MATCH
Communications in Mathematical and in Computer Chemistry

MATCH Commun. Math. Comput. Chem. **71** (2014) 575-608

ISSN 0340 - 6253

Stereoisograms of Octahedral Complexes. III. Prochirality, Pro-*RS*-Stereogenicity, and Pro-Ortho-Stereogenicity Free from the Conventional "Prochirality" and "Prostereogenicity"

Shinsaku Fujita

Shonan Institute of Chemoinformatics and Mathematical Chemistry,

Kaneko 479-7 Ooimachi, Ashigara-Kami-Gun, Kanagawa-Ken,

258-0019 Japan

E-mail: shinsaku_fujita@nifty.com

(Received January 24, 2012)

Abstract

The concept of prochirality is defined to discuss inorganic stereochemistry on the basis of enantiosphericity, which has been developed as a purely geometric formulation for organic stereochemistry (S. Fujita, *J. Am. Chem. Soc.*, **112**, 3390–3397 (1990); S. Fujita, "Symmetry and Combinatorial Enumeration in Chemistry", Springer-Verlag, Berlin-Heidelberg (1991)). In addition, the concept of pro-*RS*-stereogenicity is defined to discuss inorganic stereochemistry on the basis of *RS*-enantiotropicity (S. Fujita, *J. Math. Chem.*, **33**, 113–143 (2003); S. Fujita, *Tetrahedron*, **62**, 691–705 (2006)). These concepts are applied to the discussion on intramolecular features of octahedral complexes. Alternatively, the stereoisogram approach for organic stereochemistry (S. Fujita, *J. Org. Chem.*, **69**, 3158–3165 (2004); S. Fujita, *Tetrahedron*, **60**, 11629–11638 (2004)) is extended to discuss prochirality and pro-*RS*-stereogenicity of octahedral complexes in inorganic stereochemistry. After octahedral complexes are categorized into five types (Types I–V) by means of stereoisograms, stereoisograms for testifying prochirality and pro-*RS*-stereogenicity are proposed as alternative devices, which are an extension of the counterparts developed originally for the

symmetry criterion in organic stereochemistry (S. Fujita, *J. Comput. Aided Chem.*, **10**, 76–95 (2009)). The relational terms *enantiotopic* and *RS-diastereotopic* are introduced to make the symmetry criterion effective. Thereby, *pro-A/pro-C*-descriptors are concluded to be based on an *RS*-diastereotopic relationship. The further concept of *pro-ortho-stereogenicity* is proposed to rationalize intramolecular (in)equivalency of proligands, which cannot be characterized by *pro-A/pro-C*-descriptors.

1 Introduction

The concept of "prochirality" was originally introduced by Hanson [1] to rationalize *pro-R/pro-S*-descriptors for organic molecules. Although such *pro-R/pro-S*-descriptors are useful to characterize stereoisomeric features, the original intention of characterizing geometrical properties by *pro-R/pro-S*-descriptors have proven futile, as pointed out in convincing discussions by Mislow and Siegel [2]. Although the term *prochirality* is recommended to be used in a purely geometric meaning apart from the terms "prostereoisomerism" and "prostereogenic centers" [2], the practical usage of these terms is confused even now, because the relationship between *prochirality* and "prostereoisomerism"(or "prostereogenic centers") has not fully defined, as found in the explanation of the term "prochirality" in the IUPAC Recommendations 1996 [3]. The confusing situations have unconsciously continued and have been reinforced by explanations adopted in reviews [4, Section 3] and textbooks [5, Chapter 8]. In particular, the terms "enantiotopic" and "diastereotopic" have been misleadingly lumped together under the term "stereoheterotopic" in order to make the usage of "prochiral" and "prostereogenic" consistent [4, Subsection 3.4], just as enantiomers and diastereomers are both called stereoisomers in an oversimplified fashion (cf. [6]).

The conventional concept of "prochirality" has been applied to coordination compounds [7] to rationalize their intramolecular properties and *pro-A/pro-C*-descriptors, where the terminology developed for organic stereochemistry has been simply applied to coordination compounds of inorganic stereochemistry. This means that the confusing situations pointed out in organic stereochemistry have been brought into inorganic stereochemistry.

We have recently discussed the confusing situations concerning "prochirality" and related concepts from a viewpoint of the stereoisogram approach [8]. As a result, we have pointed out that the conventional terminology should be entirely reconsidered to restructure stereochemistry, as quoted below with additional items:

1. The term "prochirality" of the *pro-R/pro-S* system should be abandoned in the same way as the transmuted term "chirality" of the CIP system should be abandoned. In other words, the theoretical framework to be developed should define a term *prochirality* by starting from the term *chirality* of a purely geometric meaning [9, 10].

2. The term "prostereogenicity" or "prostereoisomerism" of the *pro-R/pro-S* system and the term "stereogenicity" for giving *RS*-stereodescriptors of the CIP system should be abandoned. Instead, the newly-developed theoretical framework will define pro-*RS*-stereogenicity by starting from *RS*-stereogenicity, which has recently been developed [11–14].

3. The terms "enantiotopic", "diastereotopic", and "stereoheterotopic" should be abandoned to support the *pro-R/pro-S* system, just as the terms "enantiomeric", "diastereomeric", and "stereogenic" for supporting *RS*-stereodescriptors of the CIP system should be abandoned. In particular, the term *enantiotopic* will be used only to explain geometric aspects

apart from the *pro-R/pro-S* system, while the newly-defined term *RS*-diastereotopic will be used to support the *pro-R/pro-S* system. On a similar line, the term *enantiomeric* will be used only to explain geometric aspects apart from the CIP system, while the newly-defined term *RS*-diastereomeric will be used to support *RS*-stereodescriptors of the CIP system (cf. Parts I and II of this series for *C/A*-descriptors of inorganic stereochemistry).

4. The use of the term "stereoheterotopic" should be entirely ceased to support the *pro-R/pro-S* system. Thereby, the dichotomy between enantiotopic and "diastereotopic" (for the term "stereoheterotopic") will be abandoned. The related terms such as "stereoheterotopism" or "stereoheterotopicity" [15, 16] for supporting the *pro-R/pro-S* system will be also abandoned.

5. The transmuted term "enantiotopic" [5, page 1198] (and [17, page 238] for inorganic stereochemistry) should be abandoned. The term *enantiotopic* will be used in a purely geometric meaning.

6. The term *chirotopic* introduced by Mislow and Siegel [2] does not differentiate a local site of a chiral molecule from that of an achiral molecule, so that additional concepts (e.g., the term *enantiotopic* defined purely geometrically [18] or the transmuted term "enantiotopic" [5, page 1198] & [17, page 238]) are necessary to define the term *prochiral*. In contrast, the terms concerning sphericities (homospheric, enantiospheric, and hemispheric) are able to define the concept of prochirality directly [19, 20] and to be applied to combinatorial enumerations [9, 10]. It follows that the use of the terms concerning sphericities are recommended.

7. In addition, a theoretical framework to be developed should explain the difference between the newly-defined prochirality (geometrically) and pro-*RS*-stereogenicity, just as it should explain the difference between chirality (geometrically) and *RS*-stereogenicity.

8. As such a theoretical framework, the stereoisogram approach has been introduced for organic stereochemistry [11–13] and for inorganic stereochemistry (cf. Parts I and II of this series). This approach should be extended to rationalize the concept of *prochirality* and related concepts.

The purposes of this article is to clarify that the concepts of sphericities [9, 19] and stereoisograms [11–13] are valid and useful in inorganic stereochemistry, just as they are valid and useful in organic stereochemistry targeted originally. First, by using octahedral complexes, we show that the concept of prochirality is able to be discussed in a purely geometrical fashion, i.e., without *pro-A/pro-C*-descriptors based on the attributive terms "prostereogenicity" and "prostereoisomerism" as well as without the relational terms "enantiotopic", "diastereotopic", and "stereoheterotopic". The crux is the concept of *sphericity*, which has been originally introduced to comprehend organic stereochemistry [9, 19]. Second, we shows that *pro-A/pro-C*-descriptors are determined by the concept of pro-*RS*-stereogenicity (not by the concept of prochirality). Third, the relational terms *enantiotopic* and *RS-diastereotopic* are defined by means of stereoisograms introduced in Parts I and II of this series. Thereby, we shows that the conventional terminology should be replaced as enumerated above.

2 Prochirality

2.1 Prochirality by the Concept of Sphericities

2.1.1 Terminology

In this article, the term *prochirality* is used in a purely geometric meaning according to a monograph we have published [9, Chapter 10]. A set of equivalent proligands in a promolecule constructs an orbit governed by a coset representation $\mathbf{G}(/\mathbf{G}_i)$, where the point group $\mathbf{G}$ represents the global symmetry of the promolecule and the point group $\mathbf{G}_i$ represents the local symmetry of each member (each proligand) of the orbit. The group $\mathbf{G}_i$ is a subgroup of $\mathbf{G}$, where the degree of the coset representation $\mathbf{G}(/\mathbf{G}_i)$, i.e., $|\mathbf{G}|/|\mathbf{G}_i|$, is equal to the size of the orbit, i.e., the number of the equivalent proligands. The terms concerning sphericities of orbits are defined as follows [9, 19]:

Definition 1 (Sphericities)
The orbit is defined as being *homospheric* if both $\mathbf{G}$ and $\mathbf{G}_i$ are achiral; as being *enantiospheric* if $\mathbf{G}$ is achiral and $\mathbf{G}_i$ is chiral; or as being *hemispheric* if both $\mathbf{G}$ and $\mathbf{G}_i$ are chiral.

It should be noted that the term *chirotopic* (or *achirotopic*) is concerned with a ligand (or a site) in a molecule [2], where the term represents the local symmetry of the ligand (or the site) without referring the global symmetry so that the number of ligands equivalent to the ligand at issue is not be taken into consideration. It follows that the term *chirotopic* is presumed to be used in combination with a relational term *enantiotopic*.

In contrast, the terms of sphericities (Def. 1) are more informative, because they are based on the coset representations $\mathbf{G}(/\mathbf{G}_i)$, which provide us with many pieces of information on equivalent (pro)ligands, e.g., the number of equivalent proligands in the orbit ($|\mathbf{G}|/|\mathbf{G}_i|$). In addition to such qualitative applications as discussions on prochirality (cf. Def.1), they support quantitative applications such as combinatorial enumerations of isomers [9, 10].

The term *prochiral* is defined on the basis of the term *enantiospheric* as follows [9, 19, 20]:

Definition 2 (Prochirality)
The term *prochiral* is used to refer to such an enantiospheric orbit. In an extended meaning, the term *prochiral* is used to refer to a promolecule having such an enantiospheric orbit [20].

Thus, the term *prochiral* is an attributive term to characterize the nature of the orbit or of the promolecule, which is linked to an enantiospheric orbit [21, 22].

An enantiospheric orbit governed by $\mathbf{G}(/\mathbf{G}_i)$ is divided into two halves under chiral environments, where each half has the size of $|\mathbf{G}|/2|\mathbf{G}_i|$. The relationship between the two halves is defined as follows [9, 19, 23]:

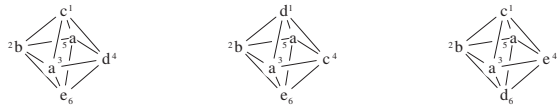
Definition 3 (Enantiotopic Relationships)
The relationship between such two halves as generated from an enantiospheric orbit is referred to as an *enantiotopic* relationship. The two halves in the enantiospheric orbit are referred to as being enantiotopic to each other.

This definition of the term *enantiotopic* is purely geometric and concerned with two or more (an even number of) members, which are divided into two halves contained in the enantiospheric orbit. The enantiotopic relationship due to Def. 3 is essentially equivalent to the original definition of the term *enantiotopic* by Mislow and Raban [18], except that the original definition is

concerned with the relationship between only two ligands, while Def. 3 is concerned with two halves of an even-membered orbit. The term "enantiotopic" of the conventional stereochemistry [5, page 1198] is also restricted to the relationship between only two ligands, where the original geometric meaning has been transmuted to have an inconsistent connotation, as described above [8].

2.1.2 Illustrative Examples

Octahedral Complexes with Achiral Proligands Only Let us examine octahedral complexes with [Ma$_2$bcde], where the letters a, b, c, d, and e represent achiral proligands and the letter M represents a central metal atom. The number of stereoisomers has been reported to be 9, where there appear six enantiomeric pairs of $\mathbf{C}_1$-promolecules and three $\mathbf{C}_s$-promolecules [24]. The latter achiral promolecules are illustrated in Fig. 1, where a central metal atom and coordination bonds are omitted, but hypothetical edges are added for sake of easy recognition.



1 ($\mathbf{C}_s$, Type IV)*‡ $\mathbf{C}_s[/\mathbf{C}_1(a_2);4/\mathbf{C}_s(b,c,d,e)]$ *OC-6-14*

2 ($\mathbf{C}_s$, Type IV)*‡ $\mathbf{C}_s[/\mathbf{C}_1(a_2);4/\mathbf{C}_s(b,c,d,e)]$ *OC-6-13*

3 ($\mathbf{C}_s$, Type IV)*‡ $\mathbf{C}_s[/\mathbf{C}_1(a_2);4/\mathbf{C}_s(b,c,d,e)]$ *OC-6-15*

Figure 1: Achiral octahedral complexes with [Ma$_2$bcde], where the point-group symmetry, the stereoisogram type, the SCR notation, and the configuration index are assigned to each complex. Each configuration index stems from the CIP priority: a > b > c > d > e. A complex with an asterisk is prochiral, while a complex with a double dagger is pro-*RS*-stereogenic.

The six substitution sites of a octahedral skeleton construct an orbit governed by the coset representation $\mathbf{O}_h(/\mathbf{C}_{4v})$. The derivations of the octahedral complexes illustrated in Fig. 1 are characterized by subductions of the coset representation (SCR) according to Table 3 of [24]:

$$\mathbf{O}_h(/\mathbf{C}_{4v}) \downarrow \mathbf{C}_s = \mathbf{C}_s(/\mathbf{C}_1) + 4\mathbf{C}_s(/\mathbf{C}_s). \tag{1}$$

Each octahedral complex depicted in Fig. 1 is derived by placing a set of achiral proligands (2a, b, c, d, and e) in accord with the SCR shown in Eq. 1. For example, the complex **1** of the $\mathbf{C}_s$-symmetry is generated by placing a$_2$ on the two-membered $\mathbf{C}_s(/\mathbf{C}_1)$-orbit as well as each of achiral proligands (b, c, d, and e) on a one-membered $\mathbf{C}_s(/\mathbf{C}_s)$-orbit. This mode of substitutions is represented by the SCR notation [25], i.e., $\mathbf{C}_s[/\mathbf{C}_1(a_2);4/\mathbf{C}_s(b,c,d,e)]$, which is commonly assigned to all of the complexes shown in Fig. 1.

The coset representation $\mathbf{C}_s(/\mathbf{C}_1)$ is enantiospheric in terms of Def. 1, because the global symmetry $\mathbf{C}_s$ is achiral and the local symmetry $\mathbf{C}_1$ is chiral. According to Def. 2, the orbit of a$_2$ in **1** (or in **2** or in **3**) is concluded to be prochiral because of enantiosphericity. Hence, the promolecules **1**, **2**, and **3** are regarded as being prochiral. The relationship between the two proligand a$_2$ in **1** (or **2** or **3**) is enantiotopic according to Def. 3.

Let us next examine octahedral complexes with [Ma$_2$b$_2$cd], where the letters a, b, c, and d represent achiral proligands and the letter M represents a central metal atom. The number of stereoisomers has been reported to be 6, where there appear two enantiomeric pairs of

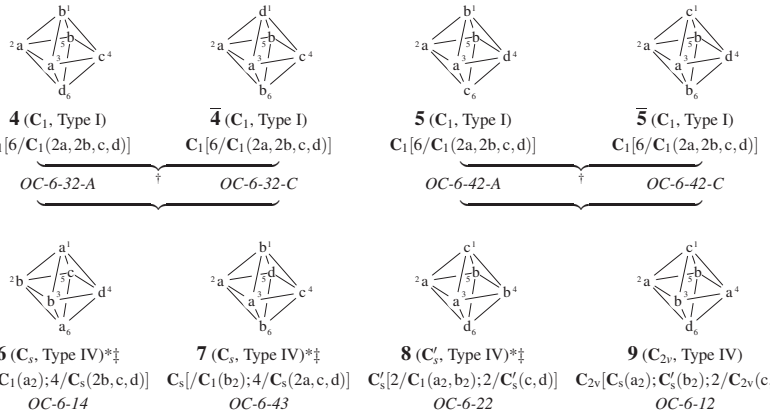


Figure 2: Octahedral complexes with $[Ma_2b_2cd]$, where the point-group symmetry, the stereoisogram type, the SCR notation, and the configuration index (with the *A/C*-descriptor) are assigned to each complex. A complex with an asterisk is prochiral, while a complex with a double dagger is pro-*RS*-stereogenic. An underbrace with a dagger indicates a pair of enantiomers, while a simple underbrace indicates a pair of *RS*-diastereomers.

$\mathbf{C}_1$-promolecules, two $\mathbf{C}_s$-promolecules, one $\mathbf{C}'_s$-promolecules, and one $\mathbf{C}_{2v}$-promolecule [24]. They are illustrated in Fig. 2.

The six substitution sites of a octahedral skeleton construct an orbit governed by the coset representation $\mathbf{O}_h(/\mathbf{C}_{4v})$, the derivations of the octahedral complexes illustrated in Fig. 2 are characterized by subductions of the coset representation (SCR) according to Table 3 of [24]:

$$\mathbf{O}_h(/\mathbf{C}_{4v}) \downarrow \mathbf{C}_1 = 6\mathbf{C}_1(/\mathbf{C}_1) \quad (2)$$

$$\mathbf{O}_h(/\mathbf{C}_{4v}) \downarrow \mathbf{C}_s = \mathbf{C}_s(/\mathbf{C}_1) + 4\mathbf{C}_s(/\mathbf{C}_s) \quad (3)$$

$$\mathbf{O}_h(/\mathbf{C}_{4v}) \downarrow \mathbf{C}'_s = 2\mathbf{C}'_s(/\mathbf{C}_1) + 2\mathbf{C}'_s(/\mathbf{C}'_s) \quad (4)$$

$$\mathbf{O}_h(/\mathbf{C}_{4v}) \downarrow \mathbf{C}_{2v} = \mathbf{C}_{2v}(/\mathbf{C}_s) + \mathbf{C}_{2v}(/\mathbf{C}'_s) + 2\mathbf{C}_{2v}(/\mathbf{C}_{2v}), \quad (5)$$

Each octahedral complex depicted in Fig. 2 is derived by placing a set of achiral proligands (2a, 2b, c, and d) in accord with one of the SCR listed in Eqs. 2 to 5. For example, the complex **6** belonging to the point group $\mathbf{C}_s$ is generated by placing a_2 on a two-membered $\mathbf{C}_s(/\mathbf{C}_1)$-orbit and four achiral proligands (2b, c, and d) on respective one-membered $\mathbf{C}_s(/\mathbf{C}_s)$-orbits in accord with Eq. 3. This mode of substitutions is represented by the SCR notation [25], i.e., $\mathbf{C}_s[/\mathbf{C}_1(a_2);4/\mathbf{C}_s(2b,c,d)]$.

Among the coset representations appearing in the right-hand sides of these equations, the coset representations $\mathbf{C}_s(/\mathbf{C}_1)$ and $\mathbf{C}'_s(/\mathbf{C}_1)$ are enantiospheric in terms of Def. 1, because the global symmetry $\mathbf{C}_s$ or $\mathbf{C}'_s$ is achiral and the local symmetry $\mathbf{C}_1$ is chiral.

According to Def. 2, the orbit of a_2 in **6**, the orbit of b_2 in **7**, and the orbit of a_2 (or b_2) in **8** are concluded to be prochiral because of enantiosphericity. Hence, the promolecules **6**, **7**, and **8** are regarded as being prochiral. The relationship between the two proligand a_2 in **6** (or between b_2 in **7** or between a_2 (or b_2) in **8**) is enantiotopic according to Def. 3.

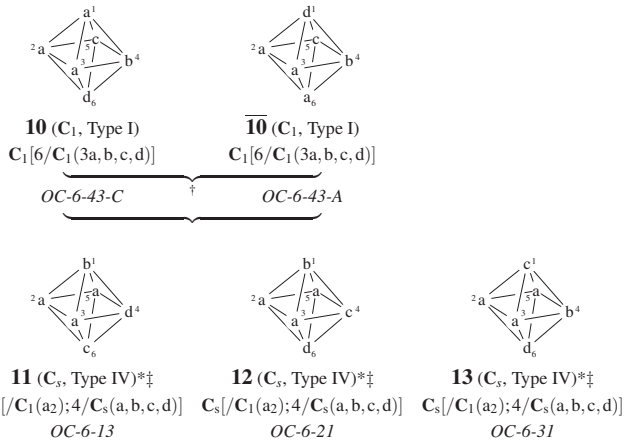


Figure 3: Octahedral complexes with $[Ma_3bcd]$, where the point-group symmetry, the stereoisogram type, the SCR notation, and the configuration index (with the *A/C*-descriptor) are assigned to each complex. A complex with an asterisk is prochiral, while a complex with a double dagger is pro-*RS*-stereogenic. An underbrace with a dagger indicates a pair of enantiomers, while a simple underbrace indicates a pair of *RS*-diastereomers.

Let us examine octahedral complexes with $[Ma_3bcd]$, where the letters a, b, c, and d represent achiral proligands and the letter M represents a central metal atom. The number of stereoisomers has been reported to be 4, where there appear one enantiomeric pair of $\mathbf{C}_1$-promolecules and three $\mathbf{C}_s$-promolecules [24]. They are illustrated in Fig. 3.

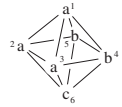
Each octahedral complex depicted in Fig. 3 is derived by placing a set of achiral proligands (3a, b, c, and d) in accord with one of the SCR listed in Eq. 3. For example, **11** ($\mathbf{C}_s$) is generated by placing a_2 on the two-membered $\mathbf{C}_s(/\mathbf{C}_1)$-orbit as well as each of achiral proligands (a, b, c, and d) on the one-membered $\mathbf{C}_s(/\mathbf{C}_s)$-orbit. This mode of substitutions is represented by the SCR notation [25], i.e., $\mathbf{C}_s[/\mathbf{C}_1(a_2);4/\mathbf{C}_s(a,b,c,d)]$, where the three a's are divided into the two a's of the $\mathbf{C}_s(/\mathbf{C}_1)$-orbit and the one 'a' of the $\mathbf{C}_s(/\mathbf{C}_s)$-orbit.

According to Def. 2, the orbit of a_2 in **11** (or **12** or **13**) is concluded to be prochiral because of its enantiosphericity. Hence, the promolecules **11**, **12**, and **13** are regarded as being prochiral. The relationship between the two proligand a_2 in each orbit is enantiotopic according to Def. 3.

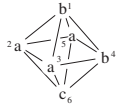
Let us examine octahedral complexes with $[Ma_3b_2c]$, where the letters a, b, and c represent achiral proligands and the letter M represents a central metal atom. The number of stereoisomers has been reported to be 3, where there appear one $\mathbf{C}'_s$-promolecule, one $\mathbf{C}_s$-promolecule, and one $\mathbf{C}_{2v}$-promolecule [24]. They are illustrated in Fig. 4.

Each octahedral complex depicted in Fig. 4 is derived by placing a set of achiral proligands (3a, b, c, and d) in accord with one of the SCR listed in Eqs. 3–5. These modes of substitutions are represented by the SCR notations [25], which are collected in Fig. 4.

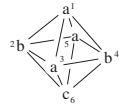
According to Def. 2, the orbits of a_2 and of b_2 in **14** (or the orbit of a_2 of **15**) are concluded to be prochiral because of their enantiosphericity. Hence, the promolecules **14** and **15** are regarded as being prochiral. The relationship between the two proligand a_2 (or b_2) in each orbit



14 ($\mathbf{C}'_s$, Type IV)*‡
$\mathbf{C}'_s[2/\mathbf{C}_1(a_2,b_2);2/\mathbf{C}'_s(a,c)]$
OC-6-32



15 ($\mathbf{C}_s$, Type IV)*‡
$\mathbf{C}_s[/\mathbf{C}_1(a_2);4/\mathbf{C}_s(a,2b,c)]$
OC-6-21



16 ($\mathbf{C}_{2v}$, Type IV)
$\mathbf{C}_{2v}[\mathbf{C}_s(a_2);\mathbf{C}'_s(b_2);2/\mathbf{C}_{2v}(a,c)]$
OC-6-31

Figure 4: Octahedral complexes with $[Ma_3b_2c]$, where the point-group symmetry, the stereoisogram type, the SCR notation, and the configuration index are assigned to each complex. A complex with an asterisk is prochiral, while a complex with a double dagger is pro-*RS*-stereogenic.

is enantiotopic according to Def. 3.

It should be noted that the proligand 'a' on the vertex 1 of **14** belongs to the one-membered $\mathbf{C}'_s(/\mathbf{C}'_s)$-orbit and different geometrically from the proligands a_2 in the two-membered enantiospheric orbit (on vertices 2 and 3). This is recognized by examining the structure of **14** or by glimpsing the SCR notation attached below the structure.

Octahedral Complexes with Chiral and Achiral Proligands Let us examine octahedral complexes with $[Ma_2bcp\overline{p}]$, where the letters a, b, and c represent achiral proligands, the letters p and $\overline{p}$ represent promolecules of an enantiomeric pair in isolation (when detached), and the letter M represents a central metal atom. The number of stereoisomers has been reported to be 10, where there appear five enantiomeric pairs of $\mathbf{C}_1$-promolecules three $\mathbf{C}_s$-promolecule, and two $\mathbf{C}'_s$-promolecule [24]. Among these octahedral complexes, five achiral promolecules are illustrated in Fig. 5.

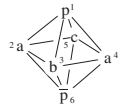
Each octahedral complex depicted in Fig. 5 is derived by placing a set of achiral proligands (2a, b, c, and p/$\overline{p}$) in accord with the SCRs listed in Eqs. 3 and 4, as indicated by the SCR notations listed below the compound numbers. Because all of these octahedral complexes (**17**–**21**) has a pair of p and $\overline{p}$ which belongs to a two-membered enantiospheric orbit (Def. 1), they are concluded to be prochiral (Def. 2). This means that a chiral reagent is capable of differentiating between p and $\overline{p}$ to generate a pair of enantiomeric complexes, although an achiral reagent cannot differentiate between p and $\overline{p}$. This type of prochirality exhibits the geometrically same situation as the above-mentioned prochirality concerning achiral proligands only (cf. Figs. 1–4).

In addition, the $\mathbf{C}'_s$-promolecule **20** (or **21**) has another enantiospheric orbit containing a_2, which can be discussed on a similar way to the enantiospheric orbit containing p/$\overline{p}$. Geometrically speaking, there is no reason to differentiate the enantiosphericity of the orbit of achiral proligands a_2 from the enantiosphericity of the orbit of chiral proligands p/$\overline{p}$.

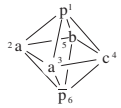
From the geometric point of view, the two a's of **17**–**19** belong to one-membered orbits separately (cf. their SCR notations), so that they are so inequivalent to be attacked selectively even by achiral reagents. This means that only geometric consideration (viz. without assigning *pro-A/pro-C*-descriptors or even without considering pro-*RS*-stereogenicity or pro-orthostereogenicity) is sufficient to discuss reactivities of the complexes **17**–**19**.

Moreover, discussions on "prochirality" and "prostereogenicity" on the basis of the conventional terminology are misleading in most cases of inorganic stereochemistry:

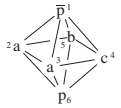
1. Because p and $\overline{p}$ are not "homomorphic" according to the conventional definition (e.g., [5, page 1200] & [17, page 238]), they are not in an "enantiotopic" relationship, if we



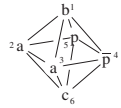
17 ($\mathbf{C}_s$, Type IV)*
$\mathbf{C}_s[/\mathbf{C}_1(p\overline{p});4/\mathbf{C}_s(2a,b,c)]$
OC-6-13



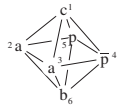
18 ($\mathbf{C}_s$, Type V)*
$\mathbf{C}_s[/\mathbf{C}_1(p\overline{p});4/\mathbf{C}_s(2a,b,c)]$
OC-6-32-A



19 ($\mathbf{C}_s$, Type V)*
$\mathbf{C}_s[/\mathbf{C}_1(p\overline{p});4/\mathbf{C}_s(2a,b,c)]$
OC-6-32-C



20 ($\mathbf{C}'_s$, Type V)*
$\mathbf{C}'_s[2/\mathbf{C}_1(a_2,p\overline{p});2/\mathbf{C}'_s(b,c)]$
OC-6-54-A



21 ($\mathbf{C}'_s$, Type V)*
$\mathbf{C}'_s[2/\mathbf{C}_1(a_2,p\overline{p});2/\mathbf{C}'_s(b,c)]$
OC-6-54-C

Figure 5: Achiral octahedral complexes with $[Ma_2bcp\overline{p}]$, where the point-group symmetry, the stereoisogram type, the SCR notation, and the configuration index are assigned to each complex. A complex with an asterisk is prochiral. A simple underbrace indicates a pair of *RS*-diastereomers.

obey the transmuted term "enantiotopic" (e.g., [5, page 1198] & [17, page 238]). Hence, the prochiralities of the octahedral complexes (**17**–**19**) are not detected in terms of the conventional stereochemistry, because the definition of "prochirality" is accordingly transmuted (e.g., [5, page 1204] & [17, page 240]).

2. In contrast, the prochiralities of the octahedral complexes (**20** and **21**) are detected in terms of the conventional stereochemistry, because a_2 are "homomorphic" according to the conventional definition (e.g., [5, page 1200] & [17, page 238]) so that they are regarded as being in an "enantiotopic" relationship (e.g., [5, page 1198] & [17, page 238]). Geometrically speaking, however, there is no reason to ignore the prochiralities of **17**–**19**.

3 Pro-*RS*-Stereogenicity

We have originally introduced the concept of tropicities in order to discuss global/local permutational-group symmetry [26], where the three terms, i.e., *homotropic*, *enantiotropic*, and *hemitropic*, were coined to characterize prostereogenicity (Note that the suffix "tropic" for the attributive terms should be differentiated from the suffix "topic" for the relational terms). However, the concept of tropicities has limitations, because the *RS*-permutation group is required to be identical with the stereogenic group. This means that the original concept of tropicities is useful mainly to tetrahedral derivatives. Later, the concept of tropicities has been restricted to a theoretically meaningful subconcept, i.e., the concept of *RS*-tropicities [27], where more definite terms *RS-homotropic*, *RS-enantiotropic*, and *RS-hemitropic* were coined to characterize pro-*RS*-stereogenicity. More strictly speaking, the concept of *RS*-tropicities should be restricted to

discussions within a stereoisogram. Hence, it has limitations for the purpose of discussing octahedral complexes, because each complex is characterized by a multiplet of stereoisograms (cf. Part II of this series). In spite of such limitations, the concept of *RS*-tropicities will be briefly introduced here in order to go further to demonstrate complicated cases of pro-*RS*-stereogenicity or prostereogenicity.

3.1 Pro-*RS*-Stereogenicity by *RS*-Tropicities

3.1.1 Terminology

According to Part I of this series, we take account of the *RS*-permutation group $\mathbf{O}_{\tilde{I}}$, which corresponds to the point group $\mathbf{O}_h$. Subgroups of the *RS*-permutation group $\mathbf{O}_{\tilde{I}}$ are categorized into *RS*-stereogenic groups and *RS*-astereogenic groups, just as subgroup of the point group $\mathbf{O}_h$ are categorized into chiral and achiral groups.

Let $\tilde{\mathbf{G}}$ be an *RS*-permutation group corresponding to the point group $\mathbf{G}$, where the groups $\tilde{\mathbf{G}}$ and $\mathbf{G}$ concurrently but independently act on a skeleton (e.g., an octahedral skeleton in the present article). A set of equivalent proligands in a promolecule constructs an orbit governed by a coset representation $\tilde{\mathbf{G}}(/\tilde{\mathbf{G}}_i)$, where the subgroup $\tilde{\mathbf{G}}_i$ corresponds to $\mathbf{G}_i$ without changing ligand chirality. The degree of the coset representation $\tilde{\mathbf{G}}(/\tilde{\mathbf{G}}_i)$, i.e., $|\tilde{\mathbf{G}}|/|\tilde{\mathbf{G}}_i|$, is equal to the size of the orbit, i.e., the number of the equivalent proligands. The terms concerning *RS*-tropicities of orbits are defined as follows [27]:

Definition 4 (*RS*-Tropicity)
The orbit is defined as being *RS-homotropic* if both $\tilde{\mathbf{G}}$ and $\tilde{\mathbf{G}}_i$ are *RS*-astereogenic; as being *RS-enantiotropic* if $\tilde{\mathbf{G}}$ is *RS*-astereogenic and $\tilde{\mathbf{G}}_i$ is *RS*-stereogenic; or as being *RS-hemitropic* if both $\tilde{\mathbf{G}}$ and $\tilde{\mathbf{G}}_i$ are *RS*-stereogenic.

The term *pro-RS-stereogenic* is defined on the basis of the attributive term *RS-enantiotropic* as follows [27]:

Definition 5 (Pro-*RS*-stereogenicity)
The term *pro-RS-stereogenic* is used to refer to such an *RS*-enantiotropic orbit. In an extended meaning, the term *pro-RS-stereogenic* is used to refer to a promolecule having such an *RS*-enantiotropic orbit [27].

Thus, the term *pro-RS-stereogenic* is an attributive term to characterize the nature of the orbit or of the promolecule, which is linked to an *RS*-enantiotropic orbit [27].

An enantiotropic orbit governed by $\tilde{\mathbf{G}}(/\tilde{\mathbf{G}}_i)$ is divided into two halves under *RS*-stereogenic environments (i.e., with no ligand permutations), where each half has the size of $|\tilde{\mathbf{G}}|/2|\tilde{\mathbf{G}}_i|$. The relationship between the two halves is defined as follows [27]:

Definition 6 (*RS*-Diastereotopic Relationships)
The relationship between such two halves as generated from an *RS*-enantiotropic orbit is referred to as an *RS-diastereotopic* relationship. The two halves in the *RS*-enantiotropic orbit are referred to as being *RS*-diastereotopic to each other.

Thus, this definition of the term *RS-diastereotopic* is independent to geometric operations, so that the terms *RS-diastereotopic* and *enantiotopic* are independent to each other. In contrast, the term "diastereotopic" of the conventional stereochemistry is dependent to the term "enantiotopic", as pointed out above [8].

3.1.2 Illustrative Examples

Octahedral Complexes with Achiral Proligands Only When we take account of achiral proligands only, the results shown in Figs. 1–4 can be easily transformed into the formats for characterizing pro-*RS*-stereogenicity. For example, the data of Fig. 1 (the achiral octahedral complexes with [Ma_2bcde]) provide us with the corresponding data as follows:

$$\mathbf{1} \quad (\tilde{\mathbf{C}}_s, \text{Type IV})\ddagger \quad \tilde{\mathbf{C}}_s[/\mathbf{C}_1(a_2); 4/\tilde{\mathbf{C}}_s(b,c,d,e)] \tag{6}$$

$$\mathbf{2} \quad (\tilde{\mathbf{C}}_s, \text{Type IV})\ddagger \quad \tilde{\mathbf{C}}_s[/\mathbf{C}_1(a_2); 4/\tilde{\mathbf{C}}_s(b,c,d,e)] \tag{7}$$

$$\mathbf{3} \quad (\tilde{\mathbf{C}}_s, \text{Type IV})\ddagger \quad \tilde{\mathbf{C}}_s[/\mathbf{C}_1(a_2); 4/\tilde{\mathbf{C}}_s(b,c,d,e)], \tag{8}$$

where the SCR notations are extended to specify the packing of proligands in accord with *RS*-tropicities. Thereby, each orbit corresponding to the coset representation $\tilde{\mathbf{C}}_s(/\mathbf{C}_1)$ is determined to be *RS*-enantiotropic, so as to accommodate two achiral ligands a_2 of the same kind. In other words, an enantiospheric orbit governed by $\mathbf{C}_s(/\mathbf{C}_1)$ (or $\mathbf{C}'_s(/\mathbf{C}_1)$) is regarded to be superposed on an *RS*-enantiotropic orbit governed by $\tilde{\mathbf{C}}_s(/\mathbf{C}_1)$. In a similar way, an enantiospheric orbit governed by $\mathbf{C}_s(/\mathbf{C}_1)$ (or $\mathbf{C}'_s(/\mathbf{C}_1)$) of each octahedral complex shown in Figs. 2–4 is regarded to be superposed on an *RS*-enantiotropic orbit governed by $\tilde{\mathbf{C}}_s(/\mathbf{C}_1)$, as denoted by a double dagger.

Octahedral Complexes with Chiral and Achiral Proligands Among the achiral octahedral complexes shown in Fig. 5, the promolecule **17** is pro-*RS*-stereogenic, because of the following *RS*-enantiotropicity:

$$\mathbf{17} \quad (\tilde{\mathbf{C}}_s, \text{TypeIV})\ddagger \quad \tilde{\mathbf{C}}_s[/\mathbf{C}_1(a_2); 4/\tilde{\mathbf{C}}_s(b,c,p,\overline{p})] \tag{9}$$

Hence, the two proligands a's accommodated in the $\tilde{\mathbf{C}}_s(/\mathbf{C}_1)$-orbit (a two-membered *RS*-enantiotropic orbit) of **17** belong separately to one-membered orbits governed by $\mathbf{C}_s(/\mathbf{C}_s)$ in a purely geometric meaning (i.e. according to the point-group symmetry).

On the other hand, the two proligands a's in each of **18**–**21** require a more elaborate treatment, which will be discussed in Section 5 after the introduction of stereoisograms for testifying prochirality and pro-*RS*-stereogenicity.

4 Stereoisograms for Testifying Prochirality and Pro-*RS*-Stereogenicity

As discussed independently in the preceding subsections, the concept of prochirality (Subsection 2.1) and the concept of pro-*RS*-stereogenicity (Subsection 3.1) are independent to each other, just as the concept of chirality and the concept of *RS*-stereogenicity are independent to each other (cf. Part I of this series). However, the concept of prochirality and the concept of pro-*RS*-stereogenicity interact, just as the concept of chirality and the concept of *RS*-stereogenicity interact. The interaction between the concept of chirality and the concept of *RS*-stereogenicity has been discussed by means of stereoisograms, as found in Part I of this series for octahedral complexes.

In addition to the criteria based on orbits (cf. Subsections 2.1 and 3.1), three types of criteria based on stereoisograms have been developed to determine prochirality and pro-*RS*-stereogenicity in organic stereochemistry, i.e., the substitution criterion [28], the membership

criterion [27, 28], and the symmetry criterion [29]. They are capable of arriving at equivalent results in organic stereochemistry as well as in inorganic stereochemistry.

In this section, we discuss transformation of stereoisograms in order to integrate the concept of prochirality (Subsection 2.1) and the concept of pro-*RS*-stereogenicity (Subsection 3.1). Among the three types of criteria based on stereoisograms, we adopt the symmetry criterion [29], which is applied to octahedral complexes selected as candidates of showing prochirality or pro-*RS*-stereogenicity.

4.1 Three Topic Relationships and Related Attributes

The conventional stereochemistry lacks the attributive terms for characterizing orbits (e.g., Defs. 1, 2, 4, and 5). Instead, the conventional terminology has depended on relational terms such as the transmuted term "enantiotopic" (e.g., [5, page 1198] & [17, page 238]) and the related terms such as "diastereotopic" and "stereoheterotopic" [4, Subsection 3.4]. To avoid the confusing situations due to the conventional terminology, we use the relational terms reported previously [29], which have been described in Defs. 3 and 6 and are summarized in Table 1.

Table 1: Three topic relationships and the corresponding attributes, which are characterized by stereoisograms for testifying prochirality and/or pro-*RS*-stereogenicity [29].

symbol	relationship	attribute	attribute for an orbit
(Concerned with reflections ◉)			
←◉→	enantiotopic [Def. 3]	prochiral [Def. 2]	enantiospheric [Def. 1]
=◉=	(self-enantiotopic)	–	–
(Concerned with *RS*-permutations ○)			
←○→	*RS*-diastereotopic [Def. 6]	pro-*RS*-stereogenic [Def. 5]	*RS*-enantiotropic [Def. 4]
=○=	(self-*RS*-diastereotopic)	–	–
(Concerned with ligand reflections ●)			
←●→	(holantitopic)[a]	(proscleral)[a]	(–)[a]
=●=	(self-holantimeric)[a]	–	–

[a] The term *holantitopic* and related terms do not appear in usual situations.

According to the stereoisogram approach [11–13], a quadruplet of *RS*-stereoisomers is characterized by a stereoisogram, which is categorized into one of the five types, i.e., Type I (the stereoisogram index $[-,-,a]$), Type II ($[-,a,-]$), Type III ($[-,-,-]$), Type IV ($[a,a,a]$), and Type V ($[a,-,-]$), as described in Part I of this series. Thereby, the concept of prochirality is concerned with conversion processes from achiral promolecules (Type VI $[\boldsymbol{a},a,a]$ and Type V $[\boldsymbol{a},-,-]$) into chiral promolecules (Type I $[\textbf{–},-,a]$, II $[\textbf{–},a,-]$, and III $[\textbf{–},-,-]$), where their features are rationalized by examining the vertical C-axes of stereoisograms. On the other hand, the concept of pro-*RS*-stereogenicity is concerned with conversion processes from *RS*-astereogenic promolecules (Type II $[-,\boldsymbol{a},-]$ and IV $[a,\boldsymbol{a},a]$) into *RS*-stereogenic promolecules (Type I $[-,\textbf{–},a]$, III $[-,\textbf{–},-]$, and V $[a,\textbf{–},-]$), where their features are rationalized by examining the horizontal S-axes of stereoisograms. Note that boldfaced letters changed from $\boldsymbol{a}$ to **–** indicate clues for exhibiting prochirality or pro-*RS*-stereogenicity.

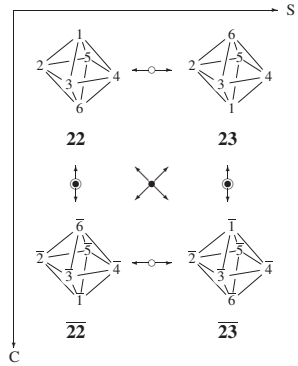


Figure 6: Reference stereoisogram for characterizing an octahedral skeleton. This stereoisogram is tentatively drawn as Type III.

The symmetry criterion adopts enantiotopic and/or *RS*-diastereotopic relationships by using stereoisograms testifying prochirality and/or pro-*RS*-stereogenicity [29]. These relational terms used in combination with stereoisograms provide us diagrammatically with definite results in equal ways to the rather abstract criteria based on orbits (cf. Subsections 2.1 and 3.1).

To exemplify the symmetry criterion, we derive such stereoisograms from a reference stereoisogram shown in Fig. 6, where the central metal atom is omitted and the numbering of vertices of **22** is tentatively selected without losing generality. According to Part I of this series, the conversion of **22** into its enantiomeric skeleton $\overline{\mathbf{22}}$ along the vertical C-axis (*C*hirality-axis) is conducted by the reflection $\overline{(1\ 6)(2)(3)(4)(5)}$, where each number with an overbar represents the reflection of ligand chirality. The conversion of **22** into its *RS*-diastereomeric skeleton **23** along the horizontal S-axis (*RS-S*tereogenicity-axis) is conducted by the *RS*-permutation $(1\ 6)(2)(3)(4)(5)$, where each number without an overbar represents no reflection of ligand chirality. The conversion of **22** into its holantimeric skeleton $\overline{\mathbf{23}}$ (along the diagonal direction) is conducted by the ligand reflection $\overline{(1)(2)(3)(4)(5)(6)}$, where no skeletal inversion occurs and each number with an overbar represents the reflection of ligand chirality.

4.2 Conversion of a Stereoisogram of Type IV into Type I

4.2.1 Test of Prochirality

As a promolecule of Type IV, let us examine **1** shown in Fig. 1, which is characterized by its enantiospheric orbit of a_2 governed by $\mathbf{C}_s(/\mathbf{C}_1)$. According to [29], the two a's of **1** are testified to determine the prochirality.

The stereoisogram of **1** shown in the left of Fig. 7 belongs to Type IV, where a quadruplet of promolecules is degenerated into a single achiral promolecule. To testify the prochirality of **1**, the two proligands a's are differentiated so as to be marked by the symbols a^{α} and a^{β}. The resulting stereoisogram is called *a testifying stereoisogram*.

As shown in the right of Fig. 7, the testifying stereoisogram belongs to Type I, where the two proligands denoted by a^{α} and a^{β} are regarded as being different tentatively and the relevant

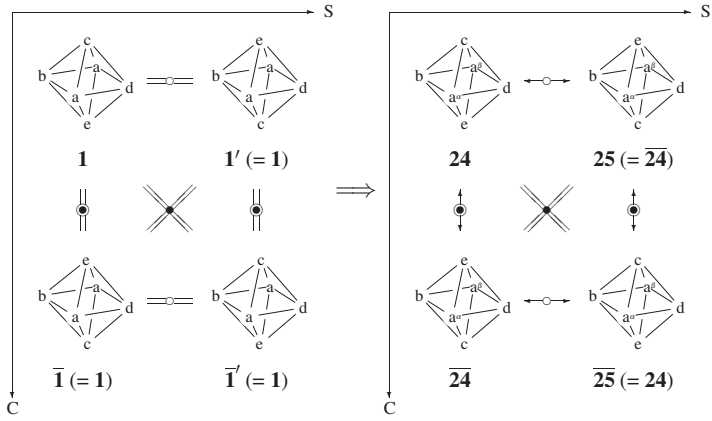


Figure 7: Stereoisogram of Type IV (left) and a testifying stereoisogram of Type I (right) due to tentative differentiation. The symbols a^{α} and a^{β} represent proligands which are generated by differentiating two proligands a's to testify prochirality (along the vertical C-axis) and pro-*RS*-stereogenicity (along the horizontal S-axis).

promolecules (**24** and $\overline{\mathbf{24}}$) are regarded tentatively as being chiral. When we focus our attention on chirality, the two tentative promolecules along the C-axis of the testifying stereoisogram, i.e., **24** and $\overline{\mathbf{24}}$, are enantiomeric to each other. Thereby, the proligands a^{α} and a^{β} are enantiotopic to each other so that the promolecule **1** is concluded to be prochiral.

It should be emphasized that the enantiotopic relationship between the proligands a^{α} and a^{β} in the promolecule **1** (= **24**) is interpreted to correspond to the enantiomeric relationship between **24** and $\overline{\mathbf{24}}$ in the testifying stereoisogram shown in Fig. 7. Thus, the intramolecular relationship is replaced by the intermolecular relationship in terms of such a testifying stereoisogram. The determination of an enantiomeric relationship by such an testifying stereoisogram (i.e., an intermolecular comparison) is obviously consistent with the determination by Def. 3 (i.e., an intramolecular comparison).

The test for determining prochirality (the symmetry criterion [29]) is confirmed by substituting the proligand a^{α} for A (and the proligand a^{β} for a) in the testifying stereoisogram (right) of Fig. 7, where the resulting pair of promolecules along the C-axis is found to be an enantiomeric pair. The resulting enantiomeric pair (**26** and $\overline{\mathbf{26}}$) are shown in Fig. 8, which is a usual reaction diagram so as to show the conversion of an achiral promolecule **1** (= **24**) into the two chiral promolecules of an enantiomeric pair (**26** and $\overline{\mathbf{26}}$). This confirmation process corresponds to the substitution criterion [28].

Because the difference (i.e., an enantiomeric relationship) between **24** and $\overline{\mathbf{24}}$ (= **25**) stems from the differentiation of the two a's into a^{α} and a^{β}, the relationship between the two a's is found to be an enantiotopic relationship. Hence, we reach the following alternative definition (cf. Def. 3):

Definition 7 (An Alternative Definition of Enantiotopic relationships)

Let us consider an achiral stereoisogram (Type IV or V) of a promolecule with two proli-

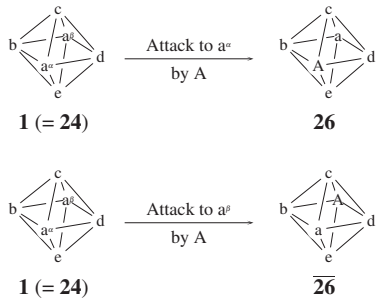


Figure 8: Conversion of an achiral promolecule **1** (= **24**) to a pair of enantiomers (**26** and $\overline{\mathbf{26}}$) in accord with the test of Fig. 7.

gands equivalent under the point group. If the differentiation of the two proligands converts the stereoisogram into a chiral one (Type I, II, or III), the two proligands are referred to as being enantiotopic.

4.2.2 Test of Pro-*RS*-Stereogenicity

To testify pro-*RS*-stereogenicity, we focus our attention on the two tentative promolecules along the S-axis of the testifying stereoisogram, i.e., **24** and **25** (= $\overline{\mathbf{24}}$), which are *RS*-diastereomeric to each other. Although the tentative *RS*-diastereomers **25** is identical with the enantiomer $\overline{\mathbf{24}}$, they are conceptually differentiated from each other in a similar way to usual stereoisograms of Type I (cf. Part I of this series). Thereby, the proligands a^{α} and a^{β} are *RS*-diastereotopic to each other so that the promolecule **1** is concluded to be pro-*RS*-stereogenic.

It should be emphasized that the *RS*-diastereotopic relationship between the proligands a^{α} and a^{β} in the promolecule **1** (= **24**) is interpreted to correspond to the *RS*-diastereomeric relationship between **24** and **25** (= $\overline{\mathbf{24}}$) in the testifying stereoisogram shown in Fig. 7. The determination of an *RS*-diastereotopic relationship by such an testifying stereoisogram (i.e., an intermolecular comparison) is obviously consistent with the determination by Def. 6 (i.e., an intramolecular comparison).

Because the difference (i.e., an *RS*-diastereomeric relationship) between **24** and **25** (=$\overline{\mathbf{24}}$) stems from the differentiation of the two a's into a^{α} and a^{β}, the relationship between the two a's is regarded as being an *RS*-diastereotopic relationship. Hence we reach an alternative definition as follows (cf. Def. 6):

Definition 8 (An Alternative Definition of *RS*-Diastereotopic relationships)

Let us consider an *RS*-astereogenic stereoisogram (Type II or IV) of a promolecule with two proligands equivalent under the *RS*-permutation group. If the differentiation of the two proligands converts the stereoisogram into an *RS*-stereogenic one (Type I, III, or V), the two proligands are referred to as being *RS*-diastereotopic.

4.2.3 Assignment of *pro-A/pro-C*-Descriptors

When the CIP priority is presumed to be a^{α} (1) > a^{β} (1′) > b (2) > c (3) > d (4) > e (5), the tentative promolecule **24** is named to be *OC-6-1′4-C*. Hence, the proligand a^{α} in **24** is characterized to be *pro-C*. On the other hand, the tentative promolecule **25** (= $\overline{\mathbf{24}}$) is named to be *OC-6-1′4-A*. Hence, the proligand a^{α} in **25** (= $\overline{\mathbf{24}}$) is characterized to be *pro-A*. This means that the proligand a^{β} in **24** is characterized to be *pro-A*. Alternatively, when the CIP priority is presumed to be a^{β} (1) > a^{α} (1′) > b (2) > c (3) > d (4) > e (5), the tentative promolecule **24** is named to be *OC-6-1′4-A*. Hence, the proligand a^{β} in **24** is characterized to be *pro-A*.

Although the present procedure of giving *pro-A/pro-C*-descriptors is based on the rules reported in [1, 7], it is based on *RS*-stereogenicity, but not on chirality, as found in the stereoisogram shown in the left of Fig. 7. This means that *pro-A/pro-C*-descriptors are specified by *RS*-diastereotopic relationships, whereas the original formulation [1, 7] has claimed that *pro-A/pro-C*-descriptors are specified by "enantiotopic" or "stereoheterotopic" relationships. This feature of *pro-A/pro-C*-descriptors in inorganic stereochemistry is equivalent to the feature of *pro-R/pro-S*-descriptors in organic stereochemistry, which are also specified by *RS*-diastereotopic relationships, not by "enantiotopic" nor "stereoheterotopic" relationships [29].

4.3 Conversion of a Stereoisogram of Type IV into Type II and into Type V

The promolecule **17** is prochiral because the orbit consisting of p and $\overline{\mathrm{p}}$ is enantiospheric (cf. Fig. 5). At the same time, the promolecule **17** is pro-*RS*-stereogenic because the orbit consisting of two a's is *RS*-enantiotropic (cf. Eq. 9). These conclusions can be confirmed by examining stereoisograms of testifying prochirality and pro-*RS*-stereogenicity.

4.3.1 Conversion of a Stereoisogram of Type IV into Type II — Test of Prochirality

Let us examine **17** as a promolecule of Type IV shown in Fig. 5, which is characterized by its enantiospheric orbit of p and $\overline{\mathrm{p}}$ governed by $\mathbf{C}_s(/\mathbf{C}_1)$. The stereoisogram of **17** shown in the left of Fig. 9 belongs to Type IV, where a quadruplet of promolecules is degenerated into a single achiral promolecule. To testify the prochirality of **17**, the pair of proligands p and $\overline{\mathrm{p}}$ are differentiated so as to be marked by the symbols p^{α} and $\overline{\mathrm{p}}^{\beta}$ (or p^{β} and $\overline{\mathrm{p}}^{\alpha}$), as shown in the testifying stereoisogram (right) of Fig. 9.

The testifying stereoisogram (the right of Fig. 9) belongs to Type II, where **27** and $\overline{\mathbf{27}}$ of a pair along the vertical C-axis are enantiomeric to each other. Accordingly, the proligand p^{α} ($\overline{\mathrm{p}}^{\beta}$) of **27** is converted into the proligand $\overline{\mathrm{p}}^{\alpha}$ (or p^{β}) of $\overline{\mathbf{27}}$ by the reflection $\overline{(1\,6)(2)(3)(4)(5)}$ (cf. Fig. 6) along the vertical C-axis. Thereby, the proligands p^{α} and $\overline{\mathrm{p}}^{\beta}$ in **27** or the proligands p^{β} and $\overline{\mathrm{p}}^{\alpha}$ in $\overline{\mathbf{27}}$ are enantiotopic to each other, so that the promolecule **27** is concluded to be prochiral.

The test for determining prochirality (the symmetry criterion [29]) is confirmed by substituting the proligand $\overline{\mathrm{p}}^{\beta}$ for A (and the proligand p^{α} for p) in the testifying stereoisogram (right) of Fig. 9, where the resulting pair of promolecules along the C-axis is found to be an enantiomeric pair. The resulting enantiomeric pair (**28** and $\overline{\mathbf{28}}$) is shown in Fig. 10, which is a usual reaction diagram so as to show the conversion of an achiral promolecule **17** (= **27**) into the two chiral promolecules of an enantiomeric pair (**28** and $\overline{\mathbf{28}}$) under the attack of chiral reagents. This confirmation process corresponds to the substitution criterion [28].

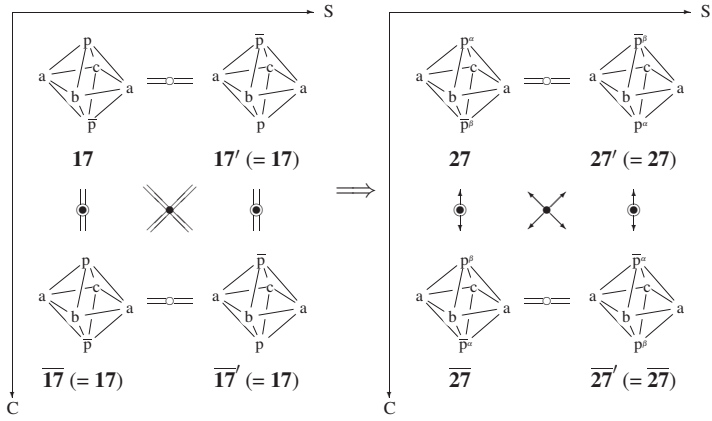


Figure 9: Stereoisogram of Type IV (left) and a testifying stereoisogram of Type II (right) due to tentative differentiation. Each pair of symbols $p^{\alpha}/\overline{p}^{\alpha}$ (or $p^{\beta}/\overline{p}^{\beta}$ represents a pair of enantiomeric proligands (in isolation) which are generated by differentiating two proligands p's (or $\overline{p}$'s) to testify prochirality (along the vertical C-axis).

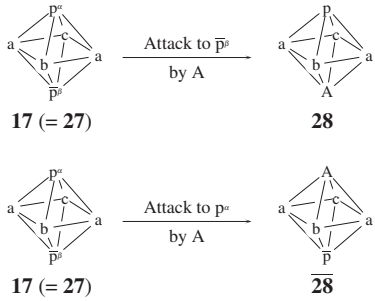


Figure 10: Conversion of an achiral promolecule **17** (= **27**) into a pair of enantiomers (**28** and $\overline{\mathbf{28}}$) in accord with the test of Fig. 9.

4.3.2 Conversion of a Stereoisogram of Type IV into Type V — Test of Pro-*RS*-Stereogenicity

Let us next examine the two a's of the promolecule **17**, which constructs a two-membered *RS*-enantiotropic orbit (cf. Eq. 9). They are differentiated by marking by the symbols α and β, so that the stereoisogram of Type IV (the left of Fig. 11) is converted into the corresponding stereoisogram for testifying pro-*RS*-stereogenicity (the right of Fig. 11).

To testify the pro-*RS*-stereogenicity, we focus our attention on the S-axis of the testifying stereoisogram of Type V (the right of Fig. 11), where the two tentative promolecules at issue,

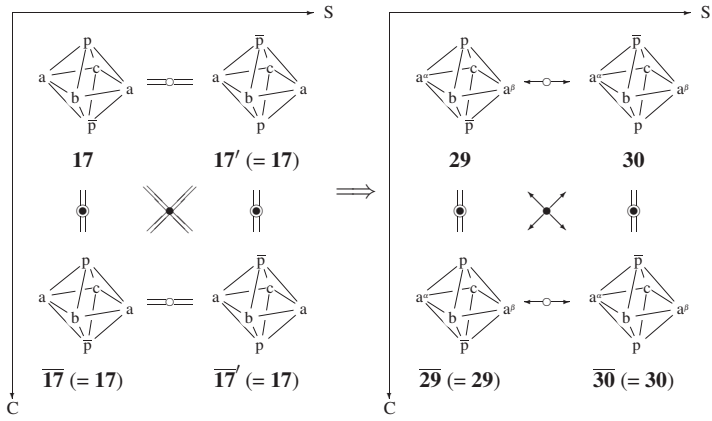


Figure 11: Stereoisogram of Type IV (left) and a testifying stereoisogram of Type V (right) due to tentative differentiation. Two proligands a's are differentiated by the symbols a^{α}/a^{β} in order to testify *RS*-stereogenicity (along the horizontal S-axis).

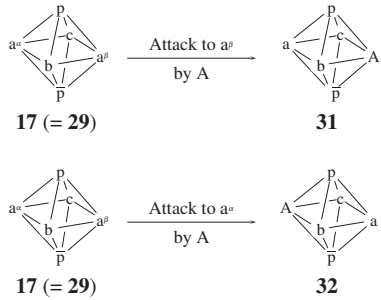


Figure 12: Conversion of an achiral promolecule **17** (= **29**) into a pair of *RS*-diastereomers (**31** and **32**) in accord with the test of Fig. 11.

i.e., **29** and **30**, are *RS*-diastereomeric to each other. Hence, the proligands a^{α} and a^{β} are *RS*-diastereotopic to each other so that the promolecule **17** is concluded to be pro-*RS*-stereogenic.

It should be emphasized, again, that the *RS*-diastereotopic relationship between the proligands a^{α} and a^{β} in the promolecule **17** is interpreted to correspond to the *RS*-diastereomeric relationship between **29** and **30** in the testifying stereoisogram shown in Fig. 11. The determination of an *RS*-diastereotopic relationship by such an testifying stereoisogram (i.e., an intermolecular comparison) is obviously consistent with the determination by Def. 6 (i.e., an intramolecular comparison and cf. Eq. 9).

The test for determining pro-*RS*-stereogenicity (the symmetry criterion [29]) is confirmed

by substituting the proligand a^{β} for A (and the proligand a^{α} for a) in the testifying stereoisogram (right) of Fig. 11, where the resulting pair of promolecules along the S-axis is found to be an *RS*-diastereomeric pair. The resulting *RS*-diastereomeric pair (**31** and **32**) are shown in Fig. 12, which is a usual reaction diagram so as to show the conversion of an achiral promolecule **17** (= **29**) into the two achiral promolecules of an *RS*-diastereomeric pair (**31** and **32**). This confirmation process corresponds to the substitution criterion [28].

It should be noted that the conversion of **17** into **31** and **32** requires no chiral conditions, because the two a's belong to one-membered homospheric orbits separately. The starting promolecule (**17**) and the resulting promolecules (**31** and **32**) in Fig. 12 are both achiral. Compare this case with the conversion of an achiral promolecule **1** into a pair of enantiomers (**26** and $\overline{\mathbf{26}}$). The latter reaction requires chiral conditions as shown in Fig. 8, because the two a's belong to a two-membered enantiospheric orbit.

4.3.3 Assignment of *pro-A/pro-C*-Descriptors

When the CIP priority is presumed to be a^{α} (1) > a^{β} (1′) > b (2) > c (3) > p (4) > $\overline{\text{p}}$ (5), the tentative promolecule **29** is named to be *OC-6-1′3-A*. Hence, the proligand a^{α} in **29** is characterized to be *pro-a*, where the lowercase letter '*a*' is used in place of the uppercase letter of *pro-A*. On the other hand, the tentative promolecule **30** is named to be *OC-6-1′3-C*. Hence, the proligand a^{α} in **30** is characterized to be *pro-c* (or *pro-C*). This means that the proligand a^{β} in **29** is characterized to be *pro-c*. Alternatively, when the CIP priority is presumed to be a^{β} (1) > a^{α} (1′) > b (2) > c (3) > p (4) > $\overline{\text{p}}$ (5), the tentative promolecule **29** is named to be *OC-6-1′4-C*. Hence, the proligand a^{β} in **29** is characterized to be *pro-c*.

Although the present procedure of giving *pro-A/pro-C*-descriptors (lowercase letters in this case) is based on the rules reported in [1, 7], it is based on *RS*-stereogenicity, but not on chirality, as found in the stereoisogram shown in the left of Fig. 11. This means that *pro-A/pro-C*-descriptors are specified by *RS*-diastereotopic relationships. In contrast, the original formulation [1, 7] has claimed that *pro-A/pro-C*-descriptors are specified by "enantiotopic" or "stereoheterotopic" relationships on case-by-case bases, where "enantiotopic" and "diastereotopic" (contained in "stereoheterotopic") are mixed up with respect to reflections and permutations. This feature of *pro-A/pro-C*-descriptors in inorganic stereochemistry is equivalent to the feature of *pro-R/pro-S*-descriptors specified by *RS*-diastereotopic relationships, not by "enantiotopic" nor "stereoheterotopic" relationships, in organic stereochemistry [29].

4.4 Conversion of a Stereoisogram of Type V into Type III

4.4.1 Test of Prochirality

As promolecules of Type V, let us examine **18** and **19** shown in Fig. 5, each of which is characterized by the presence of an enantiospheric orbit of p and $\overline{\text{p}}$ governed by $\mathbf{C}_s(/\mathbf{C}_1)$. The stereoisogram of **18** and **19** shown in the left of Fig. 13 belongs to Type V, where a quadruplet of promolecules is degenerated into two achiral promolecules, which are *RS*-diastereomeric to each other. To testify the prochirality of **18** (or **19**), the pair of proligands p and $\overline{\text{p}}$ are differentiated so as to be marked by the symbols p^{α} and $\overline{\text{p}}^{\beta}$ (or p^{β} and $\overline{\text{p}}^{\alpha}$), as shown in the testifying stereoisogram (right) of Fig. 13.

The testifying stereoisogram (the right of Fig. 13) is found to belong to Type III, where **33** and $\overline{\mathbf{33}}$ of a pair along the vertical C-axis are enantiomeric to each other. Accordingly, the proligand p^{α} ($\overline{\text{p}}^{\beta}$) of **33** is converted into the proligand $\overline{\text{p}}^{\alpha}$ (or p^{β}) of $\overline{\mathbf{33}}$ by the reflection

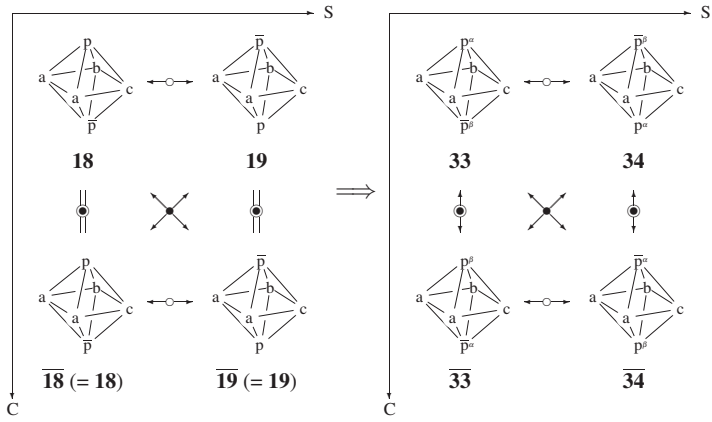


Figure 13: Stereoisogram of Type V (left) and a testifying stereoisogram of Type III (right) due to tentative differentiation. Each pair of symbols $p^{\alpha}/\overline{p}^{\alpha}$ (or $p^{\beta}/\overline{p}^{\beta}$ represents a pair of enantiomeric proligands (in isolation) which are generated by differentiating two proligands p's (or $\overline{p}$'s) to testify prochirality (along the vertical C-axis). The stereoisogram of Type V (left) already exhibits *RS*-stereogenicity (along the horizontal S-axis).

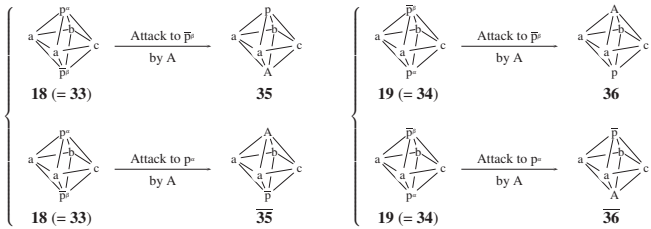


Figure 14: Conversion of an achiral promolecule **18** (= **33**) to a pair of enantiomers (**35** and $\overline{\mathbf{35}}$) as well as conversion of an achiral promolecule **19** (= **34**) to a pair of enantiomers (**36** and $\overline{\mathbf{36}}$) in accord with the test of Fig. 13.

$\overline{(1\,6)(2)(3)(4)(5)}$ (cf. Fig. 6) along the vertical C-axis. Thereby, the proligands p^{α} and $\overline{p}^{\beta}$ in **33** or the proligands p^{β} and $\overline{p}^{\alpha}$ in $\overline{\mathbf{33}}$ are enantiotopic to each other so that the promolecule **18** (= **33**) is concluded to be prochiral.

A parallel discussion is effective to another pair of **34** and $\overline{\mathbf{34}}$ along the vertical C-axis, which are tentatively regarded as being enantiomeric to each other. Hence, the proligands p^{α} and $\overline{p}^{\beta}$ in **34** or the proligands p^{β} and $\overline{p}^{\alpha}$ in $\overline{\mathbf{34}}$ are enantiotopic to each other so that the promolecule **19** (= **34**) is concluded to be prochiral.

The enantiotopic relationship between the proligands p^{α} and $\overline{p}^{\beta}$ in the achiral promolecule **18** (= **33**) or in the achiral promolecule **19** (= **34**) is interpreted to correspond to the enantiomeric

relationship between **33** and $\overline{\mathbf{33}}$ or between **34** and $\overline{\mathbf{34}}$ in the testifying stereoisogram shown in Fig. 13. Thus, the intramolecular relationship is replaced by the intermolecular relationship in terms of such a testifying stereoisogram. The determination of an enantiomeric relationship by such an testifying stereoisogram (i.e., an intermolecular comparison) is obviously consistent with the determination by Def. 3 (i.e., an intramolecular comparison).

The test for determining prochirality (the symmetry criterion [29]) is confirmed by substituting the proligand $\overline{\mathrm{p}}^{\beta}$ for A (and the proligand p^{α} for p) in the testifying stereoisogram (right) of Fig. 13, where the resulting pair of promolecules along the C-axis is found to be an enantiomeric pair. The resulting enantiomeric pair (**35** and $\overline{\mathbf{35}}$) are shown in Fig. 14 (left), which is a usual reaction diagram so as to show the conversion of an achiral promolecule **18** (= **33**) into the two chiral promolecules of an enantiomeric pair (**35** and $\overline{\mathbf{35}}$). Similarly, another enantiomeric pair (**36** and $\overline{\mathbf{36}}$) is obtained from an achiral promolecule **19** (= **34**) as shown in Fig. 14 (right). These two confirmation processes correspond to the substitution criterion [28].

4.4.2 Test of Pro-*RS*-Stereogenicity

As found in the stereoisogram of Type V shown in the left of Fig. 13, **18** and **19** are *RS*-diastereomeric to each other, so that they are already *RS*-stereogenic. Thus, a pair of *C/A*-descriptors is assigned to the *RS*-diastereomeric pair, i.e., *OC-6-32-A* to **18** and *OC-6-32-C* to **19** (cf. Fig. 5).

If we restrict our discussions to a single stereoisogram such as the left of Fig. 13, we are able to focus our attention on only the pair of proligands, p and $\overline{\mathrm{p}}$, as discussed in the preceding paragraphs. As found by the SCR notations, i.e., $\mathbf{C}_{\mathrm{s}}[/\mathbf{C}_1(\mathrm{p}\overline{\mathrm{p}}); 4/\mathbf{C}_{\mathrm{s}}(2\mathrm{a},\mathrm{b},\mathrm{c})]$ for **18** (and **19**), a purely geometric discussion indicates that two a's in **18** (or **19**) are so inequivalent as to belong to one-membered orbits separately.

If we extend our discussions to a multiplet of stereoisograms (cf. Part II of this series), more complicated treatments are required, as discussed below (Section 5).

4.5 Conversion of a Stereoisogram of Type II into Type III

The two a's of the promolecule **37** (the left of Fig. 15) constructs a two-membered *RS*-enantiotropic orbit, so that they are *RS*-diastereotopic to each other. To determine the *RS*-diastereotopic relationship, they are differentiated by marking by the symbols α and β. Thereby, the stereoisogram of Type II (the left of Fig. 15) is converted into the corresponding stereoisogram of Type III for testifying pro-*RS*-stereogenicity (the right of Fig. 15).

To testify the pro-*RS*-stereogenicity, we focus our attention on the two tentative promolecules along the S-axis of the testifying stereoisogram, i.e., **38** and **39**, which are *RS*-diastereomeric to each other. Hence, the proligands a^{α} and a^{β} are *RS*-diastereotopic to each other, so that the promolecule **37** is concluded to be pro-*RS*-stereogenic.

It should be emphasized, again, that the *RS*-diastereotopic relationship between the proligands a^{α} and a^{β} in the promolecule **37** is interpreted to correspond to the *RS*-diastereomeric relationship between **38** and **39** in the testifying stereoisogram shown in Fig. 15. The determination of an *RS*-diastereotopic relationship by such an testifying stereoisogram (i.e., an intermolecular comparison) is obviously consistent with the determination by Def. 6 (i.e., an intramolecular comparison).

The test for determining pro-*RS*-stereogenicity (the symmetry criterion [29]) is confirmed by substituting the proligand a^{β} for A (and the proligand a^{α} for a) in the testifying stereoisogram

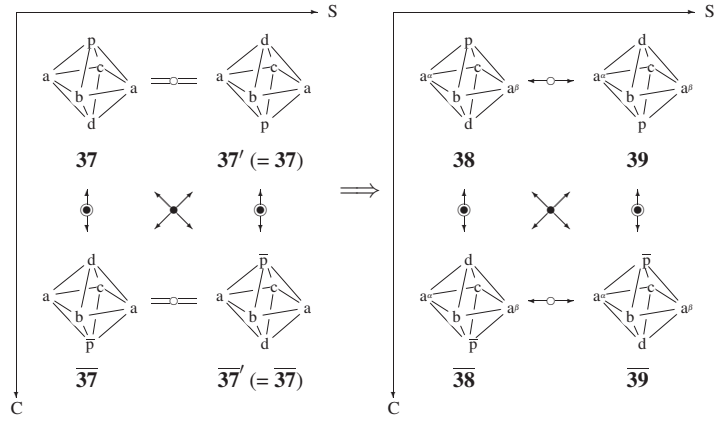


Figure 15: Stereoisogram of Type II (left) and a testifying stereoisogram of Type III (right) due to tentative differentiation. Two proligands a's are differentiated by the symbols a^{α}/a^{β} in order to testify *RS*-stereogenicity (along the horizontal S-axis). A pair of symbols p/$\overline{\text{p}}$ represents a pair of enantiomeric proligands (in isolation).

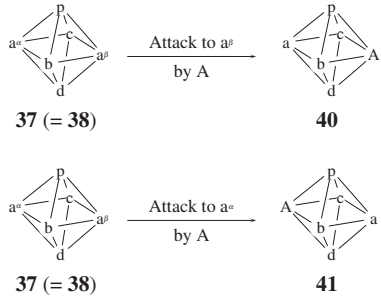


Figure 16: Conversion of a chiral promolecule **37** (= **38**) into a pair of *RS*-diastereomers (**40** and **41**) in accord with the test of Fig. 15.

(right) of Fig. 15, where the resulting pair of promolecules along the S-axis is found to be an *RS*-diastereomeric pair. The resulting *RS*-diastereomeric pair (**40** and **41**) are shown in Fig. 16, which is a usual reaction diagram so as to show the conversion of a chiral promolecule **37** (= **38**) into two chiral promolecules of an *RS*-diastereomeric pair (**40** and **41**). This confirmation process corresponds to the substitution criterion [28].

4.6 *pro-A/pro-C*-Descriptors Assigned by pro-*RS*-Stereogenicity

4.6.1 Systematic Rationalization Due to the Stereoisogram Approach

The stereoisogram approach has been applied to organic stereochemistry and concluded that each pair of *pro-R/pro-S*-descriptors is assigned to a pair of *RS*-diastereotopic proligands, which is directly linked to a pair of tentative *RS*-diastereomers appearing in the horizontal direction (the *RS*-stereogenicity axis) of each stereoisogram for testifying prochirality and/or pro-*RS*-stereogenicity [27–30]. The preceding discussions for inorganic stereochemistry have reached a parallel conclusion on *pro-A/pro-C*-descriptors, which is clarified to be assigned to a pair of *RS*-diastereotopic proligands.

Table 10.5 of [8] for *pro-R/pro-S*-descriptors in organic stereochemistry is effective to *pro-A/pro-C*-descriptors for inorganic stereochemistry, as summarized in Table 2. The discussions described in [8] are quoted as follows with some modifications required to be applied to inorganic stereochemistry.

1. **Coincident appearance of prochirality and pro-*RS*-stereogenicity**: Figure 7 shows a case of Type IV (into Type I) in which prochirality (achiral → chiral) coincides with pro-*RS*-stereogenicity (*RS*-astereogenic → *RS*-stereogenic). As summarized in Table 2, the prochirality is ascribed to the enantiotopic relationship between the two a's of **1**, while pro-*RS*-stereogenicity is ascribed to the *RS*-diastereotopic relationship between the same a's of **1**. The latter *RS*-diastereotopic relationship permits a pair of *pro-A/pro-C*-descriptors.

2. **Appearance of pro-*RS*-stereogenicity**: Figure 11 shows a case of Type IV (into Type V), which is characterized in terms of pro-*RS*-stereogenicity (*RS*-astereogenic → *RS*-stereogenic). As summarized in Table 2, pro-*RS*-stereogenicity is ascribed to the *RS*-diastereotopic relationship between the two a's of **17**, which are named by a pair of *pro-A/pro-C*-descriptors.

   On the other hand, Fig. 15 shows a case of Type II (into Type III), which is also characterized in terms of pro-*RS*-stereogenicity (*RS*-astereogenic → *RS*-stereogenic). As summarized in Table 2, pro-*RS*-stereogenicity is ascribed to the *RS*-diastereotopic relationship between the two a's of the promolecule **37** which are named by a pair of *pro-A/pro-C*-descriptors.

3. **Appearance of prochirality**: Figure 9 shows a case of Type IV (into Type II), which is characterized in terms of prochirality (achiral → chiral). As summarized in Table 2, the prochirality is ascribed to the enantiotopic relationship between p and $\overline{p}$ of the achiral **17**.

   Figure 13 shows a case of Type V (into Type III), which is characterized in terms of prochirality (achiral → chiral). As summarized in Table 2, the prochirality is ascribed to the enantiotopic relationship between p and $\overline{p}$ of the achiral **18**.

Table 2: A single criterion for giving *pro-A/pro-C*-descriptors and another single criterion for discussing prochirality in the stereoisogram approach.[a]

stereoisogram change		prochirality	pro-*RS*-stereogenicity
(achiral → chiral & *RS*-astereogenic → *RS*-stereogenic)			
Type IV → I	$[\boldsymbol{a},\boldsymbol{a},a] \rightarrow [\boldsymbol{-},\boldsymbol{-},a]$ (Fig. 7)	enantiotopic	*RS*-diastereotopic
(*RS*-astereogenic → *RS*-stereogenic)			
Type IV → V	$[a,\boldsymbol{a},a] \rightarrow [a,\boldsymbol{-},-]$ (Fig. 11)	–	*RS*-diastereotopic
Type II → III	$[-,\boldsymbol{a},-] \rightarrow [-,\boldsymbol{-},-]$ (Fig. 15)	–	*RS*-diastereotopic
(achiral → chiral)			
Type IV → II	$[\boldsymbol{a},a,a] \rightarrow [\boldsymbol{-},a,-]$ (Fig. 9)	enantiotopic	–
Type V → III	$[\boldsymbol{a},-,-] \rightarrow [\boldsymbol{-},-,-]$ (Fig. 13)	enantiotopic	–
		(chirality-faithfulness)	

[a] For a single criterion for giving *pro-R/pro-S*-descriptors in organic stereochemistry, see Table 10.5 of [8].

Table 3: Entangled criteria for giving *pro-A/pro-C*-descriptors and for discussing prochirality in the conventional approach.[a,b]

	"prostereogenicity" ("prochirality")
Type IV → I (Fig. 7)	"enantiotopic"
Type IV → V (Fig. 11)	"diastereotopic"
Type II → III (Fig. 15)	"diastereotopic"
Type IV → II (Fig. 9)	–
Type V → III (Fig. 13)	–
	"stereoheterotopic"

[a] These criteria should be replaced by a set of independent and more succinct criteria shown in Table 2.

[b] For entangled criteria for giving *pro-R/pro-S*-descriptors in organic stereochemistry, see [8].

In the preceding categorization, the relational terms for specifying the relationships between the members of an orbit (enantiotopic and RS-diastereotopic, cf. Defs. 3 and 6 as well as Defs. 7 and 8) can be replaced by the attributive terms for specifying the property of the orbit at issue (enantiospheric and *RS*-enantiotropic, cf. Defs. 1 and 4).

It is to be noted that the promolecule **17** is pro-*RS*-stereogenic with respect to the two a's (Fig. 11) while it is prochiral, at the same time, with respect to the enantiotopic pair of p and $\overline{\mathrm{p}}$ (Fig. 9). This case of **17** decisively indicates that pro-*RS*-stereogenicity and prochirality are independent concepts. It follows that the coincident appearance of prochirality and pro-*RS*-stereogenicity in **1** should be explained as above from the common standpoint that pro-*RS*-stereogenicity and prochirality are independent concepts.

4.6.2 Problematic Rationalization Due to the Conventional Approach

Because of the lack of the categorization of Types I–V, discussions based on the conventional approach (e.g., *pro-R/pro-S*-descriptors in organic stereochemistry and *pro-A/pro-C*-descriptors in inorganic stereochemistry) are incapable of arriving at categorized modes of conversions (Fig. 2).

The problematic situations of the conventional approach in inorganic stereochemistry can be more clearly demonstrated by entangled criteria summarized in Table 3, which is a modification of Table 10.6 of [8] described for organic stereochemistry. In particular, the misleading confusion of "prochirality" with "prostereogenicity" stems from a theoretical basis which overlooks the coincident appearance of prochirality and pro-*RS*-stereogenicity (Fig. 7). As found in the [Type IV → I]-row of Table 3, the "prochirality" (or the "enantiotopic" relationship) is taken into sole consideration, so that the pro-*RS*-stereogenicity (the *RS*-diastereotopic relationship) is nullified. The term "stereoheterotopic" which has been introduced to lump the terms "enantiotopic" and "diastereotopic" together (Table 3) has seemingly rationalized the nullification but rather concealed inconsistency profound in the conventional organic and inorganic stereochemistry.

5 Stereoisograms for Testifying Pro-ortho-stereogenicity

5.1 Conversion into Ortho-Stereogenic Stereoisograms

The stereoisogram of Type V shown in the left of Fig. 13 (for **18** and **19**) has an equivalent stereoisogram with the constitution $[\mathrm{Ma_2bcp\overline{p}}]$ under the stereoisomeric group, as discussed in Part II of this series (cf. Stereoisograms **261** and **279** in Fig. 13 and Eq. 68 in Part II of this series). As for **18** and **19**, Stereoisograms **42** and **43** are obtained as such equivalent stereoisograms by a permutation of vertices 2 and 3, i.e., $(1)(2\ 3)(4)(5)(6)$, as shown in Fig. 17.

First, we focus our attention on Stereoisogram **42** of Type V. When we differentiate two proligands a's in **18** by marking α and β, the corresponding stereoisogram of testifying prochirality or pro-*RS*-stereogenicity is obtained as a Type V stereoisogram, i.e., Stereoisogram **48**. Within Stereoisogram **48**, the proligands a^{α} and a^{β} are not interchangeable under the *RS*-permutation group ($\mathbf{O}_{\tilde{i}}$), the elements of which are collected in Fig. 2 of Part I of this series. Note that the permutation $(1)(2\ 3)(4)(5)(6)$ for converting **44** into **45** is not contained in $\mathbf{O}_{\tilde{i}}$. Although Stereoisogram **48** exhibits *RS*-stereogenicity just as Stereoisogram **42** exhibits *RS*-stereogenicity, the relationship between a^{α} and a^{β} is beyond the scope of Def. 6, so that it is not an *RS*-diastereotopic relationship.

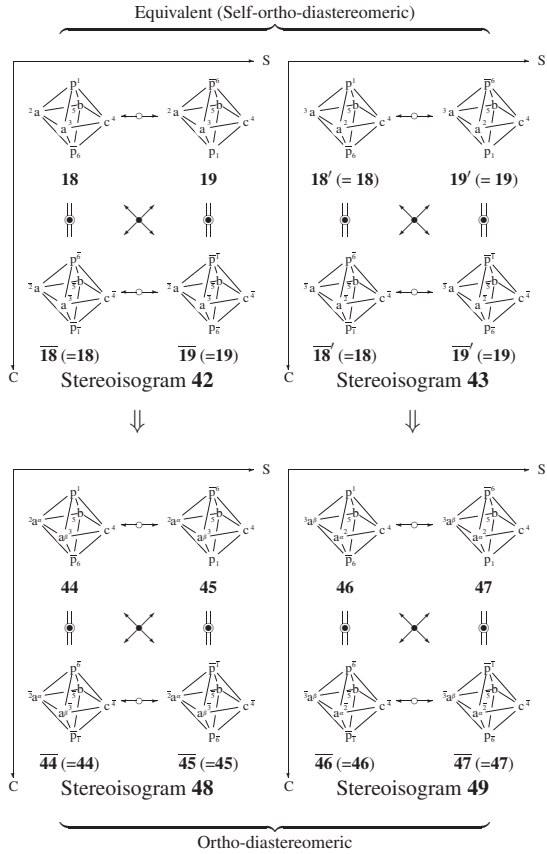


Figure 17: Stereoisograms of Type V (upperleft and upperright) equivalent to each other under the stereoisomeric group as well as testifying stereoisograms of Type V (lowerleft and lowerright) ortho-diastereomeric to each other under the stereoisomeric group. Two proligands a^{α} and a^{β} in each promolecule are not *RS*-diastereotopic in a stereoisogram, but they are orthodiastereotopic between the two stereoisograms.

In a similar way, Stereoisogram **43** of Type V, which is equivalent to Stereoisogram **42** under the stereogenic group (i.e., the symmetric group of degree 6 in this case), generates Stereoisogram **49** as the corresponding stereoisogram of testifying prochirality or pro-*RS*-stereogenicity. Although Stereoisogram **49** similarly exhibits *RS*-stereogenicity, the relationship between a^{α} and a^{β} is beyond the scope of Def. 6, so that it is not an *RS*-diastereotopic relationship.

Second, we examine the relationship between the testifying stereoisograms **48** and **49**. They are inequivalent but interchangeable by the permutation $(1)(2\,3)(4)(5)(6)$, which is an element of the stereogenic group (i.e., the symmetric group of degree 6) but does not belong to the *RS*-

permutation group ($\mathbf{O}_{\bar{i}}$). In other words, **48** and **49** are ortho-diastereomeric in terms of Def. 1 of Part II of this series.

Because the difference (i.e., an ortho-diastereomeric relationship) between **48** and **49** stems from the differentiation of the two a's into a^{α} and a^{β}, the relationship between the two a's is referred to as an ortho-diastereotopic relationship, which is defined as follows:

Definition 9 (Ortho-diastereotopic relationships and pro-ortho-stereogenicity)

Suppose that a stereoisogram of a promolecule with two proligands has an equivalent stereoisogram under the stereogenic group. If the differentiation of the two proligands makes the two stereoisograms inequivalent (i.e., ortho-stereogenic due to Def. 1 of Part II of this series), the two proligands are referred to as being *ortho-diastereotopic*. Such a promolecule as having ortho-diastereotopic proligands is referred to being *pro-ortho-stereogenic*.

By replacing the differentiated proligands a^{α} and a^{β} by proligands A and a (not changed), the stereoisograms of Type V (Fig. 17) are converted into the stereoisograms of Type V, where an *RS*-diastereomeric pair of **50** and **51** is ortho-diastereomeric to another *RS*-diastereomeric pair of **52** and **53**. They are "diastereomeric" according to the conventional terminology.

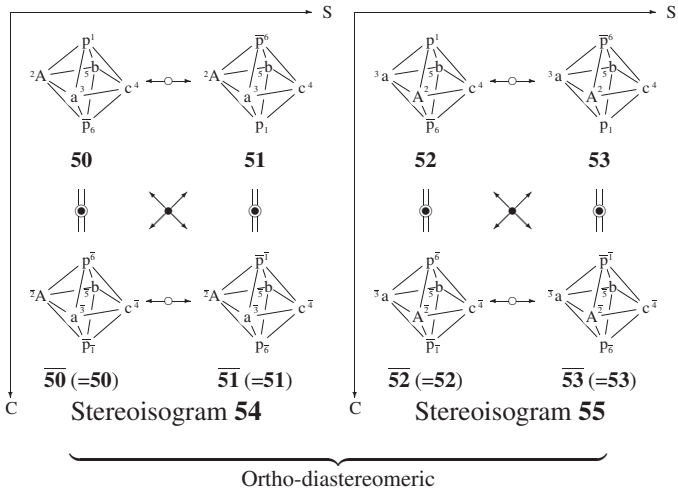


Figure 18: Stereoisograms of Type V generated from the stereoisograms of Type V (Fig. 17) by replacing a^{α} and a^{β} by A and a (not changed).

From a viewpoint of chemical reactions, the proligands a^{α} and a^{β} of **18** (= **44**) are differentiated and replaced by A and a (or vice versa) to produce **50** (or **52**). Similarly, **19** (= **45**) is capable of producing **51** or **53**, so that the following modes of conversions are possible.

$$\mathbf{18}\,(=\mathbf{44}) \;\rightarrow\; \mathbf{50}+\mathbf{52} \tag{10}$$

$$\mathbf{19}\,(=\mathbf{45}) \;\rightarrow\; \mathbf{51}+\mathbf{53} \tag{11}$$

5.2 Group-Theoretical Discussions on Pro-Ortho-Stereogenicity

5.2.1 Pro-Ortho-Stereogenicity by Ortho-Tropicities

Let us consider an octahedral complex with $[Ma_2bcd_2]$, which is generated by substituting the proligands p and $\overline{p}$ of **18** ($[Ma_2bcp\overline{p}]$ for d_2. The complex corresponds to two equivalent stereoisograms of Type IV, which are generated Stereoisograms **42** and **43** (Fig. 17) by substituting the proligands p and $\overline{p}$ for d_2. The two stereoisograms are parallel to the two stereoisograms **154** and **170** with $[Ma_2b_2cd]$, as shown in Fig. 5 of Part II of this series. They are characterized by the following stereoisomeric group:

$$\begin{aligned}\mathbf{G} \;=\; \{&(1)(2)(3)(4)(5)(6), \overline{(1\,6)}(2)(3)(4)(5),\\ &\overline{(1)(2)(3)(4)(5)(6)}, \overline{(1\,6)(2)(3)(4)(5)},\\ &(1)(2\,3)(4)(5)(6), \overline{(1\,6)(2\,3)(4)(5)},\\ &\overline{(1)(2\,3)(4)(5)(6)}, (1\,6)(2\,3)(4)(5)\},\end{aligned} \tag{12}$$

which is a subgroup of the stereoisomeric group for characterizing an octahedral skeleton. The promolecules with $[Ma_2bcd_2]$ under the group **G** are degenerated into a single promolecule.

Stereoisograms **42** and **43** (Fig. 17) are reversely generated by substituting d_2 of the complex $[Ma_2bcd_2]$ for p and $\overline{p}$, where the group **G** does not fix **42** (or **43**), because the *RS*-permutation $(1\,6)(2)(3)(4)(5)$, for example, converts the promolecule **18** into an inequivalent promolecule **19**. Note that the inequivalency is judged by considering the *RS*-stereoisomeric group, where **18** and **19** are *RS*-diastereomeric to each other.

The conversion from $[Ma_2bcd_2]$ to $[Ma_2bcp\overline{p}]$ results in the restriction of the group **G** into a subgroup as follows:

$$\begin{aligned}\mathbf{G}' \;=\; \{&(1)(2)(3)(4)(5)(6), \overline{(1\,6)(2)(3)(4)(5)},\\ &(1)(2\,3)(4)(5)(6), \overline{(1\,6)(2\,3)(4)(5)}\},\end{aligned} \tag{13}$$

which represents the symmetries of the promolecules contained in Stereoisograms **42** and **43** (Fig. 17). If we focus our attention on the promolecule **18** appearing in the Stereoisogram **42**, the group $\mathbf{G}'$ generates a quadruplet of promolecules, i.e., **18**, $\overline{\mathbf{18}}$ (=**18**), **18**′ (=**18**), and $\overline{\mathbf{18}}'$ (=**18**), which are degenerated into a single promolecule (**18**). These promolecules are collected to construct a skew-stereoisogram for characterizing ortho-stereogenicity as shown in Fig. 19, where the horizontal S-axis is concerned with a permutation which is not contained in the *RS*-permutation group. Note that the symbol □ denotes the permutation $(1)(2\,3)(4)(5)(6)$ of the group $\mathbf{G}'$ and the symbol ◘ denotes the operation $\overline{(1\,6)(2\,3)(4)(5)}$ of the group $\mathbf{G}'$ (Eq. 13). The quadruplet of promolecules in the skew stereoisogram of Fig. 19 is degenerated into a single promolecule.

Let us consider the following subgroup of $\mathbf{G}'$ to characterize the local symmetry of each proligand of the two a's:

$$\mathbf{G}'_C = \{(1)(2)(3)(4)(5)(6), \overline{(1\,6)(2)(3)(4)(5)}\}. \tag{14}$$

Obviously, the group $\mathbf{G}'_C$ fixes each proligand of the two a's.

By starting from the global symmetry $\mathbf{G}'$ (Eq. 13) and the local symmetry $\mathbf{G}'_C$, the following coset decomposition is obtained:

$$\mathbf{G}' = \mathbf{G}'_C + \mathbf{G}'_C(1)(2\,3)(4)(5)(6), \tag{15}$$

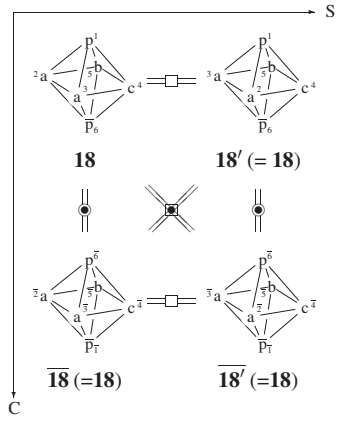


Figure 19: Skew-stereoisogram for characterizing ortho-stereogenicity, where the horizontal S-axis is concerned with a permutation (represented by □) which is not contained in the *RS*-permutation group. The quadruplet of promolecules in this skew stereoisogram is degenerated into a single promolecule.

Thereby, the coset representation $\mathbf{G}'(/\mathbf{G}'_C)$ of degree 2 ($|\mathbf{G}'|/|\mathbf{G}'_C| = 4/2 = 2$) is generated to characterize the orbit of the two a's in the promolecule **18**.

The global symmetry $\mathbf{G}'$ is regarded as being ortho-*a*stereogenic, while the local symmetry $\mathbf{G}'_C$ is regarded as being ortho-stereogenic. Hence, the coset representation $\mathbf{G}'(/\mathbf{G}'_C)$ is concluded to be ortho-enantiotropic, so that the corresponding orbit of the two a's is an ortho-enantiotropic orbit. The term *ortho-enantiotropic* is used in a parallel way to the term *RS-enantiotropic* defined in Def. 4, where a pair of *RS*-stereogenic/*RS-a*stereogenic in Def. 4 is replaced by a pair of ortho-stereogenic/ortho-*a*stereogenic. According to the ortho-enantiotropic orbit of the two a's in the promolecule **18**, the relationship between the two a's is concluded to be ortho-diastereotopic (cf. Def. 9), as well as the promolecule **18** is concluded to be pro-ortho-stereogenic.

Let us next consider the following subgroup of $\mathbf{G}'$ to discuss the pro-ortho-stereogenicity of the promolecule **18** in an alternative way:

$$\mathbf{G}'_S = \{(1)(2)(3)(4)(5)(6), (1)(2\,3)(4)(5)(6)\}, \tag{16}$$

which characterize the relationship between **18** and **18′** (**= 18**) along the S-axis of Fig. 19. When we regard the group $\mathbf{G}'_S$ is the global symmetry of **18**, each proligand of the two a's is fixed by the identity element $(1)(2)(3)(4)(5)(6)$, so that the local symmetry at issue is concluded to be $\mathbf{C}_1$ (an identity group). The orbit of the two a's is concluded to be governed by the coset representation $\mathbf{G}'_S(/\mathbf{C}_1)$, where the size of the orbit is calculated to be $|\mathbf{G}'_S|/|\mathbf{C}_1| = 2/1 = 2$. The global symmetry $\mathbf{G}'_S$ is regarded as being ortho-*a*stereogenic, while the local symmetry $\mathbf{C}_1$ is regarded as being ortho-stereogenic. Hence, the coset representation $\mathbf{G}'_S(/\mathbf{C}_1)$ is concluded to be ortho-enantiotropic, so that the corresponding orbit of the two a's is an ortho-enantiotropic orbit. On a similar way to the coset representation $\mathbf{G}'(/\mathbf{G}'_C)$, the present coset representation $\mathbf{G}'_S(/\mathbf{C}_1)$

reveals that the relationship between the two a's is concluded to be ortho-diastereotopic (cf. Def. 9), as well as the promolecule **18** is concluded to be pro-ortho-stereogenic.

5.2.2 Skew-Stereoisograms for Testifying Pro-Ortho-Stereogenicity

The pro-ortho-stereogenicity of the promolecule **18** is alternative deduced by means of a skew-stereoisogram for testifying pro-ortho-stereogenicity, as shown in Fig. 20. In a similar way to the conversion shown in Fig. 17, the two proligands a's of each promolecule in the skew-stereoisogram (Fig. 19) are differentiated by marking α and β. Thereby, the corresponding skew-stereoisogram of testifying pro-ortho-stereogenicity is obtained as shown in Fig. 20, where the self-ortho-diastereomeric relationship between **18** and **18′** (= **18**) in Fig. 19 is changed into the ortho-diastereomeric relationship between **44** and **46** in Fig. 20. It follows that the proligands a^{α} and a^{β} are ortho-diastereotopic (cf. Def. 9).

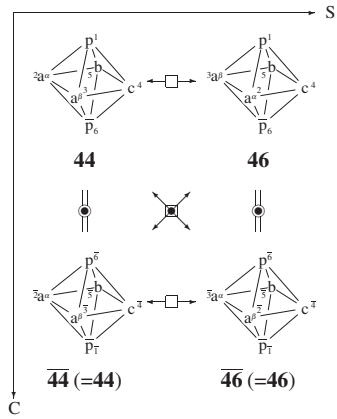


Figure 20: Skew-stereoisogram for testifying pro-ortho-stereogenicity, where the horizontal S-axis is concerned with a permutation (represented by □) which is not contained in the *RS*-permutation group. The quadruplet of promolecules in this skew stereoisogram is degenerated into two achiral promolecules.

It should be noted that the testifying skew-stereoisogram shown in Fig. 20 can be regarded as a simplified version of the testifying stereoisogram shown in Fig. 17. By replacing a^{α} and a^{β} by A and a (not changed) in Fig. 20, we are able to obtain Stereoisogram **54** shown in Fig. 18. Reversely, by replacing a^{β} and a^{α} by A and a (not changed) in Fig. 20, we are able to obtain Stereoisogram **55** shown in Fig. 18

5.3 Pro-ortho-stereogenicity and Prostereogenicity

5.3.1 New Definition of Prostereogenicity

To harmonize the present terminology with the conventional one, the term *prostereogenic* (or *diastereotopic*) is defined on the basis of the definition of the term *stereogenicity* (or *diastere-*

omeric) described in Def. 3 of Part II of this series.

Definition 10 (Diastereotopic relationships and Prostereogenicity)

Suppose that an enantiomeric pair of promolecules (or an achiral promolecule as a self-enantiomeric pair), which has two proligands, has an equivalent (self)-enantiomeric pair of promolecules under the stereogenic group. If the differentiation of the two proligands makes the two pairs (or the two promolecules) inequivalent (i.e., diastereomeric due to Def. 3 of Part II of this series), the two proligands are referred to as being *diastereotopic*. The (self)-enantiomeric pair of promolecules having such a diastereotopic pair of proligands is referred to as being *prostereogenic*.

As an example of determining a diastereotopic relationship in terms of Def. 10, the skew-stereoisogram shown in Fig. 19 is compared with the skew-stereoisogram for testifying pro-ortho-stereogenicity (Fig. 20). In Fig. 19, the achiral promolecule **18** (as a self-enantiomeric pair of promolecules) has an equivalent achiral promolecule **18′** (**=18**), where the equivalency is assured by a permutation $(1)(2\,3)(4)(5)(6)$ of the group $\mathbf{G}'_S$ (Eq. 16), which is a subgroup of the stereogenic group (i.e., the symmetric group of degree 6 in this case). The two proligands a's are differentiated by adding α and β as superscript so as to give the skew-stereoisogram for testifying pro-ortho-stereogenicity (Fig. 20). Thereby, the resulting achiral promolecules, i.e., **44** and **46** become inequivalent, because they are not interconvertible by the permutation $(1)(2\,3)(4)(5)(6)$, as found in Fig. 20. In other words, **44** and **46** are diastereomeric due to Def. 3 of Part II of this series. According to Def. 10, the two proligands a's in **18** is concluded to be diastereotopic, so that **18** is prostereogenic.

It should be emphasized that **18** is concluded to be pro-ortho-stereogenic and prostereogenic by examining the skew-stereoisogram for testifying pro-ortho-stereogenicity (Fig. 20). The concept of *pro-ortho-stereogenic* stems from quadruplets of *RS*-stereoisomers (stereoisograms), while the concept of *prostereogenic* stems from pairs of (self-)enantiomers. The concept of *prostereogenicity* due to Def. 10 consists of *pro-RS-stereogenic* (Def. 5) and *pro-ortho-stereogenic* (Def. 9), approximately speaking, i.e., if we tentatively ignore the difference between the *RS*-permutation group and the stereogenic group.

5.3.2 Newly-Defined Prostereogenicity vs. the Conventional "Prostereogenicity"

It is safe to say that the conventional concept of "prostereogenicity" has overlooked the difference between the *RS*-permutation group and the stereogenic group. In other words, the concept of "prostereogenicity" in the conventional stereochemistry ignores the presence of the *RS*-permutation group and takes no account of the intermediate concept of *RS*-stereoisomers formulated by the stereoisogram approach.

The newly-defined concept of *prostereogenicity* is independent to the concept of *prochirality* of a purely geometric meaning. The concept of *pro-RS-stereogenicity* is abstracted from the concept of *prostereogenicity*. After that, the interaction between *pro-RS-stereogenicity* and *prochirality* is discussed by means of stereoisograms for testifying prochirality and pro-*RS*-stereogenicity, where the concept of *pro-RS-stereogenicity* is independent to the concept of *prochirality* of a purely geometric meaning.

Accordingly, the achiral promolecule **1** is characterized as follows:

Def. 2:	a_2	prochiral (Type IV to I)	Fig. 7	(17)
Def. 5:	a_2	pro-*RS*-stereogenic (Type IV to I)	Fig. 7	(18)
Def. 10:	a_2	prostereogenic	Fig. 7	(19)

The orbit of two a's is characterized as being prochiral, pro-*RS*-stereogenic, and prostereogenic. The assignment of *pro-A/pro-C*-descriptors stems from the pro-*RS*-stereogenic (cf. Table 2).

In contrast, the conventional concepts of "prostereogenicity" and "prochirality" are entangled as shown in Table 3. As a result, the conventional stereochemistry has nullified the pro-*RS*-stereogenicity (Eq. 18) and prostereogenicity (Eq. 19) of the two a's in **1**. Thereby, the assignment of *pro-A/pro-C*-descriptors to the two a's in **1** is presumed to stem from "prochirality", because the two a's are regarded as being "enantiotopic" (cf. Table 3). This presumption is inconsistent with the following cases of **17** and **18**.

As for **17**, the results described above are summarized as follows:

Def. 2:	$p\overline{p}$	prochiral (Type IV to II)	Fig. 9	(20)
Def. 5:	a_2	pro-*RS*-stereogenic (Type IV to V)	Fig. 11	(21)
Def. 10:	a_2	prostereogenic	Fig. 11	(22)

The prochirality of **17** is concerned with the proligands p and $\overline{p}$, while the pro-*RS*-stereogenicity of **17** is concerned with the proligands a's. Thereby, the assignment of *pro-A/pro-C*-descriptors to the two a's in **17** stems from the pro-*RS*-stereogenicity (cf. Table 2).

As for **18**, the results described above are summarized as follows:

Def. 2:	$p\overline{p}$	prochiral (Type V to III)	Fig. 13	(23)
Def. 9:	a_2	pro-ortho-stereogenic	Figs. 17, 19, and 20	(24)
Def. 10:	a_2	prostereogenic	Figs. 19 and 20	(25)

The prochirality of **18** is concerned with the proligands p and $\overline{p}$. The two proligands a's in **18** exhibit pro-ortho-stereogenicity, where the two a's are differentiated by the attack of chemical reagents. Because they do not exhibit pro-*RS*-stereogenicity, *pro-A/pro-C*-descriptors are not been assigned to the proligands a's.

Eqs. 17–19 for **1**, Eqs. 20–22 for **18**, and Eqs. 23–25 for **19** show different modes of interaction between the newly-defined concept of *prostereogenicity* and prochirality. The different modes are more clearly specified in terms of pro-*RS*-stereogenicity (Eqs. 18 and 21) and pro-ortho-stereogenicity (Eq. 24) in the present stereoisogram approach. Hence, it is advisable to use the term *prostereogenicity* in the following restricted fashion:

1. As for cases similar to **1**, the term *prochiral* (Eq. 17) is used to characterize reactions under chiral conditions and the term *pro-RS-stereogenicity* (Eq. 18) is used to rationalize *pro-A/pro-C*-descriptors. The usage of the term *prostereogenicity* (Eq. 19) is not recommended so that the more definite term *pro-RS-stereogenicity* (Eq. 18) should be used.

2. As for cases similar to **18**, the term *prochiral* (Eq. 20) is used to characterize reactions under chiral conditions and the term *pro-RS-stereogenicity* (Eq. 21) is used to rationalize *pro-A/pro-C*-descriptors. The usage of the term *prostereogenicity* (Eq. 19) is not recommended so that the more definite term *pro-RS-stereogenicity* (Eq. 18) should be used.

3. As for cases similar to **19**, the term *prochiral* (Eq. 23) is used to characterize reactions under chiral conditions. The term *pro-ortho-stereogenicity* (Eq. 24) is used to rationalize intramolecular (in)equivalency of proligands, which cannot be characterized by *pro-A/pro-C*-descriptors. The term *prostereogenicity* (Eq. 25) may be used in the meaning of pro-ortho-stereogenicity if such usage causes no confusion.

The above-mentioned restriction of the term *prostereogenicity* meets the conventional term "prostereogenicity" halfway, so that past literature dealing with "prostereogenicity" would be effective with minor modifications. However, it should be noted that the conventional terminology based on the terms "prochirality" and "prostereogenicity" has several items of inconsistency as follows:

1. The conventional term "prostereogenicity" nullifies the prostereogenicity of Eq. 19 so that the prochirality of Eq. 17 is taken into sole consideration. This nullification results in entangled situations collected in Table 3.

2. The conventional term "prostereogenicity" does not differentiate between the prostereogenicities represented by Eq. 22 and 25. It follows that the term "prostereogenicity" is not always successful in the decision of whether *pro-A/pro-C*-descriptors can be assigned or not.

3. The conventional term "prochirality" overlooks prochirality in the cases of converting Type IV into Type II (Eq. 20) and in the cases of converting Type V to Type III (Eq. 23).

6 Conclusion

As a continuation of Part I and Part II of this series, the stereoisogram approach is extended to discuss prochirality and pro-*RS*-stereogenicity for octahedral complexes in inorganic stereochemistry. According to the formulation described previously for organic chemistry, the concept of prochirality is defined in a purely geometric fashion on the basis of enantiospheric-ity [9, 19, 20]. On the other hand, the concept of pro-*RS*-stereogenicity is defined on the basis of *RS*-enantiotropicity [26, 27]. These concepts are applied to intramolecular features of octahedral complexes, which have been enumerated previously [24] and discussed with respect to their intermolecular features in Part I and Part II of this series.

After octahedral complexes are categorized into five types (Types I–V) by means of stereoisograms, stereoisograms for testifying prochirality and pro-*RS*-stereogenicity are proposed as alternative devices, which are an extension the counterparts developed originally for the symmetry criterion in organic stereochemistry [29]. The relational terms *enantiotopic* and *RS-diastereotopic* are introduced to make the symmetry criterion effective. Thereby, *pro-A/pro-C*-descriptors are concluded to be based on an *RS*-diastereotopic relationship. The further concept of *pro-ortho-stereogenicity* is proposed to rationalize intramolecular (in)equivalency of proligands, which cannot be characterized by *pro-A/pro-C*-descriptors.

References

[1] K. R. Hanson, *J. Am. Chem. Soc.*, **88**, 2731–2742 (1966).

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

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

[4] E. L. Eliel, *Top. Curr. Chem.*, **105**, 1–76 (1982).

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

[6] S. Fujita, *Tetrahedron*, **65**, 1581–1592 (2009).

[7] G. Mestroni, E. Alessio, G. Zassinovich, and L. G. Marzilli, *Comments Inorg. Chem.*, **12**, 67–91 (1991).

[8] S. Fujita, in "Carbon Bonding and Structures. Advances in Physics and Chemistry," ed. by M. V. Putz, Springer-Verlag, Dordrecht Heidelberg London (2011) Vol. 5 of Carbon Materials: Chemistry and Physics Chapter 10, pp 227–271.

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

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

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

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

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

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

[15] H. Hirschmann and K. R. Hanson, *Eur. J. Biochem.*, **22**, 301–309 (1971).

[16] H. Hirschmann, *Trans. N. Y. Acad. Sci. Ser. II*, **41**, 61–69 (1983).

[17] A. von Zelewsky, "Stereochemistry of Coordination Compounds," John Wiley & Sons, Chichester (1996).

[18] K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1–38 (1967).

[19] S. Fujita, *J. Am. Chem. Soc.*, **112**, 3390–3397 (1990).

[20] S. Fujita, *J. Org. Chem.*, **67**, 6055–6063 (2002).

[21] S. Fujita, *Chem. Rec.*, **2**, 164–176 (2002).

[22] S. Fujita, *Bull. Chem. Soc. Jpn.*, **75**, 1863–1883 (2002).

[23] S. Fujita, *Bull. Chem. Soc. Jpn.*, **73**, 1979–1986 (2000).

[24] S. Fujita, *Polyhedron*, **12**, 95–110 (1993).

[25] S. Fujita, *Bull. Chem. Soc. Jpn.*, **63**, 315–327 (1990).

[26] S. Fujita, *J. Math. Chem.*, **33**, 113–143 (2003).

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

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

[29] S. Fujita, *J. Comput. Aided Chem.*, **10**, 76–95 (2009).

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