Group-Theoretical Discussion on the *E*/*Z*-Nomenclature for Ethylene Derivatives. Discrimination between *RS*-Stereoisomeric Groups and Stereoisomeric Groups

Shinsaku Fujita*

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyoku, Kyoto 606-8585, Japan

Received June 2, 2004

The hierarchy of point groups, *RS*-stereoisomeric groups, stereoisomeric groups, and isoskeletal groups is discussed to comprehend the chirality, *RS*-stereogenicity, stereogenicity, and isoskeletal isomerism for ethylene derivatives. The *RS*-stereoisomeric groups for ethylene derivatives have been clarified not to coincide with their stereoisomeric groups, so that diastereomers (*E*/*Z*-isomers) are not identical with *RS*-diastereomers. To discuss the relationship among *RS*-diastereomers, *m*-diastereomers, and isoskeletal isomers, we have proposed the concepts of *extended stereoisograms* and *extended stereoisogram sets*, where the term "*m*-diastereomers" is coined to show its difference from the traditional term "diastereomer". Thereby, ethylene derivatives are classified into Types II−II/II−II/II−II, IV−IV/IV−IV/IV−IV, etc. on the basis of relevant stereoisograms (Types I to V). The stereoisomerism of ethylenes has been concluded to be treated in terms of *m*-diastereomers characterized by the *E*/*Z*-nomenclature but not to be treated in terms of *RS*-diastereomers characterized by the *RS*-nomenclaure.

1. INTRODUCTION

Different systems of nomenclature have been used for specifying the stereoisomerism of molecules of ligancy 4: i.e., the *RS*-nomenclature for teterahedral molecules and allenes,[1] the *E*/*Z*-nomenclature for ethylenes,[2,3] and the other nomenclature for square-planar complexes.[4,5] For example, a tetrahedral molecule with a ligand pattern ABp$\bar{p}$ (A, B: achiral ligands; p and $\bar{p}$: a pair of enantiomeric chiral ligands) generates its diastereomer by a ligand permutation between A and B, where their relationship is characterized by *RS*-descriptors. On the other hand, an ethylene molecule with a ligand pattern AB=p$\bar{p}$ generates its enantiomer by the same ligand permutation between A and B, where their relationship is characterized by *E*/*Z*-descriptors. The traditional stereochemistry has referred to this difference only by saying that the *RS*-nomenclature describes three-dimensional situations, while the *E*/*Z*-nomenclature describes in-plance situations. However, the same permutations causing such different behaviors (diastereomers vs enantiomers) are expected to come from an inherent nature, which should be examined on the basis of a common logical framework.

The basis of the *RS*-nomenclature, which was traditionally explained in terms of chirality or stereogenicity units (centers, axes, and planes), has been clarified logically by means of the concepts of holantimer and stereoisogram.[6] However, it has not been fully rationalized why such different systems of nomenclature are necessary according to objects to be named. This situation stems from the lack of a logical framework suitable to clarify the difference, although methodologies for representating organic and inorganic structures have been widely discussed from the viewpoint of chemoinformatics and related fields.[7,8]

The concepts of holantimers and stereoisograms have been based on the concept of *RS*-stereoisomeric groups,[9] which have rationalized the basis of the *RS*-nomenclature for tetrahedral molecules and for allene derivatives. These groups, however, are incapable of clarifying the basis of the *E*/*Z*-nomenclature for ethylene derivatives, because they are insufficient to describe *E*/*Z*-stereoisomerism. Hence, a new group theoretical approach should be developed to pursue such a logical framework.

In this paper, we will study ethylene derivatives as a typical example of general cases in which stereoisomeric groups should be considered in addition to *RS*-stereoisomeric groups. Moreover, the hierarchy of groups (i.e., isoskeletal groups, stereoisomeric groups, *RS*-stereoisomeric groups, and point groups) will be discussed to obtain a balanced overview on stereochemical nomenclature. This study will reveal why ethylene derivatives are characterized by *E*/*Z*-nomenclatures but not by the *RS*-nomenclature.

2. CHARACTERIZING ETHYLENE DERIVATIVES

2.1. Numbering an Ethylene Skeleton. To give a definite formulation, an ethylene skeleton with appropriate locant numbers is taken into consideration, as shown in Figure 1. The initial numbering can be selected arbitarily. Then, an ethylene derivative is considered to be generated by placing a set of ligands (e.g., A, B, C, and D) according to a function *f*, which represents a mode of the placement: e.g., $f(1) =$ A, $f(2) =$ B, $f(3) =$ C, and $f(4) =$ D. Thereby, the skeleton **1** generates a derivative **2** of a ligand pattern ABCD. In this paper, uppercase letters such as A, B, C, and D represent achiral ligands and pairs of lowercase letters such as p and $\bar{p}$, q and $\bar{q}$, etc. represent pairs of enantiomeric ligands.

A set of locant numbers is permuted to give another set, giving twenty-four ways of numbering. The same function is applied to the resulting numbered skeletons so that a set of isomers (stereoisomers and constitutional isomers) is generated. The set of isomers is categorized by considering the actions of various groups of permutations, as discussed in the next subsection.

* Corresponding author e-mail: fujitas@chem.kit.ac.jp.

10.1021/ci040103r CCC: $27.50
Published on Web 08/24/2004

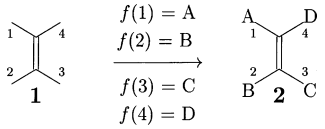


Figure 1. An initial numbering of a ethylene ethylene skeleton. A function *f* is used to form an ethylene derivative.

2.2. Groups for Characterizing an Ethylene Skeleton. To comprehend the stereochemistry of ethylene derivatives (especially their *E*/*Z*-stereoisomerism), we take into account groups collected in Figure 2, which act on the four positions of an ethylene skeleton.

1. The point group $\mathbf{D}_{2h}$ of order 8 is considered to discuss the geometrical aspect (chirality) of ethylene derivatives. Precisely speaking, the coset representation $\mathbf{D}_{2h}(/\mathbf{C}_s'')$ is taken into account.[10] This coset representation is regarded as a permutation representation, where permutations corresponding to improper rotations (rotoreflections) are designated by overbars. Thereby, it is capable of mediating the point group $\mathbf{D}_{2h}$ and the corresponding permutation group of degree 4.[10] The coset representation $\mathbf{D}_{2h}(/\mathbf{C}_s'')$ is referred to as the group $\mathbf{D}_{2h}$, if such usage causes no confusion. It should be noted that the permutations for proper rotations coincide with the permutations for improper rotations if an overbar on each locant is omitted.

2. To discuss the nomenclature aspect (stereogenicity) of ethylene, *RS*-stereogenicty is discriminated from usual-defined stereogenicity. The group for characterizing the *RS*-stereogenicity of ethylene derivatives, which can be represented by $\mathbf{S}_7^{[4]} \times \{I,\sigma\}$ (where $\sigma = \sigma_h$), coincide with the group $\mathbf{D}_{2h}$ so that each stereoisogram inherently belongs to Type II or IV.[6] This means that ethylene derivatives cannot be specified by *RS*-descriptors.

3. In addition, the permutation group $\mathbf{S}_9^{[4]}$, which is a subgroup of the symmetric group of degree 4 (i.e., $\mathbf{S}^{[4]}$), is considered to discuss the further nomenclature aspect (stereogenicity).

$$\mathbf{S}_9^{[4]} = \mathbf{S}_7^{[4]} + (1)(2\,3)(4)\mathbf{S}_7^{[4]}$$
$$= \{(1)(2)(3)(4),(1\,2)(3\,4),(1\,4)(2\,3),(1\,3)(2\,4);$$
$$(1)(2\,3)(4),(1\,2\,4\,3),(1\,4)(2)(3),(1\,3\,4\,2)\} \quad (1)$$

Obviously, this group characterizes *E*/*S*-stereoisomerism for ethylene derivatives.

4. To integrate the two aspects (chirality and stereogenicity), we define the stereoisomeric group of the ethylene skeleton as a direct product represented by $\mathbf{S}_9^{[4]} \times \{I,\sigma\}$. Note that the operation σ can be selected from rotoreflections. We can use $\sigma = \sigma_h$, which is contained in the group $\mathbf{D}_{2h}$. This group contains the point group $\mathbf{D}_{2h}$ and the permutation group $\mathbf{S}_9^{[4]}$ as normal subgroups. In addition, there emerges another normal subgroup $\mathbf{D}_{2i}$, which is called the *isomerization group*:

$$\mathbf{D}_{2i} = \{I, C_{2(3)}, C_{2(1)}, C_{2(2)}; \hat{I}, \hat{C}_{2(3)}, \hat{C}_{2(1)}, \hat{C}_{2(2)}\} \quad (2)$$
$$= \{(1)(2)(3)(4),(1\,2)(3\,4),(1\,4)(2\,3),(1\,3)(2\,4);$$
$$\overline{(1)(2\,3)(4)}, \overline{(1\,2\,4\,3)}, \overline{(1\,4)(2)(3)}, \overline{(1\,3\,4\,2)}\} \quad (3)$$

where we place $\hat{I} = \overline{(1)(23)(4)}$ to convert eq 2 into eq 3.

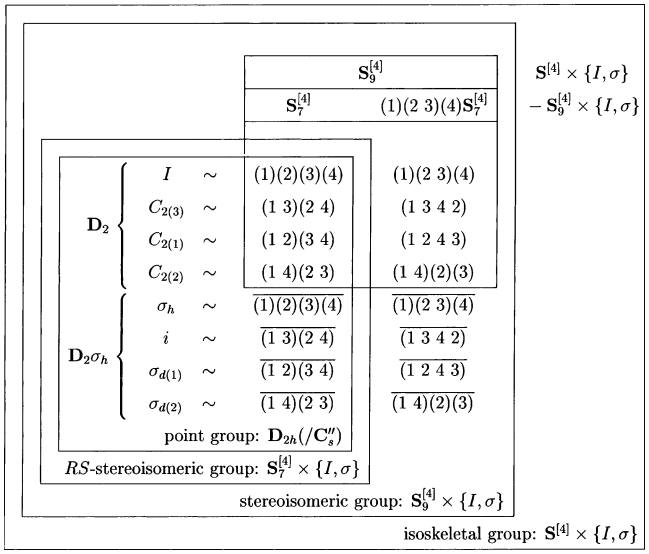


Figure 2. Point group, *RS*-stereoisomeric group, stereoisomeric group, and isoskeletal group for ethylene derivatives.

The symbol $\mathbf{D}_{2i}$ is coined to emphasize the name *isomerization group* which has the point group $\mathbf{D}_2$ as a normal subgroup.

5. We finally consider the action of the symmetric group $\mathbf{S}^{[4]}$ on the four positions of an ethylene derivative. Thereby, we can obtain constitutional isomers that have an ethylene skeleton as a common skeleton. Such isomers are called here *isoskeletal isomers*. To describe these isoskeletal isomers, we consider a direct product represented by $\mathbf{S}^{[4]} \times \{I,\sigma\}$, which is called *isoskeletal groups*.

The hierarchy for ethylene isomers is found to be as follows: isoskeletal isomers ($\mathbf{S}^{[4]} \times \{I,\sigma\}$) $\supset$ stereoisomers ($\mathbf{S}_9^{[4]} \times \{I,\sigma\}$) $\supset$ *RS*-stereoisomers ($\mathbf{S}_7^{[4]} \times \{I,\sigma\}$) = enantiomers ($\mathbf{D}_{2h}$), where the groups shown in parentheses control the respective isomers, as shown in Figure 2.

3. ISOSKELETAL GROUPS AND EXTENDED STEREOISOGRAM SETS

Let us next consider the conversions of an ethylene molecule having ligands ABCp under the action of the isoskeletal group $\mathbf{S}^{[4]} \times \{I,\sigma\}$ (Figures 4−7).

3.1. Action of Stereoisomeric Group. We have recently proposed the concept of holantimer, where two molecules based on the same skeleton are defined as being *holantimeric* if the chirality of each ligand in the one molecule is changed into the opposite one to give the other molecule based on that same skeleton.[6] As for ethylene derivatives, the holantimer (e.g., $\bar{\mathbf{3}}\mathbf{b}$) of an original molecule (e.g., **3a**) is always identical with the corresponding enantiomer (e.g., $\bar{\mathbf{3}}\mathbf{a}$) so that the *RS*-diastereomer (e.g., **3b**), which is defined as the enantiomer of the holantimer, is identical with the original molecule (e.g., **3a**). The corresponding stereoisogram (the left of Figure 3),[6] which comprises the original molecule (e.g., **3a**), its enantiomer (e.g., $\bar{\mathbf{3}}\mathbf{a}$), its holantimer (e.g., $\bar{\mathbf{3}}\mathbf{b}$), and its *RS*-diastereomer (e.g., **3b**), represents these results by equality symbols and double-headed arrows. These results stem from the fact that the *RS*-stereoisomeric group for an ethylene derivative is identical with the point group, as shown in Figure 2. As a result, the stereoisogram of each ethylene derivative need not contain the holantimer and the *RS*-diastereomer along with the S-axis, which represents *RS*-

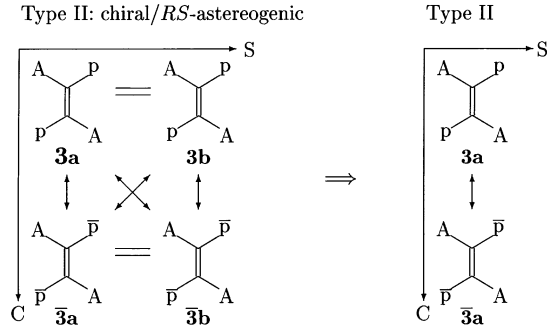


Figure 3. Stereoisogram (left) and degenerate stereoisogram (right) for an ethylene derivative with ligands A^2p^2. They are concerned with the *RS*-stereoisomeric group $\mathbf{S}_7^{[4]} \times \{I,\sigma\}$.

stereogenicity/*RS*-astereogenicity. This means that the S-axis of the stereoisogram can be degenerate so that the stereoisogram contains the original ethylene molecule and its enantiomer along with the *C*-axis, which represents chirality/achirality, as shown in the right degenerate stereoisogram of Figure 3.

For the sake of convenience, we take into account the *RS*-stereoisomeric group at the same time during the examination of the action of the stereoisomeric group. The resulting diagram containing two (degenerate) stereoisograms is called *extended stereoisogram*.

First, Figure 4 depicts the action of the stereoisomeric group $\mathbf{S}_9^{[4]} \times \{I,\sigma\}$, which is classified into four parts according to the following cosets: $\mathbf{S}_7^{[4]}$, $(1)(2\ 3)(4)\mathbf{S}_7^{[4]}$, $\overline{(1)(2)(3)(4)}\mathbf{S}_7^{[4]}$, and $\overline{(1)(2)(3)(4)}\mathbf{S}_7^{[4]}$. The numbering of the original molecule **4a** is permuted so as to place ligands in accord with the function: $f(1) = \mathrm{A}$, $f(2) = \mathrm{C}$, $f(3) = \mathrm{p}$, $f(4) = \mathrm{B}$. Thereby we obtain molecules collected in Figure 4.

Each part contains a set of homomers: the $\mathbf{S}_7^{[4]}$-part is a homomer set of the original molecule, the $(1)(2\ 3)(4)\mathbf{S}_7^{[4]}$-part is a homomer set of the *m*-diastereomer (cis/trans-isomer), the $\overline{(1)(2)(3)(4)}\mathbf{S}_7^{[4]}$-part is a homomer set of the enantiomer, and the $(1)(2)(3)(4)\mathbf{S}_7^{[4]}$-part is a homomer set of the other *m*-diastereomer (the cis/trans-isomer of the enantiomer).

It should be noted that the term "*m*-diastereomers" is coined to show its difference from the traditional term "diastereomer", where *m* represents "meta" of Greek origin. The traditional term "diastereomer" corresponds approximately to the terms "*RS*-diastereomer" plus "*m*-diastereomer" according to the present approach.

The homomer sets can be expressed by respective representatives, i.e., the original molecule **4a**, the *m*-diastereomer **5a**, the enantiomer $\bar{\mathbf{4}}\mathbf{a}$, and the other *m*-diastereomer $\bar{\mathbf{5}}\mathbf{a}$. By collecting these representatives, we are able to construct an extended stereoisogram, as shown in Figure 5. Each extended stereoisogram is represented by the *C*-axis and the S′-axis, where the S′-axis represents stereogenicity/astereogenicity. The term "extended stereoisogram" is used to designate that it contains a stereoisogram represented by the *C*-axis and the S-axis, where the S-axis is degenerate because the *RS*-stereoisomeric group becomes identical with the point groups as described above.

As found easily, the extended stereoisogram (Figure 5) contains two degenerate stereoisograms of Type II. Since they are different from each other, the extended stereoisogram is designated by the symbol II−II, which represents that this case is characterized as cis/trans- or *E*/*Z*-isomerism. Since the horizontal axis is concerned with usual stereogenicity (i.e., cis/trans- or *E*/*Z*-isomerism), it is designated by the symbol S′ so that the S′-axis is discriminated from the S-axis (for *RS*-stereogenicity), as found in Figure 5. Since the original molecule **4a** and the *m*-diastereomer **5a** are different, they are linked with a nonequality symbol (≠). If we presume the priority to be A > B > C > p, **4a** is a *Z*-isomer, while **5a** is an *E*-isomer.

3.2. Action of Isoskeletal Groups. Second, we regards the stereoisomeric group $\mathbf{S}_9^{[4]} \times \{I,\sigma\}$ as a subgroup of the isoskeletal group $\mathbf{S}^{[4]} \times \{I,\sigma\}$ (cf. Figure 2). Thereby, we can consider the corresponding coset decomposition, where one of the cosets is listed in Figure 6. Each permutation is shown in the first row of Figure 6. The resulting isomers are not stereoisomers but isoskeletal isomers (a kind of constitutional isomers) of the ethylene derivatives collected in Figure 6. If we regard the first derivative **6a** is selected as an original molecule and its numbering is adopted as an initial one, we obtain permutations shown in the second row of Figure 6.

Third, the remaining coset is similarly obtained, as listed in Figure 7, where each permutation is shown in the first row. Again, the resulting isomers are not stereoisomers but isoskeletal isomers (a kind of constitutional isomers) of the ethylene derivatives collected in Figure 4. We then regard the first derivative **8a** is selected as a third original molecule

	$\mathbf{S}_9^{[4]}$ (stabilizer: $\mathbf{S}_9^{[4]}$)							
	4a	**4b**	**4d**	**4c**	**5a**	**5b**	**5d**	**5c**
	I	$C_{2(1)}\sim$	$C_{2(2)}\sim$	$C_{2(3)}\sim$				
$\mathbf{D}_{2h}$	(1)(2)(3)(4)	(1 2)(3 4)	(1 4)(2 3)	(1 3)(2 4)	(1)(2 3)(4)	(1 2 4 3)	(1 4)(2)(3)	(1 3 4 2)
	$\bar{\mathbf{4}}\mathbf{a}$	$\bar{\mathbf{4}}\mathbf{b}$	$\bar{\mathbf{4}}\mathbf{d}$	$\bar{\mathbf{4}}\mathbf{c}$	$\bar{\mathbf{5}}\mathbf{a}$	$\bar{\mathbf{5}}\mathbf{b}$	$\bar{\mathbf{5}}\mathbf{c}$	$\bar{\mathbf{5}}\mathbf{d}$
	$\sigma_h\sim$	$\sigma_{d(1)}\sim$	$\sigma_{d(2)}\sim$	$i\sim$				
	(1)(2)(3)(4)	(1 2)(3 4)	(1 4)(2 3)	(1 3)(2 4)	(1)(2 3)(4)	(1 2 4 3)	(1 4)(2)(3)	(1 3 4 2)

Figure 4. Isomer equivalence for ABCp under $\mathbf{S}^{[4]} \times \{I,\sigma\}$ (Part 1).504

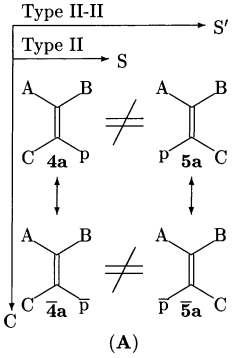


Figure 5. Extended stereoisogram (II−II) for an ethylene molecule with ABCp under the stereoisomeric group: $\mathbf{S}_9^{[4]} \times \{I,\sigma\}$. The degenerate S-axis is concerned with *RS*-astereogenicity, while the S′-axis is concerned with *m*-stereogenicity (i.e., cis/trans- or *E*/*Z*-isomerism).

and its numbering is adopted as an initial one. Thereby we obtain permutations shown in the second row of Figure 7, where these permutations allow us to generate another stereoisogram by starting from Figure 7.

3.3. Definition of Extended Stereoisogram Sets. Finally, we collect the representatives described above for Figures 4, 6, and 7 so as to give a set of three extended stereoisograms (**A**, **B**, and **C**) as shown in Figure 8, where **A** is shown in Figure 5 derived from Figure 4 and where **B** and **C** are derived from Figures 6 and 7, respectively. We call this collection *isoskeletal set of extended stereoisograms* or simply *extended stereoisogram set*.

Each stereoisogram contained in **A**, **B**, or **C** (Figure 8) is categorized into Type II (chiral/*RS*-astereogenic) according to the scheme shown in previous papers.[6,9] The designation of Type II is shown above the S-axis. The pair of enantiomers (e.g., **4a** and $\bar{\mathbf{4}}\mathbf{a}$) in each stereoisogram is converted into the corresponding pair (e.g., **5a** and $\bar{\mathbf{5}}\mathbf{a}$) under the action of the stereoisomeric group. Since the two pairs of Type II are different from each other, they are linked with nonequality symbols ($\neq$). The resulting extended stereoisogram is designated by the symbol II−II (shown above the S′-axis), which means that both of the relevant stereoisograms belong to Type II. Type II−II represents cis/trans- or *E*/*Z*-isomerism between chiral ethylene derivatives.

The three extended stereoisograms shown in Figure 8 correspond to three sets (**A**, **B**, and **C**) of constitutional isomers, where the sets are isoskeletally isomeric to each other. This type of extended stereoisogram set is designated by the symbol II−II/II−II/II−II.

Extended stereoisogram sets (II−II/II−II/II−II) similar to Figure 8 are found for ligand patterns such as ABCp, ABpq, Ap$\bar{\text{p}}$q, Apqr, p$\bar{\text{p}}$qr, and pqrs.

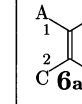
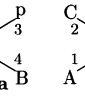
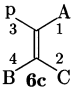
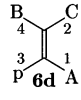
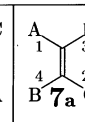
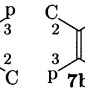
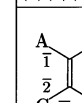
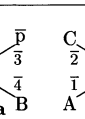
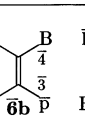
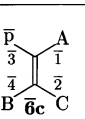
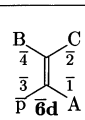
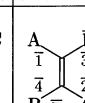
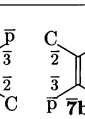
	$(1)(2)(3\ 4)\mathbf{S}_9^{[4]}$ (stabilizer: $\mathbf{S}_9^{[4]\prime}$)							
								
	6a	**6b**	**6c**	**6d**	**7a**	**7b**	**7c**	**7d**
	(1)(2)(3 4)	(1 2)(3)(4)	(1 3 2 4)	(1 4 2 3)	(1)(2 4 3)	(1 2 3)(4)	(1 3 4)(2)	(1 4 2)(3)
	I	$C_{2(1)} \sim$	$C_{2(2)} \sim$	$C_{2(3)} \sim$				
$\mathbf{D}_{2h}$	(1)(2)(3)(4)	(1 2)(3 4)	(1 3)(2 4)	(1 4)(2 3)	(1)(2 4)(3)	(1 2 3 4)	(1 3)(2)(4)	(1 4 3 2)
								
	$\bar{\mathbf{6}}\mathbf{a}$	$\bar{\mathbf{6}}\mathbf{b}$	$\bar{\mathbf{6}}\mathbf{c}$	$\bar{\mathbf{6}}\mathbf{d}$	$\bar{\mathbf{7}}\mathbf{a}$	$\bar{\mathbf{7}}\mathbf{b}$	$\bar{\mathbf{7}}\mathbf{c}$	$\bar{\mathbf{7}}\mathbf{d}$
	(1)(2)(3 4)	(1 2)(3)(4)	(1 3 2 4)	(1 4 2 3)	(1)(2 4 3)	(1 2 3)(4)	(1 3 4)(2)	(1 4 2)(3)
	$\sigma_h \sim$	$\sigma_{d(1)} \sim$	$\sigma_{d(2)} \sim$	$i \sim$				
	(1)(2)(3)(4)	(1 2)(3 4)	(1 3)(2 4)	(1 4)(2 3)	(1)(2 4)(3)	(1 2 3 4)	(1 3)(2)(4)	(1 4 3 2)

Figure 6. Isomer equivalence for ABCp under $\mathbf{S}^{[4]} \times \{I,\sigma\}$ (Part 2).

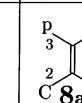
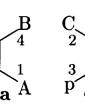
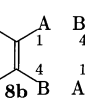
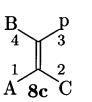
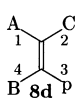
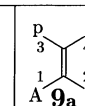
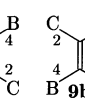
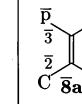
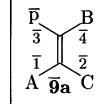
	$(1\ 3)(2)(4)\mathbf{S}_9^{[4]}$ (stabilizer: $\mathbf{S}_9^{[4]\prime\prime}$)							
								
	8a	**8b**	**8c**	**8d**	**9a**	**9b**	**9c**	**9d**
	(1 3)(2)(4)	(1 2 3 4)	(1 4 3 2)	(1)(2 3)(4)	(1 3 2)(4)	(1 2 4)(3)	(1 4 3)(2)	(1)(2 3 4)
	I	$C_{2(1)} \sim$	$C_{2(2)} \sim$	$C_{2(3)} \sim$				
$\mathbf{D}_{2h}$	(1)(2)(3)(4)	(1 4)(2 3)	(1 2)(3 4)	(1 3)(2 4)	(1 2)(3)(4)	(1 3 2 4)	(1)(2)(3 4)	(1 4 2 3)
								
	$\bar{\mathbf{8}}\mathbf{a}$	$\bar{\mathbf{8}}\mathbf{b}$	$\bar{\mathbf{8}}\mathbf{c}$	$\bar{\mathbf{8}}\mathbf{d}$	$\bar{\mathbf{9}}\mathbf{a}$	$\bar{\mathbf{9}}\mathbf{b}$	$\bar{\mathbf{9}}\mathbf{c}$	$\bar{\mathbf{9}}\mathbf{d}$
	(1 3))(2)(4)	(1 2 3 4)	(1 4 3 2)	(1)(2 4)(3)	(1 3 2)(4)	(1 2 4)(3)	(1 4 3)(2)	(1)(2 3 4)
	$\sigma_{d(1)} \sim$	$S_{4(3)} \sim$	$S_{4(3)}^3 \sim$	$\sigma_{d(6)} \sim$				
	(1)(2)(3)(4)	(1 4)(2 3)	(1 2)(3 4)	(1 3)(2 4)	(1 2)(3)(4)	(1 3 2 4)	(1)(2)(3 4)	(1 4 2 3)

Figure 7. Isomer equivalence for ABCp under $\mathbf{S}^{[4]} \times \{I,\sigma\}$ (Part 3).

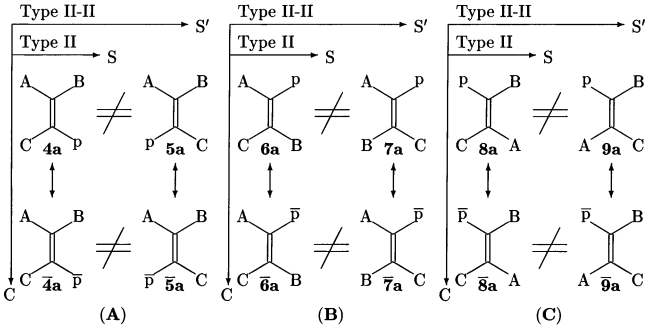


Figure 8. Extended stereoisogram set (II−II/II−II/II−II) for isoskeletal isomerism of ABCp under $\mathbf{S}^{[4]} \times \{I,\sigma\}$.

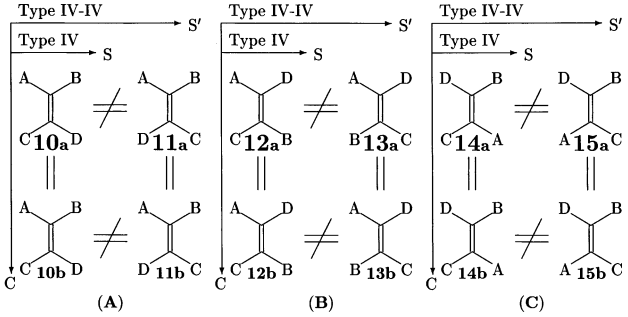


Figure 9. Extended stereoisogram set (IV−IV/IV−IV/IV−IV) for isoskeletal isomerism of ABCD under $\mathbf{S}^{[4]} \times \{I,\sigma\}$.

4. EXTENDED STEREOISOGRAM SETS OF VARIOUS TYPES

According to the example scheme for deriving an extended stereoisogram set (Figure 8), we are able to construct extended stereoisogram sets for ethylene derivatives. The exhaustive enumeration of ethylene derivatives has been reported by using the point group $\mathbf{D}_{2h}$ and the permutation group $\mathbf{S}_9^{[4]}$ separately, where the *RS*-stereoisomeric group $\mathbf{S}_7^{[4]} \times \{I,\sigma\}$ and the stereoisomeric group $\mathbf{S}_9^{[4]} \times \{I,\sigma\}$ are not taken into consideration.[11] By taking into account the numbering of the top molecule in each part listed in Figures 4, 6, and 7, four ligands are placed in accord with a respective function: $f(1)$, $f(2)$, $f(3)$, and $f(4)$. Thereby, representative molecules are easily obtained without the full consideration of permutations, so as to construct such an extended stereoisogram set.

4.1. Extended Stereoisogram Sets of IV−IV/IV−IV/IV−IV. Figure 9 shows a set of three extended stereoisograms for the isoskeletal isomerism of ligands ABCD under the isoskeletal group $\mathbf{S}^{[4]} \times \{I,\sigma\}$. According to the numbering listed in Figures 4, 6, and 7, the four ligands are placed in the respective positions in accord with the function: $f(1) = \mathrm{A}$, $f(2) = \mathrm{C}$, $f(3) = \mathrm{D}$, $f(4) = \mathrm{B}$. Thereby we obtain representative molecules collected in Figure 9.

The extended stereoisogram (**A**) of Figure 9 contains two degenerate stereoisograms of Type IV (achiral/*RS*-astereogenic). The extended stereoisogram is represented by the symbol IV−IV because of the existence of cis/trans- or *E*/*Z*-isomerism. The action of $\mathbf{S}^{[4]} \times \{I,\sigma\}$ generates extended stereoisograms **B** and **C** of Type IV−IV in addition to **A**, where they are different (isoskeletally isomeric) from each other. This type of extended stereoisogram set is designated by the symbol IV−IV/IV−IV/IV−IV.

Extended stereoisogram sets (IV−IV/IV−IV/IV−IV) similar to Figure 9 are found for ligand patterns such as ABCD and $\mathrm{p\bar{p}q\bar{q}}$. Each extended stereoisogram designated by the symbol IV−IV is concerned with cases in which achiral ethylene derivatives exhibit cis/trans- or *E*/*Z*-isomerism.

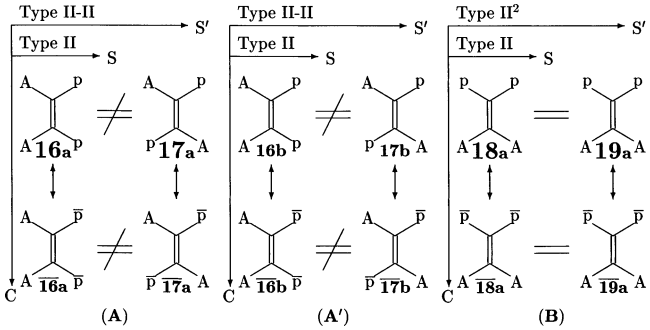


Figure 10. Extended stereoisogram set $((\mathrm{II}-\mathrm{II})^2/\mathrm{II}^2)$ for isoskeletal isomerism of $\mathrm{A^2p^2}$ under $\mathbf{S}^{[4]} \times \{I,\sigma\}$.

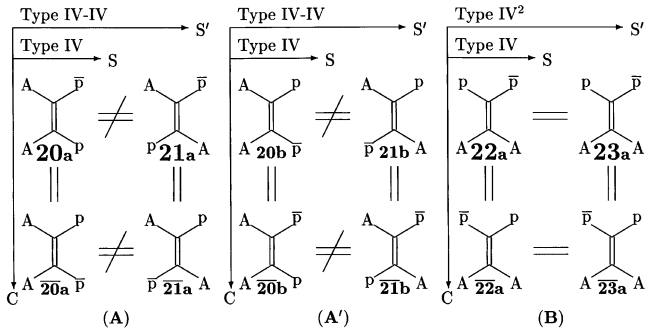


Figure 11. Extended stereoisogram set $((\mathrm{IV}-\mathrm{IV})^2/\mathrm{IV}^2)$ for isoskeletal isomerism of $\mathrm{A^2p\bar{p}}$ under $\mathbf{S}^{[4]} \times \{I,\sigma\}$.

4.2. Extended Setereoisogram Sets of $(\mathrm{II}-\mathrm{II})^2/\mathrm{II}^2$. Figure 10 shows an extended stereoisogram set for isoskeletal isomerism of $\mathrm{A^2p^2}$ under $\mathbf{S}^{[4]} \times \{I,\sigma\}$. According to the numbering listed in Figures 4, 6, and 7, the function, $f(1) = \mathrm{A}$, $f(2) = \mathrm{A}$, $f(3) = \mathrm{p}$, $f(4) = \mathrm{p}$, is used to place ligands in the respective positions. Thereby, representative molecules are obtained, as collected in Figure 10.

The extended stereoisogram **A** of Figure 10 belongs to Type II−II. The action of $\mathbf{S}^{[4]} \times \{I,\sigma\}$ generates an extended stereoisogram **A′** of Type II−II, which is identical with **A** as well as an extended stereoisogram **B** of Type II^2. This type of extended stereoisogram set is designated by the symbol $(\mathrm{II}-\mathrm{II})^2/\mathrm{II}^2$. This symbol with a slashed separation indicates that **A** (or **A′**) represented by the symbol (II−II) is isoskeletally isomeric with **B** represented by the symbol II^2. All of the participant molecules are chiral, as indicated by vertical double-headed arrows. The superscript 2 of $(\mathrm{II}-\mathrm{II})^2$ represents that the two extended stereoisograms are identical with each other. Note that the symbol II−II indicates the existence of cis/trans- or *E*/*Z*-isomerism for **A** (or **A′**). The superscript 2 of II^2 represents that the two stereoisograms in the extended stereoisogram **B** are identical with each other. This means the nonexistence of cis/trans- or *E*/*Z*-isomerism for **B**.

Stereoisogram sets $((\mathrm{II}-\mathrm{II})^2/\mathrm{II}^2)$ similar to Figure 10 are found for ligand patterns such as $\mathrm{A^2p^2}$, $\mathrm{A^2Bp}$, $\mathrm{A^2pq}$, $\mathrm{ABp^2}$, $\mathrm{p^2q^2}$, $\mathrm{Ap^2\bar{p}}$, $\mathrm{Ap^2q}$, $\mathrm{p^2\bar{p}q}$, $\mathrm{p^2q\bar{q}}$, and $\mathrm{p^2qr}$.

4.3. Extended Setereoisogram Sets of $(\mathrm{IV}-\mathrm{IV})^2/\mathrm{IV}^2$. Figure 11 shows an extended stereoisogram set for isoskeletal isomerism of $\mathrm{A^2p\bar{p}}$ under $\mathbf{S}^{[4]} \times \{I,\sigma\}$. According to the numbering listed in Figures 4, 6, and 7, the four ligands are placed in accord with the function: $f(1) = \mathrm{A}$, $f(2) = \mathrm{A}$, f

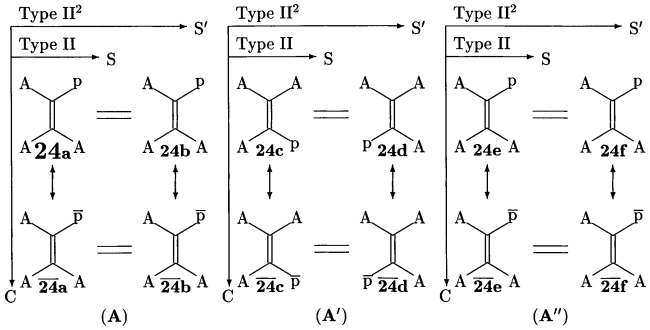


Figure 12. Extended stereoisogram set $((II^2)^3)$ for isoskeletal isomerism of A^3p under $\mathbf{S}^{[4]} \times \{I,\sigma\}$.

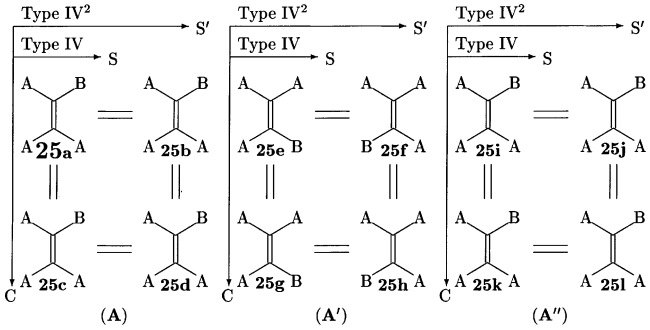


Figure 13. Extended stereoisogram set $((IV^2)^3)$ for isoskeletal isomerism of A^3B under $\mathbf{S}^{[4]} \times \{I,\sigma\}$.

$(3) = p$, $f(4) = \bar{p}$. Thereby, the molecules collected in Figure 11 are obtained as representatives.

The extended stereoisogram **A** of Figure 11 belongs to Type IV−IV. The action of $\mathbf{S}^{[4]} \times \{I,\sigma\}$ generates the equivalent extended stereoisogram **A′** of Type IV−IV as well as another extended stereoisogram of **B** of Type IV^2. This type of extended stereoisogram set is designated by the symbol $(IV-IV)^2/IV^2$.

This slashed symbol indicates that **A** (or **A′**) represented by the symbol IV−IV is isoskeletally isomeric with **B** represented by the symbol IV^2. All of the participant molecules are achiral, as indicated by vertical equality symbols. The symbol IV−IV indicates the existence of cis/trans- or *E*/*Z*-isomerism for **A** (or **A′**). The superscript 2 of the symbol $(IV-IV)^2$ represents that the two extended stereoisograms (**A** and **A′**) are identical with each other. The superscript 2 of the symbol IV^2 represents that the two stereoisograms are identical with each other in the extended stereoisogram **B**. As a result, there emerges no cis/trans-isomerism (nor *E*/*Z*-isomerism) for **B**.

Extended stereoisogram sets $((IV-IV)^2/IV^2)$ similar to Figure 11 are found for ligand patterns such as A^2B^2, $p^2\bar{p}^2$, A^2BC, and $A^2p\bar{p}$.

4.4. Extended Setereoisogram Sets of $(II^2)^3$. Figure 12 shows an extended stereoisogram set for the isoskeletal isomerism of ligands A^3p under $\mathbf{S}^{[4]} \times \{I,\sigma\}$. The function represented by $f(1) = A$, $f(2) = A$, $f(3) = A$, $f(4) = p$ is applied according to the numbering listed in Figures 4, 6, and 7 so as to give representative molecules collected in Figure 12.

The extended stereoisograms (**A**, **A′**, and **A″**) contained in Figure 12 are identical with each other under the action of $\mathbf{S}^{[4]} \times \{I,\sigma\}$ and belong to Type II^2. This type of stereoisogram set is designated by the symbol $(II^2)^3$. All of the participant molecules are chiral, as indicated by vertical double-headed arrows. The superscript 2 of the symbol II^2 represents that the two stereoisograms are identical with each other in the extended stereoisogram **A** (or **A′** or **A″**). As a result, there emerges no cis/trans-isomerism (nor *E*/*Z*-isomerism) for **A**.

Stereoisogram sets $((II^2)^3)$ similar to Figure 12 are found for ligand patterns such as p,[4] A^3p, Ap^3, $p^3\bar{p}$, and p^3q.

4.5. Extended Setereoisogram Sets of $(IV^2)^3$. Figure 13 shows an extended stereoisogram set for the isoskeletal isomerism of ligands A^3B under $\mathbf{S}^{[4]} \times \{I,\sigma\}$. The ligands A^3B are placed according to the function, $f(1) = A$, $f(2) = A$, $f(3) = A$, and $f(4) = B$, by taking into account the numbering listed in Figures 4, 6, and 7. Thereby, the molecules collected in Figure 13 are obtained as representatives.

The extended stereoisogram **A** of Figure 13 belongs to Type IV^2. The action of $\mathbf{S}^{[4]} \times \{I,\sigma\}$ generates identical extended stereoisograms **A′** and **A″** of Type IV^2. This type of extended stereoisogram set is designated by the symbol $(IV^2)^3$. All of the participant molecules are achiral, as indicated by vertical equality symbols. The superscript 2 of the symbol IV^2 represents that the two stereoisograms are identical with each other in the extended stereoisogram **A** (or **A′** or **A″**). This means the nonexistence of cis/trans-isomerism (nor *E*/*Z*-isomerism) for **A**. The ligand patterns A^3B and A^4 are obtained as examples.

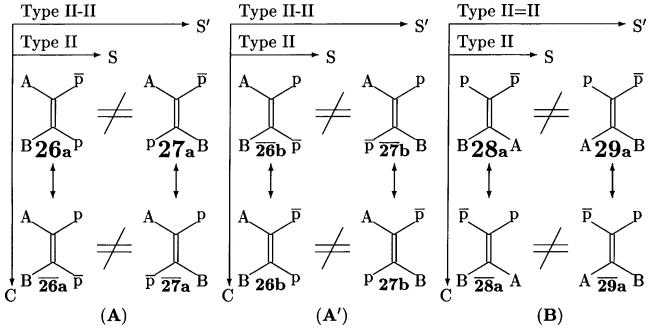


Figure 14. Extended stereoisogram set $((II-II)^2/II{=}II)$ for isoskeletal isomerism of $ABp\bar{p}$ under $\mathbf{S}^{[4]} \times \{I,\sigma\}$.

4.6. Extended Setereoisogram Sets of $(II-II)^2/II{=}II$. Figure 14 shows a special extended stereoisogram set for the isoskeletal isomerism of ligands $ABp\bar{p}$ under $\mathbf{S}^{[4]} \times \{I,\sigma\}$. According to the numbering listed in Figures 4, 6, and 7, the ligands $ABp\bar{p}$ are placed in accord with the function: $f(1) = A$, $f(2) = B$, $f(3) = p$, $f(4) = \bar{p}$. Thereby, the molecules collected in Figure 14 are obtained to construct an extended stereoisogram **A**, which belongs to Type II−II. The action of $\mathbf{S}^{[4]} \times \{I,\sigma\}$ generates stereoisograms **A′** of Type II−II, which is essentially identical with **A**. In addition, there emerges a special extended stereoisogram **B**, in which the original *Z*-isomer (**28a**) is identical with the enantiomer ($\overline{\mathbf{29a}}$) of the *E*-isomer (**29a**). Hence, this extended stereoisogram is designated by the symbol II=II. Totally, this type of extended stereoisogram set is designated by the symbol $(II-II)^2/II{=}II$, where the ligand pattern $ABp\bar{p}$ is a sole example.

Table 1. Extended Stereoisogram Sets for Ethylene Derivatives

type of an extended stereoisogram set		*E*/*Z*-isomerism yes (Y) or no (N)	ligand pattern
II−II/II−II/II−II	(Figure 8)	Y/Y/Y	ABCp, ABpq, Ap$\bar{p}$q, Apqr, $\bar{p}$pqr, pqrs
$(II-II)^2/II^2$	(Figure 10)	Y/N	A^2p^2, A^2Bp, A^2pq, ABp^2, p^2q^2, $Ap^2\bar{p}$, Ap^2q, $p^2\bar{p}q$, $p^2q\bar{q}$, p^2qr
$(II-II)^2/II{=}II$	(Figure 14)	Y/Y	AB$p\bar{p}$
$(II^2)^3$	(Figure 12)	N	p^4, A^3p, Ap^3, $p^3\bar{p}$, p^3q
IV−IV/IV−IV/IV−IV	(Figure 9)	Y/Y/Y	ABCD, p$\bar{p}$q$\bar{q}$
$(IV-IV)^2/IV^2$	(Figure 11)	Y/N	A^2B^2, $p^2\bar{p}^2$, A^2BC, $A^2p\bar{p}$
$(IV^2)^3$	(Figure 13)	N	A^3B, A^4

5. PROBLEMATIC TERMINOLOGY IN STEREOCHEMISTRY

5.1. Holantimeric and Enatiomeric Relationships. The hierarchy of groups for ethylene isomers is found to be as follows: isoskeletal groups ($\mathbf{S}^{[4]} \times \{I,\sigma\}$) $\supset$ stereoisomeric groups ($\mathbf{S}_9^{[4]} \times \{I,\sigma\}$) $\supset$ *RS*-stereoisomeric groups ($\mathbf{S}_7^{[4]} \times \{I,\sigma\}$) = point groups ($\mathbf{D}_{2h}$). It should be emphasized that *RS*-stereoisomeric groups ($\mathbf{S}_7^{[4]} \times \{I,\sigma\}$) are equal to point groups ($\mathbf{D}_{2h}$) for ethylenes. This means that *RS*-stereoisomers coincide with enantiomers for ethylenes. More precisely speaking, *holantimeric relationships for ethylenes coincide with the enantiomeric relationships*. *RS*-Diastereomeric relationships for ethylenes, on the other hand, are degenerate into identity so as to bring the *RS*-astereogenicity of ethylenes due to the stereoisograms of Type II or IV.

5.2. *E*/*Z*-Nomenclature Revisited. Each extended stereoisogram in an extended stereoisogram set reveals whether the corresponding ethylene derivative can be characterized by the *E*/*Z*-nomenclature. For example, the extended stereoisogram set of Type IV−IV/IV−IV/IV−IV shown in Figure 9 contains three extended stereoisograms of Type IV−IV, which can be characterized by the *E*/*Z*-nomenclature. Hence, it is designated by the symbol Y/Y/Y, where the letter Y stands for "yes". On the other hand, the extended stereoisogram set of Type $(II-II)^2/II^2$ shown in Figure 10 contains two extended stereoisograms of Type II−II and II^2, where the former can be characterized by the *E*/*Z*-nomenclature, but the latter cannot be characterized. Hence, it is designated by the symbol Y/N, where the letter N stands for "no". The results for the other extended stereoisogram sets examined above are collected in Table 1.

One may say that the results shown in Figures 3−14 are the ones that a chemist may derive manually with ease and without any group theory. However, the chemist has never attempted such manual derivation, probably because of the lack of such guiding principles as discussed in the present approach. Even if he has attempted, the validity of the chemist's results has never been proved *in a general and rigorous fashion*, even though his professional experience is capable of rationalizing specified results one by one. In other words, the ultimate validity of the chemist's results cannot be confirmed without such general and rigorous formulations as Figures 1−14. Moreover, the categorization summarized in Table 1 shows the generality of the present approach, which would not be obtained by the chemist's one-by-one approach.

5.3. Dichotomy Between Enantiomers and Diastereomers. In the traditional stereochemistry, diastereomers have been defined as stereoisomers that are not enantiomers.[12] This dichotomy has been widely accepted by organic chemists, as found in the definition of "stereoisomers" due to Eliel-Wilen's textbook (page 1208):[13] "Isomers of identical constitution but differing in the arrangement of their atoms in space. Subclass are Enantiomers and Diastereomers." By the inspection of the extended stereoisogram set $((II-II)^2/II{=}II)$ shown in Figure 14, we are able to find a troublesome example to the dichotomy between enantiomers and diastereomers.

The relationship between **28a** and **29a** is a cis/trans- or *E*/*Z*-isomeric one (i.e., traditionally a diastereomeric relationship), since the molecules are interconvertible by cis/trans-isomerization. At the same time, the relationship between **28a** and **29a** is an enantiomeric one, because the latter (**29a**) is identical with $\overline{\mathbf{28a}}$ which is the enantiomer of the former (**28a**). The two isomers **28a** and **29a** are *E*/*Z*-isomers (diastereomers) *and* enantiomers of each other.

If one intends to maintain the traditional dichotomy, one may say that a torsion about a double bond (a permutation between A and B or between p and $\bar{p}$) converts **28a** into its enantiomer **29a**. In this statement, however, he/she overlooks the fact that such a torsion about a double bond causes an *E*/*Z*-isomeric relationship (a diastereomeric relationship due to the traditional stereochemistry). In other words, he/she implicitly gives an enantiomeric relationship priority over a diastereomeric relationship (the cis/trans- or *E*/*Z*-isomeric one). Thereby, the relationship between **28a** and **29a** is forced to be regarded as an enantiomeric one.

To avoid confusion caused by the present extension, the term "*m*-diastereomeric" has been coined as discussed above. Hence, we can say that a *m*-diastereomeric relationship (i.e., traditionally a cis/trans- or *E*/*Z*-isomeric relationship or a diastereomeric relationship) may sometimes coincide with an enantiomeric realtionship.

5.4. Enantiomers vs Isoskeletal Isomers. Let us consider the relationship between **26a** in of Figure 14 and $\overline{\mathbf{26b}}$ in **A′** of Figure 14. The relationship is concluded to be an isoskeletal isomeric relationship. At the same time, $\overline{\mathbf{26b}}$ in **A′** of Figure 14 identical with $\overline{\mathbf{26a}}$ in **A** of Figure 14, which is in turn enantiomeric to **26a** in **A** of Figure 14. This means that the isoskeletal relationship may sometimes coincide with the enantiomeric relationship.

One may say that everyone knows that simple tetrahedral enantiomers are interconverted by detaching two substituents and reattaching each one to the other place. In this statement, he/she overlooks the fact that the operation "detaching two substituents and reattaching each one to the other place" is different from a reflection operation generating enantiomers. In other words, he/she implicitly gives the latter reflection operation priority over the former detach−reattach (permutation) operation.

According to the traditional dichotomy between enantiomers and diastereomers, permutation operations have been treated partially as compared with reflection operations. It

should be added here that a tetrahedral molecule with a ligand pattern ABp$\bar{p}$ generates its diastereomer by a ligand permutation between A and B (or p and $\bar{p}$, etc.), as discussed in a previous paper.[6] On the other hand, the torsion about a double bond (the ligand permutation between A and B or between p and $\bar{p}$) converts **28a** into its enantiomer **29a**, as described above.

The same permutations causing such different behaviors (diastereomers vs enantiomers) are consistently discussed in this paper by a common logical framework based on group theory. By taking into account the importance of permutations, the present approach provides us with a new method that can characterize *RS*-diastereomeric relationships and *m*-diastereomeric relationships. Thus, the method overcomes the oversimplified dichotomy between enantiomers and diastereomers in which the term "diastereomeric" means "being nonenantiomeric" only.

6. CONCLUSION

Chirality, *RS*-stereogenicity, stereogenicity, and isoskeletal isomerism for ethylene derivatives have been comprehensively discussed by considering point groups, *RS*-stereoisomeric groups, stereoisomeric groups, and isoskeletal groups. In the case of ethylene derivatives, *RS*-stereoisomeric groups have been clarified not to coincide with stereoisomeric groups so that *m*-diastereomers (cis/trans-isomers) are not identical with *RS*-diastereomers. To discuss the relationship among *RS*-diastereomers, *m*-diastereomers, and isoskeletal isomers, we have proposed the concepts of *extended stereoisogram* and *extended stereoisogram set*. The cis/trans-isomerism of ethylenes has been concluded to be treated in terms of *m*-diastereomers characterized by the *E*/*Z*-nomenclature but not to be treated in terms of *RS*-diastereomers characterized by the *RS*-nomenclaure.

REFERENCES AND NOTES

(1) Prelog, V.; Helmchen, G. Basic principles of the CIP-system and proposal for a revision. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 567−583.
(2) Blackwood, J. E.; Gladys, C. L.; Loening, K. L.; Petrarca, A. E.; Rush, J. E. Unambiguous specification of stereoisomerism about a double bond. *J. Am. Chem. Soc.* **1968**, *90*, 509−510.
(3) Blackwood, J. E.; Gladys, C. L.; Petrarca, A. E.; Powell, W. H.; Rush, J. E. Unique and unambiguous specification of stereoisomerism about a double bond. *J. Chem. Doc.* **1968**, *8*, 30−32.
(4) Brown, M. F.; Cook, B. R.; Sloan, T. E. Stereochemical notation in coordination chemistry. Mononuclear complexes. *Inorg. Chem.* **1975**, *14*, 4, 1273−1278.
(5) IUPAC *Nomenclature of Inorganic Chemistry, Recommendations 1990*; Blackwell Scientific: Oxford, 1990.
(6) Fujita, S. Stereogenicity revisited. Proposal of holantimers for comprehending the relationship between stereogenicity and chirality. *J. Org. Chem.* **2004**, *69*, 3158−3165.
(7) Davis, C. H.; Ruch, J. E. *Information Retrieval and Documentation in Chemistry*; Greenwood Press: Westport, 1974.
(8) Gasteiger, J., Ed. *Handbook of Chemoinformatics*; WILEY−VCH: Weinheim, 2003; Vol. 1.
(9) Fujita, S. Integrated discussion on stereogenicity and chirality for restructuring stereochemisty. *J. Math. Chem.* **2004**, *35*, 261−283.
(10) Fujita, S. *Symmetry and Combinatorial Enumeration in Chemistry*; Springer-Verlag: Berlin-Heidelberg, 1991.
(11) Fujita, S. Enantiomeric and diastereomeric relationships of ethylene derivatives. Restructuring stereochemistry by a group-theoretical and combinatorial approach. *J. Math. Chem.* **2002**, *32*, 1−17.
(12) IUPAC Recommendations 1996. Basic Terminology of Stereochemistry. *Pure Appl. Chem.* **1996**, *68*, 2193−2222.
(13) Eliel, E.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.

CI040103R