MATCH
Communications in Mathematical and in Computer Chemistry

MATCH Commun. Math. Comput. Chem. **63** (2010) 25-66

ISSN 0340 - 6253

Correlation Diagrams of Stereoisograms for Characterizing Uninuclear Promolecules. A Remedy for Over-Simplified Dichotomy in Stereochemical Terminology

Shinsaku Fujita
Shonan Institute of Chemoinformatics and Mathematical Chemistry,
Kaneko 479-7 Ooimachi, Ashigara-Kami-Gun, Kanagawa-Ken,
258-0019 Japan
E-mail: fujita-sicimc@nifmail.jp

(Received December 19, 2008)

Abstract

Correlation diagrams of stereoisograms for characterizing stereoisomers have been developed so as to provide more information on both geometric and stereoisomeric features than a separate use of a stereoisogram. They are capable of solving most problems which have been left unsolved within the traditional terminology of stereochemistry and related chemoinformatics practices, e.g., over-simplified features of the conventional dichotomy between enantiomers and diastereomers, incomplete separation of *RS*-stereogenicity from chirality, unconscious disregard of local *RS*-stereogenicity and confusion of it with local chirality, implications of reflection-invariant cases of the CIP priority system, and others.

1 Introduction

Although the terms *chirality* and *stereogenicity* have been pointed out to be conceptually distinct, they are closely related to each other so that they have caused serious confusion over stereochemical terminology and related practices of chemoinformatics. For example, the Cahn-Ingold-Prelog (CIP) priority system of giving *RS*-descriptors has initially been proposed to

specify molecular chirality, as shown by the title "Specification of Molecular Chirality" of the article [1]. The revised CIP priority system [2] has changed its basis to specify stereogenicity, which was introduced in the form of stereogenic units. This terminology based on stereogenic units (stereogens/stereoelements) has been adopted by the IUPAC Recommendations (1996) [3]. Further discussions on chirality and stereogenicity have appeared in order to clarify the relationship between them [4, 5]. In particular, Helmchen's article [5] (Paragraph 1.1.5.3.4 "Symmetry Consistency of the CIP Specification" on page 32) has described "Although the CIP system is mainly based on stereogenicity there is a high degree of symmetry consistency." and enumerated four criteria to check *RS*-descriptors for symmetry consistency.

In spite of these discussions, tetrahedral carbons having four different substituents have still been called "asymmetric centers" or "chiral centers", even though the use of the term "stereogenic centers" has become predominant [6, 7, 8, 9]. Moreover, there have still remained serious problems due to an unsolved question as to *how stereogenicity is different from and related to chirality*. One of such problems was concerned with pseudoasymmetry, where *RS*-descriptors should be or should not be used in lowercase letters (*r* and *s*). For example, Mislow-Siegel's comments [4] on "pseudoasymmetric centers" were critically cited in the Helmchen's article [5], which was again commented by Mislow [10]. The crux of the discussions is whether a pseudoasymmetric center is allowed to be present in a chiral molecule [5] or not [4], because the chemical tradition has linked pseudoasymmetric centers to achiral molecules as found in articles [11, 4] and textbooks [12, 13].

As demonstrated by Fujita [14, 15], incomplete differentiation between chirality and stereogenicity has been mainly brought about by over-simplified features of the conventional dichotomy between enantiomers and diastereomers. For the purpose of remedying such over-simplified features, Fujita has proposed the concept of *RS-stereoisomers* [16], which were subclasses of stereoisomers and categorized into *enantiomers*, *RS-diastereomers*, and *holantimers* by means of three relationships involved in *stereoisograms*, i.e., enantiomeric, *RS*-diastereomeric, and holantimeric relationships. The three relationships were correlated to three attributes, i.e., chirality (the same as the traditional term), *RS*-stereogenicity, and sclerality, so that such a stereoisogram as containing at most four *RS*-stereoisomers has been classified into one of five types (Types I–V). The five types have been specified by combining chirality (or achirality), *RS*-stereogenicity (or *RS*-astereogenicity), and sclerality (or asclerality) on the basis of *RS*-stereoisomeric groups. Thereby, the existence of only five types has been proven by showing the existence of five types of subgroups of *RS*-stereoisomeric groups [17]. The versatility of stereoisograms of Types I–V has been demonstrated by applying them to various type of compounds [18, 19, 20, 21] as well as to the problems of pseudoasymmetry [22] and prochirality [23, 24].

By virtue of the the concept of *RS*-stereoisomers, 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 in Fig. 1 [14, 15]. One of the merits provided by the paradigm shift is to discuss the problems described above by using stereoisograms (i.e., within the level of *RS*-stereoisomers), so that we are able to avoid apparent inconsistency between geometric features (e.g., chirality) and stereoisomerism (e.g., stereogenicity and *RS*-nomenclature). Thereby, the capability of giving *RS*-descriptors has been ascribed to *RS*-stereogenicity (not chirality nor stereogenicity) [16] and the capability of giving *pro-R*/*pro-S*-descriptors has been ascribed to pro-*RS*-stereogenicity (not prochirality nor prostereogenicity) [23, 15].

Although the paradigm shift shown in Fig. 1 has provided us with a new prospect over

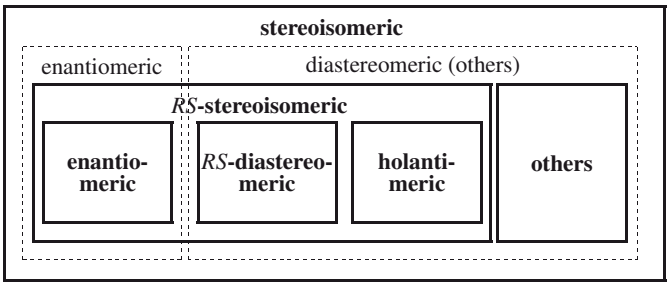


Figure 1: Paradigm shift from the conventional terminology to the present terminology for stereoisomerism. A broken-lined box represents a term of the conventional terminology, while a solid-lined box represents a term of the present terminology.

stereochemistry, the results described in the preceding paragraphs were mainly restricted to cases with one *RS*-stereogenic center (or related site) and took no direct account of cases with two or more *RS*-stereogenic centers. In other words, the results have focused mainly on the global symmetry of a given molecule, where a specific carbon center was selected to represent the molecule and then the local symmetry at the specific carbon center was examined in place of the global symmetry by means of the corresponding stereoisogram [16]. As a result, a single stereoisogram corresponding to the global symmetry of one *RS*-stereogenic center has been investigated to throw a light on problems due to the conventional paradigm (dotted boxes in Fig. 1). Multiple use of stereoisograms to investigate two or more *RS*-stereogenic centers [14] has remained within processes of trial and error so that it has not arrived at a systematic format in comparison with cases of one *RS*-stereogenic center [16]. To gain deeper insight of stereochemistry, a new device for examining local symmetries along with the global symmetry should be developed, where it is capable of covering cases of two or more *RS*-stereogenic centers by keeping balanced watch on both global and local symmetries.

The present paper is devoted to develop systematic solutions to cover such cases as requiring two or more stereoisograms. We will describe the development of *correlation diagrams of stereoisograms*, which are defined as effective sets of stereoisograms for specifying a given set of stereoisomers. They will be proven to be a versatile device for rigorous distinction between local chirality and local *RS*-stereogenicity, which have been traditionally mixed up by the term "local symmetry" or even worse by the term "local chirality". In addition, they will provide us with a conceptually well-defined tool for solving problems due to over-simplified features involved in the conventional dichotomy between enantiomers and diastereomers.

2 Results

2.1 Basic Terminology

According to previous articles [16, 25], the symbols collected in 1 are employed to indicate three relationships to draw stereoisograms. For the sake of simplicity, our discussions will be restricted to tetrahedral carbons. To introduce stereoisograms, it is important to differentiate

Table 1: Three Relationships in Stereoisograms and the Corresponding Attributes

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

between permutation operations and reflection operations.

Permutation operations A permutation operation causes the interchange of two ligands on a tetrahedral skeleton *without change of ligand chirality*. To represent this operation, the symbol ◯ is used to denote an operation of causing a skeletal change but no change of ligand chirality.

Reflection operations A reflection operation is an operation of generating the mirror image of an original object where the changing of a skeleton is accompanying with *the change of ligand chirality*. If the symbol • denotes an operation of changing ligand chirality with no skeletal change, the combination of ◯ and • means the changing of a skeleton along with ligand chirality.

In particular, the emphasized phrases concerning ligand chirality (change or no change) are crucial to understand the difference between geometric (3D structural) features and stereoisomerism. However, the change or no change of ligand chirality is often overlooked so that there has emerged unconscious confusion over the two operations, when they are applied to tetrahedral carbons.

The three relationships correspond to three pairs of attributes for characterizing a promolecule: chiral/achiral, *RS*-stereogenic/*RS*-astereogenic, and scleral/ascleral. As a result, there appear an enantiomeric pair (enantiomers) for chirality, an *RS*-diastereomeric pair (*RS*-diastereomers) for an *RS*-stereogenicity, and a holantimeric pair (holantimers) for a scleral-ity, which are collectively called *RS-stereoisomers*. Among eight modes of combination, five modes listed in 2 are effective to characterize stereoisograms, each of which contains four *RS*-stereoisomers at most.

2.2 Enantiomers vs. *RS*-Stereoisomers

To treat molecules having two or more *RS*-stereogenic centers, we here derive principles (Principles 1–4) which govern enantiomers and *RS*-stereoisomers having two or more *RS*-stereogenic centers.

2.2.1 Implied Connotations as to Enantiomers of Traditional Terminology

Promolecules for Characterizing Local Symmetries In order to discuss configurations at respective carbon centers, it is convenient to use the concepts of *proligands* and *promolecules*,

Table 2: Five Types of *RS*-Stereoisomers Specified by Stereoisograms

type	three attributes		
Type I:	chiral 	*RS*-stereogenic 	ascleral 
Type II:	chiral 	*RS*-astereogenic 	scleral 
Type III:	chiral 	*RS*-stereogenic 	scleral 
Type IV:	achiral 	*RS*-astereogenic 	ascleral 
Type V:	achiral 	*RS*-stereogenic 	scleral 

where the chirality/achirality of each ligand is only taken into consideration [26]. Let us consider *meso*-2,4-dihydroxyglutaric acid **1** as an achiral molecule (Fig. 2), where the mirror image $\overline{\mathbf{1}}$ is identical with the original molecule **1** without considering locant numbers, as shown by the symbol  . The global symmetry (achirality) is represented by the configuration at No. 3 carbon (C_3). By replacing the two chiral ligands incident to C_3 by chiral proligands r and $\bar{r}$, we are able to generate an achiral promolecule $\mathbf{1}_3$ (identical with $\overline{\mathbf{1}}_3$), which represents the global achirality of the molecule **1** (Throughout the present article, a structure number having a locant number as a subscript (e.g., $\mathbf{1}_3$) is used to designate the corresponding promolecule). Although the promolecule $\mathbf{1}_3$ (identical with $\overline{\mathbf{1}}_3$) represents the local symmetry at the C_3 atom, it also represents the global symmetry. It should be noted here that the above-mentioned global symmetry (global achirality) stems from the traditional terminology of stereochemistry up to this step, where the traditional terminology is silent about global *RS*-astereogenicity, which is part of the global symmetry from the present viewpoint.

Let us next pay attention to the configuration at the C_2 atom of **1** (and its self-enantiomeric $\overline{\mathbf{1}}$). By replacing the two chiral ligands incident to C_2 by proligands r_1 and $\bar{r}_1$, we are able to generate a chiral promolecule $\mathbf{1}_2$ from **1** and its enantiomeric promolecule $\overline{\mathbf{1}}_2$ from $\overline{\mathbf{1}}$. The local symmetry (local chirality) at the C_2 atom, which is characterized by the pair of enantiomeric promolecules $\mathbf{1}_2$ and $\overline{\mathbf{1}}_2$, is not identical with the global symmetry (achirality) of **1**. Although $\mathbf{1}_2$ and $\overline{\mathbf{1}}_2$ are different from each other, both of them represent the same entity **1**, if the proligands r_1 and $\bar{r}_1$ are returned into the original concrete forms. This is confirmed by comparing between the locant numbers of **1** and those of $\overline{\mathbf{1}}$ (appearing in the leftmost illustration of Fig. 2).

As for the configuration at the C_4 atom of **1** (and its self-enantiomeric $\overline{\mathbf{1}}$), a similar substitution of proligands r_1 and $\bar{r}_1$ generates a chiral promolecule $\mathbf{1}_4$ from **1** and its enantiomeric promolecule $\overline{\mathbf{1}}_4$ from $\overline{\mathbf{1}}$. The local symmetry (local chirality) at the C_4 atom is characterized by the pair of enantiomeric promolecules $\mathbf{1}_4$ and $\overline{\mathbf{1}}_4$ and is not identical with the global symmetry (achirality) of **1**. Although $\mathbf{1}_4$ and $\overline{\mathbf{1}}_4$ are different from each other, both of them represent the same entity **1**, if the proligands r_1 and $\bar{r}_1$ are returned into the original concrete forms. This is confirmed by comparing **1** with $\overline{\mathbf{1}}$ with respect of locant number 4 (appearing in the "molecule"-column of Fig. 2).

It should be noted again that the above-mentioned local symmetry (local chirality) for characterizing a pair of enantiomeric promolecules $\mathbf{1}_2/\overline{\mathbf{1}}_2$ or another pair of enantiomeric promolecules $\mathbf{1}_4/\overline{\mathbf{1}}_4$ cannot not be related to local *RS*-stereogenicity within the traditional terminology, because this is silent about such local *RS*-stereogenicity as being part of the local symmetry from the present viewpoint.

Throughout the present article, the term "enantiomeric" is used mainly, while the use of

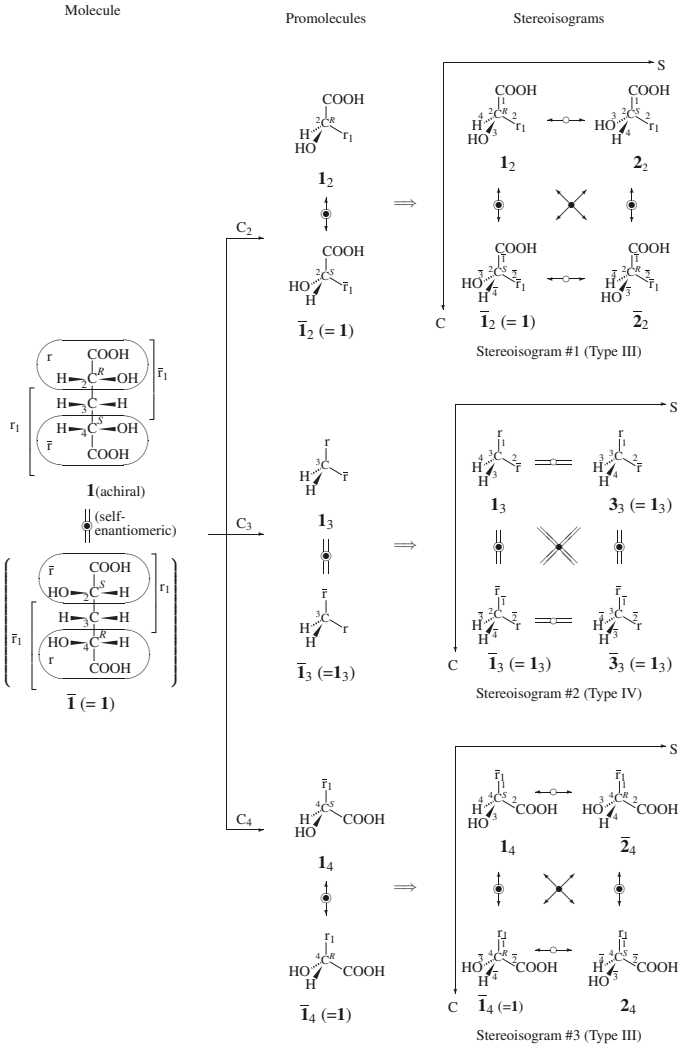


Figure 2: Transformation of an achiral molecule (*meso*-2,4-dihydroxyglutaric acid) into promolecules. The "promolecules"-column represents a pair of promolecules for characterizing local chirality/achirality, while the "stereoisograms"-column represents a quadruplet of promolecules for characterizing local chirality/achirality as well as local *RS*-stereogenicity/*RS*-astereogenicity.

the term “enantiomorphic” is avoided. This is because the introduction of the term “self-enantiomeric” paired with the term “enantiomeric” has brought about a standpoint of treating (pro)ligands and (pro)molecules in a common framework. Thus, the terms “enantiomeric” and “self-enantiomeric” are used to indicate such cases as $\mathbf{1}_2/\overline{\mathbf{1}}_2$ and $\mathbf{1}_4/\overline{\mathbf{1}}_4$ as well as to the case of $\mathbf{1}_3/\overline{\mathbf{1}}_3$, which represents the global and local symmetries at the same time.

Pairwise Appearance of Enantiomeric Promolecules As found easily, the promolecules listed in the “promolecules”-column of Fig. 2 emerge pairwise, i.e., $\mathbf{1}_3/\overline{\mathbf{1}}_3$ (a self-enantiomeric pair, i.e., $\mathbf{1}_3 = \overline{\mathbf{1}}_3$), $\mathbf{1}_2/\overline{\mathbf{1}}_2$ (an enantiomeric pair), $\mathbf{1}_4/\overline{\mathbf{1}}_4$ (an enantiomeric pair), where each pair represents the same molecular entity as **1** (= $\overline{\mathbf{1}}$). This fact can be extended into general cases:

> **(Principle 1)** [Pairwise appearance of enantiomeric promolecules] A given enantiomeric pair (or self-enantiomeric pair) of *molecules* is represented by an enantiomeric pair (or a self-enantiomeric pair) of *promolecules* generated with respect to each carbon center selected from the molecule.

Principle 1 means that a pairwise relationship between enantiomers is invariant if any *RS*-stereogenic centers or other sites are selected to be examined. It should be noted that the selected carbon center may or may not be an *RS*-stereogenic center, as exemplified by the C_3 atom of **1**. If necessary (e.g., in case of tartaric acids), an appropriate bond can be selected to generate such an enantiomeric pair (or a self-enantiomeric pair) of promolecules. One of the merits provided by the use of the concepts of proligands and promolecules is that each local symmetry can be examined in the form of a promolecule, as found by Principle 1.

Principle 1 can be also confirmed by considering a pair of chiral molecules, e.g., an enantiomeric pair of chiral 2,4-dihydroxyglutaric acids **2**/$\overline{\mathbf{2}}$ (Fig. 3), where the mirror image $\overline{\mathbf{2}}$ is different from the original molecule **2** as shown by the symbol $\leftarrow\!\!\bullet\!\!\rightarrow$. The global symmetry (chirality) is represented by the configuration at No. 3 carbon (C_3), because **2** (or $\overline{\mathbf{2}}$) is considered to have a centroidal carbon-skeleton. By replacing the two chiral ligands incident to C_3 by two chiral proligands r's (or two r̄'s), we are able to generate an enantiomeric pair of chiral promolecules $\mathbf{2}_3/\overline{\mathbf{2}}_3$, which represents the global chirality of the molecule **2** in terms of the promolecule $\overline{\mathbf{2}}_3$ or $\overline{\mathbf{2}}_3$. Although the promolecule $\mathbf{2}_3$ (or $\overline{\mathbf{2}}_3$) represents the local symmetry at the C_3 atom, it also represents the global symmetry.

The configuration at the C_2 atom of **2** (and its enantiomeric $\overline{\mathbf{2}}$) is characterized by the corresponding enantiomeric pair of promolecules $\mathbf{2}_2/\overline{\mathbf{2}}_2$ (the “promolecule”-column of Fig. 3). On a similar line, the configuration at the C_4 atom of **2** (and its enantiomeric $\overline{\mathbf{2}}$) is characterized by the corresponding enantiomeric pair of promolecules $\mathbf{2}_4/\overline{\mathbf{2}}_4$ (the “promolecule”-column of Fig. 3).

The promolecules listed in the “promolecules”-column of Fig. 3 emerge pairwise, i.e., $\mathbf{2}_3/\overline{\mathbf{2}}_3$ (an enantiomeric pair), $\mathbf{2}_2/\overline{\mathbf{2}}_2$ (an enantiomeric pair), $\mathbf{2}_4/\overline{\mathbf{2}}_4$ (an enantiomeric pair), where each pair represents the same pair of molecular entities **2**/$\overline{\mathbf{2}}$. This case is another example of Principle 1.

Appearance of Enantiomeric Pairs with a Fixed Locant Number Let us compare between Fig. 2 and Fig. 3, where the achiral molecule **1**(= $\overline{\mathbf{1}}$) and the pair of enantiomeric molecules **2**/$\overline{\mathbf{2}}$ are decided as being diastereomeric so as to construct a set of stereoisomers. To decide such diastereomeric relationships, the traditional methodology of stereochemistry only examines whether or not the two pairs of enantiomers (in this case an achiral molecule **1** and a pair

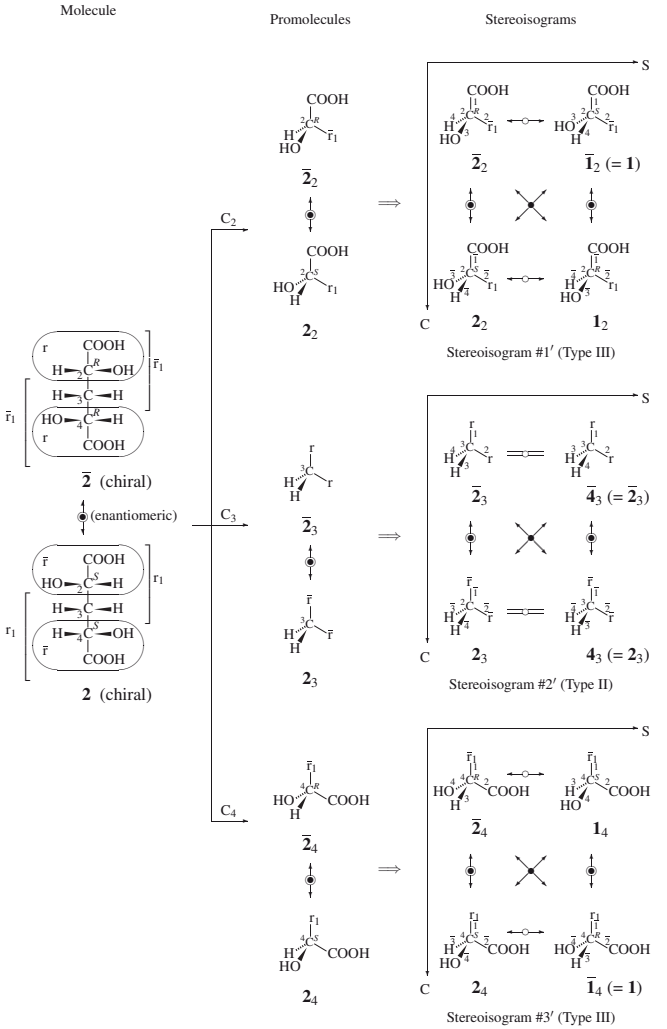


Figure 3: Transformation of chiral molecules (chiral 2,4-dihydroxyglutaric acid) into promolecules. The "promolecules"-column represents a pair of promolecules for characterizing local chirality/achirality, while the "stereoisograms"-column represents a quadruplet of promolecules for characterizing local chirality/achirality as well as local *RS*-stereogenicity/*RS*-astereogenicity.

of **2**/$\overline{\mathbf{2}}$) have the same constitution so as to give a single graph. This process of examination is qualitatively clear but have no recipe supported by mathematically well-defined operations.

The comparison between the "promolecule" column of Fig. 2 and the corresponding column of Fig. 3 gives another viewpoint which modifies the traditional methodology. Suppose that stereoisomers have carbon centers which are specified by common locant numbers. Then, the corresponding promolecules at a carbon center having a fixed locant number are collected to be examined. For example, when the C_2 atom is selected as such a carbon center, an enantiomeric pair of promolecules $\mathbf{1}_2/\overline{\mathbf{1}}_2$ (corresponding to the achiral molecule **1**) can be compared with another enantiomeric pair of promolecules $\mathbf{2}_2/\overline{\mathbf{2}}_2$ (corresponding to the pair **1**/$\overline{\mathbf{2}}$). Thereby, we find that $\mathbf{1}_2$ (or $\overline{\mathbf{1}}_2$) is convertible into $\mathbf{2}_2$ (or $\overline{\mathbf{2}}_2$) by a permutation operation. This conversion is beyond the scope of the traditional stereochemistry which lacks the concept of promolecules generated at a carbon center having a fixed locant number. Whether such a conversion is considered or not, the two enantiomeric pairs can cover the set of stereoisomers according to Principle 1.

On similar line, the C_4 atom is selected as such a carbon center, we can find that $\mathbf{1}_4$ (or $\overline{\mathbf{1}}_4$) is convertible into $\mathbf{2}_4$ (or $\overline{\mathbf{2}}_4$) by a permutation operation. According to Principle 1, the two enantiomeric pairs can cover the set of stereoisomers.

If the C_3 atom is selected as such a carbon center, an achiral promolecule $\mathbf{1}_3$ (= $\overline{\mathbf{1}}_3$) (corresponding to the achiral molecule **1**) cannot be correlated to an enantiomeric pair of promolecules $\mathbf{2}_3/\overline{\mathbf{2}}_3$ (corresponding to the pair **1**/$\overline{\mathbf{2}}$) by a permutation operation. Even in this case, $\mathbf{1}_3$ (= $\overline{\mathbf{1}}_3$) and $\mathbf{2}_3/\overline{\mathbf{2}}_3$, which are generated at the fixed C_3 atom, can cover the set of stereoisomers (i.e., **1** (= $\overline{\mathbf{1}}$) and and **2**/$\overline{\mathbf{2}}$).

In summary, once a (self-)enantiomeric pair of promolecules is formulated at a carbon center with a fixed locant number, such a (self-)enantiomeric pair can be moved to cover all of stereoisomers. This holds true for any carbon centers (or any bonds if necessary):

> **(Principle 2)** [Enantiomeric pairs with a fixed locant number to cover a stereoisomeric set] Suppose that a set of stereoisomers is classified into (self-)enantiomeric pairs and that their carbon centers (or the bond if necessary) are correlated to each other by common numbering. All of such (self-)enantiomeric pairs are exhaustively enumerated by considering enantiomeric pairs at any one of such corresponding carbon centers (or the bond if necessary).

Principle 2 can be derived only by considering a set of (self-)enantiomeric pairs of promolecules at an arbitrarily fixed carbon center (or a bond) according to the concept of promolecules. It should be noted that Principle 2 is concerned with (self-)enantiomeric pairs contained in a stereoisomeric set and that it does not refer to diastereomeric relationships.

2.2.2 Stereoisograms for Specifying Global and Local Symmetries

According to the present methodology based on stereoisograms, we can developed a more systematic way than simple use of promolecules (cf. the "promolecules"-column of Fig. 2 and Fig. 3.

A Quadruplet of Promolecules in a Stereoisogram According to the present methodology, the promolecule $\mathbf{1}_3$ (identical with $\overline{\mathbf{1}}_3$) is regarded as being involved in a Type-IV stereoisogram (Stereoisogram #2), as found in the "stereoisogram" column of Fig. 2. See 2 for the assignment of Type IV to Stereoisogram #2. The *RS*-astereogenic character of the promolecule $\mathbf{1}_3$ is shown

by the equality symbol along with the horizontal S-axis, while the achiral character $\mathbf{1}_3$ is shown by the equality symbol along with the vertical C-axis.

On the other hand, the promolecules $\mathbf{1}_2/\overline{\mathbf{1}}_2$ are regarded as two components of a Type-III stereoisogram (Stereoisogram #1), where they appear along the vertical C-axis in the first diagram of the "stereoisogram" column of Fig. 2. The *RS*-stereogenic character of the promolecule $\mathbf{1}_2$ (or $\overline{\mathbf{1}}_2$) generates another promolecule $\mathbf{2}_2$ (or $\overline{\mathbf{2}}_2$) so that they are differentiated by means of *RS*-descriptors. Thus, the priority sequence OH > COOH > r_1 > H specifies the configuration of the C_2 atom of $\mathbf{1}_2$ as being *R*, while that of $\mathbf{2}_2$ as being *S*. The other priority sequence OH > COOH > $\bar{r}_1$ > H specifies the configuration of the C_2 atom of $\overline{\mathbf{1}}_2$ as being *S*, while that of $\overline{\mathbf{2}}_2$ as being *R*.

In a similar way, promolecules $\mathbf{1}_4/\overline{\mathbf{1}}_4$ are regarded as two components of a Type-III stereoisogram (Stereoisogram #3), where they appear along the vertical C-axis in the first diagram of the "stereoisogram" column of Fig. 2. The *RS*-stereogenic character of the promolecule $\mathbf{1}_4$ (or $\overline{\mathbf{1}}_4$) generates another promolecule $\mathbf{2}_4$ (or $\overline{\mathbf{2}}_4$). Stereoisogram #3 is essentially identical to Stereoisogram #1, if the modes of locant numbering are disregarded.

On a similar line, Fig. 3 can be explained by Stereoisograms #1′, #2′, and #3′. It should be noted that Stereoisograms #1 and #1′ are essentially equivalent; and also Stereoisograms #3 and #3′ are essentially equivalent. On the other hand, Stereoisogram #2 is Type IV, while Stereoisogram #2′ is Type II.

In summary, Stereoisograms #1–#3 in Fig. 2 contain respective quadruplets which are concerned with pairs of promolecules corresponding to a common molecule $\mathbf{1}$ ($= \overline{\mathbf{1}}$). Stereoisograms #1′–#3′ in Fig. 3 contain respective quadruplets which are concerned with pairs of promolecules corresponding to a common pair of molecules $\mathbf{2}/\overline{\mathbf{2}}$.

Principle 1 is modified to cover such quadruplets as contained in stereoisograms.

> **(Principle 3)** [Quadruplet appearance of *RS*-stereoisomeric promolecules] Suppose that a given enantiomeric (or self-enantiomeric) pair of molecules corresponds to an enantiomeric (or self-enantiomeric) pair of promolecules which is generated at each carbon center (or bond or site if necessary) selected from the molecule according to Principle 1. Then, a quadruplet of *RS*-stereoisomeric promolecules at the carbon center (or bond or site) contains the enantiomeric (or self-enantiomeric) pair of promolecules and another enantiomeric (or self-enantiomeric) pair of promolecules. The two enantiomeric pairs contained in the quadruplet may be superposed to represent the same enantiomeric pair.

Principle 3 is concerned with a quadruplet of *RS*-stereoisomeric promolecules contained in a stereoisogram which is generated at the corresponding carbon center having a fixed locant number (or an appropriately fixed bond or site). This implies that local symmetry at the carbon center involves local chirality (or local achirality) and local *RS*-stereogenicity (or local *RS*-astereogenicity), both of which are specified by the stereoisogram at issue.

Stereoisograms with a Fixed Locant Number When a (self-)enantiomeric pair at a carbon center with a fixed locant number is selected from a set of stereoisomers according to Principle 2, another (self-)enantiomeric pair at the carbon center is specified to generate a quadruplet. Such a quadruplet can be specified uniquely. Next, one of the remaining (self-)enantiomeric pairs at the carbon center with a fixed locant number is selected from a set of stereoisomers, another (self-)enantiomeric pair at the carbon center is specified to generate a quadruplet. This

procedure is repeated to cover the set of stereoisomers. To formulate this procedure of repetition, Principle 2 is converted to describe quadruplets of promolecules:

> **(Principle 4)** [Appearance of quadruplets of promolecules in a stereoisomer set] Suppose that a set of stereoisomers is classified into (self-)enantiomeric pairs and that their carbon centers (or bonds or sites if necessary) are correlated to each other by common numbering. Quadruplets at any one of such commonly-numbered carbon centers (or bonds or sites if necessary) can be constructed to cover the set of stereoisomers.

2.3 Correlation Diagrams of Stereoisograms

Principles 1–4 indicate that a set of stereoisomers of which locant numbers are commonly given can be examined by means of stereoisograms which are constructed at a carbon center with a fixed locant number. The present subsection is devoted to introduce correlation diagrams of stereoisograms, which have been developed as a diagrammatical device of visualizing Principles 1–4.

2.3.1 Construction of Correlation Diagrams

To grasp total features of stereoisomeric 2,4-dihydroxyglutaric acids, we should integrate Fig. 2 and Fig. 3. First, we examine the C_3 atom of each of the stereoisomers as a central atom. Although the C_3 atom is not *RS*-stereogenic, the examination of the C_3 atom is necessary to show the achirality of **1**. A self-enantiomeric pair of promolecules (i.e., an achiral promolecule **1**) and an enantiomeric pair of promolecules (**2** and $\overline{\mathbf{2}}$) (as well as promolecules necessary to draw stereoisograms) are arranged to occupy peripheral positions, which are fixed according to Principles 1 and 2 if other central atoms are selected. Then, Stereoisograms #2 (Fig. 2) and #2′(Fig. 3) are drawn, as shown in Fig. 4. The obtained diagram is called a *correlation diagram* of stereoisograms. The common locant numbering assures the generation of stereoisogram at a fixed carbon center according to Principles 3 and 4. The subscript of each promolecule number (e.g., $\mathbf{1}_3$) indicates such a fixed central atom (e.g., C_3). Although the promolecule $\mathbf{1}_3$ and its *RS*-diastereomer $\mathbf{3}_3$ (and other pairs of promolecules linked by an equality symbol) represents the same molecular entity, they are tentatively differentiated by numbering because two hydrogens at the C_3 atom are permuted (see Stereoisograms #2 (Fig. 2) and #2′ (Fig. 3)). Such duplications are necessary to show the features of promolecules of Type II and Type IV in Fig. 4.

Let us next consider the C_2 atom of 2,4-dihydroxyglutaric acids by using the data collected in Fig. 2 and Fig. 3. The C_2 atom is *RS*-stereogenic to give the corresponding correlation diagram concerning Stereoisogram #1 and #1′, as shown in Fig. 5. Stereoisogram #1 contained in Fig. 5 is identical with Stereoisogram #1 contained in Fig. 2. On the other hand, Stereoisogram #1′ contained in Fig. 5 is different in the reference numbers from Stereoisogram #1′ contained in Fig. 2, because the correspondences between $\mathbf{3}_2$ (= **1**) and $\mathbf{3}_3$ (= **1**) and between $\mathbf{4}_2$ (= **2**) and $\mathbf{4}_3$ (= **2**) are taken into consideration.

Note that Stereoisograms #1 and #1′ contained in Fig. 5 is are equivalent, just as the counterparts listed in Fig. 2 and Fig. 3 are equivalent.

On a similar line, another epimeric correlation diagram of stereoisograms where the 4-carbon of each stereoisomer is regarded as a central atom, where Stereoisogram #3 (Fig. 2) is integrated with #3′ (Fig. 3).

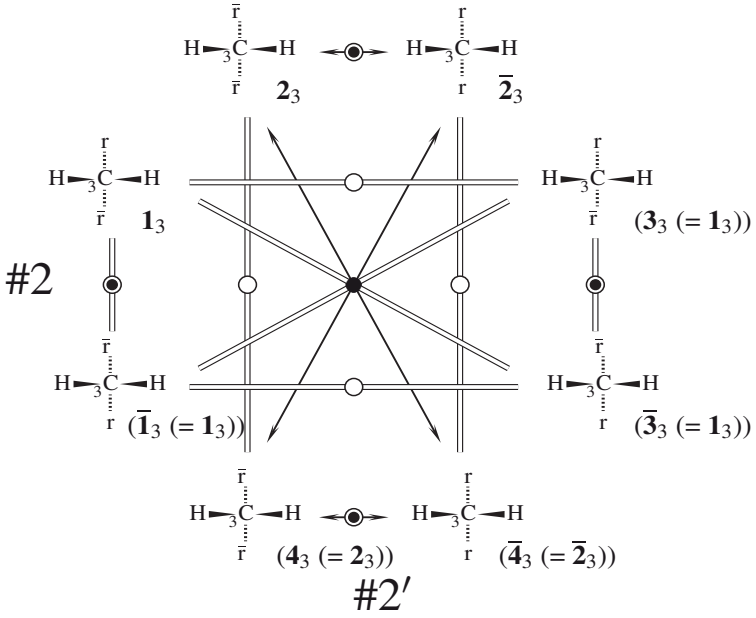


Figure 4: A main correlation diagram of stereoisograms for stereoisomeric 2,4-dihydroxyglutaric acids, where the 3-carbon of each stereoisomer is regarded as a central atom so as to give Stereoisogram #2 (Type IV) and Stereoisogram #2′ (Type II).

2.3.2 Correlation Diagrams for Three *RS*-Stereogenic Centers

In this subsection, we first draw correlation diagrams for a non-degenerate case having three *RS*-stereogenic centers, and then compare them with correlation diagrams for a degenerate case.

Pentoses as a Non-Degenerate Case We first examine a set of pentose stereoisomers (open-chain forms) having three *RS*-stereogenic carbon centers, as shown in Fig. 6. In the present methodology, the eight pentoses are pairwise considered: **5**/$\overline{\mathbf{5}}$, **6**/$\overline{\mathbf{6}}$, **7**/$\overline{\mathbf{7}}$, and **8**/$\overline{\mathbf{8}}$, where locant numbers are commonly attached to respective carbon atoms.

When we focus our attention on an *RS*-stereogenic atom of a fixed locant number appearing in each enantiomeric pair (**5**/$\overline{\mathbf{5}}$, **6**/$\overline{\mathbf{6}}$, **7**/$\overline{\mathbf{7}}$, or **8**/$\overline{\mathbf{8}}$), we obtain three correlation diagrams shown in Fig. 7(A–C).

The correlation diagram of Fig. 7(A) concerned with the C_3 atom contains two stereoisograms, where Stereoisogram #1 of Type III consists of a quadruplet of promolecules, i.e., $\mathbf{5}_3$, $\overline{\mathbf{5}}_3$, $\mathbf{7}_3$, and $\overline{\mathbf{7}}_3$; and Stereoisogram #2 of Type III consists of another quadruplet of promolecules, i.e., $\mathbf{6}_3$, $\overline{\mathbf{6}}_3$, $\mathbf{8}_3$, and $\overline{\mathbf{8}}_3$. The following items should be mentioned with respect to the capability of giving *RS*-descriptors of the CIP priority system.

1. In Stereoisogram #1 of Fig. 7(A), the *RS*-diastereomeric relationship between $\mathbf{5}_3$ and $\mathbf{7}_3$

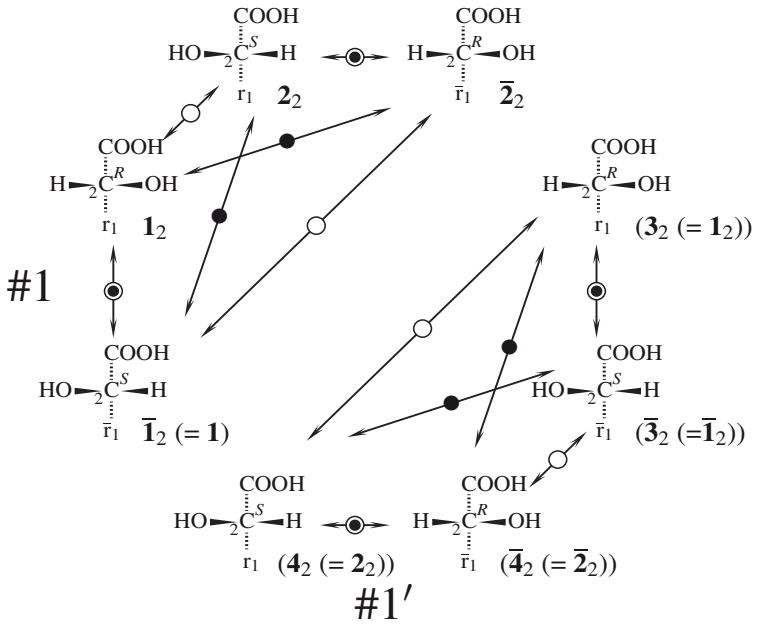


Figure 5: An epimeric correlation diagram of stereoisograms stereoisomeric 2,4-dihydroxyglutaric acids, where the 2-carbon of each stereoisomer is regarded as a central atom so as to give Stereoisogram #1 (Type III) and Stereoisogram #1′ (Type III). The two stereoisograms are degenerate.

indicates local *RS*-stereogenicity, which corresponds to *R*- and *S*-configuration in terms of the priority sequence, OH > p > q > H. On the other hand, the *RS*-diastereomeric relationship between $\overline{\mathbf{5}}_3$ and $\overline{\mathbf{7}}_3$ gives *S*- and *R*-configuration, respectively, in terms of the other priority sequence, OH > $\overline{\text{p}}$ > $\overline{\text{q}}$ > H.

2. In Stereoisogram #2 of Fig. 7(A), the *RS*-diastereomeric relationship between $\mathbf{6}_3$ and $\mathbf{8}_3$ indicates local *RS*-stereogenicity, which corresponds to *R*- and *S*-configuration because of the priority sequence, OH > $\overline{\text{p}}$ > q > H. The *RS*-diastereomeric relationship between $\overline{\mathbf{6}}_3$ and $\overline{\mathbf{8}}_3$ gives *S*- and *R*-configuration, respectively, because of the priority sequence, OH > p > $\overline{\text{q}}$ > H.

3. It should be emphasized that the enantiomeric relationship between $\mathbf{5}_3$ and $\overline{\mathbf{5}}_3$ (or their local chirality) by no means determines the *RS*-descriptors. In other words, the *R*-configuration of $\mathbf{5}_3$ have nothing to do with the *S*-configuration of $\overline{\mathbf{5}}_3$, so long as the two priority sequences (OH > p > q > H for $\mathbf{5}_3$ and OH > $\overline{\text{p}}$ > $\overline{\text{q}}$ > H for $\overline{\mathbf{5}}_3$) are different. Only after the two priority sequences are equalized, the *R*-configuration of $\mathbf{5}_3$ can be correlated to the *S*-configuration of $\overline{\mathbf{5}}_3$. This equalization is implicitly presumed by the CIP priority system.

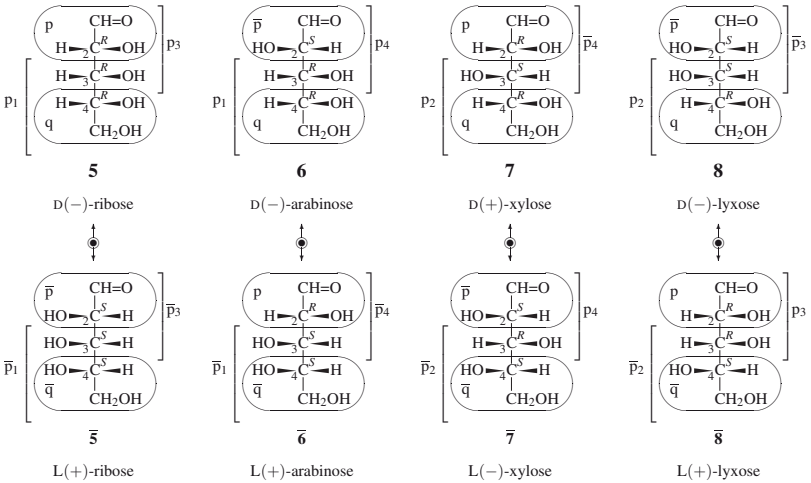


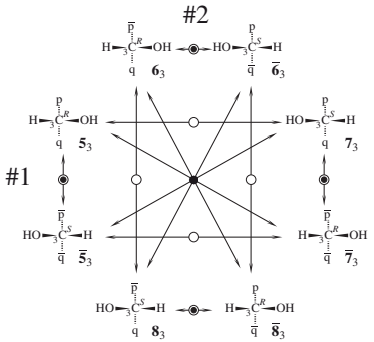
Figure 6: Four enantiomeric pairs of pentoses. Proligands for correlation diagrams of stereoisograms are designated by p, $\overline{\text{p}}$, and so on.

The correlation diagram of Fig. 7(B) for the C_2 atom, in which the position of each enantiomeric pair is correlated to that of Fig. 7 according to Principle 2, contains two stereoisograms, i.e., Stereoisogram #1 of Type III consists of a quadruplet of promolecules, i.e., $\mathbf{5}_2$, $\overline{\mathbf{5}}_2$, $\mathbf{6}_2$, and $\overline{\mathbf{6}}_2$. and Stereoisogram #2 of Type III consists of another quadruplet of promolecules, i.e., $\mathbf{7}_2$, $\overline{\mathbf{7}}_2$, $\mathbf{8}_2$, and $\overline{\mathbf{8}}_2$.

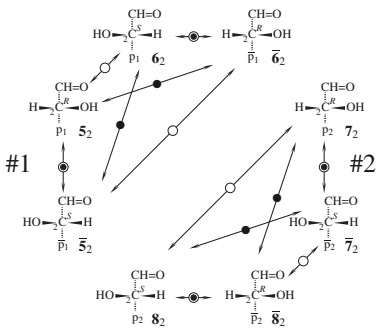
The three items described for Fig. 7(A) hold true for the stereoisograms appearing in Fig. 7(B). Thus, *RS*-diastereomeric relationships contained in Stereoisogram #1 of Fig. 7(B), i.e., $\mathbf{5}_2/\mathbf{6}_2$ (the priority sequence: OH > CH=O > p_1 > H) and $\overline{\mathbf{5}}_2/\overline{\mathbf{6}}_2$ (the priority sequence: OH > CH=O > $\overline{p}_1$ > H), as well as those contained in Stereoisogram #2 of of Fig. 7(B), i.e., $\mathbf{7}_2/\mathbf{8}_2$ (the priority sequence: OH > CH=O > p_2 > H) and $\overline{\mathbf{7}}_2/\overline{\mathbf{8}}_2$ (the priority sequence: OH > CH=O > $\overline{p}_2$ > H), represent local *RS*-stereogenicity, which is a basis of giving *RS*-descriptors. The enantiomeric relationships (or their local chirality) contained in Stereoisograms #1 and #2 of Fig. 7(B) (e.g., $\mathbf{5}_2/\overline{\mathbf{5}}_2$) are incapable of giving a basis to the determination of the *RS*-descriptors because of the difference between the participating priority sequences.

The correlation diagram of Fig. 7(C) for the C_4 atom contains two stereoisograms, i.e., Stereoisogram #1 of Type III consists of a quadruplet of promolecules, i.e., $\mathbf{5}_4$, $\overline{\mathbf{5}}_4$, $\mathbf{8}_4$, and $\overline{\mathbf{8}}_4$. and Stereoisogram #2 of Type III consists of $\mathbf{6}_4$, $\overline{\mathbf{6}}_4$, $\mathbf{7}_4$, and $\overline{\mathbf{7}}_4$.

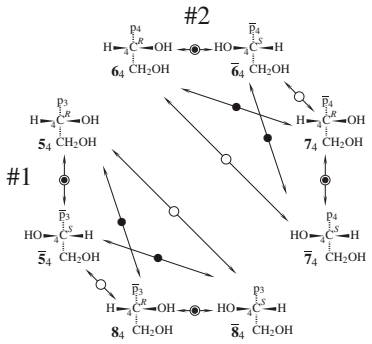
The three items described for Fig. 7(A) also hold true for the stereoisograms appearing in Fig. 7(C), where *RS*-diastereomeric relationships contained in these stereoisograms represent local *RS*-stereogenicity, which is a basis of giving *RS*-descriptors. Thus, Stereoisogram #1 Fig. 7(C) affords the following *RS*-diastereomeric pairs: $\mathbf{5}_4/\overline{\mathbf{8}}_4$ (the priority sequence: OH > p_3 > CH_2OH > H) and $\overline{\mathbf{5}}_4/\mathbf{8}_4$ (the priority sequence: OH > $\overline{p}_3$ > CH_2OH > H). On the other hand, Stereoisogram #2 Fig. 7(C) affords the following *RS*-diastereomeric pairs: $\mathbf{6}_4/\overline{\mathbf{7}}_4$ (the priority sequence: OH > p_4 > CH_2OH > H) and $\overline{\mathbf{6}}_4/\mathbf{7}_4$ (other priority sequence: OH > $\overline{p}_4$ > CH_2OH



(A) Correlation Diagram at C_3



(B) Correlation Diagram at C_2



(C) Correlation Diagram at C_4

Figure 7: Correlation diagrams of stereoisograms for pentose stereoisomers. (A) For C_3: Stereoisograms of #1 and #2 both belong to Type III, where OH > p ($\overline{p}$) > q ($\overline{q}$) > H; (B) For C_2: Stereoisograms #1 and #2 belong to Type III, where OH > CH=O > p_1 ($\overline{p}_1$) > H and OH > CH=O > p_2 ($\overline{p}_2$) > H; and (C) For C_4: Stereoisograms #1 and #2 belong to Type III, where OH > p_3 ($\overline{p}_3$) > CH_2OH > H and OH > p_4 ($\overline{p}_4$) > CH_2OH > H.

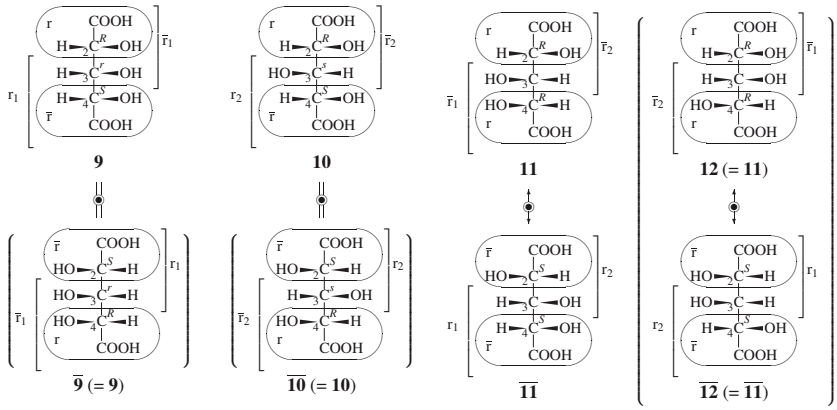


Figure 8: Two achiral isomers and one enantiomeric pair of 2,3,4-trihydroxyglutaric acids. Two formulas **9** and **9′** (or the other two formulas **10** and **10′**) represent the same entity, although the modes of numbering for carbon atoms are altered. The formulas **11** and $\overline{\mathbf{11}}$ represents an enantiomeric pair. Proligands for drawing correlation diagrams of stereoisograms are designated by r, $\bar{\mathrm{r}}$, and so on.

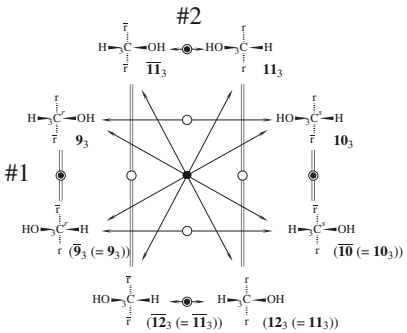
$>$ H). The enantiomeric relationships (or their local chirality) contained in Stereoisograms #1 and #2 of Fig. 7(C) (e.g., $\mathbf{5}_4/\overline{\mathbf{5}}_4$) are incapable of giving a basis to the determination of the *RS*-descriptors because of the difference between the participating priority sequences.

Degenerate Case due to Pseudoasymmetry The set of stereoisomeric 2,3,4-trihydroxyglutaric acids is composed of an achiral molecule **9**, another achiral molecule **10**, and an enantiomeric pair of molecules **11**/$\overline{\mathbf{11}}$. To show the degenerate features of this set, we add $\overline{\mathbf{9}}$ (= **9**), $\overline{\mathbf{10}}$ (= **10**), and **12**/$\overline{\mathbf{12}}$ (= **11**/$\overline{\mathbf{11}}$) in pairs of parentheses. It should be noted that the degeneration is removed when the modes of locant numbering are taken into consideration. For example, **9** and $\overline{\mathbf{9}}$ are different in their modes of locant numbering, although they represent the same molecular entity.

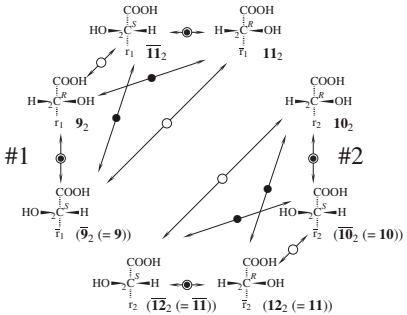
When our attention is paid to an *RS*-stereogenic atom of a fixed locant number appearing in each (self-)enantiomeric pair **9**(= $\overline{\mathbf{9}}$), **10** (= $\overline{\mathbf{10}}$) and **11**/$\overline{\mathbf{11}}$ along with the supplementary enantiomeric pair **12**/$\overline{\mathbf{12}}$, three correlation diagrams are obtained, as shown in Fig. 9(A–C).

The correlation diagram of stereoisograms shown in Fig. 9(A) is concerned with the C_3 atom of each (self-)enantiomeric pair and contains Stereoisogram #1 of Type V (a quadruplet of promolecules, i.e., $\mathbf{9}_3$, $\overline{\mathbf{9}}_3$ (identical with $\mathbf{9}_3$), $\mathbf{10}_3$, and $\overline{\mathbf{10}}_3$ (identical with $\mathbf{10}_3$)) and Stereoisogram #2 of Type II (a quadruplet of promolecules, i.e., $\mathbf{11}_3$, $\overline{\mathbf{11}}_3$, $\mathbf{12}_3$, and $\overline{\mathbf{12}}_3$, where the two enantiomeric pairs are identical with each other).

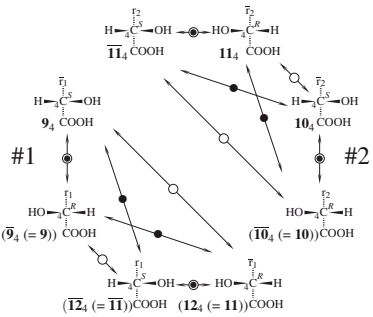
Stereoisogram #1 (Type V) of Fig. 9(A) has the *RS*-diastereomeric relationship between $\mathbf{9}_3$ and $\mathbf{10}_3$, so that the corresponding local *RS*-stereogenicity is capable of specify *r*- and *s*-configurations by means of the priority sequence, OH $>$ r $>$ $\bar{\mathrm{r}}$ $>$ H. In agreement with its Type-V character, the *RS*-diastereomeric relationship between $\overline{\mathbf{9}}_3$ and $\overline{\mathbf{10}}_3$ is identical with the one between $\mathbf{9}_3$ and $\mathbf{10}_3$ so as to represent degeneration due to pseudoasymmetry. Because the above *RS*-diastereomeric relationship concerned with the two achiral promolecules $\mathbf{9}_3$ and $\mathbf{10}_3$



(A) Correlation Diagram at C_3



(B) Correlation Diagram at C_2



(C) Correlation Diagram at C_4

Figure 9: Correlation diagrams of stereoisograms for stereoisomeric 2,3,4-trihydroxyglutaric acids. (A) For C_3: Stereoisogram #1 belongs to Type V, while Stereoisogram #2 belongs to Type II, where OH > r > $\bar{\text{r}}$ > H; (B) For C_2: Stereoisograms #1 and #2 belong to Type III. where OH > COOH > r_1 ($\bar{r}_1$) > H and OH > COOH > r_2 ($\bar{r}_2$) > H; and (C) For C_4: Stereoisograms #1 and #2 belong to Type III. where OH > COOH > r_1 ($\bar{r}_1$) > H and OH > COOH > r_2 ($\bar{r}_2$) > H.

(contained in the Stereoisogram #1 of Type V), the corresponding *RS*-descriptors are denoted by lowercase letters (*r* and *s*).

Stereoisogram #2 of Type II contained in the correlation diagram of Fig. 9(A) exhibits local *RS*-astereogenicity, because of the self-*RS*-diastereomeric relationship between $\mathbf{11}_3$ and $\mathbf{12}_3$ (i.e., $\mathbf{11}_3 \eqcirc \mathbf{12}_3$). Thus the *RS*-astereogenicity corresponds to the incapability of giving *RS*-descriptors. On a similar line, the self-*RS*-diastereomeric relationship between $\overline{\mathbf{11}}_3$ and $\overline{\mathbf{12}}_3$ gives no *RS*-descriptors.

The correlation diagram shown in Fig. 9(B) contains two stereoisograms of Type III, which can be used to discuss the configurations at the C_2 atoms. Stereoisogram #1 consists of a quadruplet of promolecules, i.e., $\mathbf{9}_2$, $\overline{\mathbf{9}}_2$, $\mathbf{11}_2$, and $\overline{\mathbf{11}}_2$, where both $\mathbf{9}_2$ and $\overline{\mathbf{9}}_2$ correspond to a single achiral molecular entity (**9**). The *RS*-diastereomeric relationship between $\mathbf{9}_2$ and $\overline{\mathbf{11}}_2$ indicates local *RS*-stereogenicity, which corresponds to *R*- and *S*-configurations by means of the priority sequence, OH > COOH > r_1 > H. The *RS*-diastereomeric relationship between $\overline{\mathbf{9}}_2$ (parenthesized to show duplication) and $\mathbf{11}_2$ gives *S*- and *R*-configurations because of the priority sequence, OH > COOH > $\bar{r}_1$ > H.

Stereoisogram #2 (Type III) of Fig. 9(B) consists of a quadruplet of promolecules, i.e., $\mathbf{10}_2$, $\overline{\mathbf{10}}_2$, $\mathbf{12}_2$, and $\overline{\mathbf{12}}_2$, where $\mathbf{10}_2$ and $\overline{\mathbf{10}}_2$ corresponds to a single achiral molecular entity (**10**). Note that the enantiomeric pair of promolecules $\mathbf{12}_2/\overline{\mathbf{12}}_2$ are parenthesized because the pair corresponds to the pair of molecules $\mathbf{12}/\overline{\mathbf{12}}$ just as the enantiomeric pair of promolecules $\mathbf{11}_2/\overline{\mathbf{11}}_2$ corresponds to the same pair $\mathbf{12}/\overline{\mathbf{12}}$. However, the proligands $r_2/\bar{r}_2$ in the former pair is different form the proligands $r_1/\bar{r}_1$ in the latter pair. The *RS*-diastereomeric relationship between $\mathbf{10}_2$ and $\overline{\mathbf{12}}_2$ indicates local *RS*-stereogenicity, which corresponds to *R*- and *S*-configuration because of the priority sequence, OH > COOH > r_2 > H. The *RS*-diastereomeric relationship between $\overline{\mathbf{10}}_2$ and $\mathbf{12}_2$ gives *S*- and *R*-configurations because of the priority sequence, OH > COOH > $\bar{r}_2$ > H.

The correlation diagram of stereoisograms shown in Fig. 9(C) is concerned with the C_4 and contains two stereoisograms of Type III, i.e., Stereoisogram #1 (a quadruplet of promolecules, i.e., $\mathbf{9}_4$, $\overline{\mathbf{9}}_4$, $\mathbf{12}_4$, and $\overline{\mathbf{12}}_4$) and Stereoisogram #2 (a quadruplet of promolecules, i.e., $\mathbf{10}_4$, $\overline{\mathbf{10}}_4$, $\mathbf{11}_4$, and $\overline{\mathbf{11}}_4$).

Stereoisogram #1 of Fig. 9(C) for the C_4 is essentially equivalent to Stereoisogram #1 of Fig. 9(B) for the C_2 because of the degenerate nature of this case. On a similar line, Stereoisogram #2 of Fig. 9(C) for the C_4 is essentially equivalent to Stereoisogram #2 of Fig. 9(B) for the C_2 because of the degenerate nature of this case.

2.3.3 Correlation Diagrams for Four *RS*-Stereogenic Centers

On a similar line to the cases having three *RS*-stereogenic centers, we first draw correlation diagrams for a non-degenerate case having four *RS*-stereogenic centers, and then compare them with correlation diagrams for a degenerate case.

Trihydroxyglutaric Acid Esters as a Non-Degenerate Case Figure 10 collects a set of 3-lactoyloxy-2,4-dihydroxyglutaric acid monomethyl esters, which are categorized into eight enantiomeric pairs. Because the eight enantiomeric pairs, **13/$\overline{13}$**, **14/$\overline{14}$**, **15/$\overline{15}$**, **16/$\overline{16}$**, **17/$\overline{17}$**, **18/$\overline{18}$**, **19/$\overline{19}$**, and **20/$\overline{20}$** are accompanied by common locant numbers, the local symmetry of each atom with a fixed locant number is examined to cover all of the enantiomeric pairs.

By focusing our attention on an *RS*-stereogenic atom of a fixed locant number appearing in each enantiomeric pair (**13/$\overline{13}$**, **14/$\overline{14}$**, **15/$\overline{15}$**, **16/$\overline{16}$**, **17/$\overline{17}$**, **18/$\overline{18}$**, **19/$\overline{19}$**, or **20/$\overline{20}$**), we obtain

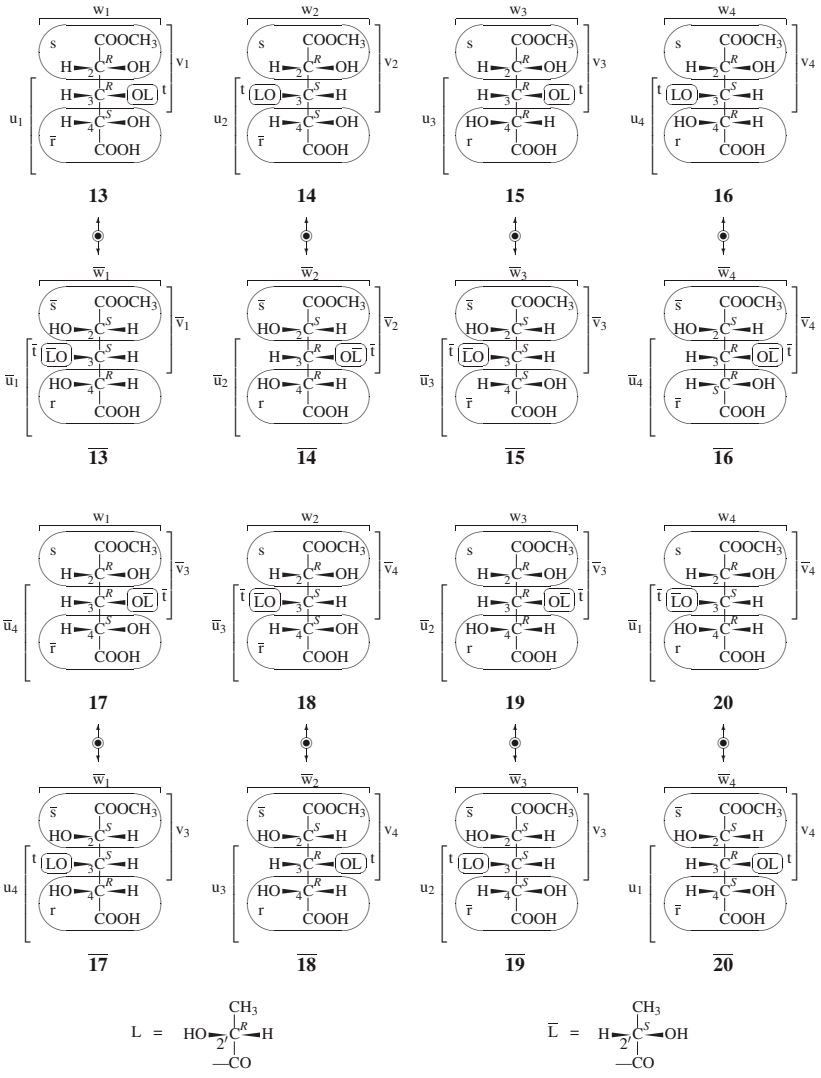


Figure 10: Eight enantiomeric pairs of 3-lactoyloxy-2,4-dihydroxyglutaric acid monomethyl esters. Proligands for drawing correlation diagrams are designated by letters r, r̄, and so on.

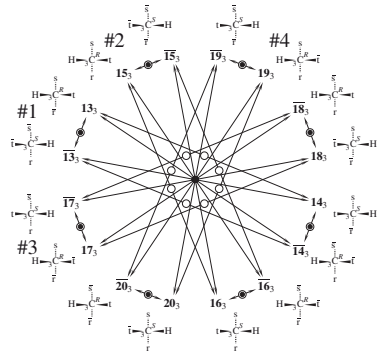
four correlation diagrams shown in Fig. 11(A–D).

The correlation diagram of Fig. 11(A) for the C_3 atom contains four stereoisograms of Type III. The three items discussed above for Fig. 7(A) also hold true for the four stereoisograms appearing in Fig. 11(A), where *RS*-diastereomeric relationships contained in each of these stereoisograms exhibit local *RS*-stereogenicity so as to be capable of giving *RS*-descriptors. The *RS*-diastereomeric relationships for giving *RS*-descriptors are as follows: (Stereoisogram #1) $\mathbf{13}_3/\mathbf{14}_3$ (the priority sequence: t > s > $\bar{\text{r}}$ > H) and $\overline{\mathbf{13}}_3/\overline{\mathbf{14}}_3$ (the priority sequence: $\bar{\text{t}}$ > $\bar{\text{s}}$ > r > H); (Stereoisogram #2) $\mathbf{15}_3/\mathbf{16}_3$ (the priority sequence: t > s > r > H) and $\overline{\mathbf{15}}_3/\overline{\mathbf{16}}_3$ (the priority sequence: $\bar{\text{t}}$> $\bar{\text{s}}$> $\bar{\text{r}}$ > H); (Stereoisogram #3) $\mathbf{17}_3/\mathbf{18}_3$ (the priority sequence: $\bar{\text{t}}$> s > $\bar{\text{r}}$ > H) and $\overline{\mathbf{17}}_3/\overline{\mathbf{18}}_3$ (the priority sequence: t > $\bar{\text{s}}$> r > H); as well as (Stereoisogram #4) $\mathbf{19}_3/\mathbf{20}_3$, (the priority sequence: $\bar{\text{t}}$> s > r > H) and $\overline{\mathbf{19}}_3/\overline{\mathbf{20}}_3$ (the priority sequence: t > $\bar{\text{s}}$> $\bar{\text{r}}$ > H).

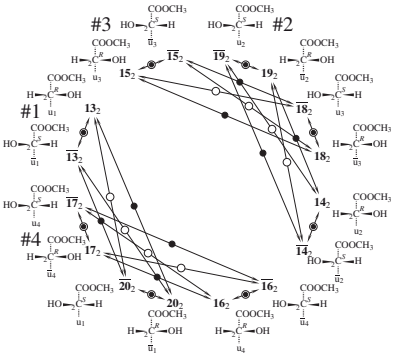
The correlation diagram of Fig. 11(B) for the C_2 atom contains four stereoisograms of Type III. The three items discussed above for Fig. 7(A) also hold true for the four stereoisograms appearing in Fig. 11(B). *RS*-Diastereomeric relationships contained in each of these stereoisograms exhibit local *RS*-stereogenicity so as to be capable of giving *RS*-descriptors as follows: (Stereoisogram #1) $\mathbf{13}_2/\overline{\mathbf{20}}_2$ (the priority sequence: OH > $COOCH_3$ > u_1 > H) and $\overline{\mathbf{13}}_2/\mathbf{20}_2$ (the priority sequence: OH > $COOCH_3$ > $\bar{\text{u}}_1$ > H); (Stereoisogram #2) $\mathbf{14}_2/\overline{\mathbf{19}}_2$ (the priority sequence: OH > $COOCH_3$ > u_2 > H) and $\overline{\mathbf{14}}_2/\mathbf{19}_2$ (the priority sequence: OH > $COOCH_3$ > $\bar{\text{u}}_2$ > H); (Stereoisogram #3) $\mathbf{15}_2/\overline{\mathbf{18}}_2$ (the priority sequence: OH > $COOCH_3$ > u_3 > H) and $\overline{\mathbf{15}}_2/\mathbf{18}_2$ (the priority sequence: OH > $COOCH_3$ > $\bar{\text{u}}_3$ > H); as well as (Stereoisogram #4) $\mathbf{16}_2/\overline{\mathbf{17}}_2$ (the priority sequence: OH > $COOCH_3$ > u_4 > H) and $\overline{\mathbf{16}}_2/\mathbf{17}_2$ (the priority sequence: OH > $COOCH_3$ > $\bar{\text{u}}_4$ > H).

To specify the configurations of the C_4 atoms of each enantiomeric pair listed in Fig. 10, we examine a correlation diagram shown in Fig. 11(C), which contains four stereoisograms of Type III. The three items discussed above for Fig. 7(A) also hold true for the four stereoisograms appearing in Fig. 11(C). *RS*-Diastereomeric relationships contained in each of these stereoisograms exhibit local *RS*-stereogenicity so that they are capable of giving *RS*-descriptors as follows: (Stereoisogram #1) $\mathbf{13}_4/\mathbf{15}_4$ (the priority sequence: OH > COOH > v_1 > H) and $\overline{\mathbf{13}}_4/\overline{\mathbf{15}}_4$ (the priority sequence: OH > COOH > $\bar{\text{v}}_1$ > H); (Stereoisogram #2) $\mathbf{14}_4/\mathbf{16}_4$ (the priority sequence: OH > COOH > v_2 > H) and $\overline{\mathbf{14}}_4/\overline{\mathbf{16}}_4$ (the priority sequence: OH > COOH > $\bar{\text{v}}_2$ > H); (Stereoisogram #3) $\mathbf{17}_4/\mathbf{19}_4$ (the priority sequence: OH > COOH > $\bar{\text{v}}_3$ > H) and $\overline{\mathbf{17}}_4/\overline{\mathbf{19}}_4$ (the priority sequence: OH > COOH > v_3 > H); as well as (Stereoisogram #4) $\mathbf{18}_4/\mathbf{20}_4$ (the priority sequence: OH > COOH > $\bar{\text{v}}_4$ > H) and $\overline{\mathbf{18}}_4/\overline{\mathbf{20}}_4$ (the priority sequence: OH > COOH > v_4 > H).

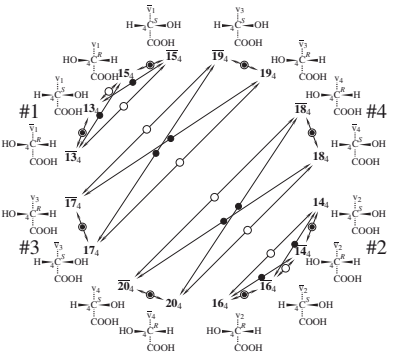
Suppose that the *RS*-stereogenic center of the lactoyloxy ligand is designated by the locant number 2′. To specify the configurations of the $C_{2'}$ atoms of each enantiomeric pair listed in Fig. 10, such a correlation diagram as shown in Fig. 11(D) should be examined. The symbols w_1–w_4 (and $\bar{\text{w}}_1$–$\bar{\text{w}}_4$) shown in Fig. 10 represent chiral proligands, where a COO function is attached to the residue which is generated by removing the OL (or $\overline{\text{OL}}$) ligand from each molecule. The correlation diagram (Fig. 11(D)) contains four stereoisograms of Type III. The three items discussed above for Fig. 7(A) also hold true for the four stereoisograms appearing in Fig. 11(D). *RS*-Diastereomeric relationships contained in each of these stereoisograms exhibit local *RS*-stereogenicity so that they are capable of giving *RS*-descriptors as follows: (Stereoisogram #1) $\mathbf{13}_{2'}/\mathbf{17}_{2'}$ (the priority sequence: OH > w_1 > CH_3 > H) and $\overline{\mathbf{13}}_{2'}/\overline{\mathbf{17}}_{2'}$ (the priority sequence: OH > $\bar{\text{w}}_1$ > CH_3 > H); (Stereoisogram #2) $\mathbf{14}_{2'}/\mathbf{18}_{2'}$ (the priority sequence: OH > w_2 > CH_3 > H) and $\overline{\mathbf{14}}_{2'}/\overline{\mathbf{18}}_{2'}$ (the priority sequence: OH > $\bar{\text{w}}_2$ > CH_3 > H); (Stereoisogram #3) $\mathbf{15}_{2'}/\mathbf{19}_{2'}$ (the priority sequence: OH > w_3 > CH_3 > H) and $\overline{\mathbf{15}}_{2'}/\overline{\mathbf{19}}_{2'}$ (the priority sequence: OH > $\bar{\text{w}}_3$



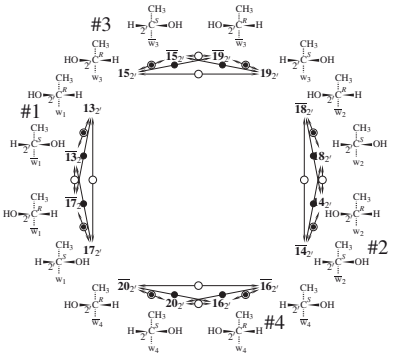
(A) Correlation Diagram at C_3



(B) Correlation Diagram at C_2



(C) Correlation Diagram at C_4



(D) Correlation Diagram at $C_{2'}$

Figure 11: Correlation diagrams of stereoisograms for characterizing stereoisomeric 3-lactoyloxy-2,4-dihydroxyglutaric acid monomethyl esters. (A) For C_3: All of the four stereoisograms (Stereoisograms #1–#4) belong to Type III, where $t(\overline{t}) > s(\overline{s}) > r(\overline{r}) > H$; (B) For C_2: All of the four stereoisograms (Stereoisograms #1–#4) belong to Type III, where $OH > COOCH_3 > u_i(\overline{u}_i) > H$ ($i = 1$–4); (C) For C_4: All of the four stereoisograms (Stereoisogram #1–#4) belong to Type III, where $OH > COOCH_3 > v_i(\overline{v}_i) > H$ ($i = 1$–4); and (D) For $C_{2'}$: All of Stereoisograms #1–#4 belong to Type III, where $OH > w_i(\overline{w}_i) > CH_3 > H$ ($i = 1$–4).

$>$ CH_3 $>$ H); as well as (Stereoisogram #4) $\mathbf{16}_{2'}/\mathbf{20}_{2'}$ (the priority sequence: OH $>$ w_4 $>$ CH_3 $>$ H) and $\overline{\mathbf{16}}_{2'}/\overline{\mathbf{20}}_{2'}$ (the priority sequence: OH $>$ $\overline{w}_4$ $>$ CH_3 $>$ H).

Degenerate Cases due to Pseudoasymmetry in Proligands We here illustrate one of reflection-invariant cases by using stereoisomeric 3-lactoyloxy-2,4-dihydroxyglutaric acids, which were once discussed by Mislow and Siegel [4] to criticize the treatment of reflection-invariant cases in the revised CIP system [2] and later discussed by Helmchen (on page 32 of Ref. [5]) to object against the Mislow-Siegel's comments [4]. Correlation diagrams of stereoisograms developed in the present paper will be proven to give balanced views on what happens under the use of the term "reflection-invariant".

Fig. 12 lists four enantiomeric pairs (**21**/$\overline{\mathbf{21}}$, **22**/$\overline{\mathbf{22}}$, **23**/$\overline{\mathbf{23}}$, and **27**/$\overline{\mathbf{27}}$) along with parenthesized pairs (**24**/$\overline{\mathbf{24}}$, **25**/$\overline{\mathbf{25}}$, **26**/$\overline{\mathbf{26}}$, and **28**/$\overline{\mathbf{28}}$) which are stereochemically duplicate but should be characterized if alternative modes of locant numbering are taken into consideration. These pairs are generated from 3-lactoyloxy-2,4-dihydroxyglutaric acid methyl esters (Fig. 10) by hypothetical partial hydrolyses. The correspondence between Fig. 12 and Fig. 10 is important to discuss degeneration due to pseudoasymmetry.

By focusing our attention on an *RS*-stereogenic atom of a fixed locant number (C_2, C_3, or C_4) appearing in each of the enantiomeric pairs listed in Fig. 12, we obtain four correlation diagrams shown in Fig. 13(A–D).

The first correlation diagrams of stereoisograms shown in Fig. 13(A) is obtained when our attention is focused on the C_3 atom of each enantiomeric pair (**21**/$\overline{\mathbf{21}}$, **22**/$\overline{\mathbf{22}}$, **23**/$\overline{\mathbf{23}}$, or **27**/$\overline{\mathbf{27}}$) along with the C_3 atom of each parenthesized pair (**24**/$\overline{\mathbf{24}}$, **25**/$\overline{\mathbf{21}}$, **26**/$\overline{\mathbf{22}}$, or **28**/$\overline{\mathbf{23}}$). The correlation diagram consists of four stereoisograms, among which two stereoisograms belong to Type III while other two belong to Type II.

The former two stereoisograms of Type III in Fig. 13(A) also behave in agreement with the three items discussed above for Fig. 7(A). *RS*-Diastereomeric relationships contained in each of these stereoisograms exhibit local *RS*-stereogenicity so that they are capable of giving *RS*-descriptors as follows: (Stereoisogram #1) $\mathbf{21}_3/\mathbf{22}_3$ (the priority sequence: $t > r > \bar{r} >$ H) and $\overline{\mathbf{21}}_3/\overline{\mathbf{22}}_3$ (the priority sequence: $\bar{t} > r > \bar{r} >$ H); as well as (Stereoisogram #3) which is duplicated to be essentially identical to Stereoisogram #1 described above.

Because the two promolecule of an enantiomeric pair $\mathbf{21}_3$ and $\overline{\mathbf{21}}_3$ are both characterized to have *R*-configuration, they are regarded as being reflection-invariant. Thereby, they are designated by a lowercase letter *r* according to CIP priority system. Because of reflection-invariance where another enantiomeric pair of $\mathbf{22}_3$ and and $\overline{\mathbf{22}}_3$ is characterized to have *S*-configuration, they are designated by a lowercase letter *s* according to CIP priority system. It should be noted, however, that the two priority sequences, i.e., $t > r > \bar{r} >$ H (for $\mathbf{21}_3$ or $\mathbf{22}_3$) and $\bar{t} > r > \bar{r} >$ H (for $\overline{\mathbf{21}}_3$ or $\overline{\mathbf{22}}_3$), are *reflection-variant* so as to be interchanged into each other by reflection.

The latter two stereoisograms of Type II in Fig. 13(A) exhibit *RS*-astereogenicity, so that the corresponding self-*RS*-diastereomeric relationships result in the incapability of giving *RS*-descriptors at the C_3 atoms. Such self-*RS*-diastereomeric relationships in Fig. 13(A) are as follows: (Stereoisogram #2) $\mathbf{23}_3 = \mathbf{24}_3$ and $\overline{\mathbf{23}}_3 = \overline{\mathbf{24}}_3$; as well as (Stereoisogram #4) $\mathbf{27}_3 = \mathbf{28}_3$ and $\overline{\mathbf{27}}_3 = \overline{\mathbf{28}}_3$. Note that the enantiomeric relationship between $\mathbf{23}_3$ and $\overline{\mathbf{23}}_3$ (or between $\mathbf{27}_3$ and $\overline{\mathbf{27}}_3$) is not a subject to be characterized by the CIP priority system.

Fig. 13(B) shows a correlation diagram of stereoisograms for determining configurations at the C_2 atoms of stereoisomers listed in Fig. 12. Among the four stereoisograms of Type III contained in Fig. 13(B), three stereoisograms are effective. They behave in agreement with the three items discussed above for Fig. 7(A). Hence, *RS*-diastereomeric relationships contained in

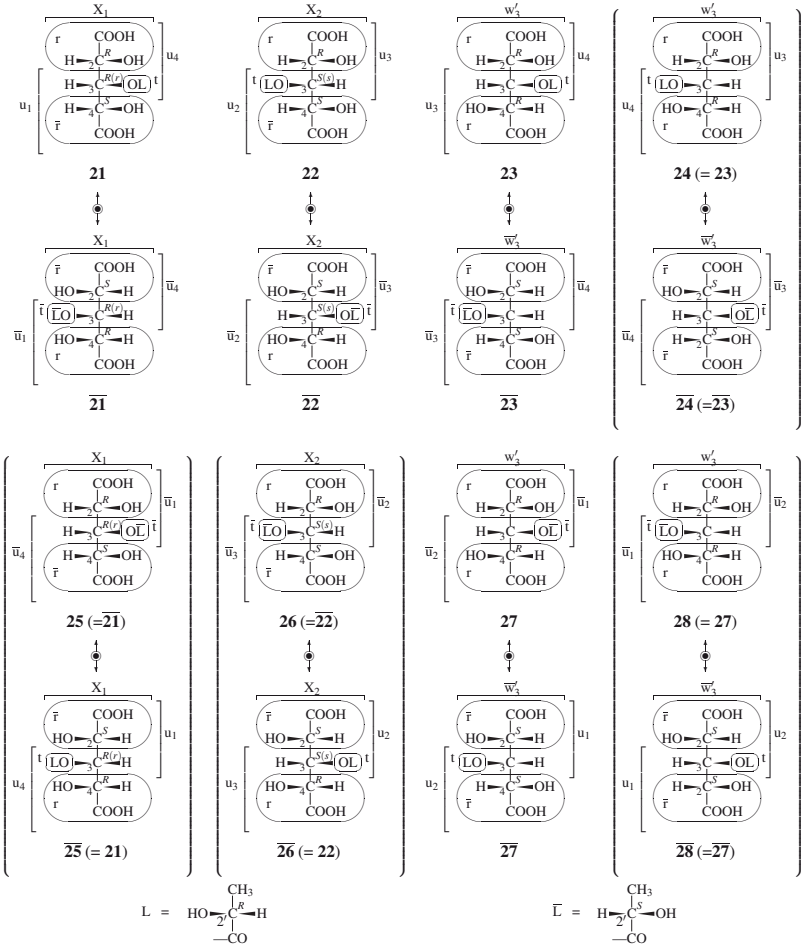
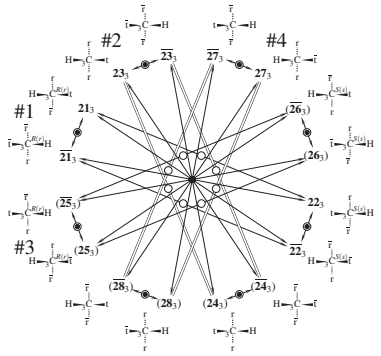
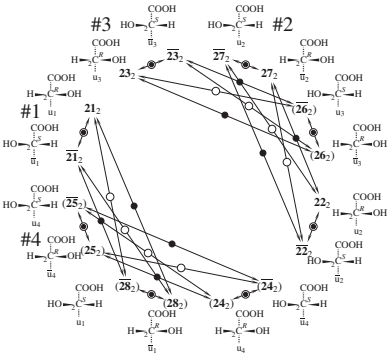


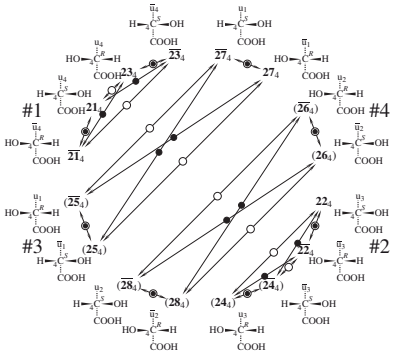
Figure 12: Four enantiomeric pairs of 3-lactoyloxy-2,4-dihydroxyglutaric acids and their duplicated structures caused by permutations or reflections (shown in pairs of parentheses). Proligands for drawing correlation diagrams of stereoisograms are designated by r, r̄, and so on.



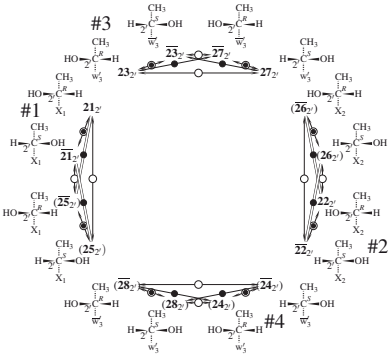
(A) Correlation Diagram at C_3



(B) Correlation Diagram at C_2



(C) Correlation Diagram at C_4



(D) Correlation Diagram at $C_{2'}$

Figure 13: Correlation diagrams of stereoisograms for characterizing stereoisomeric 3-lactoyloxy-2,4-dihydroxyglutaric acids. (A) For C_3: Stereoisograms #1 and #3 belong to Type III, while Stereoisogram #2 and #4 belong to Type II, where $t > r > \bar{r} > H$ and $\mathbf{21}_3 = \overline{\mathbf{25}}_3$, $\overline{\mathbf{21}}_3 = \mathbf{25}_3$, $\mathbf{22}_3 = \overline{\mathbf{26}}_3$, and $\overline{\mathbf{22}}_3 = \mathbf{26}_3$; (B) For C_2: All of Stereoisograms #1–#4 belong to Type III, where $OH > COOH > u_i(\overline{u}_i) > H$ ($i = 1$–4); (C) For C_4: All of Stereoisogram #1–#4 belong to Type III, where $OH > COOH > u_i(\overline{u}_i) > H$ ($i = 1$–4); and (D) For $C_{2'}$: Stereoisograms #1 and #2 belong to Type I, while Stereoisograms #3 and #4 belong to Type III, where w_3 and $\overline{w}_3$ are proligands of an enantiomeric pair ($OH > w'_3(\overline{w}'_3) > CH_3 > H$), while X_1 and X_2 are achiral proligands ($OH > X_1(X_2) > CH_3 > H$).

each of these stereoisograms exhibit local *RS*-stereogenicity so that they are capable of giving *RS*-descriptors as follows: (Stereoisogram #1) $\mathbf{21}_2/\overline{\mathbf{28}}_2$ (the priority sequence: OH > COOH > u_1 > H) and $\overline{\mathbf{21}}_2/\mathbf{28}_2$ (the priority sequence: OH > COOH > $\overline{u}_1$ > H); (Stereoisogram #2) $\mathbf{22}_2/\overline{\mathbf{27}}_2$ (the priority sequence: OH > COOH > u_2 > H) and $\overline{\mathbf{22}}_2/\mathbf{27}_2$ (the priority sequence: OH > COOH > $\overline{u}_2$ > H); as well as (Stereoisogram #3) $\mathbf{23}_2/\overline{\mathbf{26}}_2$ (the priority sequence: OH > COOH > u_3 > H) and $\overline{\mathbf{23}}_2/\mathbf{26}_2$ (the priority sequence: OH > COOH > $\overline{u}_3$ > H). Stereoisogram #4 contained in Fig. 13(B) is composed of a quadruplet of promolecules, $\mathbf{24}_2$, $\overline{\mathbf{24}}_2$, $\mathbf{25}_2$, and $\overline{\mathbf{25}}_2$, which are all parenthesized to show duplication. They are regarded to be identical with **21**, $\overline{\mathbf{21}}$, **23**, and $\overline{\mathbf{25}}$, where the C_4 atoms are focused on (cf. Stereoisogram #1 contained in Fig. 13(C)).

To determine the configurations of the C_4 atoms of each enantiomeric pair listed in Fig. 12, we examine a correlation diagram shown in Fig. 13(C). The correlation diagram contains four stereoisograms of Type III, among which three stereoisograms are effective. Their features are in agreement with the three items discussed above for Fig. 7(A). Thus, *RS*-diastereomeric relationships contained in each of these stereoisograms exhibit local *RS*-stereogenicity so that they are capable of giving *RS*-descriptors as follows: (Stereoisogram #1) $\mathbf{21}_4/\mathbf{23}_4$ (the priority sequence: OH > COOH > u_4 > H) and $\overline{\mathbf{21}}_4/\overline{\mathbf{23}}_4$ (the priority sequence: OH > COOH > $\overline{u}_4$ > H); (Stereoisogram #2) $\mathbf{22}_4/\mathbf{24}_4$ (the priority sequence: OH > COOH > u_3 > H) and $\overline{\mathbf{22}}_4/\overline{\mathbf{24}}_4$ (the priority sequence: OH > COOH > $\overline{u}_3$ > H); as well as (Stereoisogram #3) $\mathbf{25}_4/\mathbf{27}_4$ (the priority sequence: OH > COOH > $\overline{u}_1$ > H) and $\overline{\mathbf{25}}_4/\overline{\mathbf{27}}_4$ (the priority sequence: OH > COOH > u_1 > H).

Stereoisogram #1 of Fig. 13(C) is essentially equivalent to Stereoisogram #4 of Fig. 13(B) which is composed of a quadruplet of promolecules parenthesized to show duplication, i.e., $\mathbf{24}_2$, $\overline{\mathbf{24}}_2$, $\mathbf{25}_2$, and $\overline{\mathbf{25}}_2$. Stereoisogram #4 contained in Fig. 13(C) is composed of a quadruplet of promolecules, $\mathbf{26}_4$, $\overline{\mathbf{26}}_4$, $\mathbf{28}_4$, and $\overline{\mathbf{28}}_4$, which are all parenthesized to show duplication. The quadruplet is regarded as corresponding to two enantiomeric pairs of molecules, i.e., $\mathbf{22}/\overline{\mathbf{22}}$ and $\mathbf{27}/\overline{\mathbf{27}}$, where the C_2 atoms are focused on to exhibit a quadruplet of promolecules. It follows that Stereoisogram #4 of Fig. 13(C) is essentially equivalent to Stereoisogram #2 of Fig. 13(B).

The *RS*-stereogenic center of the lactoyloxy ligand of each molecule listed in Fig. 12 is designated by the locant number $2'$. The correlation diagram of Fig. 13(D) for determining the configurations of the $C_{2'}$ atoms of each enantiomeric pair contains four stereoisograms, in which the symbols X_1 and X_2 represent achiral proligands, where a CO function is attached to the residue which is generated by removing a lactoyl ligand (L or $\overline{L}$) from each molecule. On a similar line, a pair of symbols $w'_3/\overline{w}'_3$ is used to represent chiral proligands which are generated by removing the $CH_3CH(OH)$ moiety of a lactoyl ligand. The two stereoisograms belong to Type I and the other two stereoisograms of Type III (duplicated).

Stereoisogram of #1 (Type I) of Fig. 13(D) consists of a quadruplet of promolecules, $\mathbf{21}_{2'}$, $\overline{\mathbf{21}}_{2'}$, $\mathbf{25}_{2'}$, and $\overline{\mathbf{25}}_{2'}$, where the latter two promolecules are parenthesized to show degeneration in Fig. 12. Note that the proligand X_1 is achiral because of pseudoasymmetry in isolation. The *RS*-diastereomeric relationship between $\mathbf{21}_{2'}$ and $\mathbf{25}_{2'}$ is capable of giving *RS*-descriptors by mean of the priority sequence, OH > X_1 > CH_3 > H. This relationship is identical with the other *RS*-diastereomeric relationship between $\overline{\mathbf{21}}_{2'}$, (= $\mathbf{25}_{2'}$) and $\overline{\mathbf{25}}_{2'}$, (= $\mathbf{21}_{2'}$), because Stereoisogram #1 belongs to Type I.

A parallel discussion can be applied to Stereoisogram #2 (Type I) of Fig. 13(D), which consists of a quadruplet of promolecules $\mathbf{22}_{2'}$, $\overline{\mathbf{22}}_{2'}$, $\mathbf{26}_{2'}$, and $\overline{\mathbf{26}}_{2'}$. The *RS*-diastereomeric relationship between $\mathbf{22}_{2'}$ and $\mathbf{26}_{2'}$ is capable of giving *RS*-descriptors by mean of the priority sequence, OH > X_2 > CH_3 > H. This relationship is identical with the other *RS*-diastereomeric relationship between $\overline{\mathbf{22}}_{2'}$, (= $\mathbf{26}_{2'}$) and $\overline{\mathbf{26}}_{2'}$, (= $\mathbf{22}_{2'}$), because Stereoisogram #2 belongs to Type

I.

In agreement with the common nature of Type-I stereoisograms, the *RS*-diastereomeric relationship between $\mathbf{21}_{2'}$ and $\mathbf{25}_{2'}$ (or between $\mathbf{22}_{2'}$ and $\mathbf{26}_{2'}$) is superposed to the enantiomeric relationship between $\mathbf{21}_{2'}$ and $\overline{\mathbf{21}}_{2'}$ (or between $\mathbf{22}_{2'}$ and $\overline{\mathbf{22}}_{2'}$). At the same time, the enantiomer $\overline{\mathbf{21}}_{2'}$ of $\mathbf{21}_{2'}$ (or $\overline{\mathbf{22}}_{2'}$ of $\mathbf{22}_{2'}$) is identical with the *RS*-diastereomer $\mathbf{25}_{2'}$ of $\mathbf{21}_{2'}$. (or $\mathbf{26}_{2'}$ of $\mathbf{22}_{2'}$).

Stereoisogram #3 (Type III) of Fig. 13(D) is composed of a quadruplet of promolecules $\mathbf{23}_{2'}$, $\overline{\mathbf{23}}_{2'}$, $\mathbf{27}_{2'}$, and $\overline{\mathbf{27}}_{2'}$. The *RS*-diastereomeric relationship between $\mathbf{23}_{2'}$ and $\mathbf{27}_{2'}$ is capable of giving *RS*-descriptors by mean of the priority sequence, $\mathrm{OH} > \mathrm{w}'_3 > \mathrm{CH_3} > \mathrm{H}$. The other *RS*-diastereomeric relationship between $\overline{\mathbf{23}}_{2'}$ and $\overline{\mathbf{27}}_{2'}$ is also capable of giving *RS*-descriptors by mean of the priority sequence, $\mathrm{OH} > \overline{\mathrm{w}}'_3 > \mathrm{CH_3} > \mathrm{H}$.

Stereoisogram #4 (Type III) of Fig. 13(D) is composed of a quadruplet of promolecules $\mathbf{24}_{2'}$, $\overline{\mathbf{24}}_{2'}$, $\mathbf{28}_{2'}$, and $\overline{\mathbf{28}}_{2'}$, where all of the component promolecules are parenthesized to show degeneration (Fig. 12). Obviously, Stereoisogram #4 represents the same thing as Stereoisogram #3.

3 Discussion

3.1 Categorization of Stereoisomers

3.1.1 Over-Simplified Dichotomy Between Enantiomers and Diastereomers

Over-simplified features inherent in the traditional dichotomy between enantiomers and diastereomers (Fig. 1) are pointed out by discussing cases of more than one *RS*-stereogenic center. More information on these features can be obtained by using correlation diagrams of stereoisograms.

Problematic Terminology Due to Special Emphasis on Enantiomeric Relationships The traditional terminology of stereochemistry has put special emphasis on enantiomeric relationships in categorization of stereoisomers. As a result, diastereomeric relationships are regarded as being subsidiary, as found in the expression "diastereomers are stereoisomers other than enantiomers". To show what happens when we are bound by the dichotomy between enantiomers and diastereomers (dotted boxes in Fig. 1), let us examine the molecules listed in Fig. 10.

When the molecule **13** is given, for example, we can recognize a pair of enantiomers **13**/$\overline{\mathbf{13}}$. According to the dichotomy between enantiomers and diastereomers, the relationship between **13** and **14** is diastereomeric, the relationship between **13** and **15** is also diastereomeric, and so on. Thereby, the 14 relationships between the given molecule **13** and respective 14 stereoisomers other than the pair **13**/$\overline{\mathbf{13}}$ are determined to be diastereomeric. This situation holds true if a molecule other than **13** is selected. Thus, there appear one enantiomer (e.g., $\overline{\mathbf{13}}$) and 14 diastereomers (others listed in Fig. 10) when the a molecule (e.g., **13**) is fixed to be examined.

As a matter of course, we get caught in a question as to how different one diastereomeric relationship (e.g., between **13** and **14**) is from another diastereomeric relationship (e.g. between **13** and **15** or between **13** and $\overline{\mathbf{15}}$). Thus there emerge 14 questions of this type for the molecules listed in Fig. 10. These questions are unanswerable systematically so long as we rely on the dichotomy between enantiomers and diastereomers.

Obviously, this unanswerability is because the dichotomy between enantiomers and diastereomers is based on categorization in terms enantiomeric relationships only. In other words,

each pair of enantiomers is an equivalence class or (or an orbit, mathematically speaking) under the action of an appropriate group (a point group), whereas the remaining diastereomeric relationships by no means participate in generating any equivalence classes. The situation described above would become more and more diverse so as to be uncontrollable by the conventional dichotomy, if a given molecule contains more and more *RS*-stereogenic centers. Hence the conventional dichotomy between enantiomers and diastereomers is concluded to be *oversimplified*.

Diastereomers Not Qualified for Equivalence Classes It would be worthwhile to give comments on terminology concerning stereoisomerism from a viewpoint of the capability of constructing equivalence classes (orbits). Expressions such as "a set of stereoisomers" and "a set (pair) of enantiomers" have definite meanings so as to be able to specify respective equivalence classes. This means that a set of stereoisomers can be counted as just one object (one orbit, i.e., one constitutional isomer or one graph) and that a set of enantiomers can be counted as just one object (one orbit, i.e., one enantiomeric pair). In contrast, an expression "a set of diastereomers" has no definite meanings when it is expressed independently. Note that "a set of diastereomers" cannot be counted as one definite object (one orbit). This is because a diastereomeric relationship is incapable of generating an equivalence class. The use of the term "diastereomer" in a plural form (such as the expression "diastereomers are stereoisomers other than enantiomers") is permissible only in combination with "stereoisomers" and "enantiomers" as definite equivalence classes. If the term "diastereomer" is used in a singular form, the corresponding pair of enantiomers (or an achiral molecule as a self-enantiomeric pair) should be referred to as a prerequisite. For example, such an expression as "a molecule and its diastereomer" presumes the presence of a (self-)enantiomeric relationship and a stereoisomeric relationship.

Moreover, the expression "diastereomers are stereoisomers other than enantiomers" has a drawback that achiral molecules are not explicitly taken into consideration. More strictly speaking, the expression should be replaced by the expression "diastereomeric relationships are stereoisomeric relationships other than enantiomeric ones" after enantiomeric relationships are extended to contain self-enantiomeric ones in order to cover achiral molecules.

3.1.2 The Present Dichotomy Based on *RS*-Stereoisomeric Relationships

***RS*-Stereoisomers as Equivalence Classes** The present dichotomy based on *RS*-stereoisomeric relationships (solid-lined boxes in Fig. 1) provides us with a versatile tool for categorizing stereoisomers. Strictly speaking, the versatility does not depend on the dichotomy but stems from the fact that an *RS*-stereoisomeric relationship is capable of generating an equivalence class (an orbit). Chirality/achirality, *RS*-stereogenicity/*RS*-astereogenicity, and sclerality/asclerality (1) are attributes inherent in a set of *RS*-stereoisomers (a quadruplet of promolecules appearing in a stereoisogram) as an equivalence class, where these attributes can be also ascribed to each promolecule of the stereoisogram. Such a set of *RS*-stereoisomers (or a quadruplet, or a stereoisogram) is counted as just one object (one orbit). In this context, the number of such sets (quadruplets in stereoisograms) as being inequivalent under *RS*-stereoisomeric groups has been calculated combinatorially [27, 28]. This enumeration is different from widely-accepted enumerations, because the latter have been based on enantiomers as equivalence classes [29, 30].

Table 3: Correlation of **5** to *RS*-Stereoisomers

Main correlation diagram		Epimeric correlation diagrams	
Stereoisogram	Quadruplet	Stereoisogram	Quadruplet
Fig. 7(A) #1	$\mathbf{5}_3/\overline{\mathbf{5}}_3$; $\mathbf{7}_3/\overline{\mathbf{7}}_3$		
Fig. 7(A) #2	$\mathbf{6}_3/\overline{\mathbf{6}}_3$; $\mathbf{8}_3/\overline{\mathbf{8}}_3$	Fig. 7(B) #1	$\mathbf{5}_2/\overline{\mathbf{5}}_2$; $\mathbf{6}_2/\overline{\mathbf{6}}_2$
		Fig. 7(C) #1	$\mathbf{5}_4/\overline{\mathbf{5}}_4$; $\mathbf{8}_4/\overline{\mathbf{8}}_4$

Epimeric Correlation Diagrams of Stereoisograms The items discussed in the preceding paragraph can be manipulated by separate use of stereoisograms. However, correlation diagrams of stereoisograms developed in the present article are informative than stereoisograms employed separately, when a given molecule is characterized by two or more *RS*-stereogenic centers.

Let us examine the four enantiomeric pairs listed in Fig. 6 by means of the corresponding correlation diagrams of stereoisograms shown in Fig. 7(A–C), where conventional diastereomeric relationships concerning **5** are related to *RS*-diastereomeric relationships of the present methodology. For the sake of convenience, each pair of enantiomers is taken into consideration. Hence, we start from the pair $\mathbf{5}/\overline{\mathbf{5}}$, which is contained in Stereoisogram #1 of Fig. 7(A) (3). Chemically speaking, this stereoisogram shows an epimerization at C_3 atom which results in the conversion of the pair $\mathbf{5}_3/\overline{\mathbf{5}}_3$ into the pair $\mathbf{7}_3/\overline{\mathbf{7}}_3$. Principle 1 allows us to regard this conversion of promolecules as that of the corresponding molecules, i.e., $\mathbf{5}/\overline{\mathbf{5}}$ into $\mathbf{7}/\overline{\mathbf{7}}$. Hence, the process of epimerization at C_3, i.e., $\mathbf{5} \rightarrow \mathbf{7}$, is definitely expressed by Stereoisogram #1 of Fig. 7(A), where the *RS*-diastereomeric relationship between **5** and **7** emerges as a detailed version of a conventional diastereomeric relationship.

On a similar line, Stereoisogram #1 of Fig. 7(B) indicates an epimerization at the C_2, which results in the conversion of the pair $\mathbf{5}_2/\overline{\mathbf{5}}_2$ into another pair $\mathbf{6}_2/\overline{\mathbf{6}}_2$. Finally, Stereoisogram #1 of Fig. 7(C) indicates an epimerization at the C_4, which results in the conversion of the pair $\mathbf{5}_4/\overline{\mathbf{5}}_4$ into another pair $\mathbf{8}_4/\overline{\mathbf{8}}_4$.

As summarized in 3, all of the conventional diastereomers of **5** are generated by the combination of the correlation diagrams of stereoisograms shown in Fig. 7(A–C). If we select any molecule contained in Fig. 6 in place of **5**, a similar process can be traced by the combination of the correlation diagrams of stereoisograms shown in Fig. 7(A–C). This means that correlation diagrams of stereoisograms are shown to be a promising device for remedying the oversimplified dichotomy between enantiomers and diastereomers.

4 collects correlation of **9** to *RS*-stereoisomers, where all of the stereoisomers listed in Fig. 8 can be generated as *RS*-stereoisomers by the combination of correlation diagrams (Fig. 9(A–C). Similar tabulations to 4 can be obtained if we select any molecule contained in Fig. 6 in place of **5**.

Multiple Use of Epimeric Correlation Diagrams of Stereoisograms More sophisticated treatments should be conducted in case of four or more *RS*-diastereomeric centers, where multistep epimerizations should be considered. Let us examine the molecule **13** and its stereoisomers (Fig. 10) according to the present methodology by using the correlation diagrams shown in Fig. 11(A–D).

Table 4: Correlation of **9** to *RS*-Stereoisomers

Main correlation diagram		Epimeric correlation diagrams	
Stereoisogram	Quadruplet	Stereoisogram	Quadruplet
Fig. 9(A) #1	$\mathbf{9}_3(/\overline{\mathbf{9}}_3)$; $\mathbf{10}_3(/\overline{\mathbf{10}}_3)$		
Fig. 9(A) #2	$\mathbf{11}_3/\overline{\mathbf{11}}_3$; $(\mathbf{12}_3/\overline{\mathbf{12}}_3)$	Fig. 9(B) #1	$\mathbf{9}_2/\overline{\mathbf{9}}_2$; $\mathbf{11}_2/\overline{\mathbf{11}}_2$
		Fig. 9(C) #1	$\mathbf{9}_4/\overline{\mathbf{9}}_4$; $(\mathbf{12}_2/\overline{\mathbf{12}}_4)$

Table 5: Correlation of **13** to *RS*-Stereoisomers

Main correlation diagram		Epimeric correlation diagrams	
Stereoisogram	Quadruplet	Stereoisogram	Quadruplet
Fig. 11(A) #1	$\mathbf{13}_3/\overline{\mathbf{13}}_3$; $\mathbf{14}_3/\overline{\mathbf{14}}_3$		
Fig. 11(A) #2	$\mathbf{15}_3/\overline{\mathbf{15}}_3$; $\mathbf{16}_3/\overline{\mathbf{16}}_3$	Fig. 11(C) #1	$\mathbf{13}_4/\overline{\mathbf{13}}_4$; $\mathbf{15}_4/\overline{\mathbf{15}}_4$
Fig. 11(A) #3	$\mathbf{17}_3/\overline{\mathbf{17}}_3$; $\mathbf{18}_3/\overline{\mathbf{18}}_3$	Fig. 11(D) #1	$\mathbf{13}_{2'}/\overline{\mathbf{13}}_{2'}$; $\mathbf{17}_{2'}/\overline{\mathbf{17}}_{2'}$
Fig. 11(A) #4	$\mathbf{19}_3/\overline{\mathbf{19}}_3$; $\mathbf{20}_3/\overline{\mathbf{20}}_3$	Fig. 11(B) #1	$\mathbf{13}_2/\overline{\mathbf{13}}_2$; $\mathbf{20}_2/\overline{\mathbf{20}}_2$

When the molecule **13** is given, the corresponding pair of enantiomers **13**/$\overline{\mathbf{13}}$ is regarded as contained in Stereoisogram #1 of the correlation diagram shown in Fig. 11 where the C_3 atom is to be examined (5). If we take account of chemical meanings, the quadruplet of promolecules in Stereoisogram #1 of Fig. 11 shows the epimerization at the C_3 atom so as to convert the pair $\mathbf{13}_3/\overline{\mathbf{13}}_3$ into the pair $\mathbf{14}_3/\overline{\mathbf{14}}_3$, where the subscript 3 indicates the center (C_3) of the epimerization between **13**/$\overline{\mathbf{13}}$ and **14**/$\overline{\mathbf{14}}$.

On similar lines (5), the quadruplet of promolecules in Stereoisogram #1 of Fig. 11(B) shows the epimerization at the C_2 atom so as to convert the pair $\mathbf{13}_2/\overline{\mathbf{13}}_2$ into the pair $\mathbf{20}_2/\overline{\mathbf{20}}_2$; the quadruplet of promolecules in Stereoisogram #1 of Fig. 11(C) shows the epimerization at the C_4 atom so as to convert the pair $\mathbf{13}_4/\overline{\mathbf{13}}_4$ into the pair $\mathbf{15}_4/\overline{\mathbf{15}}_4$; as well as the quadruplet of promolecules in Stereoisogram #1 of Fig. 11(D) shows the epimerization at the $C_{2'}$ atom of a lactoyloxy moiety, so as to convert the pair $\mathbf{13}_{2'}/\overline{\mathbf{13}}_{2'}$ into the pair $\mathbf{17}_{2'}/\overline{\mathbf{17}}_{2'}$.

There is no direct epimerization processes from **13**/$\overline{\mathbf{13}}$ into the pair **16**/$\overline{\mathbf{16}}$. However, the combination of Stereoisogram #1 of Fig. 11(C) with Stereoisogram #2 of Fig. 11(A) (cf. 5) indicates a two-step conversion: **13**/$\overline{\mathbf{13}}$ → **15**/$\overline{\mathbf{15}}$ → **16**/$\overline{\mathbf{16}}$, where the first step is an epimerization at the C_4 and the second step is an epimerization at the C_3. Note that Principle 1 permits the omission of subscripts during the combination of Stereoisogram #1 of Fig. 11(C) with Stereoisogram #2 of Fig. 11(A). The two-step process can be confirmed by scrutinizing Fig. 10.

On a similar line, 5 shows that the combination of Stereoisogram #1 of Fig. 11(D) with Stereoisogram #3 of Fig. 11(A) indicates a two-step conversion: **13**/$\overline{\mathbf{13}}$ → **17**/$\overline{\mathbf{17}}$ → **18**/$\overline{\mathbf{18}}$, where the first step is an epimerization at the $C_{2'}$ of a lactoyloxy ligand and the second step is an epimerization at the C_3. 5 also shows that the combination of Stereoisogram #1 of Fig. 11(B) with Stereoisogram #4 of Fig. 11(A) indicates a two-step conversion: **13**/$\overline{\mathbf{13}}$ → **20**/$\overline{\mathbf{20}}$ → **19**/$\overline{\mathbf{19}}$, where the first step is an epimerization at the C_2 and the second step is an epimerization at the C_3.

Table 6: Correlation of **21** to *RS*-Stereoisomers

Main correlation diagram		Epimeric correlation diagrams	
Stereoisogram	Quadruplet	Stereoisogram	Quadruplet
Fig. 13(A) #1	$\mathbf{21}_3/\overline{\mathbf{21}}_3$; $\mathbf{22}_3/\overline{\mathbf{22}}_3$		
Fig. 13(A) #2	$\mathbf{23}_3/\overline{\mathbf{23}}_3$; ($\mathbf{24}_3/\overline{\mathbf{24}}_3$)	Fig. 13(C) #1	$\mathbf{21}_4/\overline{\mathbf{21}}_4$; $\mathbf{23}_4/\overline{\mathbf{23}}_4$
Fig. 13(A) #3	($\mathbf{25}_3/\overline{\mathbf{25}}_3$); ($\mathbf{26}_3/\overline{\mathbf{26}}_3$)	Fig. 13(D) #1	$\mathbf{21}_{2'}/\overline{\mathbf{21}}_{2'}$; ($\mathbf{25}_{2'}/\overline{\mathbf{25}}_{2'}$)
Fig. 13(A) #4	$\mathbf{27}_3/\overline{\mathbf{27}}_3$; ($\mathbf{28}_3/\overline{\mathbf{28}}_3$)	Fig. 13(B) #1	$\mathbf{21}_2/\overline{\mathbf{21}}_2$; ($\mathbf{28}_2/\overline{\mathbf{28}}_2$)

The process described above for non-degenerate cases is applicable to degenerate cases after adequate modifications. For example, stereoisomeric relationships of **21** are traced by using the corresponding correlation diagrams, as summarized in 6.

When the molecule **21** is given, we are able to find the corresponding pair of enantiomers **21**/$\overline{\mathbf{21}}$. The quadruplet of promolecules in Stereoisogram #1 of Fig. 13(A) shows the epimerization at the C_3 atom so as to convert the pair $\mathbf{21}_3/\overline{\mathbf{21}}_3$ into the pair $\mathbf{22}_3/\overline{\mathbf{22}}_3$, where the subscript 3 indicates the center (C_3) of the epimerization between **21**/$\overline{\mathbf{21}}$ and **22**/$\overline{\mathbf{22}}$.

The quadruplet of promolecules in Stereoisogram #1 of Fig. 13(B) shows the epimerization at the C_2 atom so as to convert the pair $\mathbf{21}_2/\overline{\mathbf{21}}_2$ into the pair $\mathbf{28}_2/\overline{\mathbf{28}}_2$, where the latter pair is parenthesized to show duplication. Although Stereoisogram #1 itself is ineffective, it is necessary to be combined with Stereoisogram #4 of Fig. 13(A) to indicate that the starting promolecule **21** is correlated to **27**. Thus, the combination of Stereoisogram #1 of Fig. 13(B) with Stereoisogram #4 of Fig. 13(A) indicates a two-step conversion: **21**/$\overline{\mathbf{21}}$ → (**28**/$\overline{\mathbf{28}}$) → **27**/$\overline{\mathbf{27}}$, where the first step is an epimerization at the C_2 and the second step is an epimerization at the C_3. The total process of **21** → (*RS*-diastereomeric relationship at the C_2) ($\overline{\mathbf{28}}$) → (*RS*-diastereomeric relationship at the C_3) $\overline{\mathbf{27}}$ is confirmed to give the conventional diastereomeric relationship between **21** and $\overline{\mathbf{27}}$ by scrutinizing Fig. 10. On the other hand, the total process of **21** → (*RS*-diastereomeric relationship at the C_2) ($\overline{\mathbf{28}}$) → (holantimeric relationship at the C_3) **27** is confirmed to give the diastereomeric relationship between **21** and **27** by scrutinizing Fig. 12. Because Stereoisogram #4 of Fig. 13(A) belongs to Type II, the duplicate promolecule ($\overline{\mathbf{28}}$) is identical with its *RS*-diastereomer $\overline{\mathbf{27}}$, the last step can be omitted if locant numbers are disregarded.

The quadruplet of promolecules in Stereoisogram #1 of Fig. 13(C) shows the epimerization at the C_4 atom so as to convert the pair $\mathbf{21}_4/\overline{\mathbf{21}}_4$ into the pair $\mathbf{23}_4/\overline{\mathbf{23}}_4$.

The quadruplet of promolecules in Stereoisogram #1 of Fig. 13(D) shows the epimerization at the $C_{2'}$ atom of a lactoyloxy moiety, so as to convert the pair $\mathbf{21}_{2'}/\overline{\mathbf{21}}_{2'}$ into the pair $\mathbf{25}_{2'}/\overline{\mathbf{25}}_{2'}$, where the latter pair is parenthesized to show duplication.

Although stereoisograms which are contained in a correlation diagram generated at a fixed *RS*-stereogenic center specify quadruplets of promolecules (i.e., *RS*-stereoisomers), the relationship among the quadruplets (the stereoisograms) are not specified by the correlation diagram (cf. the "main correlation diagram" column of each of 3–6). This means that there seemingly remain "unspecified diastereomeric relationships" at this step of examination. However, 3–6 shows that if additional correlation diagrams generated at other *RS*-stereogenic centers are applied at the same time (cf. the "epimeric correlation diagrams" column of each of 3–6), all of such "unspecified diastereomeric relationships" can be specified.

Equivalence Classes vs. Relationships Discussions based on separate use of stereoisograms have mainly relied on *RS*-stereoisomeric relationships (i.e., enantiomers, *RS*-diastereomers, and holantimers) according to the paradigm shift shown in Fig. 1. The present development of correlation diagrams of stereoisomers has furthermore brought about an additional paradigm shift from *relationships* to *equivalence classes*. In fact, each stereoisogram contained in a correlation diagram indicates a quadruplet of promolecules as an equivalence class. In this context, even the above-mentioned specification of "unspecified diastereomeric relationships" is based on equivalence classes derived from *RS*-stereoisomeric relationships, as implied in 3–6.

The results shown in 3–6 are, in fact, based on equivalence classes and are sufficient to understand the total features of the stereoisomerism shown in Fig. 6, Fig. 8, Fig. 10, and Fig. 12. However, terms based on relationships are often convenient and useful to clarify the oversimplified features of the traditional dichotomy between enantiomers and diastereomers, because they are more popular to organic chemists than terms on equivalence classes. For example, the results listed in 5 can be translated into 7 in terms of the three relationships listed in 1. Thereby, the fourteen diastereomeric relationships concerning **13** are specified in terms of the three relationships, among which *RS*-diastereomeric relationships and holantimeric relationships are mainly employed.

If holantimeric relationships are unfamiliar to organic chemists, they can be replaced by a combination of enantiomeric relationships and *RS*-diastereomeric ones. For example, the conventional diastereomeric relationship between **13** and $\overline{\mathbf{18}}$ can be described by a combination of an *RS*-diastereomeric relationship appearing in Stereoisogram #1 of Fig. 11(D) ($\mathbf{13}_{2'} \rightarrow \mathbf{17}_{2'}$) with a holantimeric relationship appearing in Stereoisogram #3 of Fig. 11(A) ($\mathbf{17}_3 \rightarrow \overline{\mathbf{18}}_3$). If we avoid the use of the term holantimeric so as to meet the traditional terminology, the latter use of a holantimeric relationship is divided into two operations, i.e., a permutation operation (an *RS*-diastereomeric relationship between $\mathbf{17}_3 \rightarrow \mathbf{18}_3$) and a reflection operation (an enantiomeric relationship between $\mathbf{18}_3 \rightarrow \overline{\mathbf{18}}_3$), both of which appear in Stereoisogram #3 of Fig. 11(A). The total process of **13** $\rightarrow$ (at the $C_{2'}$) **17** $\rightarrow$ (at the C_3) **18** $\rightarrow$ (at the C_3) $\overline{\mathbf{18}}$ is confirmed to give the diastereomeric relationship between **13** and $\overline{\mathbf{18}}$ by scrutinizing Fig. 10.

3.2 Global Symmetry and Local Symmetry

3.2.1 Global Symmetry Specified by Stereogenicity and by *RS*-Stereogenicity

While the term "stereogenicity" has not been directly defined in IUPAC Recommendations 1996 [3], the term "stereogenic unit" has been defined instead. This detour of direct definition is seemingly related to the absence of the term "local stereogenicity" in contrast to the presence of the term "local chirality". This situation will be discussed by means of correlation diagrams of stereoisograms.

Scope and Limitations of of the Term Stereogenicity In the traditional terminology of stereochemistry, stereoisomeric relationships are often linked to the term *stereogenicity*, which is regarded as the basis for giving *RS*-descriptors of the CIP priority system [2]. Because stereoisomeric relationships consist of enantiomeric relationships and diastereomeric relationships (the dotted boxes in Fig. 1) and because enantiomeric relationships are linked with chirality, we arrive at a seemingly plausible scheme "stereogenicity $\supset$ chirality". Hence, *RS*-descriptors of the CIP priority system have been inevitably considered to specify chirality as a part of stereogenicity in the traditional terminology of stereochemistry. Accordingly, the term "chirality center" is

Table 7: Fourteen Diastereomeric Relationships Concerning **13**

Pair	Relationship	Stereoisogram
13/$\overline{\mathbf{13}}$	enantiomeric at C_3	Fig. 11(A) #1
13/14	*RS*-diastereomeric at C_3	Fig. 11(A) #1
13/$\overline{\mathbf{14}}$	holantimeric at C_3	Fig. 11(A) #1
13/15	*RS*-diastereomeric at C_4	Fig. 11(C) #1
13/$\overline{\mathbf{15}}$	holantimeric at C_4	Fig. 11(C) #1
13/16	*RS*-diastereomeric at C_4	Fig. 11(C) #1
	and *RS*-diastereomeric at C_3	Fig. 11(A) #2
13/$\overline{\mathbf{16}}$	*RS*-diastereomeric at C_4	Fig. 11(C) #1
	and holantimeric at C_3	Fig. 11(A) #2
13/17	*RS*-diastereomeric at $C_{2'}$	Fig. 11(D) #1
13/$\overline{\mathbf{17}}$	holantimeric at $C_{2'}$	Fig. 11(D) #1
13/18	*RS*-diastereomeric at $C_{2'}$	Fig. 11(D) #1
	and *RS*-diastereomeric at C_3	Fig. 11(A) #3
13/$\overline{\mathbf{18}}$	*RS*-diastereomeric at $C_{2'}$	Fig. 11(D) #1
	and holantimeric at C_3	Fig. 11(A) #3
13/19	*RS*-diastereomeric at C_2	Fig. 11(B) #1
	and holantimeric at C_3	Fig. 11(A) #4
13/$\overline{\mathbf{19}}$	*RS*-diastereomeric at C_2	Fig. 11(B) #1
	and *RS*-diastereomeric at C_3	Fig. 11(A) #4
13/20	holantimeric at C_2	Fig. 11(B) #1
13/$\overline{\mathbf{20}}$	*RS*-diastereomeric at C_2	Fig. 11(B) #1

used widely as a subsidiary concept of "stereogenic center".

A typical example is a tetrahedral molecule CABXY, where substituents A, B, X, and Y are all achiral ligands or atoms in isolation. This molecule is specified as having *R*- or *S*-configuration by the CIP priority system, where stereogenicity for giving such *RS*-descriptors is regarded as chirality in the traditional terminology of stereochemistry. Note that enantiomers are not diastereomers because of the dichotomy between enantiomers and diastereomers (the dotted boxes in Fig. 1). Hence, the stereogenicity (the capability of giving *RS*-descriptors) for the enantiomers of CABXY has been replaced by the chirality for them and consequently disregarded.

In contrast, the configuration of the C_3 atom of **2** (or $\overline{\mathbf{2}}$) is not specified by *RS*-descriptors, even though the promolecule $\mathbf{2}_3$ (or $\overline{\mathbf{2}}_3$) exhibits chirality (Fig. 3), which corresponds to the global symmetry of **2** (or $\overline{\mathbf{2}}$). Logically speaking, the scheme (stereogenicity $\supset$ chirality) indicates that the C_3 atom of **2** (or $\overline{\mathbf{2}}$) is chiral and so stereogenic. The expression "the stereogenic C_3" is rather strange, but the C_3 atom is linked to the presence of two enantiomers $\mathbf{2}_3$ and $\overline{\mathbf{2}}_3$, which are stereoisomers in the traditional terminology of stereochemistry. However, the C_3 atom is usually regarded as constructing a non-stereogenic unit in the traditional terminol-

ogy of stereochemistry. In order to avoid such confusing discussions, the CIP priority system disregards the C_3 atom as a "chiral center" nor as a "stereogenic center" at an initial stage of treating such confusing cases [2], when the presence of the two enantiomers ($\mathbf{2}_3$ and $\overline{\mathbf{2}}_3$) is neglected by labelling the C_3 as non-stereogenic. However, the presence of the chirality without *RS*-descriptors (at the C_3 atom) shows that the term "chiral center" for the capability of giving *RS*-descriptors seems to be unconvincing.

Let us next consider a pseudoasymmetric case concerning **9** and **10** (Fig. 8). The diastereomeric relationship between them gives a basis of giving *RS*-descriptors so that the C_3 atoms are regarded as a stereogenic center in spite of the local achirality of the C_3 atoms. Hence, the capability of giving *RS*-descriptors to the C_3 atoms of **9** and **10** has been ascribed to a certain property derived by stereogenicity minus chirality.

In conclusion, the term "stereogenicity" ($\supset$ chirality) does not provide an inconsistent basis for explaining the capability of giving *RS*-descriptors, because the term "stereogenicity" (corresponding to stereoisomeric relationships) contains "chirality" (corresponding to enantiomeric relationships).

***RS*-Stereogenicity Separated from Stereogenicity** In the present terminology of stereochemistry, stereoisomeric relationships consist of *RS*-stereoisomeric relationships and others (cf. the solid-lined boxes in Fig. 1) and the latter *RS*-stereoisomeric relationships consist of the three relationships, i.e., enantiomeric, *RS*-diastereomeric, and holantimeric relationships. Then, *RS*-diastereomeric relationships are linked to the term *RS-stereogenicity*, which is regarded as the basis for giving *RS*-descriptors of the CIP priority system [16, 25]. On the other hand, enantiomeric relationships are linked to chirality, which gives no basis for giving *RS*-descriptors of the CIP priority system.

For example, the above-described tetrahedral molecule CABXY is specified as being chiral, *RS*-stereogenic, and ascleral (Type I) in the present terminology of stereochemistry. Because of the *RS*-stereogenicity, the molecule is specified as having *R*- or *S*-configuration by the CIP priority system. Although the molecule is chiral, its chirality has no relationship to the capability of giving such *RS*-descriptors. By means of the corresponding stereoisogram of Type I, the *R*- or *S*-descriptor due to *RS*-stereogenicity is subsidiarily correlated to the chirality of the molecule CABXY.

On the other hand, the configuration of the C_3 atom of **2** (or $\overline{\mathbf{2}}$) can be discussed by means of Stereoisogram #2′ of Type II (Fig. 3). The incapability of having *RS*-descriptors is explained by the *RS*-astereogenic nature, where the promolecule $\overline{\mathbf{2}}_3$ and its *RS*-diastereomeric promolecule is identical to each other, as found in the horizontal direction of Stereoisogram #2′. In contrast, the chirality of the promolecule $\overline{\mathbf{2}}_3$ is determined by vertical comparison with its enantiomeric promolecule $\mathbf{2}_3$. This means that the *RS*-astereogenicity of the promolecule $\overline{\mathbf{2}}_3$ (or $\mathbf{2}_3$) is consistent with its chirality by means of Stereoisogram #2′ of Type II.

The pseudoasymmetric case concerning **9** and **10** (Fig. 8) is examined by means of Stereoisogram #1 of Type V shown in Fig. 9(A), which consists of a quadruplet of promolecules, i.e., $\mathbf{9}_3$, $\overline{\mathbf{9}}_3$ (= $\mathbf{9}_3$), $\mathbf{10}_3$, and $\overline{\mathbf{10}}_3$ (= $\mathbf{10}_3$). The *RS*-diastereomeric relationship linked with *RS*-stereogenicity explains the capability of giving *RS* descriptors to $\mathbf{9}_3$ and $\mathbf{10}_3$. Stereoisogram #2 of Type II shown in Fig. 9(A) is another example that is chiral but exhibits *RS*-astereogenic nature so as to show the incapability of giving *RS*-descriptors.

Redefinition of Several Terms To avoid the inconsistency, the traditional terminology for characterizing global symmetry should be revised according to the present terminology developed by stereoisograms. In particular, the viewpoint based on stereoisomeric relationships linked with stereogenicity is replaced by the viewpoint based on diastereomeric relationships linked with stereogenicity:

stereoisomeric relationship	—	stereoisomerism
enantiomeric relationship	—	chirality
diastereomeric relationship	—	stereogenicity

As a result, the revised term "stereogenicity" is correlated to permutation operations defined above, but by no means to reflection operations. This revision is conceptually significant so that the scheme "stereogenicity ⊃ chirality" is replaced by the new scheme "stereoisomerism ⊃ chirality" (more strictly, stereoisomerism = chirality + stereogenicity). However, because the concept of "stereogenicity" has been defined and used in the form of "stereogenic unit" [3], the revision of "stereogenicity" does not so severely influence descriptions of previous articles. In other words, the detour of the direct definition of "stereogenicity" in IUPAC Recommendations 1996 [3] turns out to imply the new scheme. In this context, the use of the term "stereogenic unit" seems to cause an equivalent effect derived from the term "local stereogenicity", which has not been recognized as a standard term.

For the sake of strict discussions, the capability of giving *RS*-descriptors should be discussed by using *RS*-stereogenicity on the basis of the present terminology:

RS-stereoisomeric relationship	—	*RS*-stereoisomerism
enantiomeric relationship	—	chirality
RS-diastereomeric relationship	—	*RS*-stereogenicity

3.2.2 Local Symmetry Subdivided into Local Chirality and Local *RS*-Stereogenicity

Local *RS*-stereogenicity (or local *RS*-astereogenicity) has not been recognized by the traditional methodology of stereochemistry, where unrecognized local *RS*-stereogenicity/*RS*-astereogenicity has been often confused with local chirality/achirality. Remember the use of "chirality center" in place of "stereogenic center" in the CIP priority system [2]. Such unrecognized local *RS*-stereogenicity (or *RS*-astereogenicity) can be discussed comprehensively by using correlation diagrams of stereoisograms.

Correlation Diagrams of Stereoisograms for Characterizing Local Chirality and Local *RS*-Stereogenicity The present methodology is based on Principles 1–4 and on the presumption that the local symmetry of a given site (center, bond, etc.) is represented by the corresponding promolecule and a stereoisogram derived from the promolecule. This means that the local symmetry of a given site can be discussed by studying the global symmetry of the promolecule selected to represent the site.

Obviously, there exists a specific site, the local symmetry of which is considered to be the global symmetry of the molecule, or, at least, the global chirality or achirality of the molecule. If the molecule is regarded as a 3D tree of a carbon skeleton, a centroid or a bicentroid (or a center or a bicenter) is a candidate of such a specific site [31]. For example, Stereoisogram #1 of Type V shown in Fig. 9(A) shows that the C_3 atom of the promolecule $\mathbf{9}_3$ (cf. **9** of Fig. 8) is

such a specific site, because the achirality of the molecule **9** corresponds to the achirality of the promolecule $\mathbf{9}_3$. In this case, the highest attainable point-group symmetry (C_s) of the molecule **9** is equal to the point-group symmetry (C_s) of the promolecule $\mathbf{9}_3$.

Local symmetry is composed of three kinds of attributes, i.e., local chirality (or achirality), local *RS*-stereogenicity (or *RS*-astereogenicity), and local sclerality (or asclerality). This methodology is a sharp contrast to the traditional methodology in which only local chirality (or achirality) is taken into consideration. It should be emphasized that the traditional stereochemistry lacks the concept of "local stereogenicity", because the paradigm based on the dichotomy between enantiomers and diastereomers would be incapable of giving its succinct definition (cf. the above-mentioned revised definition of "stereogenicity" and the conventional paradigm shown in Fig. 1).

In contrast, by considering *RS*-stereoisomerism as a subclass of stereoisomerism (cf. the present paradigm shown in Fig. 1), the present methodology is able to define the concept of *local RS-stereogenicity* (or *RS-astereogenicity*), which is unequivocally derived from a quadruplet of promolecules contained in a stereoisogram. Moreover, the concept of *local chirality* can be examined at the same time by referring to a single stereoisogram containing a promolecule of a given site as well as a set of its enantiomer, its *RS*-diastereomer, and its holantimer.

3.2.3 Coexistence of Local Chirality and Local *RS*-Stereogenicity

Promolecules of Type I for Representing Local Symmetry Correlation diagrams of stereoisograms provides us with several merits as a versatile methodology for discussing chirality and *RS*-stereogenicity. One of such merits is concerned with promolecules of Type I. Even if such promolecules of Type I are selected to represent local symmetry, parallel discussions can be employed just as Type-I promolecules are used to represent global symmetry. The above-mentioned comments on the Type-I molecule having the formula CABXY can be extended to more sophisticated molecules having more than one *RS*-stereogenic center. For example, let us re-examine Stereoisogram of #1 of Type I in Fig. 13(D), which consists of a quadruplet of promolecules, $\mathbf{21}_{2'}$, $\overline{\mathbf{21}}_{2'}$, $\mathbf{25}_{2'}$ (= $\overline{\mathbf{21}}_{2'}$), and $\overline{\mathbf{25}}_{2'}$. (= $\mathbf{21}_{2'}$):

1. In the present methodology, the *RS*-diastereomeric relationship between $\mathbf{21}_{2'}$ and $\mathbf{25}_{2'}$ (= $\overline{\mathbf{21}}_{2'}$) is conceptually distinguished from the enantiomeric relationship $\mathbf{21}_{2'}$ and $\overline{\mathbf{21}}_{2'}$. The two relationships, however, are recognized to be superposable to each other. In other words, the enantiomer $\overline{\mathbf{21}}_{2'}$ of $\mathbf{21}_{2'}$ is regarded as being identical with the *RS*-diastereomer $\mathbf{25}_{2'}$ of $\mathbf{21}_{2'}$, although enantiomeric relationships and *RS*-diastereomeric ones are conceptually distinguished from each other.

2. Even an achiral proligand (e.g., X_1 of $\mathbf{21}_{2'}$) has internal structures so that it is conceptually or hypothetically changed into the corresponding enantiomeric proligand (e.g., $\overline{X}_1$ of $\overline{\mathbf{21}}_{2'}$). Note that the X_1 of $\mathbf{21}_{2'}$ and the $\overline{X}_1$ of $\overline{\mathbf{21}}_{2'}$) is different in their modes of locant numbering (cf. **21** and $\overline{\mathbf{21}}$ of Fig. 12). Because such modes of locant numbering are disregarded in the actual judgment of ligand equality, the $\overline{X}_1$ is regarded as being identical to the X_1. On the other hand, permutation operations bring about no changes. Thus, the X_1 of $\mathbf{21}_{2'}$ remain unchanged in the corresponding *RS*-diastereomeric promolecule (e.g., X_1 of of $\mathbf{25}_{2'}$). Note that there appears no changes of internal structures even when the modes of locant numbering are taken into consideration (cf. **21** and **25** of Fig. 12).

3. According to the coexistence of *RS*-diastereomeric relationships and enantiomeric ones, the corresponding attributes, i.e., chirality and *RS*-stereogenicity, coexist even in stereo-

isograms of Type I. The *RS*-stereogenicity is capable of giving *RS*-descriptors, while the chirality is a basis of describing 3D-structures.

The traditional terminology is a sharp contrast to the present terminology in treating Type-I cases:

1. In the traditional methodology, a permutation operation changes the promolecule $\mathbf{21}_{2'}$ into $\mathbf{25}_{2'}$ (cf. Stereoisogram of #1 of Type I in Fig. 13(D)). Because the latter $\mathbf{25}_{2'}$ is identical to $\overline{\mathbf{21}}_{2'}$, the promolecules $\mathbf{21}_{2'}$ and $\mathbf{25}_{2'}$ (= $\overline{\mathbf{21}}_{2'}$) are concluded to be in an enantiomeric relationship. As a result, permutation operations are unconsciously mixed up with reflection operations.

2. Because of the dichotomy between enantiomers and diastereomers, the traditional methodology presumes that such permutation operations as described above are correlated to enantiomeric relationships, but not to diastereomeric relationships. This is inconsistent with the fact that permutation operations provide diastereomeric relationships even in the traditional methodology (e.g., Type-III and Type-V cases).

3. Because of the dichotomy between enantiomers and diastereomers, only the enantiomeric relationship between $\mathbf{21}_{2'}$ and $\overline{\mathbf{21}}_{2'}$ (= $\mathbf{25}_{2'}$) can exist so as to provide a basis of giving *RS*-descriptors.

4. Both enantiomeric relationships and diastereomeric relationships are capable of giving *RS*-descriptors in the traditional methodology. The two relationships are subclasses of stereoisomeric relationships which are linked with stereogenicity. This means the scheme "stereogenicity $\supset$ chirality" in the traditional terminology. This is inconsistent with the statement that chirality and stereogenicity are distinct concepts.

Promolecules of Type III for Representing Local Symmetry Just as Type-III promolecules are used to represent global symmetry, Type-III promolecules involved in a correlation diagram can be used to discuss local symmetry, where Type III indicates local chirality, local *RS*-stereogenicity, and local sclerality.

For example, let us examine the stereoisogram of Type III shown in Fig. 7(A) which consists of a quadruplet of promolecules, i.e., $\mathbf{5}_3$, $\overline{\mathbf{5}}_3$, $\mathbf{7}_3$, and $\overline{\mathbf{7}}_3$. The stereoisogram exhibits local chirality, local *RS*-stereogenicity, and local sclerality.

The assignment of the *R*-configuration of $\mathbf{5}_3$ and the *S*-configuration of $\mathbf{7}_3$ is based on the local *RS*-stereogenicity, which is linked to the *RS*-diastereomeric relationship between them, where the common priority sequence, OH $>$ p $>$ q $>$ H, is effective. On the other hand, the *S*-configuration of $\overline{\mathbf{5}}_3$, which is enantiomeric to $\mathbf{5}_3$, is determined in terms of another priority sequence, OH $>$ $\overline{\text{p}}$ $>$ $\overline{\text{q}}$ $>$ H. Note that this assignment is based on the *RS*-diastereomeric relationship between $\overline{\mathbf{5}}_3$ and $\overline{\mathbf{7}}_3$, but not on the enantiomeric relationship between $\mathbf{5}_3$ and $\overline{\mathbf{5}}_3$.

As a result, the priority sequence OH $>$ p $>$ q $>$ H for determining the *R*-configuration of $\mathbf{5}_3$ is different from the priority sequence OH $>$ $\overline{\text{p}}$ $>$ $\overline{\text{q}}$ $>$ H for determining the *S*-configuration of its enantiomer $\overline{\mathbf{5}}_3$. Strictly speaking, the determination of the *R*-configuration of $\mathbf{5}_3$ has nothing to do with the determination of the *S*-configuration of its enantiomer $\overline{\mathbf{5}}_3$. In the traditional methodology, the priority sequence OH $>$ p $>$ q $>$ H is unconsciously equalized to the priority sequence OH $>$ $\overline{\text{p}}$ $>$ $\overline{\text{q}}$ $>$ H, because the latter sequence can be derived from the former one, and vice versa.

The traditional methodology, however, is silent on this unconscious equalization, because it pays attention only to the enantiomeric pair **5**/$\overline{\mathbf{5}}$ as molecules and no attention to *RS*-diastereomeric pair $\mathbf{5}_3/\mathbf{6}_3$ as promolecules. To understand how *RS*-descriptors are assigned to promolecules, it is safe to consult such a stereoisogram as specifying a quadruplet of promolecules.

Promolecules of Type V for Representing Local Symmetry Even when promolecules of Type V are selected to represent local symmetry (local achirality, local *RS*-stereogenicity, and local sclerality), they can be examined on a similar line to Type-V promolecules selected to represent global symmetry.

For example, let us examine the stereoisogram of Type V shown in Fig. 9, which consists of a quadruplet of promolecules, i.e., $\mathbf{9}_3$, $\overline{\mathbf{9}}_3$ (= $\mathbf{9}_3$), $\mathbf{10}_3$, and $\overline{\mathbf{10}}_3$ (= $\mathbf{10}_3$). Although both $\mathbf{9}_3$ and $\mathbf{10}_3$ are achiral, their *RS*-stereogenicities correspond to the *RS*-diastereomeric relationship between them so as to give *RS*-descriptors. Because of global achirality, their descriptors are designated in lowercase letters (*r* and *s*) so as to emphasize pseudoasymmetry. The determination of the *r*- and *s*-configuration is based on the same priority sequence, OH > r > $\bar{\mathrm{r}}$ > H.

What Do *RS*-Descriptors Specify? The answer is simply *RS-stereogenicity* or more strictly *local RS-stereogenicity*, which determines the configuration of a given promolecule and that of its *RS*-diastereomer. The answer is not "chirality" nor "stereogenicity", which is frequently referred to as a standard answer in the traditional stereochemistry.

To gain this succinct answer, the paradigm shift shown in Fig. 1 is necessary so as to provide us with stereoisograms as a versatile device for discussing chirality, *RS*-stereogenicity, and sclerality. Because promolecules contained in stereoisograms of Type I, Type III, or Type V are characterized to be *RS*-stereogenic, they are capable of being specified by *RS*-descriptors. They may be chiral (Type I and Type III) or achiral (Type V) so that it is safe to consult such stereoisograms in order to grasp how a quadruplet of promolecules is correlated to *RS*-descriptors.

It should be noted, however, that although the present approach provides us with a conceptual change (cf. the paradigm shift of Fig. 1), it does not influence practical applications and assignment results of the CIP priority system.

3.3 Correlation Diagrams With and Without Degeneration

3.3.1 Number of Stereoisograms in Each Correlation Diagram Without Degeneration

When stereoisomers are given as a set, the locant numbers of their *RS*-stereogenic sites (centers, bonds, etc.) are presumed to be given commonly. A correlation diagram of stereoisograms can be drawn by collecting respective stereoisograms for specifying the local symmetry of an *RS*-stereogenic site of a fixed locant number in each stereoisomer. Suppose that n of *RS*-stereogenic centers generate 2^n stereoisomers without degeneration. Then, there appear totally 2^n promolecules in the correlation diagram, where every four promolecules construct one stereoisogram in an appropriate way. If such a promolecule correlated to a stereoisogram is run to cover all the stereoisomers of the set, there appear 2^{n-2} (= $2^n/4$) of stereoisograms in the corresponding correlation diagram.

For example, the set of stereoisomeric pentoses listed in Fig. 6 is characterized by three *RS*-stereogenic centers so that there appear three correlation diagrams, i.e., Fig. 7(A) for C_3, Fig. 7(B) for C_2, and Fig. 7(C) for C_4. Because this case exhibits no degeneration, each of the three correlation diagrams contains two (= $2^{3-2} = 2^3/4$) stereoisograms.

Another example without degeneration is shown in Fig. 10, where each stereoisomer is characterized by four *RS*-stereogenic centers so that there appear 16 (= 2^4) stereoisomers. Because of four *RS*-stereogenic centers, the set of 16 stereoisomers is characterized by four correlation diagrams, i.e., Fig. 11(A) for C_3, Fig. 11(B) for C_2, Fig. 11(C) for C_4, and Fig. 11(D) for $C_{2'}$. Because this case exhibits no degeneration, each of the four correlation diagrams contains four (= $2^{4-2} = 2^4/4$) stereoisograms.

3.3.2 Comparisons Between Correlation Diagrams With and Without Degeneration

Correlation diagrams with degeneration can be discussed in comparison with correlation diagrams without degeneration. For example, when we discuss correlation diagrams for the molecules shown in Fig. 8 (three *RS*-stereogenic centers with degeneration), supplemental parenthesized molecules are added by referring to Fig. 6 (three *RS*-stereogenic centers without degeneration). As a result, Fig. 9(A) for the C_3 can be compared with Fig. 7(A); Fig. 9(B) for the C_2 can be discussed in comparison with Fig. 7(B); and Fig. 9(C) for the C_4 can be discussed by referring to Fig. 7(C).

Similarly, correlation diagrams with degeneration for describing the molecules listed in Fig. 12 can be discussed by comparing them with the counterpart diagrams for the molecules listed in Fig. 10 which corresponds to cases without degeneration: Fig. 13(A) vs. Fig. 11(A) for the C_3, Fig. 13(B) vs. Fig. 11(B) for the C_2, Fig. 13(C) vs. Fig. 11(C) for the C_4, and Fig. 13(D) vs. Fig. 11(D) for the $C_{2'}$,

3.3.3 Pseudoasymmetric Cases and Reflection-Invariant Cases

The State of the Art Concerning These Cases The term *pseudoasymmetry* has suffered verbal transmutation as pointed out by Mislow [10]. This transmutation can be unequivocally traced by the present terminology based on stereoisograms [22].

The original meaning of pseudoasymmetry by Fischer [32] was concerned with Type-V promolecules (achiral, *RS*-stereogenic, and scleral), although Fischer himself did not coined the term. The IUPAC 1968 rule extended pseudoasymmetry to specify Type-V promolecules as well as a special group of Type-III promolecules (chiral, *RS*-stereogenic, and scleral), e.g., **21** and **22** [33]. Pseudoasymmetry concerned with Type-V promolecules was geometrically formulated by Prelog and Helmchen [11]. According to this formulation, the IUPAC 1974 rule restricted pseudoasymmetry to specify Type-V promolecules and excluded such a special group of Type-III promolecules [34]. The extended pseudoasymmetry for specifying Type-V promolecules and the special group of Type-III promolecules was reinforced by Hirschmann and Hanson [35]. Although they referred to Hirschmann-Hanson's discussion [35] as being unjustified, Prelog and Helmchen [2] implemented the concept of "reflection-invariance" into the revised CIP priority system so as to treat Type-V promolecules and the special group of Type-III promolecules commonly. This means that they discarded their geometric formulation concerning Type-V promolecules at least in the application of the CIP priority rule [11]. Mislow and Siegel [4] discussed the term "pseudoasymmetric" so as to conclude that the term lacks meaningful reference to symmetry and geometry; and they commented on the application of *RS*-descriptors to the special kind of Type-III promolecules. Mislow-Siegel's comments [4] on the application of the CIP priority system to the special kind of Type-III promolecules were criticized by Helmchen [5]. Finally, Mislow stated discontents with stereochemical terminology concerning pseudoasymmetry [10].

Broader and Balanced Prospects Provided by Correlation Diagrams After the proposal of stereoisograms [16], the term "pseudoasymmetry" was discussed by Fujita [22] so that it should be used only to specify Type-V promolecules. Correlation diagrams of stereoisograms developed in the present paper provides us with broader and balanced prospects to pseudoasymmetric and reflection-Invariant cases.

Stereoisogram #1 of Type III (Fig. 13(A)) consists of two pairs of enantiomers, $\mathbf{21}_3/\overline{\mathbf{21}}_3$ and $\mathbf{22}_3/\overline{\mathbf{22}}_3$. The *R*-configuration (or *r*-configuration due to the CIP system) of $\mathbf{21}_3$ is invariant by reflection. It should be noted that the reflection-invariance is only concerned with *RS*-descriptors. The following features should be pointed out by consulting Stereoisogram #1 of Type III contained in the correlation diagram shown in Fig. 13(A):

1. Stereoisogram #1 (Type III) shown in Fig. 13(A) is characterized by a quadruplet of promolecules, $\mathbf{21}_3$, $\overline{\mathbf{21}}_3$, and $\mathbf{22}_3$, and $\overline{\mathbf{22}}_3$, which are different from each other. This feature is common to all Type-III promolecules. The *R*- (or *r*-)configuration of $\mathbf{21}_3$ is determined in comparison with the *S*- (or *s*-)configuration of $\mathbf{22}_3$, where the comparison is based on the corresponding *RS*-diastereomeric relationship by using the common priority sequence, $\mathrm{t} > \mathrm{r} > \bar{\mathrm{r}} > \mathrm{H}$. This comparison has nothing to do with the reflection-invariance of the *R*- (or *r*-)descriptor of $\mathbf{21}_3$.

2. The reflection-invariance of the *R*-configuration (or *r*-configuration due to the CIP system) of $\mathbf{21}_3$ means that $\mathbf{21}_3$ is converted by reflection into its enantiomeric promolecule $\overline{\mathbf{21}}_3$, which has also *R*-configuration (or *r*-configuration due to the CIP system). In other words, the configuration of $\mathbf{21}_3$ itself (a promolecule with proligands t, r, $\bar{\mathrm{r}}$, and H) is reflection-variant so as to be converted into that of the enantiomer $\overline{\mathbf{21}}_3$ (a promolecule with proligands $\bar{\mathrm{t}}$, r, $\bar{\mathrm{r}}$, and H).

3. Although the promolecules are characterized to have *R*- (or *r*)-configuration, the local chirality of the C_3 atom of $\mathbf{21}_3$ is opposite to the local chirality of the C_3 atom of $\overline{\mathbf{21}}_3$. This behavior is common to Type-III promolecules.

4. In this reflection-invariant case, the *R*- (or *r*-)configuration of $\mathbf{21}_3$ is determined by the priority sequence $\mathrm{t} > \mathrm{r} > \bar{\mathrm{r}} > \mathrm{H}$, while the *R*- (or *r*-)configuration of $\overline{\mathbf{21}}_3$ is determined by the different priority sequence $\bar{\mathrm{t}} > \mathrm{r} > \bar{\mathrm{r}} > \mathrm{H}$. In other words, the priority sequences are reflection-variant.

These features are different from Type-V promolecules exhibiting typical pseudoasymmetry (e.g., Stereoisogram #1 of Type V shown in Fig. 9(A))

On the other hand, the concept of reflection-invariance can be discussed from an alternative viewpoint by comparing two or more correlation diagrams of stereoisograms which represent the same set of stereoisomers (e.g., Fig. 13(A) vs. Fig. 13(D)).

5. Let us examine the achiral proligands (X_1 and X_2) contained in the correlation diagram (Fig. 13(D)), where the concrete structures of X_1 and X_2 are shown in Fig. 12. Note that the promolecule $\mathbf{21}_{2'}$ etc. contained in Stereoisogram #1 or #2 (Type I) are alternative representations of the molecule **21** etc. to be examined. In order to determine the achirality of X_1 or X_2, the proligand r$\bar{\mathrm{r}}$CH-OCO— (= X_1 or X_2) should be preliminarily examined by regarding it as exhibiting typical pseudoasymmetry.

6. The examination of the proligand r$\bar{\mathrm{r}}$CH-OCO— is equivalent to the examination of a tentative promolecule r$\bar{\mathrm{r}}$CH-OCO—R, where R is a tentative achiral proligand. As found

easily, this examination is equivalent to that of Type-V promolecule. This examination would provide an equivalent result to the examination of reflection-invariance described above with an appropriate presumption.

The above-mentioned discussion reveals that the use of lowercase letters (or uppercase letters) is not based on its correctness. Rather, the selection of lowercase letters (or uppercase letters) depends on practical purposes. If we put emphasis on the items No. 1–4, *RS*-descriptors for such reflection-invariant cases are decided to be written in uppercase letters (*R* or *S*) just as Type-III promolecules are designated by uppercase letters. If we put emphasis on the items No. 5 and 6, *RS*-descriptors for such reflection-invariant cases of Type III are decided to be written in lowercase letters (*r* or *s*). With respect to the latter decision, especially to items No. 5 and 6, see Criterion 1 described in the enumerations of alkanes [36] and monosubstituted alkanes [37].

Finally, correlation diagrams of stereoisograms teach us that the term "pseudoasymmetric" should be used to specify Type-V promolecules or isolated proligands belonging to Type V. This usage is able to support the original meaning of the term "pseudoasymmetric" as well as most parts of the extended meaning due to "reflection-invariance" even if items 1–4 along with items 5 and 6 are taken into consideration. The extended meaning due to "reflection-invariance" is indirectly supported via such isolated proligands belonging to Type V. Even if we adopt this modification, there would appear troublesome cases (e.g., a proligand —Cp$\overline{\text{p}}$q contained in a promolecule Cp$\overline{\text{p}}$q$\overline{\text{q}}$ of Type I). Hence, the use of lowercase letters *r* and *s* for specifying such special Type-III promolecules that are characterized by the term "reflection-invariance" should be regarded as a rule for the sake of convenience, but not as an authority for equalizing Type-V molecules and such special Type-III promolecules. Although the CIP priority system has adopted the lowercase letters (*r* or *s*) for describing reflection-invariant cases of Type III, it should be remembered that the reflection-invariant cases of Type III are quite different from pseudoasymmetric cases of Type V (cf. items No. 1–4). If the former Type-III cases are differentiated from the latter Type-V cases, the use of $r's'$ or $r_{\text{III}}s_{\text{III}}$ would be practical, although more rigorous discussions are required.

4 Conclusion

Correlation diagrams of stereoisograms for characterizing stereoisomers have been developed so as to provide us with more information on geometric and stereoisomeric features than a single use of a stereoisogram. A correlation diagram of stereoisograms is constructed at an *RS*-stereogenic center or related site whose locant number is given commonly to respective stereoisomers having a common constitution. The correlation diagram contains a definite number of stereoisograms, each of which characterizes a set of *RS*-stereoisomers as an equivalence class among the stereoisomers of a common constitution. Thereby, each stereoisogram represents the local chirality/achirality and the local *RS*-stereogenicity/*RS*-astereogenicity of the *RS*-stereogenic center (or related site) so that the corresponding correlation diagram indicates total features of such local symmetries. If such an *RS*-stereogenic center (or related site) runs over all of *RS*-stereogenic centers (or related sites), a set of correlation diagrams can be obtained to characterize the set of stereoisomers having a common constitution. By means of correlation diagrams of stereoisograms, several problems of the traditional stereochemistry have been discussed, e.g., the over-simplified feature of the conventional dichotomy between enantiomers

and diastereomers, implications of reflection-invariant cases of the CIP priority system, unconscious mixing-up of local chirality and local *RS*-stereogenicity.

References

[1] R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Int. Ed. Eng.*, **5**, 385–415 (1966).

[2] V. Prelog and G. Helmchen, *Angew. Chem. Int. Ed. Eng.*, **21**, 567–583 (1982).

[3] IUPAC Organic Chemistry Division, *Pure Appl. Chem.*, **68**, 2193–2222 (1996).

[4] K. Mislow and J. Siegel, *J. Am. Chem. Soc.*, **106**, 3319–3328 (1984).

[5] G. Helmchen A. General Aspects. 1. Nomenclature and Vocabulary of Organic Stereochemistry, in "Stereoselective Synthesis. Methods of Organic Chemistry (Houben-Weyl). Workbench Edition E21," 4 ed., ed. by G. Helmchen, R. W. Hoffmann, J. Mulzer, and E. Schaumann, Georg Thieme, Stuttgart New York (1996) Vol. 1 pp 1–74.

[6] S. R. Buxton and S. M. Roberts, "Guide to Organic Stereochemistry," Addison Wesley Longman, New York (1996).

[7] E. L. Eliel, *Chirality*, **9**, 428–430 (1997).

[8] G. Helmchen, *Enantiomer*, **2**, 315–318 (1997).

[9] D. G. Morris, "Stereochemistry," Royal Soc. Chem., Cambridge (2001).

[10] K. Mislow, *Chirality*, **14**, 126–134 (2002).

[11] V. Prelog and G. Helmchen, *Helv. Chim. Acta*, **55**, 2581–2598 (1972).

[12] E. Eliel and S. H. Wilen, "Stereochemistry of Organic Compounds," John Wiley & Sons, New York (1994).

[13] N. North, "Principles and Applications of Stereochemistry," Stanley Thornes, Cheltenham (1998).

[14] S. Fujita, *MATCH Commun. Math. Comput. Chem.*, **61**, 11–38 (2009).

[15] S. Fujita, *Yuki Gosei Kagaku Kyokai-Shi/J. Synth. Org. Chem. Jpn.*, **66**, 995–1004 (2008).

[16] S. Fujita, *J. Org. Chem.*, **69**, 3158–3165 (2004).

[17] S. Fujita, *MATCH Commun. Math. Comput. Chem.*, **54**, 39–52 (2005).

[18] S. Fujita, *J. Math. Chem.*, **35**, 265–287 (2004).

[19] S. Fujita, *MATCH Commun. Math. Comput. Chem.*, **52**, 3–18 (2004).

[20] S. Fujita, *MATCH Commun. Math. Comput. Chem.*, **53**, 147–159 (2005).

[21] S. Fujita, *Memoirs of the Faculty of Engineering and Design, Kyoto Institute of Technology*, **53**, 19–38 (2005).

[22] S. Fujita, *Tetrahedron*, **60**, 11629–11638 (2004).

[23] S. Fujita, *Tetrahedron*, **62**, 691–705 (2006).

[24] S. Fujita, *MATCH Commun. Math. Comput. Chem.*, **61**, 39–70 (2009).

[25] S. Fujita, *Chem. Educ. J.*, **8**, Registration No. 8–8 (2005).

[26] S. Fujita, *Tetrahedron*, **47**, 31–46 (1991).

[27] S. Fujita, *MATCH Commun. Math. Comput. Chem.*, **58**, 611–634 (2007).

[28] S. Fujita, *MATCH Commun. Math. Comput. Chem.*, **61**, 71–115 (2009).

[29] S. Fujita, "Symmetry and Combinatorial Enumeration in Chemistry," Springer-Verlag, Berlin-Heidelberg (1991).

[30] S. Fujita, "Diagrammatical Approach to Molecular Symmetry and Enumeration of Stereoisomers," University of Kragujevac, Faculty of Science, Kragujevac (2007).

[31] S. Fujita, *J. Math. Chem.*, **43**, 141–201 (2008).

[32] E. Fischer, *Ber. Dtsch. chem. Ges.*, **24**, 1836–1845 (1891).

[33] The Commission on the Nomenclature of Organic Chemistry of IUPAC, *J. Org. Chem.*, **35**, 2849–2867 (1970).

[34] The Commission on the Nomenclature of Organic Chemistry of IUPAC, *Pure and App. Chem.*, **45**, 11–30 (1976).

[35] H. Hirschmann and K. R. Hanson, *Tetrahedron*, **30**, 3649–3656 (1974).

[36] S. Fujita, *MATCH Commun. Math. Comput. Chem.*, **59**, 509–554 (2008).

[37] S. Fujita, *Bull. Chem. Soc. Jpn.*, **81**, 193–219 (2008).