeric relationships and stereoisomeric relationships are reduced to generate a single equivalence class is shown in Figure 6a. There is such a single equivalence class that contains an achiral molecule (e.g., **9**) on the action of reflection. This situation is frequently referred to by saying that there are no enantiomers. As for stereoisomeric relationships in this case, a multiplet of stereoisomers consists of a single equivalence class which contains an achiral molecule (e.g., **9**). This situation is frequently referred to by saying that there are no stereoisomers. The term 'non-stereoisomerous' is tentatively used to denote this situation.

To discuss the pair of the terms 'stereoisomerous/non-stereoisomerous' or the pair of the terms 'stereogenic/non-stereogenic', a single set of operations should be defined to formulate

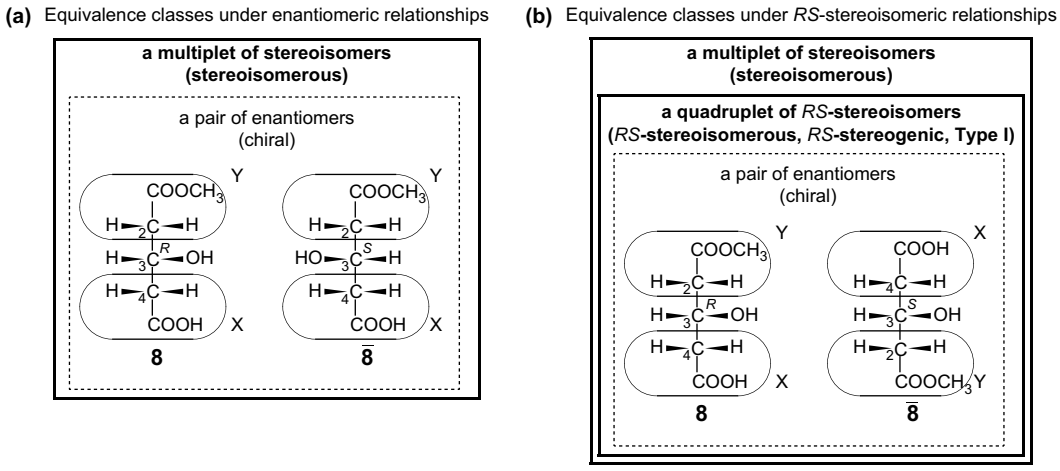

Figure 5. Equivalence classes of stereoisomeric 3-hydroxyglutaric acid monomethyl esters. (a) Under the action of enantiomeric relationships, equivalence classes to be considered are generated by enantiomeric and stereoisomeric relationships. (b) Under the action of *RS*-stereoisomeric relationships, equivalence classes are generated by enantiomeric, *RS*-stereoisomeric, and stereoisomeric relationships.

stereoisomerism or stereogenicity, just as the pair of chirality/achirality is discussed successfully by employing point groups which formulate chirality. But the direct formulation of stereoisomerism or stereogenicity is difficult so that the present approach takes an alternative way in which an appropriate part to be formulated (i.e., *RS*-stereoisomerism or *RS*-stereogenicity described below) is extracted from the whole domain of stereoisomerism or stereogenicity.

3. Paradigm shift from enantiomers to *RS*-stereoisomers as relationships

3.1. Reflection operations and permutation operations

3.1.1. Possible confusion over the two operations

Reflection operations and permutation operations are akin to each other, but definitely different in altered or unaltered configurations of ligands. For example, compare the conversion (reflection) of **4** into $\overline{\mathbf{4}}$ with the conversion (permutation) of **4** into **5**. Although the terms *proligand* and *promolecule* are used in place of terms *ligand* and *molecule* in order to treat more general cases,[27] they are not so strictly differentiated in most cases.

The chiral molecule **8** shown in Figure 5a provides a more confusing situation, which is frequently overlooked. The chiral molecule **8** is converted into its enantiomer $\overline{\mathbf{8}}$ on the action of a reflection operation. On the other hand, a permutation operation (on H/OH or on X/Y) converts **8** into $\overline{\mathbf{8}}'$, which should be finally equalized to $\overline{\mathbf{8}}$ (Fig. 7).

A stereochemical convention usually adopts the reflection operation on **8** and disregards the permutation operation on **8**. However, if we pay attention to H^{α} (*pro-S*)/H^{β} (*pro-R*) in the ligand X of **8**, they are converted into H^{α} (*pro-S*)/H^{β} (*pro-R*) in X of $\overline{\mathbf{8}}'$ along the horizontal direction, while they are differently converted into H^{α} (*pro-R*)/H^{β} (*pro-S*) in $\overline{\mathrm{X}}$ of $\overline{\mathbf{8}}$ along the vertical direction. To equalize $\overline{\mathbf{8}}'$ to $\overline{\mathbf{8}}$, we must put $\mathrm{X} = \overline{\mathrm{X}}$(and $\mathrm{Y} = \overline{\mathrm{Y}}$).

The processes illustrated in Figure 7 indicate the importance of the internal structures of the ligands X and Y. Although Figure 5a contains a reflection operation only (in the form of an enantiomeric relationship), the concealed action of such a permutation operation should be explicitly taken into consideration. Thereby, Figure 5a can be treated on the same line as Figures 3a and 4a. This point

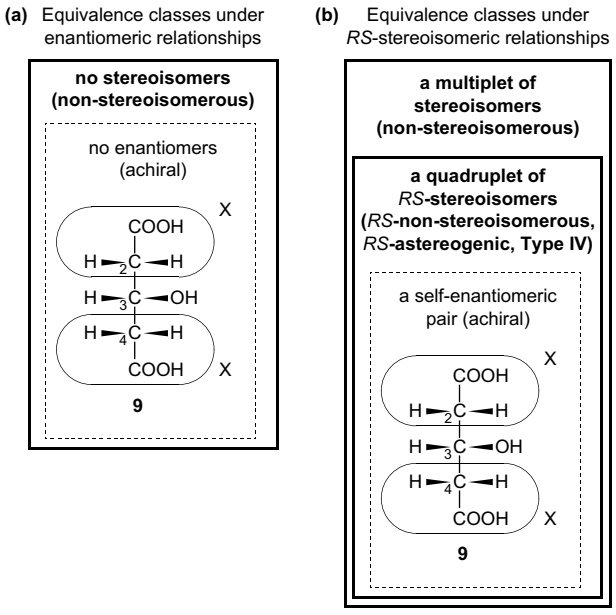

Figure 6. A single equivalence class for 3-hydroxyglutaric acid. (a) Under the action of enantiomeric relationships, a single equivalence class is generated by enantiomeric and stereoisomeric relationships. (b) Under the action of *RS*-stereoisomeric relationships, a single equivalence class is generated even by enantiomeric, *RS*-stereoisomeric, and stereoisomeric relationships.

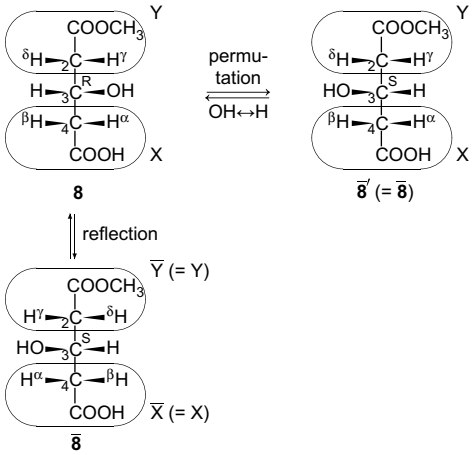

Figure 7. A permutation operation and a reflection operation applied to a chiral molecule (**8**). The former permutation operation is usually hidden behind the latter reflection operation in the conventional stereochemistry.

would be confirmed if the molecule **4** shown in Figure 4a is tested according to the scheme of Figure 7 after the molecule **4** is generated by the substitution of OH for H^{α} (in X) and H^{γ} (in Y) of **8**.

Remember that the permutation operation converting **8** into $\overline{\mathbf{8}}'$ along the horizontal direction of Figure 7 is the same kind as the operation participating in the conversion of **1** into **2** (Fig. 3a). Even though the latter operation generates a diastereomeric relationship between **1** and **2**, the pair of **8** and $\overline{\mathbf{8}}'(=\overline{\mathbf{8}})$ generated by the same operation is regarded only as being enantiomeric. Thus, such a phrase as "With the case of ligands H, OH, X, and Y, both reflection and permutation yield the enantiomer" (Phrase 1) is frequently used, even though the enantiomeric relationship is tested by reflection, but not by permutation. Although this phrase is allowable, it tends to be misunderstood as if the permutation operation converting **8** into $\overline{\mathbf{8}}'$ (Fig. 7) is ignored or at most regarded as inferior to a reflection operation. As a result, it is unclear that permutation operations correspond to which parts of stereoisomeric relationships in contrast to the fact that reflection operations exactly correspond to enantiomeric relationships. An answer to this question has been provided by the separation of *RS*-stereoisomeric relationships from stereoisomeric relationships, where stereoisograms have been developed as a versatile device for realizing such separation.[14,22]

3.2. Construction of stereoisograms

3.2.1. Three relationships defined newly

We have reported a new paradigm shown in Figure 1 (straight-lined boxes), where three relationships (enantiomeric, *RS*-diastereomeric, and holantimeric relationships) have been proposed to develop the concept of *RS*-stereoisomers.[14,22] The concept has been intuitionally demonstrated by means of stereoisograms, each of which consists of four (pro)molecules recognized as a quadruplet linked by three relationships.

According to previous articles,[14,22] we use the symbols collected in Figure 8. Three relationships (enantiomeric, *RS*-diastereomeric, and holantimeric relationships) correspond to three attributes (chirality, *RS*-stereogenicity, and sclerality). Just as chirality is accompanied with achirality, *RS*-stereogenicity is accompanied with *RS*-astereogenicity as well as sclerality is accompanied with asclerality.

When three sets of attributes, which are contained in stereoisograms (i.e., chiral/achiral, *RS*-stereogenic/*RS*-astereogenic, and scleral/ascleral) are combined, there appear eight possibilities (2^3=8). Among them, there exist five types of stereoisograms (Types I–V).[14,18,22] The existence of five types has been proved by using the group theory.[15] Such stereoisograms can be categorized by considering whether they are able or unable to be specified by *RS*-descriptors of the CIP system.

3.2.2. Stereoisograms capable of being specified by RS-descriptors

Among five possible types of stereoisograms, Figure 9 illustrates three types, which exhibit *RS*-stereogenicity, which shows the capability of giving *RS*-descriptors. Thus, one of the important conclusions derived from the concept of *RS*-stereoisomers is as follows:

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

Figure 8. Three relationships and the corresponding attributes appearing in stereoisograms.[22]

The CIP system gives an R- or S-descriptor to each RS-stereogenic molecule (Types I, III, and V). In other words, a pair of R and S-descriptors is given to two molecules in an RS-diastereomeric relationship.

For example, the enantiomeric pair (**8** and $\overline{\mathbf{8}}$) shown in Figure 5a generates a single stereoisogram shown in Figure 9a, which is characterized by a set of attributes: chiral/*RS*-stereogenic/ascleral (Type I). For the sake of convenience, a symbol such as [–, –, *a*] is used to designate the combination of chiral/*RS*-stereogenic/ascleral (Type I).

The two promolecules (**8a** and $\overline{\mathbf{8}}$**a**) of the enantiomeric pair are also in an *RS*-diastereomeric relationship (in order to emphasize promolecules generated from molecules, the suffix **a** is attached, e.g., promolecule **8a** from molecule **8**). Hence, an enantiomeric relationship and an *RS*-diastereomeric relationship appear simultaneously in a Type-I promolecule. The present approach demonstrates that the CIP system is applied to the horizontal axis (*C*-axis)

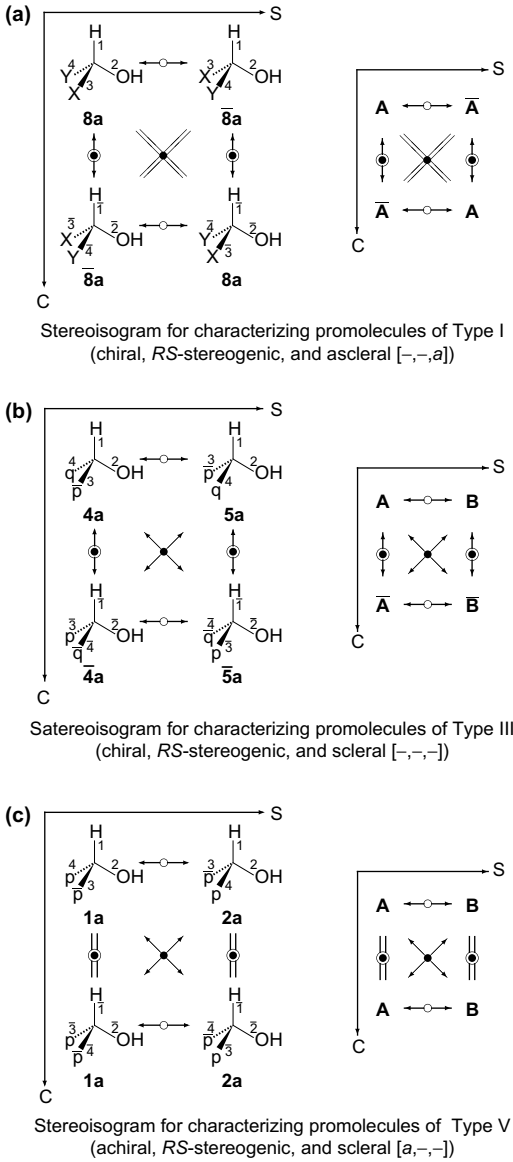

Figure 9. Stereoisograms for characterizing promolecules of Types I (A), III (B), and V (C), which are capable of being specified by *RS*-descriptors due to *RS*-stereogenicity. Each left diagram shows an illustrative example, while each right diagram shows a general expression. Each pair $\mathbf{A}/\overline{\mathbf{A}}$ or $\mathbf{B}/\overline{\mathbf{B}}$ represents a pair of enantiomers. If each pair is degenerate to give a single promolecule, it represents an achiral promolecule.

and that *R*- and *S*-descriptors are given to **8a** and $\overline{\mathbf{8}}\mathbf{a}$ in an *RS*-diastereomeric relationship by means of the priority sequence, OH>Y>X>H.

In this case, however, the conventional stereochemistry puts exclusive emphasis on an enantiomeric relationship so as to disregard any diastereomeric relationships because of the dichotomy between enantiomers and diastereomers. From the present viewpoint, *RS*-diastereomeric relationships (extracted from diastereomeric relationships) appear together with enantiomeric relationships. Even within the conventional stereochemistry, Figure 7 indicates that a diastereomeric relationship (due to a permutation operation) and an enantiomeric relationship (due to a reflection operation) are conceptually distinct from each other so as to appear simultaneously in Type I promolecules. It follows that the exclusive emphasis of enantiomeric relationships causes confusion.

The stereoisogram shown in Figure 9b belongs to Type III, which is characterized by a set of attributes: chiral/*RS*-stereogenic/scleral or [–, –, –]. This stereoisogram is a diagrammatical expression of the discussions described for Figure 4a. The C-3 atoms of **4** and **5**, which are aligned along the horizontal axis are pairwise characterized to have *R*- and *S*-configurations by employing a priority sequence OH > q > $\overline{\text{p}}$ > H. On the other hand, the configurations of the C-3 atoms of $\overline{\mathbf{4}}$ and $\overline{\mathbf{5}}$, which are aligned along the horizontal axis are pairwise characterized to have *S*- and *R*-configurations by employing another priority sequence (OH > $\overline{\text{q}}$ > p > H).

The pseudoasymmetric cases (**1** and **2**) shown in Figure 3a are joined so as to generate a single stereoisogram shown in Figure 9c. This stereoisogram is characterized by the fact that each self-enantiomeric relationship along the vertical axis (*C*-axis) is represented by an equality symbol. This means that it is specified by a set of attributes: achiral/*RS*-stereogenic/scleral or [*a*, –, –] (Type V).

Figure 9c reveals that an *RS*-diastereomeric relationship along the horizontal axis is a source of the capability of being named by the CIP system. The C-3 (*r*) of **1** and the C-3 (*s*) of **2** are specified by considering the same priority sequence OH > p > $\overline{\text{p}}$ > H. The lowercase descriptors (*r* and *s*) stem from the equality along the vertical axis (*C*-axis), which exhibits pseudoasymmetry (Type V).

Comparison of panels a–c of Figure 9 indicates that *RS*-stereogenicity is a common attribute to Types I, III, and V so that the capability of giving *RS*-descriptors of the CIP system is ascribed to the *RS*-stereogenicity. The differences between chirality and *RS*-stereogenicity exhibit various features:

(1) [Type I] This conclusion forces us to issue a statement that is seemingly contrary to the conventional dichotomy between enantiomers and diastereomers:

The enantiomeric relationship between two promolecules of each equivalence class of Type I is superposed on the RS-diastereomeric relationship between them. The RS-diastereomeric relationship is the basis of giving RS-descriptors, while the enantiomeric relationship is the basis of characterizing the chirality of them.

It should be emphasized again that an enantiomeric relationship coexists with an *RS*-diastereomeric relationship in a Type I promolecule.

(2) [Type III] Two *RS*-diastereomeric molecules of Type III are pairwise characterized by *RS*-descriptors. Although *RS*-descriptors are often misunderstood to be given pairwise to two enantiomers of Type III, the misunderstanding should be cleared up because of the presence of such reflection-invariant cases as described below.

(3) [Type V] Two *RS*-diastereomeric molecules of Type V are pairwise characterized by *RS*-descriptors. They are both achiral and should be recognized to be pseudoasymmetric molecules.

These characteristics of *RS*-stereogenic molecules (i.e., Types I, III, and V) indicate that the capability of generating *RS*-descriptors cannot be ascribed to chirality/achirality.

3.2.3. *Stereoisograms incapable of being specified by RS-descriptors*

The enantiomeric pair (**3** and $\overline{\mathbf{3}}$) shown in Figure 3a generates a single stereoisogram as shown in Figure 10a, which is characterized by a set of attributes: chiral/*RS*-astereogenic/scleral (Type II). The *RS*-astereogenic nature results in the appearance of equality symbols along the horizontal axis (*S*-axis). Thus, the two molecules (**3** and $\overline{\mathbf{3}}$) of the enantiomeric pair are characterized to be self-*RS*-diastereomeric because of the *RS*-astereogenicity. Because they are self-*RS*-diastereomeric, they are incapable of being specified by *RS*-descriptors.

The achiral molecule (**9**) shown in Figure 6a generates a single stereoisogram shown in Figure 10b, which is characterized by a set of attributes: achiral/*RS*-astereogenic/ascleral (Type IV). The four molecules contained in the stereoisogram are identical so that all the relationships contained in the stereoisogram are represented by equality symbols.

As found in Figure 10, *chiral* molecules of Type II are not characterized by *RS*-descriptors (cf. Fig. 10a) as well as *achiral* molecules of Type IV are not characterized by *RS*-descriptors (cf. Fig. 10b). This means that the incapability of generating *R*- or *S*-descriptors cannot be ascribed to chirality/achirality. Instead, such molecules Types II and IV are characterized as being *RS*-astereogenic so that the incapability of generating *R*- or *S*-descriptors should be ascribed to *RS*-astereogenicity. As a result (Figs. 9 and 10), the capability and

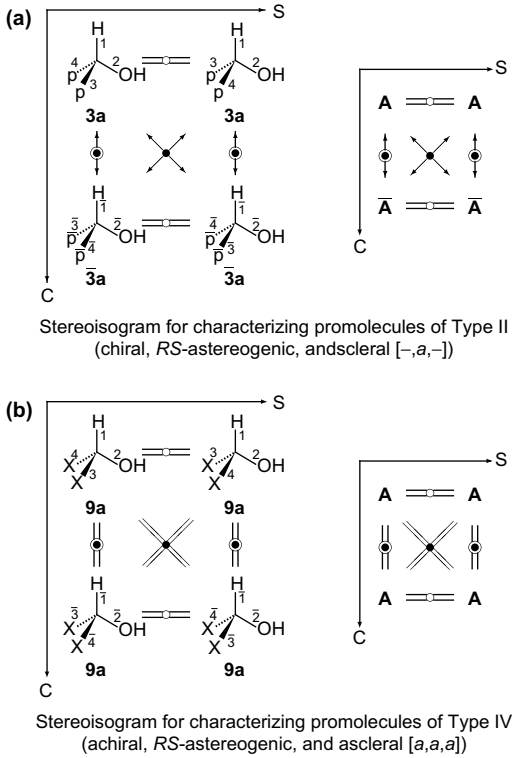

Figure 10. Stereoisograms for characterizing promolecules of Types II (A) and IV (B), which are incapable of being specified by *RS*-descriptors because of *RS*-astereogenicity. Each left diagram shows an illustrative example, while each right diagram shows a general expression. Each pair **A**/$\overline{\mathbf{A}}$ or **B**/$\overline{\mathbf{B}}$ represents a pair of enantiomers.

incapability of generating *R*- or *S*-descriptors have nothing to do with chirality/achirality.

4. Paradigm shift from enantiomers to *RS*-stereoisomers as equivalence classes

4.1. Quadruplets of *RS*-stereoisomers as equivalence classes

The paradigm shift shown in Figure 1 (the straight-lined boxes) is concerned with *RS*-stereoisomeric *relationships* separated from the conventional stereoisomeric *relationships*. A more important result derived from the paradigm shift is that a quadruplet of *RS*-stereoisomers contained in each stereoisogram constructs an equivalence class under *RS*-stereoisomeric relationships (or on the action of an *RS*-stereoisomeric group), just as a pair of enantiomers constructs an equivalence class under enantiomeric relationships (or on the action of an appropriate point group). Consequently, the equivalence classes illustrated in Figure 2a are substantially extended into equivalence classes due to *RS*-stereoisomers, as shown in Figure 2b.

A new viewpoint derived by comparing Figure 2b with Figure 2a brings about another paradigm shift concerning equivalence classes in addition to the aforementioned paradigm shift concerning relationships (the straight-lined boxes of Fig. 1). Such a quadruplet can be regarded as being composed of two enantiomeric pairs (containing self-enantiomeric pairs for achiral promolecules), of two *RS*-diastereomeric pairs (containing self-*RS*-diastereomeric pairs for *RS*-astereogenic promolecules), or of two holantimeric pairs (containing self-holantimeric pairs for ascleral promolecules). Among them, Figure 2b illustrates the first viewpoint concerning enantiomeric pairs in order to harmonize the present approach with the conventional one represented by Figure 2a. Types I–V assigned to stereoisograms can be used to categorize the corresponding quadruplets as well as each component promolecule of a quadruplet.

4.2. Equivalence classes under *RS*-stereoisomeric relationships

4.2.1. Participation of Type II and Type V promolecules

In agreement with Figure 2b, Figure 3a showing equivalence classes due to the conventional stereochemistry is modified to Figure 3b, where there emerge two stereoisograms (Types V and II), which generate two equivalence classes due to the present approach, i.e., a quadruplet (Type V) concerned with **1** and **2** and another quadruplet (Type II) concerned with **3** and $\overline{\mathbf{3}}$.

The former quadruplet (Type V) surrounded by an inner bold-line box (Fig. 3b) is characterized to be an equivalence class generated by such a stereoisogram of Type V as shown in Figure 9c, where the quadruplet is reduced to generate two achiral *RS*-diastereomers (**1** and **2**). It should be noted that the two equivalence classes of the conventional stereochemistry (Fig. 3a) coalesce into the single equivalence class of the present approach (Fig. 3b).

Just as stereoisomerism (being stereoisomerous) is correlated to stereoisomeric relationships, the term *RS*-stereoisomerism (being *RS*-stereoisomerous) is coined to indicate the capability of generating promolecules in an *RS*-stereoisomeric relationship.

Relationship	Attribute for the corresponding equivalence classes
RS-Stereoisomeric	*RS*-Stereoisomerism (*RS*-Stereoisomerous, *RS*-non-stereoisomerous)
Enantiomeric	Chirality (Chiral, achiral)
RS-Diastereomeric	*RS*-Stereogenicity (*RS*-Stereogenic, *RS*-astereogenic)

Then, the molecule **1** (or **2**) is characterized as being *RS*-stereoisomerous (as exhibiting *RS*-stereoisomerism) and as being *RS*-stereogenic, as well as being achiral and scleral (Type V). Note that the capability of generating an *R*- or *S*-descriptor for each C-3 atom stems from the *RS*-stereogenic nature of **1** (or **2**).

On the other hand, the latter quadruplet (Type II) surrounded by another inner bold-line box (Fig. 3b) is characterized to be another equivalence class generated by such a stereoisogram of Type II as shown in Figure 10a, where the quadruplet is reduced to generate a pair of enantiomers (**3** and $\overline{\mathbf{3}}$). The single equivalence class of the conventional stereochemistry (Fig. 3a) remains as the single equivalence class (Fig. 3b), although the latter involves an additional criterion due to *RS*-stereoisomerism of the present approach. Then, **3** (or $\overline{\mathbf{3}}$) is characterized as being *RS*-stereoisomerous and *RS*-astereogenic as well as being chiral and scleral (Type II). Note that the incapability of generating an *R*- or *S*-descriptor for each C-3 atom stems from the *RS*-astereogenic nature of **3** (or $\overline{\mathbf{3}}$).

Finally, the two quadruplets (Types II and V) construct a multiplet (an equivalence class) of stereoisomers as a single equivalence class under a stereoisomeric relationship, as shown in Figure 3b. Once we have abstracted the two quadruplets (Types II and V), the relationship between the two quadruplets is characterized to be diastereomeric. Note that the *RS*-stereoisomeric relationships (for characterizing each of Types II and V) and such a diastereomeric relationship (for characterizing the two quadruplets) construct the stereoisomeric relationship. This terminology implies that such a diastereomeric relationship corresponds to the boldfaced term 'others' in Figure 1 (straight-lined boxes). However, a rational explanation of the latter diastereomeric relationship requires a more general discussion, which is open to future investigation.

4.2.2. Participation of Type III promolecules

On the same line, Figure 4a showing equivalence classes due to the conventional stereochemistry is modified into Figure 4b in agreement with Figure 2b. Two stereoisograms of Type III (e.g., Fig. 9b) can be drawn to generate two equivalence classes due to the present approach, i.e., a quadruplet of $\mathbf{4}/\overline{\mathbf{4}}$ and $\mathbf{5}/\overline{\mathbf{5}}$ and a quadruplet of $\mathbf{6}/\overline{\mathbf{6}}$ and $\mathbf{7}/\overline{\mathbf{7}}$. Finally, the two quadruplets of Type III construct a multiplet of stereoisomers as a single equivalence class under a stereoisomeric relationship, as shown in Figure 4b.

Once we have abstracted the two quadruplets of Type III, the relationship between the two quadruplets is characterized to be diastereomeric. Note that the *RS*-stereoisomeric relationships (for characterizing each molecule of Type III) and such a diastereomeric relationship (for characterizing the two quadruplets) construct the stereoisomeric relationship.

4.2.3. Participation of Type I promolecules

On the same line, Figure 5a showing a single equivalence class due to the conventional stereochemistry is modified into Figure 5b in agreement with Figure 2b. Although the single equivalence class of Figure 5b remains as a single one of Figure 5b, a further categorization due to the concept of *RS*-stereoisomers is added, where a pair of enantiomers $\mathbf{8}/\overline{\mathbf{8}}$ is alternatively regarded as a quadruplet of *RS*-stereoisomers (Type I).

Comparison between Figure 5a (due to the conventional viewpoint) and Figure 5b (due to the present viewpoint) shows how important the development of stereoisograms is. Even in Figure 5b of the present viewpoint, a pair of enantiomers $\mathbf{8}/\overline{\mathbf{8}}$ is represented as a single equivalence class so that we tend to overlook the fact that an enantiomeric relationship and an *RS*-diastereomeric relationship are superposed to each other (cf. Fig. 9a).

4.2.4. Participation of a Type IV promolecule

In agreement with Figure 2b, the single equivalence class shown in Figure 6a remains as a single equivalence class, as found in Figure 6b.

The difference between Figure 6a and Figure 6b stems from an addition of an *RS*-stereoisomeric relationship. The Type IV quadruplet of *RS*-stereoisomers in Figure 6b contains only one molecule **9**, which is achiral, *RS*-astereogenic, and ascleral (cf. Fig. 10b).

5. Perspectives

5.1. Categorization of tetrahedral promolecules

Figure 11 collects promolecules derived from a tetrahedral skeleton, which are categorized into five types. Each single molecule shown in Figure 11 is an achiral molecule or an arbitrary representative selected from a pair of enantiomers. Two molecules linked with an underbrace are in *RS*-diastereomeric relationships so that they construct a stereoisogram after relevant molecules are added to generate a quadruplet of *RS*-stereoisomers.

Promolecules of Types I, III, and V are characterized by *RS*-descriptors of the CIP system. If a promolecule of Type I (**10** or **11**) is characterized to be *R* under a priority sequence A>B>X>Y or $p > \overline{p} > q > \overline{q}$, the corresponding enantiomer (omitted) is specified to have *S*-configuration. It should be noted, however, that each enantiomeric relationship is superposable on an *RS*-diastereomeric relationship and that the latter relationship gives a basis of giving an *R*- or *S*-descriptor.

Two Type III promolecules linked with each brace are pairwise specified by the CIP system. For example, if **27** is specified as having an *R*-configuration under a priority sequence A>B>X>p, the counterpart molecule **28** is ascribed to an *S*-configuration under the same sequence. The enantiomer (*S*) of **27** and the enantiomer (*R*) of **28** are pairwise specified by the CIP system under a relevant priority sequence $A > B > X > \overline{p}$. The case of **31** and **32** exhibits reflection-invariant nature, which will be discussed in the next subsection.

Two Type V promolecules **45** and **46** are pairwise specified by the CIP system. Because they are achiral, the *RS*-descriptors are represented in lowercase letters, e.g., *r* for **45** and *s* for **46** under a tentative priority sequence $A > B > p > \overline{p}$.

5.2. Reflection-invariant cases

It is worthy here to mention the term 'reflection-invariant' introduced by the revised CIP system.[11] For succinct comments on the historical aspects of the term 'reflection-invariant' and the related term 'pseudoasymmetry', see Mislow's review.[6] The new paradigm

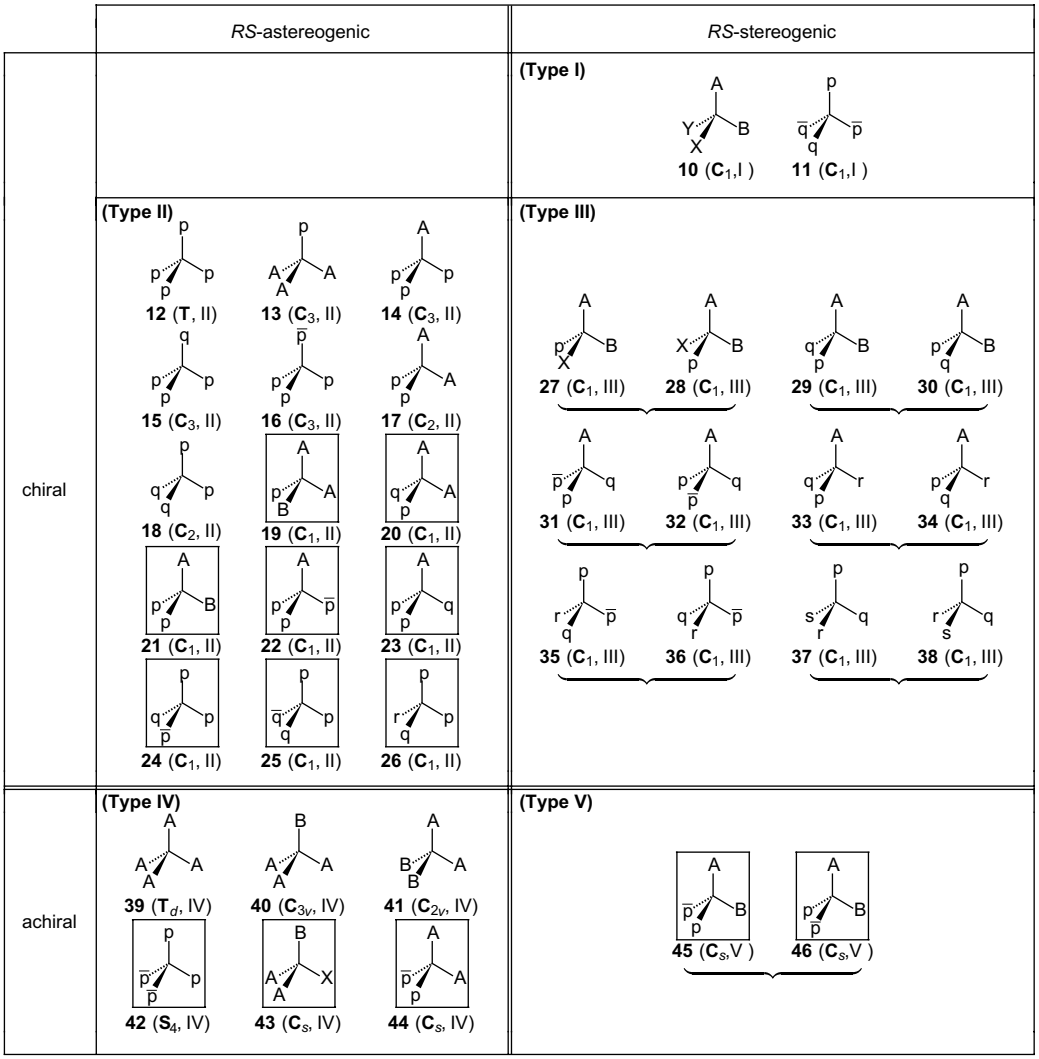

Figure 11. Five *RS*-stereoisomeric types (Types I–V) for tetrahedral molecules.[22] The symbols A, B, X, and Y represent atoms or achiral (pro)ligands. The symbols p, q, r, and s represent chiral (pro)ligands, while each symbol with an overbar represents the corresponding chiral (pro)ligand with the opposite chirality. Each promolecule surrounded by a box is a prochiral and/or pro-*RS*-stereogenic one.

shown in Figure 2b throws a more balanced light on the entangled situation of the term 'reflection-invariant'.

Suppose that the OH group of **1** is replaced by Oq (q and $\overline{q}$ are enantiomeric in isolation) to give a chiral molecule represented by C(Oq)$\overline{p}$pH (**47**), as shown in Figure 12. Molecule **47** has *R*-(or *r*-)configuration if we postulate a priority sequence Oq > p > $\overline{p}$ > H. The corresponding enantiomer is represented by C(O$\overline{q}$)$\overline{p}$pH(**$\overline{47}$**), which has *R*-(or *r*-)configuration because of the corresponding priority sequence O$\overline{q}$ > p > $\overline{p}$ > H. Because the enantiomers **47** and **$\overline{47}$** are ascribed to the same *R*-(or *r*-)configuration, their descriptors are reflection-invariant so that they are changed into lowercases according to the CIP system.

It should be noted, however, that the priority sequence Oq > p > $\overline{p}$ > H for **47** is different from the priority sequence O$\overline{q}$ > p > $\overline{p}$ > H for **$\overline{47}$** in ligand species (Oq vs O$\overline{q}$). Strictly speaking, the priority sequence Oq > p > $\overline{p}$ > H should be used to examine pairwise **47** and **48** along the horizontal axis of Figure 12, just as the priority sequence O$\overline{q}$ > p > $\overline{p}$ > H should be used to examine pairwise **$\overline{47}$** and **$\overline{48}$** on the same line.

The usage of lowercase letters for such a non-classical type as shown in Figure 12 (the leftmost stereoisogram of Type III) turns out to conceal the fact that there are four chiral molecules participating in the stereoisogram, just as four chiral molecules are contained in a usual Type III stereoisogram (cf. Fig. 9b). On the other hand, a stereoisogram for a classical type using lowercase letters contains two achiral molecules, as found in Figure 9c.

Compare the double-headed arrows along the vertical axis (*C*-axis) in Figure 12 with the equality symbols along the vertical axis (*C*-axis) in Figure 9c. Then we can safely say that the term 'reflection-invariant' is concerned only with *RS*-descriptors, not with the alternation of molecular configurations (e.g., **47** and **$\overline{47}$**). Note that the ligand Oq in **47** and the ligand OO$\overline{q}$ in **$\overline{47}$** differently influence the C-3 atoms at issue even though the C-3 atoms seem to be alike.

The equalization of such two types in the revised CIP system results in the equalization of such stereoisograms as represented by Figure 9c and Figure 12 (the leftmost stereoisogram). If the two types are referred to by lowercase descriptors (*r* or *s*), the revised CIP system would run a risk of disregarding such quantitative differences of stereoisomer numbers as exemplified in Figure 9c (two stereoisomers) and the leftmost stereoisogram of Figure 12 (four stereoisomers).

As for the term 'pseudoasymmetry', the capability of producing two stereoisomers (due to degeneration) would be a quantitative criterion to judge whether pseudoasymmetric or not. In this context, Criterion 1 described in enumerations of alkanes[28] and monosubstituted alkanes[29] would be helpful for further investigations.

5.3. Prochirality and *pro-RS*-stereogenicity

Because chirality and stereogenicity have been not so well distinguished in stereochemistry, related pairwise terms 'prochirality' and 'prostereogenicity' have been left in a more confused situation, as pointed out by the glossary section (the term 'prochirality') in the IUPAC 1996 recommendations on 'Basic Terminology of Stereochemistry'.[2] The concept of stereoisograms has proved versatile to settle completely the long-standing confusion on the term 'prochirality', where pairwise concepts of *prochirality* and *pro-RS*-stereogenicity have been proposed[16,23] by using stereoisograms on the analogy of the pairwise concepts *chirality* and *RS*-stereogenicity described here.

Among the molecules listed in Figure 11, each molecule in a straight-lined frame is prochiral and/or *pro-RS*-stereogenic.[23] As a matter of course from the present viewpoint, prochirality appears in achiral molecules (i.e., Types IV and V), while *pro-RS*-stereogenicity appears in *RS*-astereogenic molecules (i.e., Types II and IV). It should be noted that there are several molecules of Type IV exhibiting both prochirality and *pro-RS*-stereogenicity because Type IV is characterized as being achiral and *RS*-astereogenic. Their behaviors have been investigated by using stereoisograms.[16,23] One of the important conclusions is that *pro-R*/*pro-S*-descriptors proposed by Hanson[30] specify *pro-RS*-stereogenicity, but neither prochirality nor prostereogenicity, where an approach based on relationships[23] and another approach based on equivalence classes[16] have been exploited to reach the conclusion. This is parallel to the present conclusion that *RS*-descriptors of the CIP system[10,11] specify *RS*-stereogenicity, but neither chirality nor stereogenicity described in the terminology of stereochemistry, where an approach based on relationships[24] and another approach based on equivalence classes (based on separate stereoisograms)[14,15,19,20] have been exploited to reach the conclusion.

5.4. Equivalence classes for combinatorial enumerations

Even if we rely on the conventions of stereochemistry, discussions based on equivalence classes (cf. Fig. 2a) provide us with more definitive conclusions than those based on relationships (cf. the broken-lined boxes of Fig. 2). The merit of the use of equivalence classes has emerged more clearly when we have been engaged in

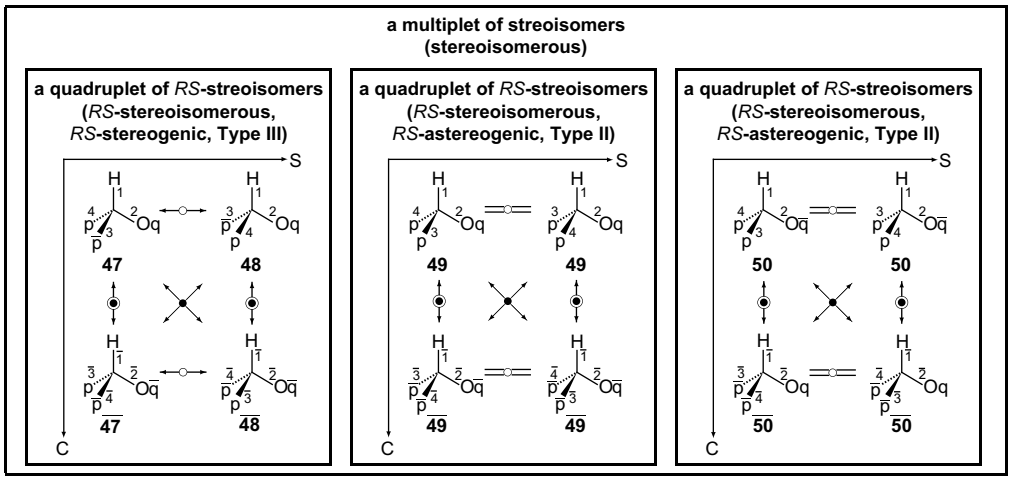

Figure 12. Stereoisogram for characterizing a reflection-invariant case (Type III) and related stereoisograms of Type II. The quadruplet of Type III is composed of two pairs of enantiomers, while each of the quadruplets of Type II is composed of one pair of enantiomers.

quantitative investigations such as enumerations of stereoisomers, where equivalence classes of ligands in a molecule are characterized by their attributes, i.e., *sphericities* (homospheric, enantiospheric, and hemispheric equivalence classes).[31,32] By employing the concept of stereoisograms, the concept of *RS-stereoisomeric relationships* is introduced as a superior concept to the concept of *enantiomeric relationships* (cf. straight-lined boxes of Fig. 2). As a matter of course, the corresponding scheme concerned with equivalence classes (cf. Fig. 2b) is applicable to qualitative discussions described in the present paper. Moreover, it turns out to be applicable to quantitative investigation on enumerations of monosubstituted alkanes[29] and alkanes,[28] where Type I and Type III molecules are related to asymmetric centers while Type V molecules are related to pseudoasymmetric centers.

6. Conclusion

Conventional approaches based on accumulation of definition terms have frequently caused 'transmutation' of the meanings of stereochemical terms, as pointed out in reviews.[6,33] In contrast, the present approach based on stereoisograms as a diagrammatical tool[14] provides us with a succinct viewpoint to stereoisomerism, where the capability of generating *RS*-descriptors is clearly ascribed to *RS*-stereogenicity.

The conventional viewpoint to stereoisomerism has relied on the hierarchy of two kinds of relationships: enantiomeric relationships and stereoisomeric relationships. On the other hand, the present viewpoint has inserted *RS*-stereoisomeric relationships as an additional kind, which is superior to enantiomeric relationships and inferior to stereoisomeric relationships. Moreover, the *RS*-stereoisomeric relationships are subdivided into three kinds of relationships: enantiomeric, *RS*-diastereomeric, and holantimeric relationships.

The introduction of stereoisograms inevitably provides a paradigm shift from the conventional viewpoint to the present one. More intimately engaged in the conventional terminology of stereochemistry, the present ideas (especially an *RS*-diastereomeric relationship superposable on an enantiomeric relationship in each Type I molecule) would be more difficult to be accepted. If one gets skillful in drawing stereoisograms, however, he/she will be able to grasp the gist of the paradigm shift.

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