Bull. Chem. Soc. Jpn., 75, 1863–1883 (2002)

Accounts

Sphericity beyond Topicity in Characterizing Stereochemical Phenomena. Novel Concepts Based on Coset Representations and Their Subductions

Shinsaku Fujita

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

(Received November 28, 2001)

Fundamental concepts proposed for comprehending stereochemical phenomena are described in order to bring out a more systematized format to conventional concepts and terminologies. The concept of coset representation (CR), the symbol of which is $\mathbf{G}(/\mathbf{G}_i)$, is intuitively introduced by considering the global symmetry $\mathbf{G}$ and the local symmetry $\mathbf{G}_i$ for an orbit of stereochemically equivalent objects (e.g. atoms in a molecule). The SCR (set-of-coset-representations) notation for classifying molecular symmetries is proposed to remedy the usual insufficient classification based on point groups. According to the chirality/achirality of $\mathbf{G}$ and $\mathbf{G}_i$, the sphericity concept (homospheric, enantiospheric, and hemispheric) and the relevant concept of chirality fittingness are proposed to specify the stereochemical phenomena of the $\mathbf{G}(/\mathbf{G}_i)$-orbit. The sphericity terms are shown to be superior to the well-known topicity terms (homotopic, enantiotopic, and heterotopic; chirotopic and achirotopic) especially in comprehending complicated stereochemical phenomena. In fact, the topicity terms as well as the terms "stereogenicity and prostereogenicity" and "prochirality" can be derived subsidiarily from the sphericity terms. The concept of subduction of CRs, for which the symbol $\mathbf{G}(/\mathbf{G}_i) \downarrow \mathbf{G}_i$ has been coined, is proposed to characterize the desymmetrization of molecules. Thereby, the design of high-symmetry molecules is discussed in term of desymmetrization by atom replacement and by bond replacement. In order to characterize the stereochemistry of non-rigid molecules with rotatable ligands, the concept of proligand/promolecule is proposed; here biphenyl derivatives, methane derivatives, ethane derivatives, and ferrocene derivatives are examined in terms of matched and mismatched molecules. Applications to combinatorial enumeration, symmetry adapted functions, flexible six-membered cyclic compounds, and symmetry numbers are also described.

Stereochemical phenomena have rationally been treated on the basis of polyhedral skeletons such as a tetrahedral model proposed by van't Hoff[1] for organic chemistry and an octahedral model proposed by Werner[2] for inorganic chemistry. Thereby, an enormous accumulation of experimental results has been categorized into several specified fields, which have been disccussed thoroughly but distinctly. As a result, each one of the fields has developed a distinct methodology, as summarized in reviews and textbooks on organic[3,4] and inorganic stereochemistry.[5] Although such distinct methodologies have been of course related to each other, they have little been discussed from an integrated standpoint based on logical or mathematical foundations. Such an integrated standpoint should cover the following items of various features:

1. The integrated standpoint should treat *stereochemistry in a molecule* successfully. In other words, it should be capable of giving a common foundation to (1) conventional terms such as "asymmetric carbon center" and "pseudoasymmetric carbon center",[6,7] (2) the sequence rule proposed by Cahn, Ingold, and Prelog (the CIP system)[8] and its application to the "prochirality" by Hanson,[9–11] (3) the terms "prochiral, pseudoasymmetric, and propseudoasymmetric centers" defined by Prelog et al.,[12–14] (4) the terms "elements of chirality" and "elements of prochirality",[15–17] (5) the topicity terms ("enantiotopic" and "diastereotopic") introduced by Mislow and Raban[18] and relevant terms "equitopic" (by Nakazaki[19,20]), "homotopic" (by Hirschmann and Hanson[10]), and "heterotopic" (by Eliel[21]), (6) the term "chirotopic" proposed by Mislow and Siegel,[22] (7) the term "local (site) symmetries" discussed by Flurry,[23] (8) the term "framework group" proposed by Pople,[24] (9) the terms "stereogenic" and "prostereogenic" proposed earlier by McCasland[25] and revised by several groups,[26–30] (10) the term "symmetry number",[31] and (11) the terms "anisochronous"[32,33] and "anisogamous".[34]

2. The integrated standpoint should explain *stereoisomerism among molecules*. A repertoire of this item involves the following conventional subjects: (1) the point-group symmetries of molecules,[35–39] (2) the terms "enantiomeric" and "dias-

tereomeric",[7] (3) the conformation of cyclic compounds,[40,41] (4) the symmetries of molecules with rotatable ligands such as ethanes[42,43] and ferrocene,[44] (5) the term "highest attainable symmetry",[45,46,18] (6) the terms "residual diastereoisomerism"[47] and "residual isomer",[48] (7) chirality functions,[49–51] (8) permutation isomerism,[52–54] (9) dynamic stereochemistry,[55,56] and (10) the configuration symmetry group.[57]

3. The integrated standpoint should support *combinatorial enumeration of isomers and stereoisomers*. This item is concerned with (1) Pólya's theorem,[58–62] Redfield's method,[63–65] and related tools for chemical combinatorics,[66–68] (2) isomer enumerations (not concerned with stereoisomers),[69–71] (3) graph enumerations,[72–74] (4) enumeration by double cosets,[75,76] (5) enumeration of rigid isomers,[77–79] (6) enumeration of nonrigid isomers,[80,81] and (7) enumeration of stereoisomers considering formulas and symmetries.[82–87]

4. The integrated standpoint should be applicable to both organic and inorganic stereochemistry. It should be so extensible as to be applied to models other than teterahedral and octahedral ones.

None of the conventional approaches have succeeded in covering all of the items listed above. Thus, although the methods cited above as the conventional approaches have been suitable to discuss the distinct subjects at which they aimed originally, they have possessed restricted capablilities of explaining other subjects. For example, the stereochemistry (Item 1) has been frequently discussed apart from stereoisomerism (Item 2), as exemplified by the section title "stereochemistry without stereoisomerism" (by Mislow and Siegel[22]). Moreover, the concepts and terminologies described above for the stereochemistry (Item 1) have not supported the combinatorial enumeration of stereoisomers (Item 3). The methods reported for Item 3 are ineffective for Items 1 and 2.

We have proposed the sphericity of an orbit as an integrated standpoint to cover Items 1 to 4, where the orbit composed of equivalent objects is considered to be governed by a coset representation (CR), as published in our monograph.[88] In this paper, the superiority of the sphericity concept to other concepts is clarified by using illustrative examples after intuitive definitions and introductory remarks. This paper is also devoted to show further aspects developed recently.

1 Orbits and Coset Representations

A set of equivalent objects (atoms, bonds, faces, ligands, edges, etc.) in a molecule is called an orbit (or an equivalence class).[89,88] Let us consider the hydrogen atoms of adamantane-2,6-dione of $\mathbf{D}_{2d}$-symmetry (Fig. 1). As found easily, the hydgrogen atoms are classified into a set of eight bridge hydrogens and another set of four bridgehead ones, which respectively construct two orbits, Δ_1 (Eq. 1) and Δ_2 (Eq. 2).

$$\Delta_1 = \{\mathrm{H}^{(a)}, \mathrm{H}^{(b)}, \mathrm{H}^{(c)}, \mathrm{H}^{(d)}; \mathrm{H}^{(a')}, \mathrm{H}^{(b')}, \mathrm{H}^{(c')}, \mathrm{H}^{(d')}\} \quad (1)$$

$$\Delta_2 = \{\mathrm{H}^{(A)}, \mathrm{H}^{(B)}, \mathrm{H}^{(C)}, \mathrm{H}^{(D)}\} \quad (2)$$

The orbit Δ_1 is assigned to a coset representation (CR) denoted by a symbol $\mathbf{D}_{2d}(/\mathbf{C}_1)$, since the global symmetry of adamantane-2,6-dione is found to be $\mathbf{D}_{2d}$ and the local symmetry of each hydrogen of the orbit Δ_1 is decided to be $\mathbf{C}_1$ (= $\{I\}$).

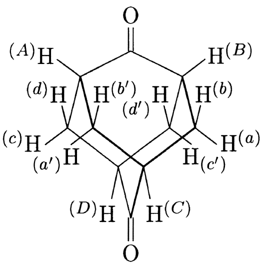


Fig. 1. Orbits in adamantane-2,6-dione.

The local symmetry $\mathbf{C}_1$ is the point group that fixes a hydrogen of Δ_1. Thus, any operation other than an identity operation (I) converts the hydrogen into one of the remaining hydrogens of Δ_1. On the other hand, the orbit Δ_2 is assigned to a CR $\mathbf{D}_{2d}(/\mathbf{C}_s)$, since the local symmetry of each hydrogen of the orbit Δ_2 is decided to be $\mathbf{C}_s$ (= $\{I,\sigma_v\}$), where an appropriate one of conjugate subgroups is selected as a representative. For example, if a mirror plane (σ_v) is selected to involve $\mathrm{H}^{(A)}$ and $\mathrm{H}^{(B)}$, a reflection with the mirror keeps the hydrogen $\mathrm{H}^{(A)}$ (or $\mathrm{H}^{(B)}$) immobile. Hence, the local symmetry for the Δ_2 is determined to be $\mathbf{C}_s$.

Although such CRs as $\mathbf{D}_{2d}(/\mathbf{C}_1)$ and $\mathbf{D}_{2d}(/\mathbf{C}_s)$ are here obtained by the intuitive method described above, they are a kind of permutation representations that are rigorously defined algebraically by means of mark tables,[89,88] which have been introduced by Burnside.[90] The algebraic method will not be discussed in this paper, because the intuitive method of this section is sufficient for understanding most of the subjects of this paper. For brief comments on mathematical foundations and illustrative examples, see Appendices A1 and A2.

In general, an orbit is governed by a CR $\mathbf{G}(/\mathbf{G}_i)$, where $\mathbf{G}$ is the global symmetry of the molecule and $\mathbf{G}_i$ ($\subset \mathbf{G}$) is the local symmetry of each atom of the orbit. The symbols such as $\mathbf{G}(/\mathbf{G}_i)$ have been coined by us to show that the permutation nature of the orbit is governed by the coset decomposition of the global symmetry $\mathbf{G}$ by the local symmetry $\mathbf{G}_i$.[91] The number of members accommodated by each orbit is equal to $|\mathbf{G}|/|\mathbf{G}_i|$, where the symbols $|\mathbf{G}|$ and $|\mathbf{G}_i|$ designate the orders of the subgroups.

2 SCR Notation

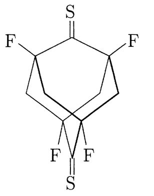
The discussion described in the preceding section reveals that a set of orbits (and the corresponding set of CRs) characterizes the symmetry of the molecule at issue. In the light of this result, we have proposed the SCR (set-of-coset-representations) notation of molecular symmetry.[92,93] The SCR notation takes explicit account of orbits, where the members of each orbit are designated. Thus, the symmetry of adamantane-2,6-dione (**1**) is designated by the following SCR notation:

$$\mathbf{D}_{2d}[/\mathbf{C}_1(\mathrm{H}_8); /\mathbf{C}_2{}'(\mathrm{C}_4); 2/\mathbf{C}_s(\mathrm{H}_4, \mathrm{C}_4); 2/\mathbf{C}_{2v}(\mathrm{C}_2, \mathrm{O}_2)],$$

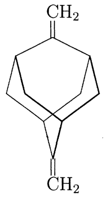
where each semicolon is used to differentiate the orbits of the mother skeleton. For example, the symbol $2/\mathbf{C}_s(\mathrm{H}_4, \mathrm{C}_4)$ with a semicolon in the SCR notation expresses that each of the two four-membered orbits governed by $\mathbf{D}_{2d}(/\mathbf{C}_s)$ contains equivalent H_4 or C_4. The character (e.g. 2) before the slash may be omitted without any confusion, since it is obtained by counting elements in parentheses. The number of members in each orbit is equal to $|\mathbf{D}_{2d}|/|\mathbf{C}_s| = 8/2 = 4$, where the symbols $|\mathbf{D}_{2d}|$ and $|\mathbf{C}_s|$ designate the orders of the subgroups.

The usual point-group approach mentioned in most textbooks on stereochemistry[94] and on chemical group theory[35–39,95–97] has a disadvantage that it is incapable of discriminating molecules of the same point group. This essential disadvantage is exemplified by a variety of $\mathbf{D}_{2d}$-molecules depicted in Fig. 2, where their symmetries are decided to be the same within the usual point-group approach. The disadvantage can be remedied by the SCR notation by considering orbits and the corresponding CRs.

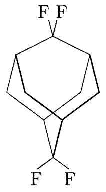
The top row of Fig. 2 illustrates a variety of adamantane derivatives belonging to the same $\mathbf{D}_{2d}$-symmetry. They are discriminated from each other and from **1** by virtue of the SCR notations accompanying the formulas. Hetera-adamantane derivatives depicted in the middle row of Fig. 2 are assigned to distinct SCR notations, although they belong to the same $\mathbf{D}_{2d}$-symmetry within the point-group approach. The bottom row of Fig. 2 illustrates other $\mathbf{D}_{2d}$-molecules, which are discriminated from each other by virtue of the SCR notations. While allene (**8**) and a biphenyl (**9**) can be regarded as rigid compounds, pentaerythritol (**10**) is a flexible molecule with rotatable ligands. The symmetry of **10** is decided to be $\mathbf{D}_{2d}$ in the highest attainable symmetry.



2



3

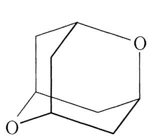


4

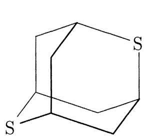
2: $\mathbf{D}_{2d}[/\mathbf{C}_1(\mathrm{H}_8); /\mathbf{C}'_2(\mathrm{C}_4); 2/\mathbf{C}_s(\mathrm{F}_4, \mathrm{C}_4); 2/\mathbf{C}_{2v}(\mathrm{C}_2, \mathrm{S}_2)]$

3: $\mathbf{D}_{2d}[/\mathbf{C}_1(\mathrm{H}_8); /\mathbf{C}'_2(\mathrm{C}_4); 3/\mathbf{C}_s(2\mathrm{H}_4, \mathrm{C}_4); 2/\mathbf{C}_{2v}(2\mathrm{C}_2)]$

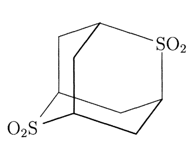
4: $\mathbf{D}_{2d}[/\mathbf{C}_1(\mathrm{H}_8); /\mathbf{C}'_2(\mathrm{C}_4); 3/\mathbf{C}_s(\mathrm{H}_4, \mathrm{C}_4, \mathrm{F}_4); /\mathbf{C}_{2v}(\mathrm{C}_2)]$



5



6

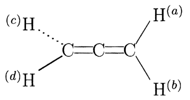


7

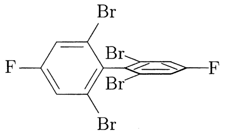
5: $\mathbf{D}_{2d}[/\mathbf{C}_1(\mathrm{H}_8); /\mathbf{C}'_2(\mathrm{C}_4); 2/\mathbf{C}_s(\mathrm{H}_4, \mathrm{C}_4); /\mathbf{C}_{2v}(\mathrm{O}_2)]$

6: $\mathbf{D}_{2d}[/\mathbf{C}_1(\mathrm{H}_8); /\mathbf{C}'_2(\mathrm{C}_4); 2/\mathbf{C}_s(\mathrm{H}_4, \mathrm{C}_4); /\mathbf{C}_{2v}(\mathrm{S}_2)]$

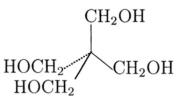
7: $\mathbf{D}_{2d}[/\mathbf{C}_1(\mathrm{H}_8); /\mathbf{C}'_2(\mathrm{C}_4); 3/\mathbf{C}_s(\mathrm{H}_4, \mathrm{C}_4, \mathrm{O}_4); /\mathbf{C}_{2v}(\mathrm{S}_2)]$



8



9



10

8: $\mathbf{D}_{2d}[/\mathbf{C}_s(\mathrm{H}_4); /\mathbf{C}_{2v}(\mathrm{C}_2); /\mathbf{D}_{2d}(\mathrm{C})]$

9: $\mathbf{D}_{2d}[4/\mathbf{C}_s(\mathrm{H}_4, 2\mathrm{C}_4, \mathrm{Br}_4); 3/\mathbf{C}_{2v}(2\mathrm{C}_2, \mathrm{F}_2)]$

10: $\mathbf{D}_{2d}[/\mathbf{C}_1(\mathrm{H}_8); 3/\mathbf{C}_s(\mathrm{H}_4, \mathrm{C}_4, \mathrm{O}_4); /\mathbf{D}_{2d}(\mathrm{C})]$

Fig. 2. SCR Notations for molecules of $\mathbf{D}_{2d}$-symmetry.

Although Pople's method based on "framework groups",[24] some revision pointed out by Brocas,[85] and Flurry's method based on local symmetries[23] have been reported to remedy the drawback of the point-group approach, they have not explicitly taken account of orbits. In contrast, the SCR notation proposed by us[92] is more systematically defined by means of orbits and CRs. One of the merits of the SCR notation stems from the fact that it is closely linked with combinatorial enumeration of isomers and stereoisomers, as discussed in terms of the USCI (unit-subduced-cycle-index) approach.

3 Sphericity

3.1 Chirality Fittingness by Sphericity. Suppose that an orbit of objects (atoms, ligands, faces, or others) in a molecule (or another object) is assigned to a coset representation (CR) $\mathbf{G}(/\mathbf{G}_i)$, where $\mathbf{G}$ is the global symmetry of the molecule and $\mathbf{G}_i$ is the local symmetry of each object of the orbit. Note that $\mathbf{G}_i$ is a subgroup of $\mathbf{G}$ and that the $\mathbf{G}(/\mathbf{G}_i)$ is a kind of permutation representations.[88] The comparison between the chirality/achirality of $\mathbf{G}$ and that of $\mathbf{G}_i$ reveals the presence of three cases (Table 1), which are specified by the sphericity terms (*homospheric, enantiospheric*, and *hemispheric*) proposed by us.[89] The stereochemical property specified by these terms is called *sphericity*. For a more mathematical definition of the concept of sphericity, see Appendix A1. The $\mathbf{G}(/\mathbf{G}_i)$-orbit accommodates $|\mathbf{G}|/|\mathbf{G}_i|$ of objects, where the sphericity of the orbit controls the chirality/achirality of the objects and the mode of accommodation (packing). This effect is called the *chirality fittingness* of an orbit.

Let us consider the orbits in adamantane-2,6-dione, i.e. Δ_1 (bridge hydrogens, Eq. 1) and Δ_2 (bridgehead hydrogens, Eq. 2), as shown in Fig. 1.

The orbit Δ_2 is governed by $\mathbf{D}_{2d}(/\mathbf{C}_s)$, which is decided to be homospheric in terms of the criteria listed in Table 1. In order to maintain the $\mathbf{D}_{2d}$-symmetry, the $\mathbf{D}_{2d}(/\mathbf{C}_s)$-orbit should accommodate four achiral objects such as hydrogen atoms, where the size of the orbit is calculated to be $|\mathbf{D}_{2d}|/|\mathbf{C}_s| = 8/2 = 4$. If the homospheric $\mathbf{D}_{2d}(/\mathbf{C}_s)$-orbit accommodates a set of four chiral ligands (Q) of the same chirality, the symmetry of the resulting molecule (**11**) is reduced into $\mathbf{D}_2$ as a result of the violation of the chirality fittingness (Fig. 3).[89,88]

Table 1. Sphericities of Orbits[89]

$\mathbf{G}$	$\mathbf{G}_i$	Sphericity of $\mathbf{G}(/\mathbf{G}_i)$	Chirality fittingness (objects allowed)
achiral	achiral	homospheric	achiral
achiral	chiral	enantiospheric	achiral,[a)] chiral[b)]
chiral	chiral	hemispheric	achiral,[c)] chiral

a) An achiral object is restricted to be chiral. The half and the other half of the orbit are superimposable by a rotoreflection operator of $\mathbf{G}$.

b) The orbit accommodates the half number ($|\mathbf{G}|/2|\mathbf{G}_i|$) of chiral objects and the same number of chiral objects of opposite chirality so as to accomplish compensated chiral packing.

c) An achiral object is restricted to be chiral.

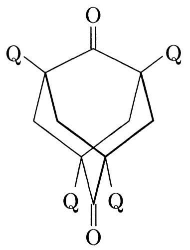


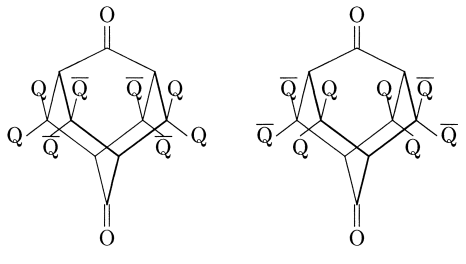
Fig. 3. $\mathbf{D}_2$-Derivative of adamantane-2,6-dione.

On the other hand, the CR $\mathbf{D}_{2d}(/\mathbf{C}_1)$ for the orbit Δ_1 is determined to be enantiospheric so that the eight hydrogen atoms ($|\mathbf{D}_{2d}|/|\mathbf{C}_1| = 8/1 = 8$) are devided into two halves ($\{H^{(a)}, H^{(b)}, H^{(c)}, H^{(d)}\}$ and $\{H^{(a')}, H^{(b')}, H^{(c')}, H^{(d')}\}$ in Eq. 1) under no rotoreflection operations. In order to maintain the $\mathbf{D}_{2d}$-symmetry, the enantiospheric $\mathbf{D}_{2d}(/\mathbf{C}_1)$-orbit can accommodate eight achiral objects such as hydrogen atoms in terms of the criteria listed in Table 1.

The enantiosphericity of the $\mathbf{D}_{2d}(/\mathbf{C}_1)$-orbit permits another mode of packing shown in Fig. 4, where one half accommodates four chiral ligands (Q) and the other half accommodates four ligands ($\bar{\mathrm{Q}}$) of the opposite chirality. Thereby, two diastereomers (**12** and **13**) are generated. A packing such as this mode is called *compensated chiral packing*.[89,88]

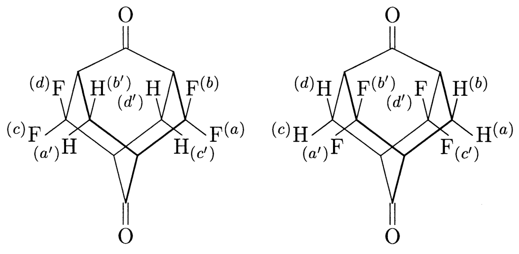
3.2 Prochirality Based on Sphericity. The sphericity concept has been successfully used to redefine prochirality.[89] Thus, *a molecule (or object) is prochiral if the molecule contains at least one enantiospheric orbit.* For example, the orbit Δ_1 (bridge hydrogens, Eq. 1) in adamantane-2,6-dione (**1**) is governed by $\mathbf{D}_{2d}(/\mathbf{C}_1)$ (Fig. 1) and determined to be enantiospheric by virtue of the criteria listed in Table 1. Moreover, the four bridge *carbons* of **1** also have an enantiospheric nature because they belong to a $\mathbf{D}_{2d}(/\mathbf{C}_2{}')$-orbit, as found in the SCR notation. Thereby, adamantane-2,6-dione (**1**) is concluded to be prochiral. Since the $\mathbf{D}_{2d}(/\mathbf{C}_1)$-orbit is divided into two halves under an external chiral environment, either half can be replaced by a set of fluorine atoms to produce either one of enantiomers (**14a** or **14b**) shown in Fig. 5.

The members of such an enantiospheric orbit may be objects of any types, as exemplified in Fig. 6. The methylene hydrogens ($H^{(a)}$ and $H^{(a')}$) of ethanol (**15**) construct an orbit governed by $\mathbf{C}_s(/\mathbf{C}_1)$, which is determined to be enantiospheric by virtue of the criteria listed in Table 1. Hence, ethanol is concluded to be prochiral. It should be noted that the prochirality is concerned with the *orbit* of the methylene hydrogens.



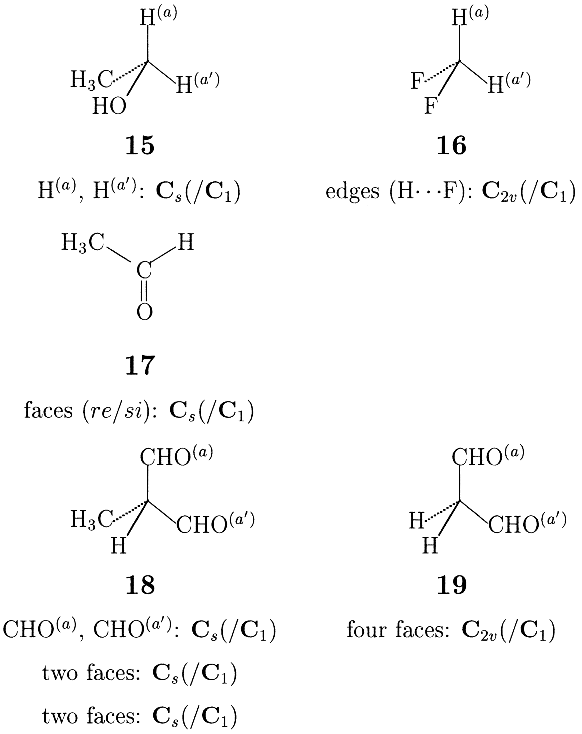
12 **13**

Fig. 4. $\mathbf{D}_{2d}$-Derivatives of adamantane-2,6-dione.



14a **14b**

Fig. 5. Enantiomeric $\mathbf{D}_2$-Derivatives of adamantane-2,6-dione.



15

$H^{(a)}$, $H^{(a')}$: $\mathbf{C}_s(/\mathbf{C}_1)$

16

edges (H$\cdots$F): $\mathbf{C}_{2v}(/\mathbf{C}_1)$

17

faces (*re*/*si*): $\mathbf{C}_s(/\mathbf{C}_1)$

18

CHO$^{(a)}$, CHO$^{(a')}$: $\mathbf{C}_s(/\mathbf{C}_1)$

two faces: $\mathbf{C}_s(/\mathbf{C}_1)$

two faces: $\mathbf{C}_s(/\mathbf{C}_1)$

19

four faces: $\mathbf{C}_{2v}(/\mathbf{C}_1)$

Fig. 6. Prochirality by sphericity.

On the other hand, the two hydrogens ($H^{(a)}$ and $H^{(a')}$) of difluoromethane (**16**) construct a homospheric $\mathbf{C}_{2v}(/\mathbf{C}_s)$-orbit. This means that difluoromethane (**16**) is not prochiral with respect to this orbit. However, the four edge relationships (H···F) can be regarded as objects that construct an orbit. Since the orbit of the four edge relationships (H···F) is assigned to a CR $\mathbf{C}_{2v}(/\mathbf{C}_1)$, it is decided to be enantiospheric. Hence, difluoromethane (**16**) is prochiral with respect to the $\mathbf{C}_{2v}(/\mathbf{C}_1)$-orbit.[89]

The two faces above and below the carbonyl group of acetaldehyde (**17**) can also be regarded as objects that construct an orbit. Quantum-chemically speaking, the two faces correspond to π-electron lobes of opposite signs. They belong to a $\mathbf{C}_s(/\mathbf{C}_1)$-orbit, which is decided to be enantiospheric by virtue of the criteria listed in Table 1. Hence, acetaldehyde (**17**) is concluded to be prochiral with respect to the $\mathbf{C}_s(/\mathbf{C}_1)$-orbit.

Methylmalonaldehyde (**18**) has two carbonyl ligands

($CHO^{(a)}$ and $CHO^{(a')}$), which construct an orbit governed by $\mathbf{C}_s(/\mathbf{C}_1)$. The enantiosphericity of the $\mathbf{C}_s(/\mathbf{C}_1)$-orbit means that methylmalonaldehyde (**18**) is prochiral. Note that this prochirality is concerned with the orbit of ligands (or substituents).

If we take the faces of the two carbonyl ligands into consideration, we can treat methylmalonaldehyde (**18**) in an alternative way. One face of the $CHO^{(a)}$ and an appropriate face of $CHO^{(a')}$ are so equivalent as to construct a $\mathbf{C}_s(/\mathbf{C}_1)$-orbit, while the remaining faces of the $CHO^{(a)}$ and the $CHO^{(a')}$ construct another $\mathbf{C}_s(/\mathbf{C}_1)$-orbit. Each of these $\mathbf{C}_s(/\mathbf{C}_1)$-orbits is enantiospheric to characterize the prochirality of **18** with respect to the faces.

The two carbonyl ligands ($CHO^{(a)}$ and $CHO^{(a')}$) of malonaldehyde (**19**) construct an orbit governed by $\mathbf{C}_{2v}(/\mathbf{C}_s)$, which is homospheric. Hence, malonaldehyde (**19**) is not prochiral with respect to the $\mathbf{C}_{2v}(/\mathbf{C}_s)$-orbit of ligands. However, the four faces produced by the two carbonyl ligands construct a $\mathbf{C}_{2v}(/\mathbf{C}_1)$-orbit, which is found out to be enantiospheric by virtue of the criteria listed in Table 1. Hence, malonaldehyde (**19**) is concluded to be prochiral when we take the orbit of faces.

It should be noted that the behavior of faces for methylmalonaldehyde (**18**) is different from that for malonaldehyde (**19**). In methylmalonaldehyde (**18**), one face of the $CHO^{(a)}$ belongs to one of the $\mathbf{C}_s(/\mathbf{C}_1)$-orbits, while the other face of the $CHO^{(a)}$ belongs to the other one of the $\mathbf{C}_s(/\mathbf{C}_1)$-orbits. This means that the two faces of the $CHO^{(a)}$ are chemically non-equivalent (diastereotopic). They can be differentiated chemically, i.e., without any external chiral conditions, so as to produce a racemic mixture for either one of possible diastereomers. On the other hand, the four faces involved in malonaldehyde (**19**) construct an enantiospheric $\mathbf{C}_{2v}(/\mathbf{C}_1)$-orbit. Hence, they cannot be differentiated chemically and require external chiral conditions in order to generate stereochemical selectivity.

The present definition of prochirality is free from "prochiral, pseudoasymmetric, and propseudoasymmetric centers" defined by Prelog et al.[12–14] as well as "elements of chirality and of prochirality" defined by Hirschmann.[15–17] In other words, the concepts of "centers" and "elements" are replaced by the concept of orbits governed by CRs. Although the direct specification of right and left requires the sequence rule proposed by Cahn, Ingold and Prelog (the CIP system)[8] and its application to the "prochirality" by Hanson,[9–11] the presence/absence or the possibility of such handedness can be fully discussed by virtue of the terms based on the sphericity concept derived from CRs.

3.3 Topicity Derived from Sphericity.

The topicity terms ("enantiotopic" and "diastereotopic") introduced by Mislow and Raban[18] and relevant terms "homotopic" (by Hirschmann and Hanson[10]) and "heterotopic" (by Eliel[21]) have been widely accepted by organic chemists. These terms deal with the relationship between *two* related atoms (or molecular environments) in a molecule. In other words, the topicity is concerned with *pairwise relationships*.

On the other hand, the sphericity terms (enantiospheric, homospheric, and hemispheric) proposed by us[89] are *attributes* of orbits governed by CRs. This feature enables us to derive the topicity terms from the sphericity terms, where the membership criterion has been proposed.[89] It should be emphasized here that the sphericity terms are sufficient to discuss stereochemical phenomena so that we can do well without the topicity terms. However, since organic chemists have been familiar with the topicity terms, a meeting point is to show a way for translating the sphericity terms into the topicity ones. Thereby, we can get a deeper insight than when we rely only on the topicity terms.

Table 2 summarizes the membership criterion based on the sphericity concept along with other criteria proposed earlier.

In order to characterize the topicity relationships, a replacement criterion (substitution or addition criterion) and a symmetry criterion have been described by Mislow and Raban,[18] where the former criterion is essentially equivalent to the one described by Hanson[9] to test prochirality. Table 2 summarizes these criteria with brief explanations. A flow chart for the classification of topic

Table 2. Criteria for Determining Topicities[99]

Topicity	Membership criterion[89,88]	Replacement criterion[18,21]	Symmetry criterion[18,21]
Homotopic	Homospheric orbit,[a)] Either half of enatiospheric orbit,[b)] or Hemispheric orbitb)	Pairwise replacement gives identical (homomeric) products	Pair interchanged by proper rotations
Enantiotopic	Two halves of an enantiospheric orbit	Pairwise replacement gives enantiomeric products	Pair interchanged by improper rotations but not by proper rotations
Diastereotopic	Two related orbits governed by the same kind of coset representations.	Pairwise replacement gives diastereomeric products	Pair not interchanged by improper rotations or by proper rotations

a) Holotopic. b) Hemitopic.

relationships has been reported in the form of a decision tree, each decision step of which is based on a distinct symmetry criterion.[22,98] Since replacement processes for the replacement criterion (substitution or addition criterion) and symmetry operations for the symmetry criterion are involved in the present processes for assigning orbits to CRs (and sphericities), the membership criterion based on the sphericity concept is more convienient and fruitful than the earlier criteria.

In the light of the membership criterion, the two methylene hydrogens ($H^{(a)}$ and $H^{(a')}$) in difluoromethane **15** are homotopic because they are the members of a homospheric $\mathbf{C}_{2v}(/\mathbf{C}_s)$-orbit, the size of which is calculated to be $|\mathbf{C}_{2v}|/|\mathbf{C}_s| = 4/2 = 2$. This decision based on the membership criterion is simpler than those due to the earlier criteria (for the replacement criterion and the symmetry criterion applied to dichloromethane, see Section 8-3 of Eliel-Willen's textbook[4]).

According to the membership criterion, an enantiotopic relationship is defined as a relationship between a member of one half and another member of the other half of an enatiospheric orbit. For example, the relationship between the two methylene hydrogens ($H^{(a)}$ and $H^{(a')}$) in ethanol (**15**) is decided to be enantiotopic, because they construct an enantiospheric $\mathbf{C}_s(/\mathbf{C}_1)$-orbit.

An enantiotopic relationship decided by the membership criterion has an extended meaning that one half of an enantiospheric orbit is defined to be enantiotopic to the other half of the enantiospheric orbit. In other words, it is concerned with a pairwise relationship between *two halves* of the enantiospheric orbit. Let us examine, for example, the relationship between eight hydrogen atoms on the bridge positions of adamantane-2,6-dione (**1**), where the orbit of them is governed by a CR $\mathbf{D}_{2d}(/\mathbf{C}_1)$. This orbit is enantiospheric so that the two halves ($\{H^{(a)}, H^{(b)}, H^{(c)}, H^{(d)}\}$ and $\{H^{(a\prime)}, H^{(b')}, H^{(c')}, H^{(d')}\}$ in Eq. 1) are enantiotopic to each other.

Since the replacement criterion and the symmetry criterion take no account of such an orbit as described in the preceding paragraph, the researchers should inspect atom by atom to decide the topicity relationships. For example, when we focus on $H^{(a)}$, we should inspect four candidate pairs, i.e., $H^{(a)}$ and $H^{(a')}$; $H^{(a)}$ and $H^{(b')}$; $H^{(a)}$ and $H^{(c')}$; and $H^{(a)}$ and $H^{(d')}$. Each of these pairs is determined to be enantiotopic by the replacement criterion or the symmetry criteiron. On the same line, we have another set of four candidate pairs, i.e., $H^{(b)}$ and $H^{(a')}$; $H^{(b)}$ and $H^{(b')}$; $H^{(b)}$ and $H^{(c')}$; and $H^{(b)}$ and $H^{(d')}$, when we focus on $H^{(b)}$; etc., etc.

To make matters more complicated for organic chemists, the topicity terms have two distinct connotations after the introduction of the terms "chirotopic" and "achirotopic".[22] The first type of topicity terms (homotopic, enantiotopic, diastereotopic, and heterotopic) represents equivalent or non-equivalent *relationships* between two sites, while the second type (chirotopic and achirotopic) represents the nature of each site. This means that the local symmetry of a molecule is discussed distinctly apart from the global symmetry. As a result, a chirotopic site may be homotopic, enantiotopic, and diastereotopic to another site, where each case should be described by such a combination as "chirotopic and homotopic". This feature indicates that the topicity terms are not so suitable to discuss such complicated cases as examined in the present paper.

To overcome the situation described above, our approach primarily adopts the sphericity terms to designate attributes. However, in case we would put a stress on relationships, we can use the terms "holotopic" and "hemitopic"[88,99] in place of two cases of the combination of "chirotopic and homotopic" so as to avoid the usage of chirotopic/achirotopic.

On the other hand, the sphericity terms provide us with a common and integrated basis for discussing the local symmetry and the global symmetry of a molecule. Such a combination as "chirotopic and homotopic" is replaced by either of the sphericity terms, "hemispheric" or "enantiospheric", according to the nature of the orbit at issue.

3.4 Stereogenicity and Prostereogenicity. The term "prochiral" due to the IUPAC Rule E-4.12(a) and Rule E-4.12(b),[100] the latter of which has been defined as the successor of Hanson's proposal, has polysemous nature, as discussed by us.[101] We use the revised definition of prochirality, as described in Subsection 3.2. Thereby, the term *prochirality* has purely stereochemical meanings so that it can be used to describe the global symmetry of a molecule. Note that the prochirality is concerned with an appropriate enantiospheric orbit, the objects of which can be atoms, bonds, faces, etc. We summarized our idea in three rules as follows.[102]

Rule A (Prochiral). The prochirality defined by Rule E-4.12(a) is preserved to be the revised definition of the term *prochiral*. This means that such a description as "a molecule is prochiral" is permitted like the one "a molecule is chiral". In terms of the sphericity concept (Table 1), *a molecule containing at least one enantiospheric orbit is defined to be prochiral.*[89] This point has already been discussed in detail in Subsection 3.2.

Rule B (Prostereogenic). The term "prochiral center" defined by Rule E-4.12(b)[103] is replaced by the term *prostereogenic center*. In terms of the sphericity concept (Table 1), *if a center or atom has two ligands that are indistinguishable in isolation and belong to the distinct halves of an enantiospheric orbit or to two distinct homospheric, hemispheric or enantiospheric orbits, it is called a prostereogenic center*. If the topicity terms are used (this way is not recommended), the condition can be replaced by the expression, "if a center or atom has two ligands that are indistinguishable in isolation and not homotopic (i.e. either enantiotopic, diastereotopic or heterotopic) in a molecule".

Rule C (Stereogenic). In addition, the term "chiral center"[8,104] is replaced by the term *stereogenic center*.[25] Thus, the term *stereogenic center* is defined by starting from Rule B. *If a center or atom has two ligands that are distinguishable in isolation and if it can be transformed* (even if virtually) *into a prostereogenic center where the ligands are converted into two ligands indistinguishable in isolation, it is called a stereogenic center.*[105]

The tests for prochirality, prostereogenicity, and stereogenicity can be systematically carried out by the tools derived from the sphericity concept (Tables 1 and 2).[102]

1. Consider an appropriate conformer of the highest attainable symmetry **G** or the corresponding promolecule belonging

to **G**.

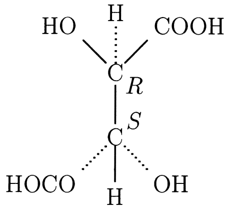
2. Collect equivalent ligands to give a respective orbit.
3. Assign each orbit to a CR $\mathbf{G}(/\mathbf{G}_i)$.
4. Classify the sphericity of the orbit according to Table 1.
5. Assign the topic relationship between a pair of orbits to be considered by virtue of Table 2. This step can be omitted if the topicity terms are not used, as is preferable.
6. Refer to Rule A for prochirality, to Rule B for prostereogenicity, or to Rule C for stereogenicity.

To illustrate Rule A, let us consider a staggered conformtion ($\mathbf{C}_i$) of meso-tartaric acid (**20**), as shown in Fig. 7. The two hydrogens on the carbon centers constuct a $\mathbf{C}_i(/\mathbf{C}_1)$-orbit, which is enantiospheric. Hence, **20** is concluded to be prochiral by virtue of Rule A. The same conclusion is also obtained by considering an eclipsed confomation ($\mathbf{C}_s$) as the highest attainable symmetry of meso-tartaric acid, because a $\mathbf{C}_s(/\mathbf{C}_1)$-orbit for the staggered conformation is found out to be enantiospheric.

An alternative explanation is based on the concept of promolecule. When the ligands *R*-CH(OH)COOH and *S*-CH(OH)COOH in meso-tartaric acid (**20** in Fig. 7) are considered to be proligands p and $\bar{\mathrm{p}}$, they constuct an enantiospheric $\mathbf{C}_{\infty h}(/\mathbf{C}_{\infty})$-orbit. Hence, meso-tartaric acid (**20**) is determined to be prochiral with respect to the $\mathbf{C}_{\infty h}(/\mathbf{C}_{\infty})$-orbit (Rule A). See also Fig. 24.

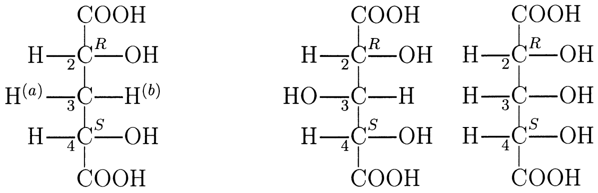
In the light of the CIP nomenclature, the local symmetry ($\mathbf{C}_1$) of each carbon in meso-tartaric acid is primarily considered. Each of the ligands (H, OH, COOH, and the remaining part) constructs a one-membered $\mathbf{C}_1(/\mathbf{C}_1)$-orbit when considering the local symmetry. Then, Rule C indicates that each carbon of **20** is a stereogenic center. It should be emphasized that the CIP nomenclature and related ones are concerned with the local symmetry of a so-called "center".

To illustrate Rule B, let us examine *meso*-2,4-dihydroxyglutaric acid (**21**), which belongs to $\mathbf{C}_s$-symmetry in its highest attainable conformation (Fig. 8). The two hydrogens $H^{(a)}$ and $H^{(b)}$ on the central carbon belong to distinct one-membered $\mathbf{C}_s(/\mathbf{C}_s)$-orbits, which are determined to be homospheric. Hence, Rule B indicates that the central carbon with $H^{(a)}$ and $H^{(b)}$ is prostereogenic.



20 $\mathbf{C}_i$ (or $\mathbf{C}_s$)

Fig. 7. *meso*-Tartaric acid.



21 **22** **23**

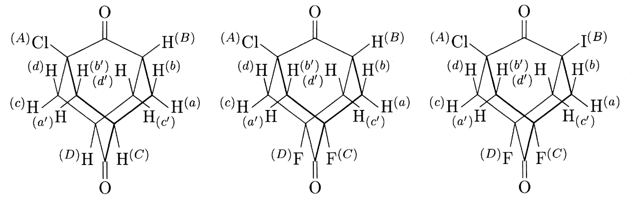
Fig. 8. *meso*-2,4-Dihydroxyglutaric acid and related compounds.

The stereogenicity of the central carbon atom (C_3) in **22** or **23** can be decided by virtue of Rule C. The relationship between **21** and a pair of **22** and **23** will be discussed later.

4 General Aspects of Desymmetrization

4.1 Desymmetrization of Orbits. A process of substitution by starting from a mother skeleton can be regarded as a desymmetrization of the skeleton. For example, monochlorination at the hydrogen $H^{(A)}$ of **1** generates a $\mathbf{C}_s$-derivative (**24**), where the $\mathbf{D}_{2d}$-symmetry of the mother skeleton **1** is reduced into $\mathbf{C}_s$. In addition to **24**, Fig. 9 depicts various $\mathbf{C}_s$-derivatives of adamantane-2,6-dione, where the same mode of desymmetrization should occur. But what does the same mode mean? Thus, the next problem is to abstract common features from the desymmetrization processes generating these $\mathbf{C}_s$-derivatives. The solution is obtained by examining the behaviors of orbits under the desymmetrization processes.

Let us first inspect 1-chloroadamantane-2,6-dione (**24**), which is generated by monochlorination of adamantane-2,6-dione (**1**). Then we find that the 1-chlorine atom ($\{Cl^{(A)}\}$) constructs a $\mathbf{C}_s(/\mathbf{C}_s)$-orbit, because it is involved in the mirror plane to determine its local symmetry $\mathbf{C}_s$. The remaining bridgehead hydrogens are found out in a similar manner to construct a $\mathbf{C}_s(/\mathbf{C}_s)$-orbit ($\{H^{(B)}\}$) and a $\mathbf{C}_s(/\mathbf{C}_1)$-orbit ($\{H^{(C)}, H^{(D)}\}$). These orbits can be considered to be generated from the original $\mathbf{D}_{2d}(/\mathbf{C}_s)$-orbit ($\Delta_2$) of adamantane-2,6-dione (**1**) as a result of the desymmetrization process from $\mathbf{D}_{2d}$ to $\mathbf{C}_s$. This

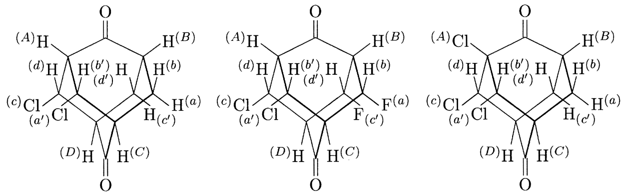


24 **25** **26**

24: $\mathbf{C}_s[8/\mathbf{C}_1(5H_2, 3C_2); 8/\mathbf{C}_s(H, 4C, 2O, Cl)]$

25: $\mathbf{C}_s[8/\mathbf{C}_1(4H_2, 3C_2, F_2); 8/\mathbf{C}_s(H, 4C, 2O, Cl)]$

26: $\mathbf{C}_s[8/\mathbf{C}_1(4H_2, 3C_2, F_2); 8/\mathbf{C}_s(4C, 2O, Cl, I)]$



27 **28** **29**

27: $\mathbf{C}_s[8/\mathbf{C}_1(4H_2, 3C_2, Cl_2); 8/\mathbf{C}_s(2H, 4C, 2O)]$

28: $\mathbf{C}_s[8/\mathbf{C}_1(3H_2, 3C_2, F_2, Cl_2); 8/\mathbf{C}_s(2H, 4C, 2O)]$

29: $\mathbf{C}_s[8/\mathbf{C}_1(4H_2, 3C_2, Cl_2); 8/\mathbf{C}_s(H, 4C, 2O), Cl]$

Fig. 9. $\mathbf{C}_s$-Derivatives of adamantane-2,6-dione.

process can be symbolically designated by the following equation:

$$\mathbf{D}_{2d}(/\mathbf{C}_s) \downarrow \mathbf{C}_s = \mathbf{C}_s(/\mathbf{C}_1) + 2\mathbf{C}_s(/\mathbf{C}_s), \qquad (3)$$

where we have the sums of the sizes for the participating orbits: $|\mathbf{D}_{2d}|/|\mathbf{C}_s| = 8/2 = 4$ for the left-hand side and $|\mathbf{C}_s|/|\mathbf{C}_1| + 2|\mathbf{C}_s|/|\mathbf{C}_s| = 2/1 + 2 \times (1/1) = 4$ for the right-hand side. Symbols such as $\mathbf{D}_{2d}(/\mathbf{C}_s) \downarrow \mathbf{C}_s$ have been coined by us in order to assign desymmetrization processes to the subduction of CRs.[91] The desymmetrization process of the bridgehead carbons (from **1** to **24**) is also controlled by Eq. 3.

According to the monochloro-substitution, the $\mathbf{D}_{2d}(/\mathbf{C}_1)$-orbit ($\Delta_1$) of the bridge hydrogens in **1** is also influenced so as to be divided into four orbits: $\{H^{(a)}, H^{(c')}\}$, $\{H^{(b)}, H^{(d')}\}$, $\{H^{(c)}, H^{(a')}\}$, and $\{H^{(d)}, H^{(b')}\}$. All of the resulting orbits are distinct from each other but are assigned to the same CR $\mathbf{C}_s(/\mathbf{C}_1)$. As a result, this process corresponds to the subduction represented by

$$\mathbf{D}_{2d}(/\mathbf{C}_1) \downarrow \mathbf{C}_s = 4\mathbf{C}_s(/\mathbf{C}_1). \qquad (4)$$

On the same line, the desymmetrization of the bridge carbons is controlled by Eq. 5, while those of the carbonyl carbons and the carbonyl oxygens are controlled by Eq. 6.

$$\mathbf{D}_{2d}(/\mathbf{C}_2{}') \downarrow \mathbf{C}_s = 2\mathbf{C}_s(/\mathbf{C}_1) \qquad (5)$$

$$\mathbf{D}_{2d}(/\mathbf{C}_{2v}) \downarrow \mathbf{C}_s = 2\mathbf{C}_s(/\mathbf{C}_s) \qquad (6)$$

The results designated by Eqs. 3 to 6 are summarized in terms of the SCR notation shown in Fig. 9.

By the inspection of **25** and **26** shown in the top row of Fig. 9, one sees that the replacement of the brigde-head hydrogens (Δ_2) by a set of $\{Cl;H;F_2\}$ or $\{Cl;I;F_2\}$ is controlled by Eq. 3 in the same way as **24** characterized by a set of $\{Cl;H;H_2\}$.

The bottom row of Fig. 9 shows the dichloro-subsititution on the $\mathbf{D}_{2d}(/\mathbf{C}_1)$-orbit ($\Delta_1$), which is divided in the light of Eq. 4 to produce $\{H^{(a)}, H^{(c')}\}$, $\{H^{(b)}, H^{(d')}\}$, $\{Cl^{(c)}, Cl^{(a')}\}$, and $\{H^{(d)}, H^{(b')}\}$. Equations 4 to 6 also explain the divisions of other orbits in **27**, **28**, and **29**.

4.2 Subduction of Coset Representations. As discussed in the preceding subsection, the desymmetrization process of adamantane-2,6-dione into any derivative of $\mathbf{C}_s$-symmetry is controlled by Eqs. 3 to 6. These equations can be derived algebraically by the subduction of CRs and tabulated as a subduction table, although the concrete procedure of derivation is omitted in this article. See Chapter 9 of Ref. 88 for detailed discussion. Table 3 shows the subduction table for $\mathbf{D}_{2d}$, where each equation (Eqs. 4 to 6) appears at the intersection of the corresponding column and row.

Once we have obtained a subduction table such as Table 3, we can predict the mode of substitution for any derivative of a given symmetry. Let us consider the derivation of allene (**8**), where the $\mathbf{D}_{2d}(/\mathbf{C}_s)$-orbit of hydrogens is taken into consideration. To obtain a derivative of $\mathbf{D}_2$-symmetry, we examine the intersection of the $\mathbf{D}_{2d}(/\mathbf{C}_s)$-row and the $\mathbf{D}_2$-column in Table 3. Then, we find the subduction result $\mathbf{D}_2(/\mathbf{C}_1)$, the local symmetry of which is decided to be $\mathbf{C}_1$. Since the resulting $\mathbf{D}_2(/\mathbf{C}_1)$-orbit is hemispheric, its chirality fittingness allows the orbit to accommodate chiral ligands (Qs) of the same kind according to Table 1. Hence, we obtain **30** as a $\mathbf{D}_2$-derivative (Fig. 10). Note that achiral ligands do not give a $\mathbf{D}_2$-derivative but a $\mathbf{D}_{2d}$-derivative.

Let us next obtain a derivative of $\mathbf{S}_4$-symmetry. The intersection of the $\mathbf{D}_{2d}(/\mathbf{C}_s)$-row and the $\mathbf{S}_4$-column in Table 3 shows the subduction result $\mathbf{S}_4(/\mathbf{C}_1)$, the local symmetry of which is found out to be $\mathbf{C}_1$. Since the resulting $\mathbf{S}_4(/\mathbf{C}_1)$-orbit is enantiospheric, it should accommodate chiral ligands in a manner of compensated chiral packing, as found in Table 1. Hence, we obtain **31** as a $\mathbf{S}_4$-derivative.

On the same line, the derivatives discussed in the preceding section can now been obtained by the combination of the subduction table (Table 3) with the chirality fittingness listed in Table 1.

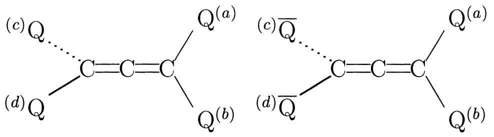
5 Desymmetrization by Atom Replacement

5.1 Derivation from Various Skeletons. One of the strategies of generating derivatives is that an orbit in an achiral (or a chiral skeleton) of a given symmetry **G** is replaced by an appropriate set of *atoms*. If the subduction table for the **G**-symmetry is obtained in advance, we can predict what symmetries can be realized as such derivatives. Thus, we have dealt with the following symmetries: $\mathbf{C}_{2v}$ (oxirane, etc.[92]), $\mathbf{D}_{2d}$ (allene[106] and adamantane-2,6-dione[107]), $\mathbf{D}_{3h}$ (a trigonal bipyramid, an iceane skeleton, and a prismane skeleton[108]), $\mathbf{T}_d$ (adamantane[109]), $\mathbf{D}_{6h}$ (benzene[110] and superphane[93]), $\mathbf{O}_h$ (octahedral

Table 3. Subduction of Coset Representations (CRs) for $\mathbf{D}_{2d}$ Point Group[88]

	$\downarrow \mathbf{C}_1$	$\downarrow \mathbf{C}_2$	$\downarrow \mathbf{C}_2{}'$	$\downarrow \mathbf{C}_s$	$\downarrow \mathbf{S}_4$	$\downarrow \mathbf{C}_{2v}$	$\downarrow \mathbf{D}_2$	$\downarrow \mathbf{D}_{2d}$
$\mathbf{D}_{2d}(/\mathbf{C}_1)$	$8\mathbf{C}_1(/\mathbf{C}_1)$	$4\mathbf{C}_2(/\mathbf{C}_1)$	$4\mathbf{C}_2{}'(/\mathbf{C}_1)$	$4\mathbf{C}_s(/\mathbf{C}_1)$	$2\mathbf{S}_4(/\mathbf{C}_1)$	$2\mathbf{C}_{2v}(/\mathbf{C}_1)$	$2\mathbf{D}_2(/\mathbf{C}_1)$	$\mathbf{D}_{2d}(/\mathbf{C}_1)$
$\mathbf{D}_{2d}(/\mathbf{C}_2)^*$	$4\mathbf{C}_1(/\mathbf{C}_1)$	$4\mathbf{C}_2(/\mathbf{C}_2)$	$2\mathbf{C}_2{}'(/\mathbf{C}_1)$	$2\mathbf{C}_s(/\mathbf{C}_1)$	$2\mathbf{S}_4(/\mathbf{C}_2)$	$2\mathbf{C}_{2v}(/\mathbf{C}_2)$	$2\mathbf{D}_2(/\mathbf{C}_2)$	$\mathbf{D}_{2d}(/\mathbf{C}_2)$
$\mathbf{D}_{2d}(/\mathbf{C}_2{}')$	$4\mathbf{C}_1(/\mathbf{C}_1)$	$2\mathbf{C}_2(/\mathbf{C}_1)$	$\mathbf{C}_2{}'(/\mathbf{C}_1)$ $+\mathbf{C}_2{}'(/\mathbf{C}_1)$	$2\mathbf{C}_s(/\mathbf{C}_1)$	$\mathbf{S}_4(/\mathbf{C}_1)$	$\mathbf{C}_{2v}(/\mathbf{C}_1)$	$\mathbf{D}_2(/\mathbf{C}_2{}')$ $+\mathbf{D}_2(/\mathbf{C}_2{}'')$	$\mathbf{D}_{2d}(/\mathbf{C}_2{}')$
$\mathbf{D}_{2d}(/\mathbf{C}_s)$	$4\mathbf{C}_1(/\mathbf{C}_1)$	$2\mathbf{C}_2(/\mathbf{C}_1)$	$2\mathbf{C}_2{}'(/\mathbf{C}_1)$	$\mathbf{C}_s(/\mathbf{C}_1)$ $+2\mathbf{C}_s(/\mathbf{C}_s)$	$\mathbf{S}_4(/\mathbf{C}_1)$	$\mathbf{C}_{2v}(/\mathbf{C}_s)$ $+\mathbf{D}_{2v}(/\mathbf{C}_2{}')$	$\mathbf{D}_2(/\mathbf{C}_1)$	$\mathbf{D}_{2d}(/\mathbf{C}_s)$
$\mathbf{D}_{2d}(/\mathbf{S}_4)^*$	$2\mathbf{C}_1(/\mathbf{C}_1)$	$2\mathbf{C}_2(/\mathbf{C}_2)$	$\mathbf{C}_2{}'(/\mathbf{C}_1)$	$\mathbf{C}_s(/\mathbf{C}_1)$	$2\mathbf{S}_4(/\mathbf{S}_4)$	$\mathbf{C}_{2v}(/\mathbf{C}_2)$	$\mathbf{D}_2(/\mathbf{C}_2)$	$\mathbf{D}_{2d}(/\mathbf{S}_4)$
$\mathbf{D}_{2d}(/\mathbf{C}_{2v})$	$2\mathbf{C}_1(/\mathbf{C}_1)$	$2\mathbf{C}_2(/\mathbf{C}_2)$	$\mathbf{C}_2{}'(/\mathbf{C}_1)$	$2\mathbf{C}_s(/\mathbf{C}_s)$	$\mathbf{S}_4(/\mathbf{C}_2)$	$2\mathbf{C}_{2v}(/\mathbf{C}_{2v})$	$\mathbf{D}_2(/\mathbf{C}_2)$	$\mathbf{D}_{2d}(/\mathbf{C}_{2v})$
$\mathbf{D}_{2d}(/\mathbf{D}_2)^*$	$2\mathbf{C}_1(/\mathbf{C}_1)$	$2\mathbf{C}_2(/\mathbf{C}_2)$	$2\mathbf{C}_2{}'(/\mathbf{C}_2{}')$	$\mathbf{C}_s(/\mathbf{C}_1)$	$\mathbf{S}_4(/\mathbf{C}_2)$	$\mathbf{C}_{2v}(/\mathbf{C}_2)$	$2\mathbf{D}_2(/\mathbf{D}_2)$	$\mathbf{D}_{2d}(/\mathbf{D}_2)$
$\mathbf{D}_{2d}(/\mathbf{D}_{2d})$	$\mathbf{C}_1(/\mathbf{C}_1)$	$\mathbf{C}_2(/\mathbf{C}_2)$	$\mathbf{C}_2{}'(/\mathbf{C}_2{}')$	$\mathbf{C}_s(/\mathbf{C}_s)$	$\mathbf{S}_4(/\mathbf{S}_4)$	$\mathbf{C}_{2v}(/\mathbf{C}_{2v})$	$\mathbf{D}_2(/\mathbf{D}_2)$	$\mathbf{D}_{2d}(/\mathbf{D}_{2d})$

*Forbidden CR. See Chapter 7 of Ref. 88.



30 **31**

Fig. 10. $\mathbf{D}_2$- and $\mathbf{S}_4$-Derivative of allene.

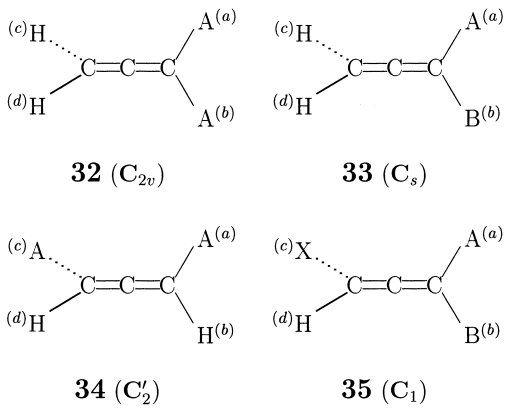
complexes[111]), and $\mathbf{I}_h$ (dodecahedrane[112] and soccerane[113]).

5.2 Allowed and Forbidden Derivations. Let us consider allene derivatives with achiral ligands only (A, B, X, and H). Under this condition, we can obtain a $\mathbf{C}_{2v}$-(**32**), a $\mathbf{C}_s$-(**33**), a $\mathbf{C}_2{}'$-(**34**), and a $\mathbf{C}_1$-derivative (**35**), as shown in Fig. 11. However, derivatives of $\mathbf{D}_2$-, $\mathbf{S}_4$-, and $\mathbf{C}_2$-symmetry are by no means generated under this condition because of their sphericities.

Allowed molecules and forbidden ones are rationalized by virtue of a subgroup lattice such as Fig. 12 for $\mathbf{D}_{2d}$, where each subgroup is characterized by the relevant subduction.[92] Although the sphericity of each CR controls the allowance, a more delicate examination is necessary. We have here arrived at a criterion for determining allowed and forbidden molecules: *A molecule of a subgroup is allowed if the subduction for the subgroup is discriminated from that for its supergroup; otherwise, it is forbidden.* Strictly speaking, this criterion is concerned with promolecules (cf. Subsection 7.2), where the descrimination is determined by comparing the sizes and the sphericities of the CRs at issue. The matching/mismatching properties should also be considered after the introduction of the concept of promolecule/molecule.

For example, let us examine the subgroup $\mathbf{S}_4$ with an orbit $\mathbf{S}_4$(/$\mathbf{C}_1$), where the size of the orbit is calculated to be $|\mathbf{S}_4|/|\mathbf{C}_1| = 4 = |\mathbf{D}_{2d}|/|\mathbf{C}_s|$. Hence, $\mathbf{S}_4$(/$\mathbf{C}_1$) cannot be discriminated from $\mathbf{D}_{2d}$(/$\mathbf{C}_s$) by considering achiral ligands only, even if the symmetry of each achiral ligand can be restricted to the local symmetry of $\mathbf{C}_1$. Similarly, a $\mathbf{C}_2$-derivative cannot be generated by comparing its orbits with those of its supergroup $\mathbf{C}_{2v}$ (Fig. 12). On the other hand, a $\mathbf{C}_2{}'$-derivative (**34**) can be generated by considering achiral ligands only, according to the criterion.

If we take account of chiral and achiral ligands, we can obtain a $\mathbf{D}_2$-(**30**) and an $\mathbf{S}_4$-derivative (**31**), as have been shown in Fig. 10. We are also able to generate a $\mathbf{C}_2$-derivative (**36**), as shown in Fig. 13. Under this condition, compensated-chiral-packing procedures give further $\mathbf{C}_s$-derivatives (**37**, **38**, and **39**) in addition to **33**. Note that each pair of Q and $\bar{Q}$ in **37**, **38**, or **39** constructs an enantiospheric $\mathbf{C}_s$(/$\mathbf{C}_1$)-orbit and that the derivatives (**37** to **39**) are so-called *meso*-compounds. In accord with chirality fittingness, a $\mathbf{C}_2{}'$-(**40**) and a $\mathbf{C}_1$-derivative (**41**) having chiral ligands can also be generated.



32 ($\mathbf{C}_{2v}$) **33** ($\mathbf{C}_s$)

34 ($\mathbf{C}_2'$) **35** ($\mathbf{C}_1$)

Fig. 11. Allowed derivatives of allene with achiral ligands.

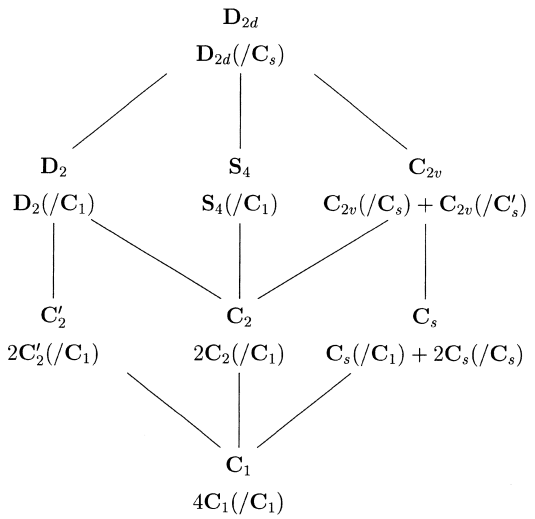
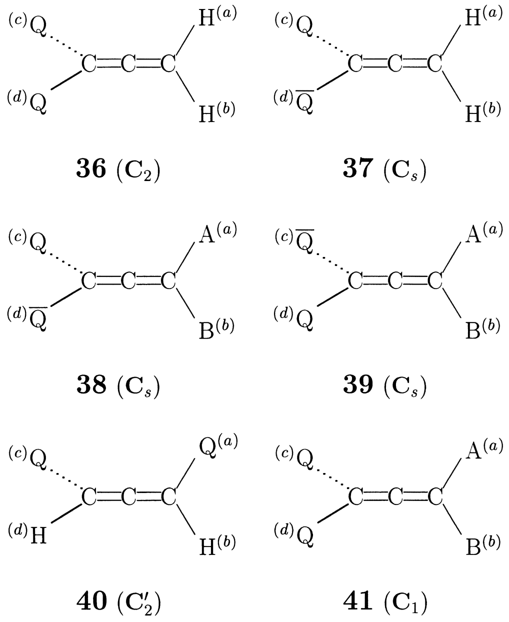


Fig. 12. Subgroup lattice of $\mathbf{D}_{2d}$ for a $\mathbf{D}_{2d}$ (/$\mathbf{C}_s$)-orbit.[114]



36 ($\mathbf{C}_2$) **37** ($\mathbf{C}_s$)

38 ($\mathbf{C}_s$) **39** ($\mathbf{C}_s$)

40 ($\mathbf{C}_2'$) **41** ($\mathbf{C}_1$)

Fig. 13. Allowed derivatives of allene with achiral and chiral ligands.

5.3 Design of High-Symmetry Molecules. For the design of chiral molecules of high symmetry, a set of substitution positions in an achiral skeleton of **G**-symmetry are replaced by chiral ligands (or proligands) of the same kind so that there emerge three criteria of generating chiral molecules (or promolecules).[115] Thus, Criterion 1 controls the desymmetrization of a homospheric orbit in an achiral skeleton, where the orbit accommodates chiral ligands (or strictly speaking, proligands) of the same chirality. The resulting molecule (or strictly speaking, promolecule) is determined to belong to the maximum chiral subgroup of **G** in agreement with a size-invariant subduction. For example, the $\mathbf{D}_2$-derivatives (**11**) shown in Fig. 3 and **30** shown in Fig. 10 are generated from the respective $\mathbf{D}_{2d}$-skeletons according to Criterion 1.

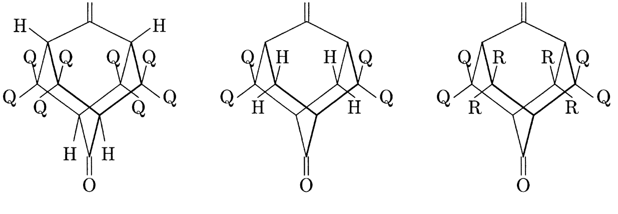
Criterion 2 controls the desymmetrization of an enantiospheric orbit, where the orbit accommodates chiral ligands (or strictly speaking, proligands) of the same chirality. It follows that the resulting molecule is determined to belong to the maximum chiral subgroup of **G** and that the original enantiospheric orbits are divided into two hemispheric orbits of equal size. For example, a $\mathbf{D}_2$-derivative (**42**) shown in Fig. 14 is generated from the $\mathbf{D}_{2d}$-skeleton according to Criterion 2, where the $\mathbf{D}_{2d}(/\mathbf{C}_1)$-orbit of **1** is transformed into the two $\mathbf{D}_2(/\mathbf{C}_1)$-orbits of **14**.

Criterion 3 deals with a chiral skeleton, where substitution by chiral ligands (or strictly speaking, proligands) of the same kind is examined as the transformation of the hemispheric orbit in the skeleton. Although no change of symmetry occurs from a group-theoretical point of view, the transformation is shown to be important chemically, since relevant ligands alter the stereochemical properties. For example, the chiral derivative **14a** shown in Fig. 5 is considered to be a starting skeleton of $\mathbf{D}_2$-symmetry, where the four fluorine atoms belonging to a hemispheric $\mathbf{D}_2(/\mathbf{C}_1)$-orbit are replaced by four Qs of the same chirality. The resulting derivative (**43**) shown in Fig. 14 also belongs to $\mathbf{D}_2$-symmetry in agreement with Criterion 3. The four hydrogens of **43** are further replaced by the four chiral Rs of the same chirality to give **44** of the same $\mathbf{D}_2$-symmetry according to Criterion 3.

Mono-substitution causes the division of an orbit, as exemplified by **24** in Fig. 9. A general treatment of such mono-substitution has been discussed in detail by virtue of the subduction of CRs.[116]

Two types of derivations of molecules, subductive and inductive, have been proposed to design molecules of high symmetry.[106] A subductive derivation consists of placing another set of atoms on a parent molecule; on the other hand, an inductive derivation is composed of providing a parent skeleton with a set of ligands that have three-dimensional structure. These derivations are discussed on the basis of subduction and induction of CRs.

The concept of size-invariant subductions has been proposed to design prochiral molecules.[117,118] Thus, an even-membered homospheric orbit has been proved to be desymmetrized into an enantiospheric orbit, where the sizes of the relevant orbits remain invariant. The concept has been applied to methanes, allenes, adamantanes, and biphenyls. It has proved effective in designing a wide variety of prochiral molecules. For example, the allene drivative **31** shown in Fig. 10 can be generated by placing a set of $\{\mathrm{Q}, \mathrm{Q}, \bar{\mathrm{Q}}, \bar{\mathrm{Q}}\}$ on the homospheric $\mathbf{D}_{2d}(/\mathbf{C}_s)$-orbit. These prochiral molecules have been shown to be extrinsic meso compounds. Intrinsic meso compounds have also been discussed as another type of prochiral molecule. For example, **12** and **13** shown in Fig. 4 are intrinsic meso compounds, where they are generated by starting from an enantiospheric $\mathbf{D}_{2d}(/\mathbf{C}_1)$-orbit.



42 **43** **44**

Fig. 14. $\mathbf{D}_2$-Derivatives of adamantane-2,6-dione.

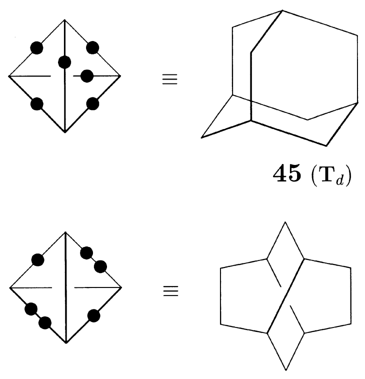
6 Desymmetrization by Bond Replacement

Another strategy for generating derivatives is that an orbit of bonds (or edges) in an achiral (or a chiral skeleton) of a given symmetry **G** is replaced by an appropriate set of *bond objects*. We can predict what symmetries are realized as such derivatives by using the subduction table prepared for **G** in advance.

Tricyclic isomers of adamantane ($C_{10}H_{16}$) have been generated in the light of the bond strategy, where they are characterized by polymethylene indices (PMIs) and molecular symmetry.[119] This idea is illustrated in Fig. 15, where polymethylenes are selected as bond objects. The PMI is a partition denoted as $[1^{m_1}, 2^{m_2}, \ldots, 6^{m_6}]$ $(m_1 + m_2 + \ldots + m_6 = 6)$, in which each integer is the length of a polymethylene unit and the power (m_r) denotes the number of the units. The isomers are then enumerated by starting from tetrahedrane ($\mathbf{T}_d$) and cyclobutadiene ($\mathbf{D}_{2h}$) as parent skeletons, in which the edges are considered to be substituted by polymethylenes. For example, Fig. 15 shows that PMI $[1^6]$ applied to the tetrahedrane ($\mathbf{T}_d$) corresponds to adamantane (**45**) itself, where a solid circle on each edge represents a methylene unit to be added. Since the six edges of the tetrahedrane skeleton construct an orbit governed by $\mathbf{T}_d(/\mathbf{C}_{2v})$, the application of the PMI $[1^6]$ is controlled by the following subduction:

$$\mathbf{T}_d(/\mathbf{C}_{2v}) \downarrow \mathbf{T}_d = \mathbf{T}_d(/\mathbf{C}_{2v}), \tag{7}$$

though this is rather trivial because the $\mathbf{T}_d$-symmetry remains unchanged during this derivation. When PMI $[1^2 2^2]$ is applied to the tetrahedrane skeleton, it can generate twistane (**46**), where the $\mathbf{T}_d$-symmetry is reduced into $\mathbf{D}_2$ during this derivation. The $\mathbf{T}_d(/\mathbf{C}_{2v})$-orbit of the six edges is desymmetrized in



46 (D_2)

Fig. 15. Edge strategy for tricyclic derivatives.

accord with the following subduction:

$$\mathbf{T}_d(/\mathbf{C}_{2v}) \downarrow \mathbf{D}_2 = \mathbf{D}_2(/\mathbf{C}_2) + \mathbf{D}_2(/\mathbf{C}_2') + \mathbf{D}_2(/\mathbf{C}_2''), \qquad (8)$$

where the resulting CRs correspond to the two ethylene bridges (for the term 2^2 of the PMI), the two methylene bridges (for the term 1^2 of the PMI), and the two unchanged edges (for an implicit term 0^2 of the PMI). Since the twistane molecule is chiral ($\mathbf{D}_2$), the formula **46** shows an arbitrary one of the enantiomers.

From the tetrahedrane skeleton, there emerge 32 isomers of adamantane ($C_{10}H_{16}$), which are classified in terms of PMIs and subsymmetries of $\mathbf{T}_d$. The full list of enumerated isomers has been shown in the original paper[119] and our book.[88]

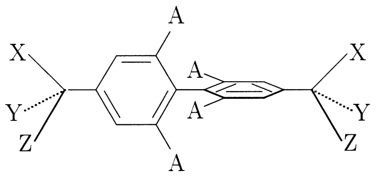
In the light of the same strategy, the cyclobutadiene skeleton has been shown to yield 89 isomers classified by PMIs and subsymmetries of $\mathbf{D}_{2h}$. Isomer enumerations have been also discussed with respect to noradamantane and homoadamantane.[119]

The edge strategy has been discussed to characterize bond-differentiating reactions.[120] After preparing the subduction table of $\mathbf{I}_\mathrm{h}$, derivatives of fullerene (C_{60}) are combinatorially enumerated in an itemized manner concerning symmetries and molecular formulas. The symmeterical properties of the derivatives are discussed by virtue of the sphericity concept. Bond-differentiating reactions are formulated in order to clarify possible routes to derivatives of several subsymmetries of $\mathbf{I}_h$.

7 Non-Rigid Molecules with Rotatable Ligands

7.1 Highest Attainable Symmetry. In the preceding discussions, we have mainly dealt with rigid molecules. Even when we have considered non-rigid molecules with rotatable ligands, we have regarded them as fixed conformers with the highest attainable symmetry. For example, ethanol (**15**) has been fixed to belongs to $\mathbf{C}_s$-symmetry in the above-mentioned discussion (Fig. 6). Although this fixation is convenient to discuss the methylene hydrogens of **15**, it causes such troubles that the three hydrogens of the methyl ligand are no longer equivalent under the $\mathbf{C}_s$-symmetry. This means that the highest attainable symmetry cannot fully characterize such flexibility.

Another troublesome compound (**47**) has been reported to be a meso-compound containing only $\mathbf{C}_1$-conformers (i.e. asymmetric conformers), where the rotation around the central bond is forbidden by the steric hindrance of As (Fig. 16).[45] The biphenyl part of this molecule has $\mathbf{D}_{2d}$ symmetry (cf. **9**), which is incompatible with the symmetries of terminal chiral ligands. Hence, the compound **47** belongs to $\mathbf{C}_1$-symmetry at the highest attainable symmetry, whereas **47** is achiral because of internal rotations of the terminal ligands. However, this type of stereochemical phenomenon is rather more generally observed than the original report[45] has claimed, so that *cis*-1,2-dimethylcyclohexane etc. behave in a similar way, as pointed out by a critical review.[121] Since the original discussion[45] as well as the critical review[121] are complicated for us to follow, a more straight-forward explanation is desirable.



47

Fig. 16. *meso*-Compound with $\mathbf{C}_1$-conformers.

In order to begin such a more straight-forward explanation, we have proposed the concept of proligand/promolecule as well as the related concept of matched/mismatched molecule.[114] These concepts enable us to discuss the items described above from a deeper and broader point of view.

7.2 Proligands and Promolecules. 7.2.1 Definitions. To overcome the drawbacks described in the preceding subsection, we have proposed the concept of proligand/promolecule.[114] *Proligands* are defined as hypothetical ligands which are structureless but have chirality/achirality. A *promolecule* consists of a skeleton and such proligands.

> The crux of organic chemistry is the recognition of a molecule as a mother skeleton with substituents, as reflected typically in the IUPAC nomenclature system. The symbols A, B, Q, R, etc. have been used to represent such substituents or ligands in most articles and books of chemical fields. (We use the word "ligand" in place of "substituent" in order to take account of chelated compounds.) Their definitions, however, have not been well-described from a group-theoretical point of view. When we use the symbols (A, B, Q, R, etc.) to denote proligands on the basis of the present definition, each proligand is always considered to obey a local symmetry decided by a CR.

To explain the behavior of **47**, we should comprehend the behaviors of relevant molecules along with **47** itself in the light of the concept of proligand/promolecule. To do this task, we here consider a biphenyl skeleton with two substitution positions (the terminal position of each phenyl), where a set of ligands selected from achiral proligands (X and Y) and chiral proligands (Q and $\bar{\mathrm{Q}}$) are substituted for the positions to produce a promolecule. Since the two substitution positions construct an orbit governed by $\mathbf{D}_{2d}(/\mathbf{C}_{2v})$, we first prepare a subgroup lattice for the $\mathbf{D}_{2d}(/\mathbf{C}_{2v})$-orbit, as shown in Fig. 17.

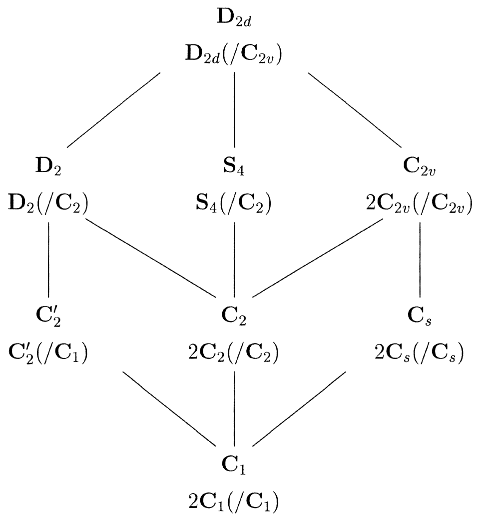


Fig. 17. Subgroup lattice of $\mathbf{D}_{2d}$ for a $\mathbf{D}_{2d}$ $(/\mathbf{C}_{2v})$-orbit.

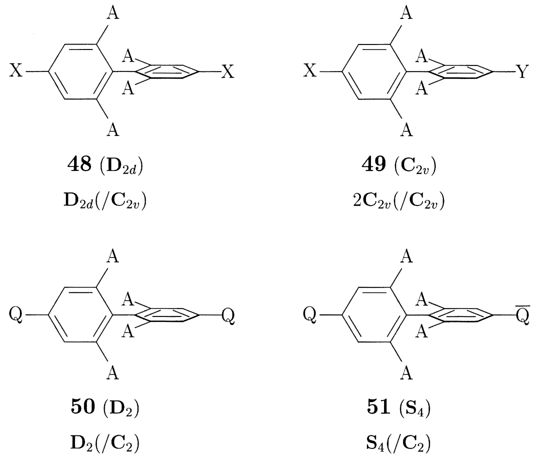
On the basis of the subgroup lattice (Fig. 17), the criterion for determining allowed and forbidden molecules is applied to the present case of promolecules. Thereby, we find promolecules depicted in Fig. 18. The CR $\mathbf{D}_{2d}(/\mathbf{C}_{2v})$ is reduced into the respective CR shown below each of the resulting promolecules. For example, the pair of $\{\mathrm{Q}, \bar{\mathrm{Q}}\}$ in **51** is assigned to an $\mathbf{S}_4(/\mathbf{C}_2)$-orbit.

7.2.2 Matched Molecules. By starting from the promolecules listed in Fig. 18, we can generate the corresponding molecules of the same symmetries, as shown in Fig. 19. These cases are called *matched molecules*, since each local symmetry is conserved.[114] We here use boron-containing cyclic ligands as ligands of $\mathbf{C}_{2v}$- and lower-symmetries, although they have not been synthesized.

The local symmetry of the $\mathbf{D}_{2d}(/\mathbf{C}_{2v})$-orbit in the promolecule (**48**) is $\mathbf{C}_{2v}$ so that the achiral proligand X can be replaced by a three-membered cyclic ligand of $\mathbf{C}_{2v}$-symmetry without desymmetrization. Hence, an achiral molecule **52** is generated.

Each of the proligands (X and Y) in **49** belongs to a one-membered $\mathbf{C}_{2v}(/\mathbf{C}_{2v})$-orbit. Hence, the achiral proligands X and Y can be replaced by three-membered cyclic ligands of different $\mathbf{C}_{2v}$-symmetries so as to give an achiral molecule **53** without desymmetrization.

The local symmetry of the $\mathbf{D}_2(/\mathbf{C}_2)$-orbit in the promolecule (**50**) is determined to be $\mathbf{C}_2$. Hence, the chiral proligand Q can be replaced by a three-membered cyclic ligand of $\mathbf{C}_2$-symmetry without desymmetrization, giving a chiral molecule **54**. The resulting molecule (**54**) has $\mathbf{D}_2$-symmetry.[115]



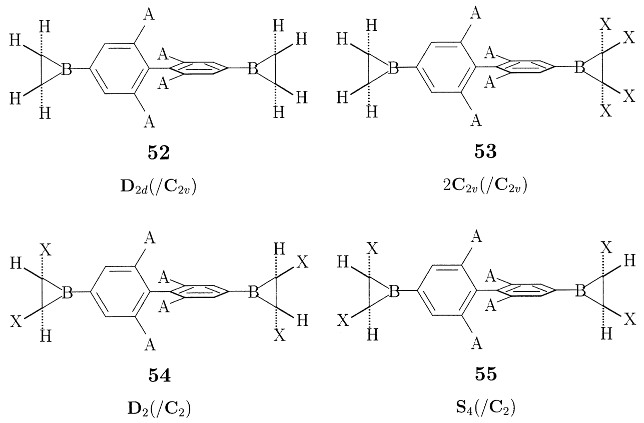
48 (D_{2d}) $\mathrm{D}_{2d}(/\mathrm{C}_{2v})$

49 (C_{2v}) $2\mathrm{C}_{2v}(/\mathrm{C}_{2v})$

50 (D_2) $\mathrm{D}_2(/\mathrm{C}_2)$

51 (S_4) $\mathrm{S}_4(/\mathrm{C}_2)$

Fig. 18. Promolecules from a biphenyl skeleton.



52 $\mathrm{D}_{2d}(/\mathrm{C}_{2v})$

53 $2\mathrm{C}_{2v}(/\mathrm{C}_{2v})$

54 $\mathrm{D}_2(/\mathrm{C}_2)$

55 $\mathrm{S}_4(/\mathrm{C}_2)$

Fig. 19. Biphenyl derivatives (matched molecules).

On the same line, the $\mathbf{S}_4(/\mathbf{C}_2)$-orbit of the promolecule (**51**) accommodates an enantiomeric pair of three-membered cyclic ligands of $\mathbf{C}_2$-symmetry in a fashion of compensated chiral packing. Thereby, an achiral molecule **55** is generated without desymmetrization.

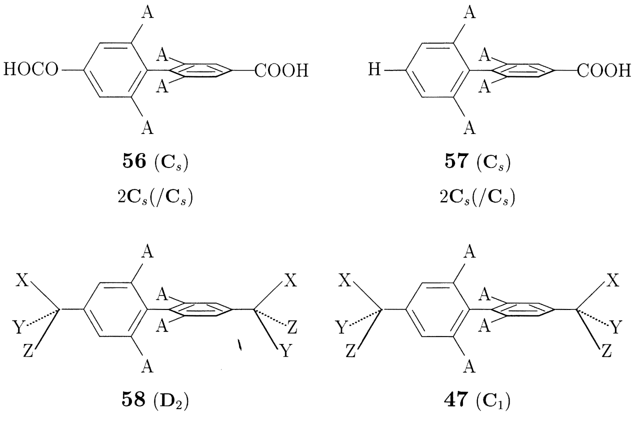
Obviously, the highest attainable symmetry of a matched molcule is equal to that of the corresponding promolecule, because the ligand can be placed so as not to violate the local symmetry in the promolecule.

7.2.3 Mismatched Molecules. When a ligand symmetry is lower than the local symmetry of an orbit of a promolecule, the global symmetry is no longer conserved. These cases are called *mismatched molecules*.[114] Figure 20 shows such mismatched molecules derived from the promolecules listed in Fig. 18.

Let us consider the two carboxyl ligands of the promolecule **56** shown in Fig. 20. Each of them has $\mathbf{C}_s$-symmetry in isolation, while the local symmetry of the $\mathbf{D}_{2d}(/\mathbf{C}_{2v})$-orbit in the promolecule (**48**) is $\mathbf{C}_{2v}$. Since the $\mathbf{C}_s$ is lower than the local symmetry $\mathbf{C}_{2v}$, the resulting molecule (**56**) no longer belongs to $\mathbf{D}_{2d}$ but belongs to $\mathbf{C}_s$ by virtue of the subgroup lattice (Fig. 17), so that the resulting local symmetry is matched to the original symmetry in isolation. As a result, the two carboxyl ligands of **56** are non-equivalent under fixed conditions because each of them constructs a distinct one-membered $\mathbf{C}_s(/\mathbf{C}_s)$-orbit. The non-equivalency is more clearly demonstrated by substituting a hydrogen for one of them, produing **57**. The symmetry of **57** can be explained in a similar way by starting from the promolecule **49**.

When chiral ligands of $\mathbf{C}_1$-symmetry (e.g. Q = CXYZ) are substituted for the Qs of **50**, the resulting molecule no longer belongs to $\mathbf{D}_2$, but is desymmetrized into $\mathbf{C}_2'$.[122] The two Qs construct a $\mathbf{C}_2'(/\mathbf{C}_1)$-orbit in agreement with the subgroup lattice (Fig. 17).

When the $\mathbf{S}_4(/\mathbf{C}_2)$-orbit of the promolecule (**51**) accommodates an enantiomeric pair of ligands of $\mathbf{C}_1$-symmetry (e.g. Q



56 (C_s) $2\mathrm{C}_s(/\mathrm{C}_s)$

57 (C_s) $2\mathrm{C}_s(/\mathrm{C}_s)$

58 (D_2) $\mathrm{C}_2'(/\mathrm{C}_1)$

47 (C_1) $2\mathrm{C}_1(/\mathrm{C}_1)$

Fig. 20. Mismatched molecules from a biphenyl skeleton (under fixed conditions).

= CXYZ and its enantiomeric ligand), desymmetrization occurs to give a molecule of $\mathbf{C}_1$-symmetry according to the subgroup lattice (Fig. 17). This case corresponds to the molecule **47** cited above. The inspection of mismatched molecules indicates that *the equivalency of ligands in such a molecule is determined at promolecule level.* Consequently, *the chirality/achirality of such a molecule is determined by the chirality/achirality of the corresponding promolecule.*[114] Thus, we should take account of the promolecule **51** of $\mathbf{S}_4$-symmetry in considering the chirality/achirality of **47**.

It is worthwhile to cite a typical explanation for such a molecule as **47** (e.g. the Mislow–Bolstad molecule[46]) from the Eliel–Wilen textbook[4] (p. 92): "Finally, we may consider the Mislow-Bolstad molecule. The molecule written is asymmetric ($\mathbf{C}_1$, order 1). There appear to be four pertinent conformations, generated by rotating the biphenyl moiety through successive angles of 90°. The order of the group is thus $1 \times 4 = 4$, which corresponds to the order of $\mathbf{S}_4$ and, indeed, it seems intuitively reasonable that the nonrigid point group of the molecule would be $\mathbf{S}_4$ (see ...)." However, the four rotating operations are by no means identical with the operation of the $\mathbf{S}_4$ so that the explanation "four pertinent conformations" is not so well-defined as to claim the $\mathbf{S}_4$-symmetry as the "nonrigid point group" of the molecule. Another explanation has been reported on the basis of topology, where the Mislow–Bolstad molecule is regarded as a Euclidean rubber glove, as mentioned to be "a molecule which can change itself into its mirror image but cannot be rotated to its mirror image".[123,124] Obviously, these approaches take account of global symmetries only and overlooks local symmetries so that they are incapable of discussing matched/mismatched molecules.

The concept of proligand/promolecule provides us with a versatile tool for treating flexible molecules as a kind of rigid molecules at promolecule level. Thus the promolecule **51** can be rigorously assigned to the $\mathbf{S}_4$-symmetry in the light of our approach. Since our approach takes global and local symmetries into consideration, it brings about a common and sound basis to discuss matched molecules such as **55** and mismatched molecules such as **47**. Moreover, the discussion in this subsection indicates that **47** as a meso-compound with $\mathbf{C}_1$-conformers is not a rare case, but has been proved to be an example of mismatched molecules defined by us.[114]

8 Promolecules from a Tetrahedral Skeleton

8.1 Methane Derivatives. Promolecules derived from a tetrahedral skeleton of $\mathbf{T}_d$-symmetry have been combinatorially enumerated, as shown in Fig. 21.[114] We use the symbols A, B, C, and D for achiral ligands and p, $\bar{\text{p}}$, q, $\bar{\text{q}}$, r, and s for chiral ligands, where a pair of p and $\bar{\text{p}}$ and another pair of q and $\bar{\text{q}}$ respectively represent enantiomeric ligand pairs in isolation.

The derivation of these promolecules rigorously obey the subduction of CRs, which is listed as a subduction table for $\mathbf{T}_d$ group in our book.[88] For example, the derivation of the $\mathbf{S}_4$-promolecule (**63**) is accomplished in agreement with the following subduction:

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{S}_4 = \mathbf{S}_4(/\mathbf{C}_1). \tag{9}$$

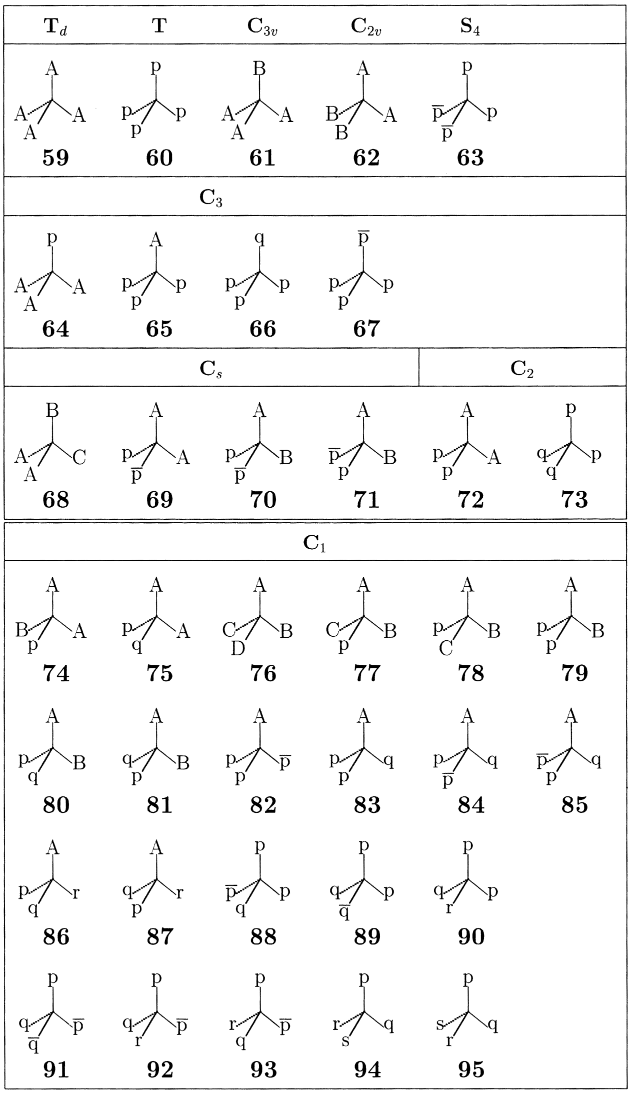


Fig. 21. Promolecules from a tetrahedral skeleton.[114]

The resulting CR $\mathbf{S}_4(/\mathbf{C}_1)$ is enantiospheric. Hence, the $\mathbf{S}_4(/\mathbf{C}_1)$-orbit accommodates two chiral ligands of the same kinds (p_2) and the corresponding ligands of the opposite chirality ($\bar{\text{p}}_2$) in a fashion of compensated chiral packing.

On the same line, promolecules derived from an allene skeleton of $\mathbf{D}_{2d}$-symmetry have been combinatorially enumerated to give a full list of such promolecules.[114,125]

8.2 Matched and Mismatched Tetrahedral Molecules. By starting from the promolecule CAAAA (**59**) of $\mathbf{T}_d$-symmetry, we can generate matched deriatives on the same line as described in the preceding section.[114] Since the orbit of the four As is governed by the CR $\mathbf{T}_d(/\mathbf{C}_{3v})$, it can accommodate a set of ligands of $\mathbf{C}_{3v}$-symmetrywithout reducing the $\mathbf{T}_d$-symmetry. For example, when we put methyl ligands in place of As, we can generate tetramethylmethane (2,2-dimethylpropane), the symmetry of which is determined to be $\mathbf{T}_d$ as the highest attainable symmetry. The $\mathbf{C}_{3v}$-symmetry of the methyl ligand is compatible to the local symmetry of the $\mathbf{T}_d(/\mathbf{C}_{3v})$-orbit.

Pentaerythritol (**10**) discussed above belongs to $\mathbf{D}_{2d}$ in the hightest attainable symmetry. This is alternatively considered to be derived from the promolecule **59** of $\mathbf{T}_d$-symmetry in a mismatched fashion. Since the hydroxymethyl ligand (CH_2OH) belongs to $\mathbf{C}_s$, the $\mathbf{T}_d$-symmetry is reduced into $\mathbf{D}_{2d}$ during this derivation so that the original $\mathbf{T}_d(/\mathbf{C}_{3v})$-orbit is subduced in agreement with the following equation:

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{D}_{2d} = \mathbf{D}_{2d}(/\mathbf{C}_s). \tag{10}$$

The local symmetry of the resulting CR $\mathbf{D}_{2d}(/\mathbf{C}_s)$ is compatible to the $\mathbf{C}_s$-symmetry of the CH_2OH ligand.

The symmetry of tetraphenylmethane can be regarded as another type of mismatched molecule in the light of the present approach. Thus, the $\mathbf{C}_{2v}$-symmetry of each phenyl ligand in isolation is restricted to $\mathbf{C}_s$ when incorporated in the molecule. Note that the intersection between the local symmery of the $\mathbf{T}_d(/\mathbf{C}_{3v})$-orbit and the in-isolation ligand symmetry is calculated to be $\mathbf{C}_{3v} \cap \mathbf{C}_{2v} = \mathbf{C}_s$, which corresponds to the local symmetry in the tetraphenylmethane molecule. As a result, the symmetry of tetraphenylmethane is also restricted to $\mathbf{D}_{2d}$ in agreement with eq.10. Possible point-group symmetries of tetraphenylmethane have been alternatively discussed by directly inspecting conformational changes of the four phenyl ligands.[126]

The promolecule Cpppp of **T**-symmetry (**60**) can generate a matched molecule by substituting a ligand of $\mathbf{C}_3$-symmetry for each p, according to the local symmetry of the corresponding $\mathbf{T}(/\mathbf{C}_3)$-orbit. As a ligand of $\mathbf{C}_3$-symmetry, we can use 2-(1*S*, *3S*, *5R*, 6*S*, 8*R*, 10*R*)-$\mathbf{D}_3$-trishomocubanylbuta-1,3-diynyl ligand. This ligand has been used by Nakazaki et al.[127] to synthesize (+)-1,3,5,7-tetrakis[2-(1*S*, 3*S*, 5*R*, 6*S*, 8*R*, 10*R*)-$\mathbf{D}_3$-trishomocubanylbuta -1,3-diynyl]adamantane as a molecule of **T**-symmetry. Note that the four bridgehead hydrogens of adamantane construct a $\mathbf{T}(/\mathbf{C}_3)$-orbit that is identical with that of the four p's in **60**.

If we select ligands of a symmetry lower than $\mathbf{C}_3$, a resulting molecule (a mismatched one) no longer belongs to **T**.[115] For example, we obtain a molecule **96** by selecting Q = CXYZ as a ligand of $\mathbf{C}_1$-symmetry. The resulting molecule **96**, which is schematically represented by the diagram **97** (Fig. 22), belongs to $\mathbf{D}_2$-symmetry in agreement with the following equation:

$$\mathbf{T}(/\mathbf{C}_3) \downarrow \mathbf{D}_2 = \mathbf{D}_2(/\mathbf{C}_1). \tag{11}$$

The local symmetry of the resulting CR $\mathbf{D}_2(/\mathbf{C}_1)$ is compatible to the $\mathbf{C}_1$-symmetry of the CXYZ ligand. Note here that the diagram **97** indicates a comformer of $\mathbf{D}_2$-symmetry as the highest attainable symmetry in a fixed condition. As a result, the sets of four X's, of four Y's, and of four Z's construct respective four-membered $\mathbf{D}_2(/\mathbf{C}_1)$-orbits in the fixed conformation. If we select the corresponding enantiomeric ligand ($\bar{p} = \bar{C}XYZ$), we can design the enantiomer of the molecule **97**. Pentaerythritol tetera(−)-menthyloxyacetate has been reported by McCasland et al.[128] as an example of this type of $\mathbf{D}_2$-molecules.

8.3 So-called *meso*-Compounds. Let us consider the promolecule **69** listed in Fig. 21.[105,102] The derivation of **69** is controlled by the following subduction:

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{C}_s = \mathbf{C}_s(/\mathbf{C}_1) + 2\mathbf{C}_s(/\mathbf{C}_s). \tag{12}$$

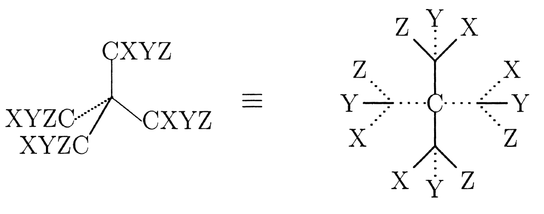
Hence, a pair of p and $\bar{p}$ constructs an enantiospheric $\mathbf{C}_s(/\mathbf{C}_1)$-orbit. On the other hand, one A belongs to a one-membered $\mathbf{C}_s(/\mathbf{C}_s)$-orbit in **69** and the other A belongs to another one-membered $\mathbf{C}_s(/\mathbf{C}_s)$-orbit. When p and $\bar{p}$ are replaced by *R*-CH(OH)COOH and *S*-CH(OH)COOH (two chiral ligands of opposite chiralities) and As are replaced by hydrogens, meso-2,4-dihydroxyglutaric acid (**21**) is generated as a molecule of $\mathbf{C}_s$-symmetry (Fig. 8). Since the effects of the enantiomeric chiral ligands are cancelled in **21**, this achiral molecule (**21**) is a so-called meso-compound.

The two hydrogens $H^{(a)}$ and $H^{(b)}$ on the central carbon of meso-2,4-dihydroxyglutaric acid (**21** in Fig. 8) are designated by the symbol *pro-s* and *pro-r* respectively by means of Hanson's criteria.[9] Although this differentiation is useful, $H^{(a)}$ and $H^{(b)}$ belong to distinct one-membered $\mathbf{C}_s(/\mathbf{C}_s)$-orbits. As a result, they can be differentiated chemically (*without any chiral conditions*) to generate two diastereomeric products such as **22** and **23**, which corespond to promolecules **70** and **71**.

On the other hand, a chiral condition can distinguish two chiral ligands, *R*-CH(OH)COOH and *S*-CH(OH)COOH, to generate either of enantiomeric (chiral) products, as shown in Fig. 23. When we consider a plausible oxidation (and a subsequent decarboxylation) of either ligand under chiral conditions, we can obtain either one of the products, **98** and **99**, which correspond to the promolecule CAABp or CAAB$\bar{p}$ (**74**) listed in Fig. 21.

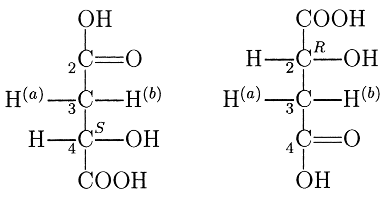
9 Promolecules from $\mathbf{D}_{\infty h}$-Skeletons

9.1 Infinite Groups. A more delicate discussion should be done in discussing the stereochemistry of ethane or ferrocene derivatives. Let us consider *meso*-tartaric acid (**20**) shown in Fig. 24. A conventional methodology is to regard **20** as a derivative of ethane, the symmetry of which is considered to be $\mathbf{D}_{3d}$ (for a staggered conformation) or $\mathbf{D}_{3h}$ (for an eclipsed



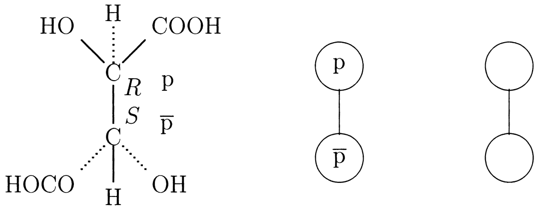
96 **97** ($\mathbf{D}_2$)

Fig. 22. Mismatched methane derivative with chiral ligands of the same kind.



98 **99**

Fig. 23. Enantiomeric products from *meso*-2,4-dihydroxyglutaric acid.



20 $\mathbf{C}_i$ (or $\mathbf{C}_s$) molecule **100** $\mathbf{C}_{\infty h}$ promolecule **101** $\mathbf{D}_{\infty h}$ skeleton

Fig. 24. Promolecule derived from a $\mathbf{D}_{\infty h}$-skeleton.

conformation).[4] In other words, it is based on the highest attainable symmetry for each fixed conformer and takes no account of rotations around the central bond. For example, the formula **20** is depicted as a staggered conformer of $\mathbf{C}_i$-symmetry, but can belong to $\mathbf{C}_s$-symmetry as an eclipsed conformer. Moreover, a rotation by 120° around the central bond generates a $\mathbf{C}_1$-conformer even by considering either of the conformations. Hence, this treatment is unsuitable to discuss the average nature and the isomer enumeration of such flexible derivatives.

According to our approach based on the concept of proligand/promolecule,[114] the chiral ligands of **20** (*R*-CH(OH)-COOH and *S*-CH(OH)COOH) are replaced by the corresponding proligands (p and p̄) to give a promolecule **100**. The promolecule is in turn considered to be derived from a $\mathbf{D}_{\infty h}$-skeleton (**101**) by putting a pair of p and p̄ on the two positions that can be assigned to a CR $\mathbf{D}_{\infty h}(/\mathbf{C}_{\infty v})$.[101,129]

When we place a pair of proligands selected from achiral proligands (A and B) and chiral ones (p, p̄, and q), we can obtain promolecules depicted in Fig. 25, where their symmetries are shown to be appropiate subgroups of $\mathbf{D}_{\infty h}$. Although the subgroups have infinite elements, CR such as $\mathbf{D}_{\infty}(/\mathbf{C}_{\infty})$ can be assigned to the resulting orbits. For example, the $\mathbf{D}_{\infty h}(/\mathbf{C}_{\infty v})$-orbit is subduced into $\mathbf{C}_{\infty h}$ according to the following equation:[101]

$$\mathbf{D}_{\infty h}(/\mathbf{C}_{\infty v}) \downarrow \mathbf{C}_{\infty h} = \mathbf{C}_{\infty h}(/\mathbf{C}_{\infty}). \tag{13}$$

Since the resulting $\mathbf{C}_{\infty h}(/\mathbf{C}_{\infty})$-orbit is enantiospheric, it can accommodate a pair of enantiomeric proligands (p and p̄) in a fashion of compensated chiral packing, generating the promolecule **100**.

To avoid difficulties due to the infinite nature of $\mathbf{D}_{\infty h}$, we can use the corresponding factor group:[101,129]

$$\mathbf{K}\ (= \mathbf{K}_5) = \mathbf{D}_{\infty h}/\mathbf{C}_{\infty} = \{\mathbf{C}_{\infty}, \mathbf{C}_{\infty}C_2, \mathbf{C}_{\infty}\sigma_{\mathrm{v}}, \mathbf{C}_{\infty}\sigma_{\mathrm{h}}\}, \tag{14}$$

which is isomorphic to $\mathbf{C}_{2v}$. The results of the infinite group $\mathbf{D}_{\infty h}$ and of the factor group **K** are shown in Fig. 25.

9.2 Ethanes. In the light of combinatorial enumeration based on the factor group **K** shown in Fig. 25, we can comprehend the stereoisomerism of ethane derivatives with atoms U, V, W, X, Y, and Z.[129] For example, we can predict that there are one U^5V-isomer, one U^4V^2-isomer, one U^4VW-isomer, two U^3V^3-isomers, two U^3V^2W-isomers, three $U^2V^2W^2$-isomers, and two U^2V^2WX-isomers, all of which belong to $\mathbf{K}_3[\mathbf{H}^{(a)};\mathbf{H}^{(a')}]$-symmetry (**105**). The symbol $\mathbf{K}_3[\mathbf{H}^{(a)};\mathbf{H}^{(a')}]$ represents a $\mathbf{K}_3$-isomer with achiral ligands (A and B) of $\mathbf{H}^{(a)}$- and $\mathbf{H}^{(a')}$-symmetry. They are depicted in Fig. 26, where the symbol $\mathbf{K}_3[\mathbf{C}_{3v};\mathbf{C}_s]$, for example, represents the case in which the molecule contains a $\mathbf{C}_{3v}$-ligand and a $\mathbf{C}_s$-ligand. An abreviated form $\mathbf{K}_3[\mathbf{C}_s]$ is used in place of the symbol $\mathbf{K}_3[\mathbf{C}_s;\mathbf{C}_s]$.

Each ligand (A or B) in the promolecule **105** belongs to a one-membered $\mathbf{K}_3(/\mathbf{K}_3)$-orbit (or $\mathbf{C}_{\infty v}(/\mathbf{C}_{\infty v})$-orbit), so the local symmetry of A (or B) is $\mathbf{K}_3$, which corresponds to $\mathbf{C}_{\infty v}$. Hence, all of the molecules shown in Fig. 26 are mismatched ones because the ligand symmetries, $\mathbf{C}_{3v}$ and $\mathbf{C}_s$, are subgroups of the local symmetry $\mathbf{C}_{\infty v}$.

9.3 Ferrocenes. Derivatives of ferrocene (**107**) can be

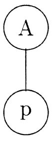
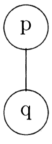
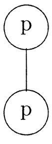
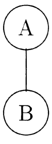
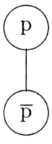
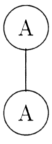
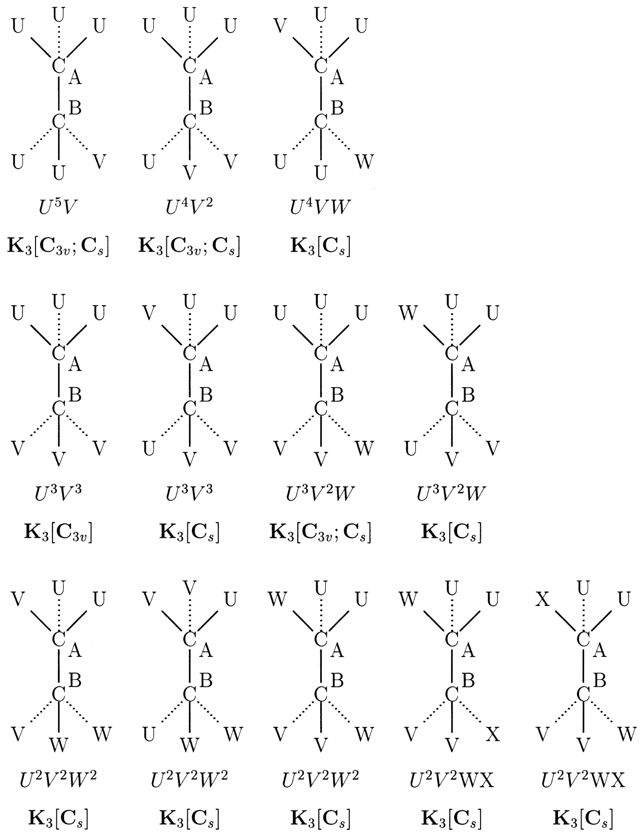
Promolecule	  **102** **103**	 **104**	 **105**	 **100**	 **106**
Point Group: $\mathbf{D}_{\infty h}$	$\mathbf{C}_{\infty}$	$\mathbf{D}_{\infty}$	$\mathbf{C}_{\infty v}$	$\mathbf{C}_{\infty h}$	$\mathbf{D}_{\infty h}$
$\mathbf{D}_{\infty h}(/\mathbf{C}_{\infty v}) \downarrow \mathbf{G}_i$	$2\mathbf{C}_{\infty}(/\mathbf{C}_{\infty})$	$\mathbf{D}_{\infty}(/\mathbf{C}_{\infty})$	$2\mathbf{C}_{\infty v}(/\mathbf{C}_{\infty v})$	$\mathbf{C}_{\infty h}(/\mathbf{C}_{\infty})$	$\mathbf{D}_{\infty h}(/\mathbf{C}_{\infty v})$
Factor Group: $\mathbf{K} = \mathbf{K}_5$	$\mathbf{K}_1$ $= \mathbf{C}_{\infty}/\mathbf{C}_{\infty}$	$\mathbf{K}_2$ $= \mathbf{D}_{\infty}/\mathbf{C}_{\infty}$	$\mathbf{K}_3$ $= \mathbf{C}_{\infty v}/\mathbf{C}_{\infty}$	$\mathbf{K}_4$ $= \mathbf{C}_{\infty h}/\mathbf{C}_{\infty}$	$\mathbf{K}_5$ $= \mathbf{D}_{\infty h}/\mathbf{C}_{\infty}$
$\mathbf{K}(/\mathbf{K}_3) \downarrow \mathbf{K}_i$	$2\mathbf{K}_1(/\mathbf{K}_1)$	$\mathbf{K}_2(/\mathbf{K}_1)$	$2\mathbf{K}_3(/\mathbf{K}_3)$	$\mathbf{K}_4(/\mathbf{K}_1)$	$\mathbf{K}(/\mathbf{K}_3)$
USCI-CF	b_1^2	b_2	a_1^2	c_2	a_2

Fig. 25. Promolecules of $\mathbf{D}_{\infty h}$ and Subgroups of Factor Group $\mathbf{K}$[129].

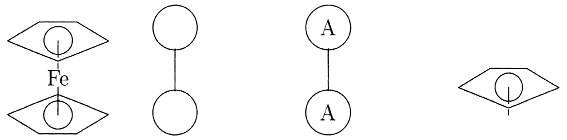


U^5V $\mathbf{K}_3[\mathbf{C}_{3v}; \mathbf{C}_s]$ — U^4V^2 $\mathbf{K}_3[\mathbf{C}_{3v}; \mathbf{C}_s]$ — U^4VW $\mathbf{K}_3[\mathbf{C}_s]$

U^3V^3 $\mathbf{K}_3[\mathbf{C}_{3v}]$ — U^3V^3 $\mathbf{K}_3[\mathbf{C}_s]$ — U^3V^2W $\mathbf{K}_3[\mathbf{C}_{3v}; \mathbf{C}_s]$ — U^3V^2W $\mathbf{K}_3[\mathbf{C}_s]$

$U^2V^2W^2$ $\mathbf{K}_3[\mathbf{C}_s]$ — $U^2V^2W^2$ $\mathbf{K}_3[\mathbf{C}_s]$ — $U^2V^2W^2$ $\mathbf{K}_3[\mathbf{C}_s]$ — U^2V^2WX $\mathbf{K}_3[\mathbf{C}_s]$ — U^2V^2WX $\mathbf{K}_3[\mathbf{C}_s]$

Fig. 26. Derivatives with $\mathbf{K}_3[\mathbf{H}^{(a)};\mathbf{H}^{(a')}]$.[129]

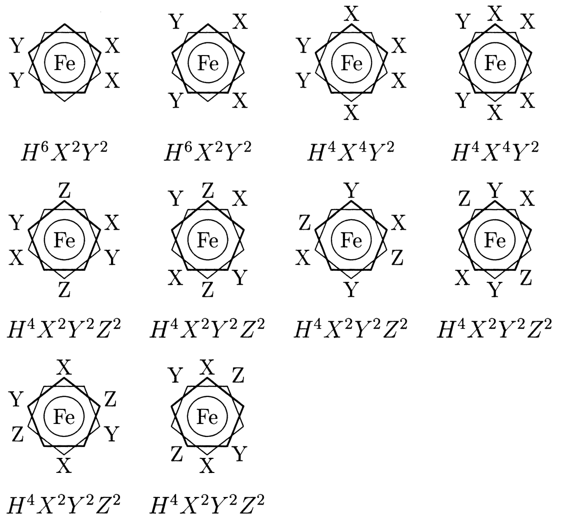


107 ferrocence — **101** skeleton — **106** promolecule with proligands A — **108** ligand for proligand A

Fig. 27. Ferrocene and promolecule.

generated from the $\mathbf{D}_{\infty h}$-skeleton (**101**), as shown in Fig. 27.[130] Ferrocene (**107**) itself is generated by putting the cyclopentadienyl ligand (**108**) on **101** via the corresponding promolecule **106**. When the cyclopendadienyl ligand (**108**) is substituted by a given set of atoms, the resulting ligand belongs to a subsymmetry of $\mathbf{C}_{5v}$, which is chiral ($\mathbf{C}_1$ or $\mathbf{C}_5$) or achiral ($\mathbf{C}_s$ or $\mathbf{C}_{5v}$) in accord with the substitution pattern. According to the conversion process of the ligand symmetry, the proligand A is considered to be converted into a chiral proligand (p) or another achiral one (B). Thereby, a promolecule substituted by the resulting proligands is generated so that it belongs to a subsymmetry of $\mathbf{D}_{\infty h}$.

We can use the promolecules of $\mathbf{D}_{\infty h}$ and its subsymmetries listed in Fig. 25. To enumerate ferrocene derivatives, each of the proligands is replaced by a substituted cyclepentadienyl anion as a ligand. The chirality/achirality nature of such proligands is maintained in this treatment.



$H^6X^2Y^2$ — $H^6X^2Y^2$ — $H^4X^4Y^2$ — $H^4X^4Y^2$

$H^4X^2Y^2Z^2$ — $H^4X^2Y^2Z^2$ — $H^4X^2Y^2Z^2$ — $H^4X^2Y^2Z^2$

$H^4X^2Y^2Z^2$ — $H^4X^2Y^2Z^2$

Fig. 28. Several ferrocene derivatives of $\mathbf{K}_4$-symmetry.[130]

So-called meso-derivatives of ferrocene are characterized by the $\mathbf{K}_4$-symmetry in the present approach. The $\mathbf{K}_4$-symmetry is symbolically represented by p–$\bar{\text{p}}$, where p and $\bar{\text{p}}$ are enantiomeric to each other. A combinatorial enumeration has shown that the $\mathbf{K}_4$-symmetry is realized in two isomers with $H^6X^2Y^2$, two isomers with $H^4X^4Y^2$, and six isomers with $H^4X^2Y^2Z^2$, which are depicted in Fig. 28.

10 Mathematical Aspects with Applications

10.1 Symmetry Adapted Functions. A CR $\mathbf{G}(/\mathbf{G}_i)$, which is defined algebraically by a coset decomposition of a finite group $\mathbf{G}$ by its subgroup $\mathbf{G}_i$, has been shown to bring out a method for the decomposition of a regular body into its point group orbits.[131] This proof also shows that each member of the $\mathbf{G}(/\mathbf{G}_i)$-orbit belongs to the $\mathbf{G}_i$ site-symmetry. In addition, a general equation concerning the multiplicities of such CRs is derived and shown to involve Brester's equations[31] and the *k*-value equations of framework groups[24] as special cases of our formulation. The relationship between the CR and the site-symmetry gives a general procedure for obtaining symmetry adapted functions.[131]

10.2 USCI Approach for Combinatorial Enumeration. We have derived unit subduced cycle indices (USCIs) from the subduction of CRs.[91] Thereby, we have developed four methods for combinatorial enumeration concerning both molecular formulas and symmetries. They are the subduced-cycle-index (SCI) method,[91] the partial-cycle index (PCI) method,[132] the elementary-superposition method,[133] and the partial-superposition method.[133] They are collectively called *the USCI approach*, since they start from unit subduced cycle indices (USCIs) obtained by the subduction of CRs.

We have derived Pólya's cycle indices from USCIs.[134] We have proposed USCIs with chirality fittingness (USCI-CFs) and have applied them to enumeration of chemical structures with achiral and chiral ligands.[135,109] We have shown the versatility of the USCI method by applying it to systematic enumerations of various chemical objects: highly symmetric cage-shaped molecules,[136] adamantane isomers,[119] compounds derived from $\mathbf{D}_{3h}$-skeletons,[108] dodecahedrane derivatives,[112] soccerane derivatives,[113] non-rigid molecues,[137,138] octahedral complexes,[111] benzene derivatives,[110] digraphs,[132] polyhedrons,[139] C_{60}-adducts,[120] and superphanes.[93]

10.3 Characteristic Monomials for Combinatorial Enumeration. In addition, Pólya's theorem has been shown to stem from dominant representations and dominant markaracters (mark-character) that have been defined as the CRs and the marks for cyclic subgroups.[140,141] Dominant representations have been correlated to $\mathbf{Q}$-conjugacy representations and the subduction of the latter has been shown to give characteristic monomials (CMs) for combinatorial enumeration.[142,143] Mathematical foundations for the characteristic-monomial (CM) method have been clarified.[144–147] The CM method has been applied to various isomer enumerations.[148–150]

10.4 Pseudo-Point Groups. After the proposal of pseudo-point groups, the USCI method is also applied to the enumeration of flexible six-membered rings such as cyclohexanes,[151,152] tetrahydropyran and 1,3-dioxane derivatives,[153] 1,4-dioxane and 1,4-oxathiane derivatives,[154] spiro[5.5]undecane derivaitves,[155] and piperidine derivatives.[156]

10.5 Symmetry Number. The symmetry number σ is important in the computation of entropy. It is defined as the number of indistinguishable but nonincidental positions into which the molecule can be turned by rigid rotations.[4] The symmetry number for a finite chiral point group is usually regarded as being equal to the order of the group, while it is one-half the order for a finite achiral point group. Obviously, this method cannot be applied to infinite groups such as $\mathbf{C}_{\infty h}$ and $\mathbf{D}_{\infty h}$, which are treated as exceptions, as found in 4-6.c in Ref. 4. This means that the order of a group cannot be directly linked to the symmetry number of the group.

In our approach,[157] a factor group $\mathbf{G}/\mathbf{G}_j$ (= $\mathbf{K}$) is used in place of the symmetry $\mathbf{G}$ of a molecule, where the infinite nature of $\mathbf{G}$ is concealed by the infinite chiral subgroup $\mathbf{G}_j$ *without violating the sphericities of all positions* (*strictly speaking, all orbits*) *in the molecule*, as discussed in Subsection 9.1. For example, $\mathbf{K}_5$ (= $\mathbf{D}_{\infty h}/\mathbf{C}_{\infty}$; order 4) and $\mathbf{K}_3$ (= $\mathbf{C}_{\infty v}/\mathbf{C}_{\infty}$; order 2) are used respectively in place of $\mathbf{D}_{\infty h}$ and $\mathbf{C}_{\infty v}$. If $\mathbf{G}$ is a finite group, the corresponding factor group $\mathbf{G}/\mathbf{C}_1$ (= $\mathbf{G}$) is used.

Let $\mathbf{K}_i$ (= $\mathbf{G}_i/\mathbf{G}_j \subset \mathbf{K}$) be the smallest cyclic subgroup corresponding to an achiral subgroup $\mathbf{G}_i$ of $\mathbf{G}$. Suppose that $\mathbf{K}_i^{(max)}$ (= $\mathbf{G}_i^{(max)}/\mathbf{G}_j$) is the maximal subgroup of $\mathbf{K}$ and corresponds to the maximal chiral subgroup $\mathbf{G}_i^{(max)}$. When $\mathbf{G}$ is chiral, we place $\mathbf{K}_i = \mathbf{K}_i^{(max)} = \mathbf{G}_j/\mathbf{G}_j$. Then, the symmetry number of $\mathbf{K}$ (and also $\mathbf{G}$) is calculalted as follows:

$$\sigma = |\mathbf{K}| \times \frac{|\mathbf{K}_i^{(max)}|}{|\mathbf{K}_i|} = \frac{|\mathbf{G}|}{|\mathbf{G}_j|} \times \frac{|\mathbf{G}_i^{(max)}|}{|\mathbf{G}_i|} \tag{15}$$

For example, the symmetry number for $\mathbf{D}_{\infty h}$ is calculated to be $|\mathbf{K}_5| \times (|\mathbf{K}_1|/|\mathbf{K}_3|) = 4 \times (1/2) = 2$; for $\mathbf{T}_d$, it is calculated to be $(|\mathbf{T}_d|/|\mathbf{C}_1|) \times (|\mathbf{C}_1|/|\mathbf{Cs}|) = 24 \times (1/2) = 12$; and for $\mathbf{S}_4$, it is calculated to be $(|\mathbf{S}_4|/|\mathbf{C}_1|) \times (|\mathbf{C}_2|/|\mathbf{S}_4|) = 4 \times (2/4) = 2$.

11 Conclusion

A set of equivalent objects (atoms, ligands, faces, etc.) in a molecule $\mathbf{G}$ is considered to construct an orbit (equivalence class) governed by a coset representation (CR), where the symbol of the CR is coined to be $\mathbf{G}(/\mathbf{G}_i)$ by virtue of the global symmetry $\mathbf{G}$ and the local symmetry $\mathbf{G}_i$ of the orbit. The SCR (set-of-coset-representations) notation is proposed to classify molecules more specifically than the usual point groups can. The sphericity concept (homospheric, enantiospheric, and hemispheric) and the relevant concept of chirality fittingness are proposed according to the chirality/achirality of $\mathbf{G}$ and $\mathbf{G}_i$ and these concepts are applied to the characterization of the stereochemical phenomena of the $\mathbf{G}(/\mathbf{G}_i)$-orbit and the revised definition of the well-known topicity terms (homotopic, enantiotopic, and heterotopic; chirotopic and achirotopic) as well as the specification of terms "stereogenicity and prostereogenicity" and "prochirality". The concept of subduction of CRs is proposed to characterize the desymmetrization of molecules, where the design of high-symmetry molecules is discussed in term of desymmetrization by atom replacement and by bond replacement. The concept of proligand/promolecule is proposed in order to characterize the stereochemistry of non-rigid molecules with rotatable ligands, where biphenyl derivatives, methane derivatives, ethane derivatives, and ferrocene derivatives are examined in terms of matched and mismatched molecules. Applications to combinatorial enumeration, symmetry adapted functions, flexible six-membered cyclic compounds, and symmetry numbers are also described by starting from the concept of subduction of CRs.

Appendix. Coset Representations and Related Concepts. Mathematical Foundations and Illustrative Examples

A1. Mathematical Foundations. Suppose that a position of a given skeleton of symmetry $\mathbf{G}$ is stabilized (fixed) under the action of $\mathbf{G}_i$ that is a subgroup of $\mathbf{G}$. Then consider the following coset decomposition:

$$\mathbf{G} = \mathbf{G}_i g_1 + \mathbf{G}_i g_2 + \dots + \mathbf{G}_i g_s, \tag{16}$$

where the symbols g_j ($j = 1, 2, \dots, s$) represent a transversal of representatives ($g_1 = I$; identity). Each set $\mathbf{G}_i g_j$ is called a coset. Thereby, the position and its equivalent positions under $\mathbf{G}$ correspond in one-to-one fashion to the cosets appearing on the right-hand side of Eq. 16. For any $g \in \mathbf{G}$, the set of cosets $\mathbf{G}_i g_j$ are converted into another set of cosets $\mathbf{G}_i g_j g$, where the former set is equal to the latter set, but the ordering of the cosets of the former is different from that of the latter. It follows that the action of g corresponds to a permutation represented by the following equation:

$$\pi_g = \begin{pmatrix} \mathbf{G}_i g_1 & \mathbf{G}_i g_2 & \dots & \mathbf{G}_i g_s \\ \mathbf{G}_i g_1 g & \mathbf{G}_i g_2 g & \dots & \mathbf{G}_i g_s g \end{pmatrix}. \tag{17}$$

If the original set of cosets $\mathbf{G}_i g_j$ is sequentially numbered from 1 to s, the permutation represented by Eq. 17 is regarded as a permutation of an ordered set of numbers. Since g runs over $\mathbf{G}$, the permutations of degree s (π_g where $g \in \mathbf{G}$) construct a representation of $\mathbf{G}$. This is called a coset representation (CR), which is designated by the symbol $\mathbf{G}(/\mathbf{G}_i)$. The CR $\mathbf{G}(/\mathbf{G}_i)$ controls the equivalence classe (orbit) that is composed of the position and its equivalent positions in the $\mathbf{G}$-skeleton. Accordingly, the orbit is called a $\mathbf{G}(/\mathbf{G}_i)$-orbit. It should be emphasized that $\mathbf{G}$ represents the global symmetry of the skeleton while $\mathbf{G}_i$ is the local symmetry of the orbit of equivalent positions.

Mathematically speaking, a $\mathbf{G}(/\mathbf{G}_i)$-orbit represents the congruence nature with regard to $\mathbf{G}_i$ as a modulus. In other words, the

Table 4. Coset Representations $\mathbf{D}_{2d}(/\mathbf{C}_1)$ and $\mathbf{D}_{2d}(/\mathbf{C}_s)$[88]

Element		CR	CR	Subgroup (up to conjugacy)							
of $\mathbf{D}_{2d}$		$\mathbf{D}_{2d}(/\mathbf{C}_1)$	$\mathbf{D}_{2d}(/\mathbf{C}_s)$	$\mathbf{C}_1$	$\mathbf{C}_2$	$\mathbf{C}_2{}'$	$\mathbf{C}_s$	$\mathbf{S}_4$	$\mathbf{C}_{2v}$	$\mathbf{D}_2$	$\mathbf{D}_{2d}$
I	~	(1)(2)(3)(4)(5)(6)(7)(8)	(1)(2)(3)(4)	x	x	x	x	x	x	x	x
$C_{2(1)}$	~	(12)(34)(56)(78)	(12)(34)			x				x	x
$C_{2(2)}$	~	(13)(24)(57)(68)	(13)(24)							x	x
$C_{2(3)}$	~	(14)(23)(58)(67)	(14)(23)		x			x	x	x	x
$\sigma_{d(1)}$	~	$\overline{(1\,5)(2\,7)(3\,6)(4\,8)}$	$\overline{(1)(2\,3)(4)}$				x		x		x
S_4	~	$\overline{(1\,7\,4\,6)(2\,5\,3\,8)}$	$\overline{(1\,2\,4\,3)}$					x			x
$S_4{}^3$	~	$\overline{(1\,6\,4\,7)(2\,8\,3\,5)}$	$\overline{(1\,3\,4\,2)}$					x			x
$\sigma_{d(2)}$	~	$\overline{(1\,8)(2\,6)(3\,7)(4\,5)}$	$\overline{(1\,4)(2)(3)}$						x		x

cosets on the right-hand side of Eq. 16 are regarded as residue classes modulo $\mathbf{G}_i$. By keeping this in mind, the sphericity is defined as the congruence of such a $\mathbf{G}(/\mathbf{G}_i)$-orbit with regard to the chirality/achirality of $\mathbf{G}_i$ as a modulus. As a result, the cosets on the right-hand side of eq.16 are congruent so that, if $\mathbf{G}$ is achiral and $\mathbf{G}_i$ is chiral, the cosets are classified into a set of cosets containing only proper rotations and another set of cosets containing only improper rotations; if both $\mathbf{G}$ and $\mathbf{G}_i$ are achiral, the cosets give a set of cosets containing both proper and improper rotations; and, rather trivially, the cosets give a set of cosets containing proper rotations if both $\mathbf{G}$ and $\mathbf{G}_i$ are chiral. These cases corespond respectively to enantiospheric, homospheric, and hemispheric cases listed in Table 1. A more general treatment has been reported in terms of subductions represented by $\mathbf{G}(/\mathbf{G}_i) \downarrow \mathbf{G}^{(max)}$ or double coset decompositions represented by $\Sigma_g \mathbf{G}_i g \mathbf{G}^{(max)}$, where the symbol $\mathbf{G}^{(max)}$ represents the maximal chiral subgroup of $\mathbf{G}$.[139]

A2. Illustrative Examples. Each permutation represened by Eq. 17 can be alternatively in the form of a product of cycles, e.g.,

$$\begin{pmatrix} 1\,2\,3\,4 \\ 1\,3\,2\,4 \end{pmatrix} = (1)(2\,3)(4) \tag{18}$$

Let us examine the orbit Δ_2 (Eq. 2) of the four bridgehead positions of adamantane-2,6-dione of $\mathbf{D}_{2d}$-symmetry. Since the local symmetry of the orbit is $\mathbf{C}_s$, Eq. 16 for this case is represented by the following coset decomposition:

$$\mathbf{D}_{2d} = \mathbf{C}_s + \mathbf{C}_s C_{2(1)} + \mathbf{C}_s C_{2(2)} + \mathbf{C}_s C_{2(3)} \tag{19}$$

As a result, we obtain the following permutation for the proper rotation $C_{2(1)}$:

$$\begin{aligned} C_{2(1)} &\sim \begin{pmatrix} \mathbf{C}_s & \mathbf{C}_s C_{2(1)} & \mathbf{C}_s C_{2(2)} & \mathbf{C}_s C_{2(3)} \\ \mathbf{C}_s C_{2(1)} & \mathbf{C}_s C_{2(1)}^2 & \mathbf{C}_s C_{2(2)} C_{2(1)} & \mathbf{C}_s C_{2(3)} C_{2(1)} \end{pmatrix} \\ &= \begin{pmatrix} \mathbf{C}_s & \mathbf{C}_s C_{2(1)} & \mathbf{C}_s C_{2(2)} & \mathbf{C}_s C_{2(3)} \\ \mathbf{C}_s C_{2(1)} & \mathbf{C}_s & \mathbf{C}_s C_{2(3)} & \mathbf{C}_s C_{2(2)} \end{pmatrix} \\ &= \begin{pmatrix} 1 & 2 & 3 & 4 \\ 2 & 1 & 4 & 3 \end{pmatrix} = (1\,2)(3\,4) \end{aligned} \tag{20}$$

Similarly, we can obtain permutations for the other operations of $\mathbf{D}_{2d}$. They construct a CR $\mathbf{D}_{2d}(/\mathbf{C}_s)$ collected in Table 4 in the form of products of cycles. Since each permutation for an improper rotation corresponds to the conversion into a mirror image, it is designated by an overline. The resulting CR $\mathbf{D}_{2d}(/\mathbf{C}_s)$ is assigned to the orbit Δ_2 shown in Fig. 1 by placing as follows:

$$\Delta_2 \begin{cases} \mathrm{H}^{(A)} & \mathrm{H}^{(B)} & \mathrm{H}^{(C)} & \mathrm{H}^{(D)} \\ 1 & 4 & 2 & 3 \end{cases}$$

Table 4 also contains the concrete form of the CR $\mathbf{D}_{2d}(/\mathbf{C}_1)$. The correspondence between the CR and the orbit Δ_1 (Fig. 1) is confirmed by placing as follows:

$$\Delta_1 \begin{cases} \mathrm{H}^{(a)} & \mathrm{H}^{(b)} & \mathrm{H}^{(c)} & \mathrm{H}^{(d)} & \mathrm{H}^{(a')} & \mathrm{H}^{(b')} & \mathrm{H}^{(c')} & \mathrm{H}^{(d')} \\ 1 & 3 & 4 & 2 & 8 & 7 & 5 & 6 \end{cases}$$

The subduction of CRs are accomplished by such data as collected in Table 4. For example, the subduction $\mathbf{D}_{2d}(/\mathbf{C}_s) \downarrow \mathbf{C}_s$ (cf. Eq. 3) is conducted by selecting the permutations for $\mathbf{C}_s$ from Table 4. The resulting group $\mathbf{C}_s = \{(1)(2)(3)(4), \overline{(1)(2\,3)(4)}\}$ brings out the division into three sets of positions, i.e., 1; 2 and 3; and 4. The two one-membered sets are assigned to the CR $\mathbf{C}_s(/\mathbf{C}_s)$, while the two-membered set corresponds to the CR $\mathbf{C}_s(/\mathbf{C}_1)$. This algebraic process is represented by Eq. 3, which has once been obtained intuitively. The subduction data collected in Table 3 have been obtained in a similar but more algebraic method.[88]

References

1 J. H. van't Hoff, *Arch. Neerl. Sci. Exactes Nat.*, **9**, 445 (1874).

2 A. Werner, *Anorg. Chem.*, **3**, 267 (1893).

3 A. M. Rouhi, *Chem. Eng. News*, (Sept. 6), 28 (1999).

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

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

6 F. M. Jaeger, "Spacial Arrangements of Atomic Systems and Optical Activity," McGraw-Hill, New York (1930).

7 J. K. O'Loane, *Chem. Rev.*, **80**, 41 (1980).

8 R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).

9 K. R. Hanson, *J. Am. Chem. Soc.*, **88**, 2731 (1966).

10 H. Hirschmann and K. R. Hanson, *Eur. J. Biochem.*, **22**, 301 (1971).

11 H. Hirschmann and K. R. Hanson, *J. Org. Chem.*, **36**, 3293 (1971).

12 V. Prelog, *Chem. Brit.*, **4**, 382 (1968).

13 V. Prelog and G. Helmchen, *Helv. Chim. Acta*, **55**, 2581 (1972).

14 V. Prelog, *Science*, **193**, 17 (1976).

15 H. Hirschmann and K. R. Hanson, *Tetrahedron*, **30**, 3649 (1974).

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

17 H. Hirschmann and K. R. Hanson, *Top. Stereochem.*, **14**, 183 (1983).

18 K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

19 M. Nakazaki, *Kagaku (Kyoto)*, **23**, 614 (1968), in Japanese.

20 M. Nakazaki, *Kagaku no Ryoiki (Tokyo)*, **22**, 1057 (1968), in Japanese.

21 E. L. Eliel, *J. Chem. Educ.*, **57**, 52 (1980).

22 K. Mislow and J. Siegel, *J. Am. Chem. Soc.*, **106**, 3319 (1984).

23 R. L. Flurry, *J. Am. Chem. Soc.*, **103**, 2901 (1981).

24 J. A. Pople, *J. Am. Chem. Soc.*, **102**, 4615 (1980).

25 G. E. McCasland, "A New General System for the Naming of Stereoisomers," Chemical Astracts, Columbus (1953).

26 V. Prelog and G. Helmchen, *Angew. Chem., Int. Ed. Engl.*, **21**, 567–583 (1982).

27 E. L. Eliel, *Top. Curr. Chem.*, **105**, 1 (1982).

28 P. Mata, A. M. Lobo, C. Marshall, and A. P. Johnson, *Tetrahedron: Asymmetry*, **4**, 657 (1993).

29 M. Perdih and M. Razinger, *Tetrahedron: Asymmetry*, **5**, 835 (1994).

30 P. Mata and R. B. Nachbar, *Tetrahedron: Asymmetry*, **6**, 693 (1995).

31 R. M. Silverstein, G. C. Bassler, and T.C. Morrill, "Infrared and Raman Spectra of Polyatomic Molecules," Van Nostrand, New York (1945).

32 W. B. Jenning, *Chem. Rev.*, **75**, 307 (1975).

33 R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectroscopic Identification of Organic Compounds," 4th ed, John & Wiley, New York (1981).

34 G. Binsch, E. L. Eliel, and H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **10**, 570 (1971).

35 H. H. Jaffé and M. Orchin, "Symmetry in Chemistry," Wiley, Chichester (1965).

36 L. H. Hall, "Group Theory and Symmetry in Chemistry," McGraw-Hill, New York (1969).

37 F. A. Cotton, "Chemical Applications of Group Theory," Wiley-International, New York (1971).

38 D. M. Bishop, "Group Theory and Chemistry," Clarendon, Oxford (1973).

39 I. Hargittai and H. Hargittai, "Symmetry through the Eyes of a Chemist," VCH, Weinheim (1986).

40 E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "The Conformational Analysis," John-Wiley & Sons, New York (1965).

41 J. B. Lambert and S. I. Featherman, *Chem. Rev.*, **75**, 611 (1975).

42 R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, **63**, 602 (1965).

43 M. Nakamura, M. Oki, and H. Nakanishi, *J. Am. Chem. Soc.*, **95**, 7169 (1973).

44 K. Schlögel, *Top. Stereochem.*, **1**, 39 (1967).

45 K. Mislow, *Science*, **120**, 232 (1954).

46 K. Mislow and R. Bolstad, *J. Am. Chem. Soc.*, **77**, 6712 (1955).

47 P. Finocchiaro, D. Gust, and K. Mislow, *J. Am. Chem. Soc.*, **96**, 3198 (1974).

48 E. L. Eliel, *Israel J. Chem.*, **15**, 7 (1976/1977).

49 E. Ruch, *Acc. Chem. Res.*, **5**, 49 (1972).

50 E. Ruch, *Angew. Chem., Int. Ed. Engl.*, **16**, 65 (1977).

51 C. A. Mead, *Top. Curr. Chem.*, **49**, 1 (1974).

52 I. Ugi, D. Marquading, H. Klusacek, G. Gokel, and P. Gillespie, *Angew. Chem., Int. Ed.*, **9**, 703 (1970).

53 I. Ugi, J. Dugundji, R. Kopp, and D. Marquarding, "Perspectives in Theoretical Stereochemistry," Springer-Verlag, Berlin-Heidelberg (1984).

54 I. Ugi, *Chimia*, **40**, 340 (1986).

55 J. Brocas, M. Gielen, and R. Willem, "The Permutational Approach to Dynamic Stereochemistry," McGraw-Hill International, New York (1983).

56 "The Permutation Group in Physics and Chemistry (Lecture Notes in Chemistry 12)," ed by J. Hinze, Springer-Verlag, Berlin Heidelberg (1979).

57 J. G. Nourse, *J. Am. Chem. Soc.*, **101**, 1210 (1979).

58 G. Pólya, *Compt. Rend.*, **201**, 1167 (1935).

59 G. Pólya, *Helv. Chim. Acta*, **19**, 22 (1936).

60 G. Pólya, *Z. Kristal. (A)*, **93**, 415 (1936).

61 G. Pólya, *Acta Math.*, **68**, 145 (1937).

62 N. G. de Bruijn, *Indag. Math.*, **21**, 59 (1959).

63 J. H. Redfield, *Amer. J. Math.*, **49**, 433 (1927).

64 J. H. Redfield, *J. Graph Theory*, **8**, 205 (1984).

65 R. A. Davidson, *J. Amer. Chem. Soc.*, **103**, 312 (1981).

66 R. C. Read, *J. London Math. Soc.*, **34**, 417 (1959).

67 R. C. Read, *J. London Math. Soc.*, **35**, 344 (1960).

68 R. C. Read, *Canad. J. Math.*, **20**, 808 (1968).

69 D. H. Rouvray, *Chem. Soc. Rev.*, **3**, 355 (1974).

70 F. Harary, E. M. Palmer, R. W. Robinson, and R. C. Read, in "Chemical Aplications of Graph Theorey," ed by A. T. Balaban, Academic, London (1976), pp. 11–24.

71 K. Balasubramanian, *Chem. Rev.*, **85**, 599 (1985).

72 "Chemical Applications of Graph Theory," ed by A. T. Balaban, Academic Press, London (1976).

73 G. Pólya, R. E. Tarjan, and D. R. Woods, "Notes on Introductory Combinatorics," Birkhäuser, Boston (1983).

74 G. Pólya and R. C. Read, "Combinatorial Enumeration of Groups, Graphs, and Chemical Compounds," Springer-Verlag, New York (1987).

75 E. Ruch, W. Hässelbarth, and B. Richter, *Theor. Chim. Acta*, **19**, 288 (1970).

76 E. Ruch and D. J. Klein, *Theor. Chim. Acta*, **63**, 447 (1983).

77 W. J. Taylor, *J. Chem. Phys.*, **11**, 532 (1943).

78 T. L. Hill, *J. Chem. Phys.*, **11**, 294 (1943).

79 D. H. McDaniel, *Inorg. Chem.*, **11**, 2678 (1972).

80 J. E. Leonard, *J. Phys. Chem.*, **81**, 2212 (1977).

81 J. R. L. Flurry, *J. Chem. Educ.*, **61**, 663 (1984).

82 J. Sheehan, *Canad. J. Math.*, **20**, 1068 (1968).

83 A. Kerber and K.-J. Thürlings, in "Combinatorial Theory," ed by D. Jngnickel and K. Vedder, Springer, Berlin (1982), pp. 191–211.

84 W. Hässelbarth, *Theor. Chim. Acta*, **67**, 339 (1985).

85 J. Brocas, *J. Am. Chem. Soc.*, **108**, 1135 (1986).

86 C. A. Mead, *J. Am. Chem. Soc.*, **109**, 2130 (1987).

87 E. K. Lloyd, *J. Math. Chem.*, **11**, 207 (1992).

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

89 S. Fujita, *J. Am. Chem. Soc.*, **112**, 3390 (1990).

90 W. Burnside, "Theory of Groups of Finite Order," 2nd ed, Cambridge University Press, Cambridge (1911).

91 S. Fujita, *Theor. Chim. Acta*, **76**, 247 (1989).

92 S. Fujita, *Bull. Chem. Soc. Jpn.*, **63**, 315 (1990).

93 S. Fujita, *Memoirs of the Faculty of Engineering and Design, Kyoto Institute of Technology*, **47**, 111 (1999).

94 H. B. Kagan, "La Stéréochimie Organique," Presses Universitaires de France (1975).

95 S. F. A. Kettle, "Symmetry and Structure," Wiley, Chichester (1985).

96 D. C. Harris and M. D. Bertolucci, "Symmetry and Spectroscopy," Dover, New York (1989).

97 M. F. C. Ladd, "Symmetry in Molecules and Crystals," Ellis Horwood, Chichester (1989).

98 K. Mislow, *Bull. Soc. Chim. Belg.*, **86**, 595 (1977).

99 S. Fujita, *Bull. Chem. Soc. Jpn.*, **73**, 1979 (2000).

100 The Commission on the Nomenclature of Organic Chemistry of IUPAC, *Pure Appl. Chem.*, **45**, 11 (1976).

101 S. Fujita, *J. Chem. Inf. Comput. Sci.*, **32**, 354 (1992).

102 S. Fujita, *Tetrahedron*, **56**, 735 (2000).

103 As a result, the term "prochiral center" defined by Hanson[9] is replaced by the term prostereogenic center. The terms "prochiral centers" and "propseudoasymmetric centers"[13] are replaced by the term prostereogenic center.

104 As a result, the term "chiral center" by Hirschmann–Hanson[10] is replaced by the term stereogenic center. The terms "chiral center" and "pseudoasymmetric center"[13] are replaced by the term stereogenic center.

105 S. Fujita, *Tetrahedron*, **46**, 5943 (1990).

106 S. Fujita, *J. Chem. Inf. Comput. Sci.*, **31**, 540 (1991).

107 S. Fujita, *Bull. Chem. Soc. Jpn.*, **63**, 2770 (1990).

108 S. Fujita, *Bull. Chem. Soc. Jpn.*, **63**, 1876 (1990).

109 S. Fujita, *Bull. Chem. Soc. Jpn.*, **63**, 203 (1990).

110 S. Fujita, *J. Chem. Inf. Comput. Sci.*, **39**, 151 (1999).

111 S. Fujita, *Polyhedron*, **12**, 95 (1993).

112 S. Fujita, *Bull. Chem. Soc. Jpn.*, **63**, 2759 (1990).

113 S. Fujita, *Bull. Chem. Soc. Jpn.*, **64**, 3215 (1991).

114 S. Fujita, *Tetrahedron*, **47**, 31 (1991).

115 S. Fujita, *Bull. Chem. Soc. Jpn.*, **73**, 2679 (2000).

116 S. Fujita, *Bull. Chem. Soc. Jpn.*, **74**, 1015 (2001).

117 S. Fujita, *Bull. Chem. Soc. Jpn.*, **73**, 2009 (2000).

118 For Erratum for S. Fujita, *Bull. Chem. Soc. Jpn.*, **73**, 2009 (2000), see *Bull. Chem. Soc. Jpn.*, **74**, 1163 (2001).

119 S. Fujita, *Tetrahedron*, **46**, 365 (1990).

120 S. Fujita, *J. Chem. Inf. Comput. Sci.*, **36**, 270 (1996).

121 M. Nakazaki, "Bunshi no Katachi to Taisho—Sono Hyoji Hou," Nankodo, Tokyo (1969).

122 The global symmetry of **50** has been erroneously assigned to $\mathbf{C}_1$ in Ref. 115. For $\mathbf{C}_1$ read $\mathbf{C}_2'$.

123 D. Walba, in "Chemical Applications of Topology and Graph Theory," ed by R. B. King, Elsevier, Amsterdam (1983), Vol. 28 of Studies in Physical and Theoretical Chemistry, pp. 17–32.

124 E. Flapan, "When Topology Meets Chemistry. A Topological Look at Molecular Chirality," Cambridge Univ. Press, Cambride (2000), pp. 19–21 and pp. 110–111.

125 S. Fujita, *J. Chem. Inf. Comput. Sci.*, **40**, 135 (2000).

126 M. G. Hutchings, J. D. Andose, and K. Mislow, *J. Am. Chem. Soc.*, **97**, 4553 (1975).

127 M. Nakazaki, K. Naemura, and Y. Hokura, *J. Chem. Soc., Chem. Commun.*, **1982**, 1245.

128 G. E. McCasland, R. Horvat, and M. R. Roth, *J. Am. Chem. Soc.*, **81**, 2399 (1959).

129 S. Fujita, *J. Chem. Inf. Comput. Sci.*, **40**, 426 (2000).

130 S. Fujita, *Bull. Chem. Soc. Jpn.*, **72**, 2409 (1999).

131 S. Fujita, *Theor. Chim. Acta*, **78**, 45 (1990).

132 S. Fujita, *J. Math. Chem.*, **12**, 173 (1993).

133 S. Fujita, *Theor. Chim. Acta*, **82**, 473 (1992).

134 S. Fujita, *J. Math. Chem.*, **5**, 99 (1990).

135 S. Fujita, *J. Math. Chem.*, **5**, 121 (1990).

136 S. Fujita, *Bull. Chem. Soc. Jpn.*, **62**, 3771 (1989).

137 S. Fujita, *Theor. Chim. Acta*, **77**, 307 (1990).

138 S. Fujita, *Bull. Chem. Soc. Jpn.*, **63**, 2033 (1990).

139 S. Fujita, *J. Graph Theory*, **18**, 349 (1994).

140 S. Fujita, *Theor. Chem. Acta*, **91**, 291 (1995).

141 S. Fujita, *Theor. Chem. Acta*, **91**, 315 (1995).

142 S. Fujita, *Theor. Chem. Acc.*, **99**, 224 (1998).

143 S. Fujita, *Bull. Chem. Soc. Jpn.*, **71**, 1587 (1998).

144 S. Fujita, *Bull. Chem. Soc. Jpn.*, **71**, 2071 (1998).

145 S. Fujita, *Bull. Chem. Soc. Jpn.*, **71**, 2309 (1998).

146 S. Fujita, *Theor. Chem. Acc.*, **99**, 404 (1998).

147 S. Fujita, *Theor. Chem. Acc.*, **101**, 409 (1999).

148 S. Fujita, *Bull. Chem. Soc. Jpn.*, **72**, 13 (1999).

149 S. Fujita, *Bull. Chem. Soc. Jpn.*, **72**, 2403 (1999).

150 S. Fujita, *J. Chem. Inf. Comput. Sci.*, **40**, 1101 (2000).

151 S. Fujita, *Bull. Chem. Soc. Jpn.*, **67**, 2935 (1994).

152 S. Fujita, *Bull. Chem. Soc. Jpn.*, **67**, 2927 (1994).

153 S. Fujita, *J. Chem. Soc., Faraday Trans.*, **94**, 2515 (1998).

154 S. Fujita, *J. Chem. Inf. Comput. Sci.*, **38**, 876 (1998).

155 S. Fujita, *J. Chem. Soc., Faraday Trans.*, **94**, 3197 (1998).

156 S. Fujita, *Bull. Chem. Soc. Jpn.*, **72**, 1759 (1999).

157 S. Fujita, unpublished data.

Shinsaku Fujita was born in Kita-Kyushu City, Japan in 1944. He received his undergraduate training at Kyoto University and a Master's degree at the same place in 1968. He then started as a research instructor and received a Dr. Eng. degree at Kyoto University under the guidance of Prof. Hitosi Nozaki. In 1972, he joined Research Laboratories, Ashigara, Fuji Photo Film Co., Ltd. He was awarded Synthetic Organic Chemistry Award in 1982. From 1997, he has been Professor of Information Materials Technology at Kyoto Institute of Technology. His research interests have included reactive intermediates (nitrenes), synthetic organic chemistry (cylophanes, strained heterocycles, and organic compounds for photography), organic photochemistry, organic stereochemistry (theoretical approach), mathematical organic chemistry (combinatorial enumeration), and organic reaction database (imaginary transition structures). He is the author of *Symmetry and Combinatorial Enumeration in Chemistry* (Springer-Verlag, 1991), XΥMTEX—*Typesetting Chemical Structural Formulas* (Addison-Wesley Japan, 1997), *Computer-Oriented Representation of Organic Reactions*, (Yoshioka Shoten, 2001), and several books on TEX/LATEX. His homepage on World Wide Web is located at http://imt.chem.kit.ac.jp/fujita/fujitas/fujita.html