Characterization of Prochirality and Classification of *Meso*-Compounds by Means of the Concept of Size-Invariant Subductions

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The concept of size-invariant subductions has been proposed to design prochiral molecules. 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. These prochiral molecules have been shown to be extrinsic *meso* compounds. Intrinsic meso compounds have also been discussed as another type of prochiral molecule.

Prochirality is a key concept in stereochemistry, especially in the field of asymmetric syntheses. However, the presence of two definitions of prochirality has provided organic chemists with some confusion. One such definition is the IUPAC Rule E-4.12(b),[1,2] which is the adoption of Hirschmann–Hanson's one,[3—5] while another one is the IUPAC Rule E-4.12(a). They are conceptually different. This difference has been a source of contention ever since.[6—8] In order to give a consistent basis to the definition of prochirality, the topicity terms ("enantiotopic" and "diastereotopic" introduced by Mislow and Raban,[9] "equitopic" proposed by Nakazaki[10,11] and "homotopic" given by Hirschmann and Hanson[4]) have been used to characterize the relationship between two sites of a molecule, i.e., stereochemical equivalence or non-equivalence. These topicity terms have been widely accepted by organic chemists and biochemists, as described in various reviews.[12—15] However, these terms have been insufficient to grasp the total aspect of prochirality. To remedy this situation, Mislow and Siegel[16] have discussed local chirality and proposed the terms "chirotopic" and "achirotopic". This proposal has resulted in two connotations for the suffix "topic". Thus, such dual expressions as "homotopic and chirotopic" and "homotopic and achirotopic" are necessary to describe chiral and achiral molecules precisely, whereas the expression "enantiotopic and chirotopic" is not necessary because "enantiotopic" relationships implies "chirotopic" attributes in achiral molecules.

These situations concerning prochirality and the relevant matters have stemmed from the lack of an appropriate mathematical or logical framework. To supply such lack, we have discussed stereochemical relationships in terms of the concept of promolecules,[17,18] where we have emphasized the importance of a coset representation $\mathbf{G}(/\mathbf{G}_i)$ and of its subduction.[19] We have coined the sphericity terms (homospheric, enantiospheric, and hemispheric) on the basis of the chirality of the groups $\mathbf{G}$ and $\mathbf{G}_i$ appearing in the coset representation. Then we have applied them to the redefinition of prochirality,[20,21] topicity,[22,23] stereogenicity,[23] and anisochrony.[24] However, further studies on stereochemical relationships are necessary to determine whether a given skeleton provides prochiral molecules or not. The target of the present paper is the proposal of size-invariant subductions to solve such problems. Thereby, we discuss the classification of meso compounds as one category of prochiral molecules.

Results

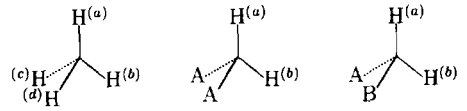
1 Sphericity and Prochirality Revisited. Throughout the present paper, we use the sphericity terms in place of the topicity terms so that we can clarify the consistency provided by the sphericity terms. To avoid the usage of the topicity terms, some essential items related to the sphericity concept shall be revisited briefly.

A set of equivalent atoms (or objects) in a molecule is called an orbit (or an equivalence class), which corresponds to a coset representation $\mathbf{G}(/\mathbf{G}_i)$.[20] A coset representation is shown to be a kind of permutation representation, the degree of which is calculated to be $|\mathbf{G}|/|\mathbf{G}_i|$ and is equal to the number of the equivalent atoms (or objects), where $|\mathbf{G}|$ and $|\mathbf{G}_i|$ represent the orders of the groups $\mathbf{G}$ and $\mathbf{G}_i$. Although the precise methods of mathematical treatment are somewhat complicated,[22] we have reported an intuitive method of the assignment of such coset representations as $\mathbf{G}(/\mathbf{G}_i)$.[22] According to the latter method, we find a point group $\mathbf{G}$ to express the global symmetry of the molecule and a point group $\mathbf{G}_i$ to express the local symmetry of each atom of the orbit. Note that $\mathbf{G}_i$ is a subgroup of $\mathbf{G}$. Then, the sphericity of the orbit $\mathbf{G}(/\mathbf{G}_i)$ is determined by the criterion listed in Table 1.[20] Thereby, *the prochirality is ascribed to the presence of at least one enantiospheric orbit.*[20]

For example, the four hydrogens of methane (**1**) shown in Fig. 1 construct a four-membered orbit ascribed to a coset

Table 1. Sphericity of $G(/G_i)$[20]

G	G_i	Sphericity of $G(/G_i)$	Chirality fittingness (Ligands allowed)
Achiral	Achiral	Homospheric	Achiral
Achiral	Chiral	Enantiospheric	Achiral, chiral
Chiral	Chiral	Hemispheric	Achiral, chiral



1 **2** **3**

$T_d(/C_{3v})$ $C_{2v}(/C_s)$ $C_s(/C_1)$

Fig. 1. Coset representations for hydrogens of methane derivatives.

representation $T_d(/C_{3v})$. This is determined to be homospheric according to the criterion listed in Table 1, since both the global symmetry T_d and the local symmetry C_{3v} are achiral. The set of two hydrogens in **2** (A = an achiral ligand) belongs to a $C_{2v}(/C_s)$-orbit, which is homospheric. The set of two hydrogens in **3** (A and B = achiral ligands) belongs to a $C_s(/C_1)$-orbit, which is determined to be enantiospheric. The last orbit ascribed to the enantiospheric $C_s(/C_1)$ is an origin of prochirality.

From a stricter point of view, the derivatives listed in Fig. 1 should be regarded as promolecules with proligands (H, A, and B). Note that a proligand has been defined as a 3D object that is structureless but has chirality.[17] For example, let us consider a tetrasubstituted methane CA_4 (H = A in **1**). If the derivative CA_4 is regarded as a molecule of T_d, then each A should be a ligand of C_{3v} or a higher symmetry. This is because the local symmetry of A in the CA_4 is C_{3v} according to the coset representation $T_d(/C_{3v})$. If a lower symmetry than C_{3v} is selected, the resulting molecule no longer exhibits the full symmetry of T_d. For example, pentaerythritol ($C(CH_2OH)_4$) derived from a ligand CH_2OH (C_s), cannot maintain T_d symmetry, but becomes restricted to D_{2d} symmetry. Such complicated situations can be avoided by the adoption of proligands and promolecules. Thus, the restriction due to a ligand need not considered when A is regarded as an achiral proligand, because of the structureless nature of proligands.

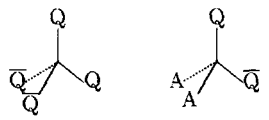
On the other hand, a simpler situation appears if a local symmetry is ascribed to C_s. For example, the achiral proligands A's in **2** belong to a two-membered $C_s(/C_s)$-orbit, while the achiral proligands A and B in **3** belong to respective one-membered $C_s(/C_s)$-orbits. Thus, local symmetries of the promolecules are both found to be C_s. The proligands A (and B) can be replaced by achiral ligands (e.g. CH_2OH) to give a molecule without decreasing the global symmetries, as found in propane-1,3-diol of C_{2v}-symmetry. Note that both achiral ligands and achiral proligands are matched in general to the local symmetries (both C_s).

2 Size-Invariant Subductions. The prochirality of an achiral promolecule (or molecule) is characterized by the capability of generating a chiral promolecule (or molecule) by desymmetrization. The capability is in turn characterized by the presence of at least one enantiospheric orbit of proligands (or ligands). When we take account of chiral proligands, there appears another type of prochirality. For example, Fig. 2 shows such prochiral promolecules, in which half the proligands are chiral ones (Q) and the remaining half are enantiomeric ones ($\overline{Q}$). The comparison between Figs. 1 and 2 gives a hint to characterize size-invariant subductions.

The set of four hydgrogens in **1** is replaced by a set of two Q's and two $\overline{Q}$'s to give a derivative of S_4 symmetry (**4**), where the latter set constructs a four-membered orbit ascribed to the coset representation $S_4(/C_1)$. The resulting derivative (**4**) is prochiral, since the $S_4(/C_1)$-orbit is determined to be enantiospheric by virtue of the criterion listed in Table 1. Note that the two Q's coincide with the two $\overline{Q}$'s by means of improper rotations involved in the point group S_4. In other words, the Q's and the $\overline{Q}$'s are equivalent to each other under the action of S_4. The comparison between **1** and **4** indicates the effect of the desymmetrization from T_d into S_4, where the sizes of the relevant orbits are conserved, i.e. $|T_d|/|C_{3v}| = 24/6 = 4$ for the $T_d(/C_{3v})$-orbit of **1** and $|S_4|/|C_1| = 4/1 = 4$ for the $S_4(/C_1)$-obrbit of **4**.

The derivative **5** belongs to C_s symmetry, where one Q and one $\overline{Q}$ construct a two-membered enantiospheric orbit ascribed to the coset representation $C_s(/C_1)$. Hence, the derivative **5** is prochiral, where the Q and the enantiomeric $\overline{Q}$ are equivalent so as to coincide with each other under the action of C_s. During the desymmetrization from C_{2v} (**2**) into C_s (**5**), the sizes of the participant orbits are conserved, i.e. $|C_{2v}|/|C_s| = 4/2 = 2$ for **2** and $|C_s|/|C_1| = 2/1 = 2$ for **5**. The resulting derivatives (**4** and **5**) are *meso* compounds, which are here called *extrinsic meso* compounds, since a size-invariant subduction and a pairwise packing with Q's and $\overline{Q}$'s are necessary to give each prochiral molecule.

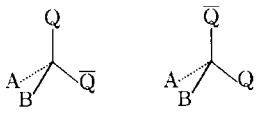
On the other hand, the $C_s(/C_1)$-orbit of $H^{(a)}$ and $H^{(b)}$ in **3** is originally enantiospheric so that **3** itself is prochiral. This has earlier been discussed in terms of a compensated chiral packing in Chapter 8 of our book.[22] Thus, there are two ways of the replacement by one Q and one $\overline{Q}$, producing two diastereomeric derivatives (**6** and **7**), of which the symmetries remain C_s (Fig. 3). Each set of Q and $\overline{Q}$ also constructs a $C_s(/C_1)$-orbit in **6** or **7**. Hence, each of the resulting orbits is enantiospheric, so that each of the derivatives **6** and **7** is determined to be prochiral. The resulting derivatives (**6** and **7**) are *meso* compounds, which are here called *intrinsic meso* compounds, since the prochirality does not always requires a pairwise packing with Q and $\overline{Q}$.



4 **5**

$S_4(/C_1)$ $C_s(/C_1)$

Fig. 2. Prochiral methane derivatives (extrinsic *meso*-type).



6 **7**

$C_s(/C_1)$ $C_s(/C_1)$

Fig. 3. Prochiral methane derivatives (intrinsic *meso*-type).

The intuitive examinations described above show that so-called meso compounds can be categorized into two classes: "extrinsic meso" and "intrinsic meso". Thus, the extrinsic class (e.g. **4** and **5**) stems from size-invariant subductions, while the intrinsic class (e.g. **6**) does not require such size-invariant subductions. In the following sections, we discuss these classes from a more primary but stricter point of view.

3 Extrinsic *Meso* Compounds. 3.1 General Treatment. The extrinsic cases (from **1** to **4** and from **2** to **5**) can be extended into general ones. Let us consider an even-membered homospheric orbit governed by the coset representation $\mathbf{G}(/\mathbf{G}_i)$, where the size of the orbit is represented by an even number $|\mathbf{G}|/|\mathbf{G}_i|$. Let $\mathbf{G}^{\max}$ be the maximal chiral subgroup of $\mathbf{G}$ and let $\mathbf{G}_i^{\max}$ be the maximal chiral subgroup of $\mathbf{G}_i$, where $|\mathbf{G}| = 2|\mathbf{G}^{\max}|$ and $|\mathbf{G}_i| = 2|\mathbf{G}_i^{\max}|$. Equation 11.16 of our book[22] has indicated

$$\mathbf{G}(/\mathbf{G}_i) \downarrow \mathbf{G}^{\max} = \mathbf{G}^{\max}(/\mathbf{G}_i^{\max}), \tag{1}$$

where we have $|\mathbf{G}|/|\mathbf{G}_i| = |\mathbf{G}^{\max}|/|\mathbf{G}_i^{\max}|$. This equation indicates a size-invariant subduction, which means that $|\mathbf{G}^{\max}|/|\mathbf{G}_i^{\max}|$ is an even number. As a result, the order $|\mathbf{G}^{\max}|$ is also an even number. This result and the relationship $|\mathbf{G}| = 2|\mathbf{G}^{\max}|$ are combined to indicate that the order of the group $\mathbf{G}$, i.e. $|\mathbf{G}|$, is a multiple of 4.

Since the order of the chiral subgroup $\mathbf{G}^{\max}$ is even, there exists a $\mathbf{C}_2$ as a subgroup of the chiral group $\mathbf{G}^{\max}$. The subduction into the group $\mathbf{C}_2$ is represented by

$$\mathbf{G}^{\max}(/\mathbf{G}_i^{\max}) \downarrow \mathbf{C}_2 = \frac{|\mathbf{G}^{\max}|}{2|\mathbf{G}_i^{\max}|}\mathbf{C}_2(/\mathbf{C}_1). \tag{2}$$

Equations 1 and 2 are combined to give

$$\mathbf{G}(/\mathbf{G}_i) \downarrow \mathbf{C}_2 = [\mathbf{G}(/\mathbf{G}_i) \downarrow \mathbf{G}^{\max}] \downarrow \mathbf{C}_2 = \mathbf{G}^{\max}(/\mathbf{G}_i^{\max}) \downarrow \mathbf{C}_2 = \frac{|\mathbf{G}^{\max}|}{2|\mathbf{G}_i^{\max}|}\mathbf{C}_2(/\mathbf{C}_1). \tag{3}$$

as found in Fig. 4(a). When we select one object from each of the resulting $\mathbf{C}_2(/\mathbf{C}_1)$-orbits, we obtain one half of the $\mathbf{G}(/\mathbf{G}_i)$-orbit; and we have the other half of the $\mathbf{G}(/\mathbf{G}_i)$-orbit by collecting the remaining one object from every $\mathbf{C}_2(/\mathbf{C}_1)$-orbit. The size of each half is calculated to be $|\mathbf{G}|/(2|\mathbf{G}_i|) = |\mathbf{G}^{\max}|/(2|\mathbf{G}_i^{\max}|)$. The two halves coincide with each other by the operations of $\mathbf{C}_2$. Suppose that the one half is filled up with chiral ligands of the same chirality (Q) and the other half with their enantiomeric ligands ($\overline{\text{Q}}$), as shown in Fig. 4(b). Then, the resulting promolecule ((b) of Fig. 4) coincides with itself by the combination of C_2 with the operation of ligand-chirality change. Since an alternative packing shown in Fig. 4(b′) coincides with (b) by the operation C_2, they are

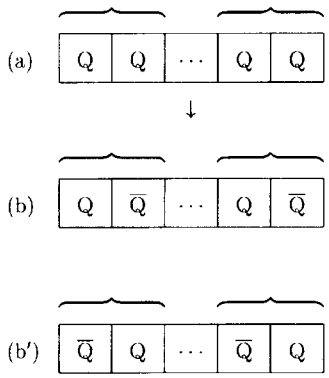


Fig. 4. A model for size-invariant subduction.

regarded as a single promolecule. Note that the operation C_2 is not always an element of the point group that characterizes the symmetry of the promolecule (b) or (b′).

Let us next examine such operations as considered for Fig. 4(b) in terms of subgroups of $\mathbf{G}$. For this purpose, we compare $\mathbf{G}(/\mathbf{G}_i)$ with $\mathbf{G}(/\mathbf{G}_i^{\max})$. While $\mathbf{G}(/\mathbf{G}_i)$ is homospheric, the coset representation $\mathbf{G}(/\mathbf{G}_i^{\max})$ is enantiospheric, where $2|\mathbf{G}|/|\mathbf{G}_i| = |\mathbf{G}|/|\mathbf{G}_i^{\max}|$. Suppose that the half of the $\mathbf{G}(/\mathbf{G}_i^{\max})$-orbit is packed with the number $|\mathbf{G}|/|\mathbf{G}_i|$ of Q and the remaining half is packed with the same number of $\overline{\text{Q}}$ as shown in Fig. 5. where the global symmetry is maintained as $\mathbf{G}$.

When each column of Q and $\overline{\text{Q}}$ is considered to be a single object, the above packing is considered to be governed by the coset representation $\mathbf{G}(/\mathbf{G}_i)$, compare this with Fig. 4(a). Suppose that we pick up the Q's and $\overline{\text{Q}}$'s in the frames. This operation is essentially the same as that of Fig. 4(b). The resulting sets of the proligands are equivalent to each other under an appropriate achiral group $\mathbf{G}'$ ($\subset\mathbf{G}$). This means that the size of the corresponding orbit $\mathbf{G}'(/\mathbf{G}_i')$ is equal to that of the original orbit $\mathbf{G}(/\mathbf{G}_i)$, where $\mathbf{G}_i'$ is a chiral group ($\mathbf{G}_i' \subset \mathbf{G}_i$). Since $\mathbf{G}'$ is achiral and $\mathbf{G}_i'$ is chiral, the orbit $\mathbf{G}'(/\mathbf{G}_i')$ is determined to be enantiospheric. This result is summarized as a theorem as follows:

Theorem 1 (Size-Invariant Subduction of a Homospheric Orbit). *An even-membered homospheric orbit governed by* $\mathbf{G}(/\mathbf{G}_i)$ *can be desymmetrized into an enantiospheric orbit governed by* $\mathbf{G}'(/\mathbf{G}_i')$, *where we have* $\mathbf{G} \supset \mathbf{G}'$ *and* $\mathbf{G}_i \supset \mathbf{G}_i'$; *and the size of the starting orbit* ($|\mathbf{G}|/|\mathbf{G}_i|$) *is equal to that of the resulting orbit* ($|\mathbf{G}'|/|\mathbf{G}_i'|$).

The desymmetrization due to Theorem 1 is now called a *size-invariant subduction*, which is represented by

$$\mathbf{G}(/\mathbf{G}_i) \downarrow \mathbf{G}' = \mathbf{G}'(/\mathbf{G}_i'). \tag{4}$$

Theorem 1 is a basis of designing prochiral molecules that are conventionally called *meso* compounds (extrinsic types).

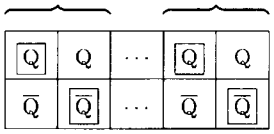


Fig. 5. Size-invariant subduction in $\mathbf{G}$.

The following examples illustrate that Theorem 1 covers a variety of *meso* compounds.

3.2 Methane Derivatives. Let us consider the desymmetrization of methane (**1**), where the $\mathbf{T}_d(/\mathbf{C}_{3v})$-orbit is taken into consideration. From the subduction table of $\mathbf{T}_d$,[22] we select size-invariant subductions as follows:

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{S}_4 = \mathbf{S}_4(/\mathbf{C}_1), \tag{5}$$

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{D}_2 = \mathbf{D}_2(/\mathbf{C}_1), \tag{6}$$

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{D}_{2d} = \mathbf{D}_{2d}(/\mathbf{C}_s), \tag{7}$$

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{T} = \mathbf{T}(/\mathbf{C}_3), \tag{8}$$

where the concept of size-invariant subductions is used in a broader manner than in Theorem 1. Among these subductions, the orbit corresponding to $\mathbf{S}_4(/\mathbf{C}_1)$ is enantiospheric, in agreement with Theorem 1, so as to produce the $\mathbf{S}_4$-derivative (**4**) as a prochiral promolecule. Then we obtain a molecule **8** by selecting Q = CXYZ and its enantiomer $\overline{\mathrm{Q}}$ = $\overline{\mathrm{C}}$XYZ as ligands of $\mathbf{C}_1$-symmetry. The methane derivative is schematically represented by the diagram **9** (Fig. 6), which is a top-view convention for drawing such methane derivatives. It should be noted here that the diagram **9** shows a comformer of $\mathbf{S}_4$-symmetry as the highest attainable symmetry in a fixed condition. As a result, the sets of the four X's, of the four Y's, and of the four Z's respectively construct four-membered $\mathbf{S}_4(/\mathbf{C}_1)$-orbits in the fixed conformation.

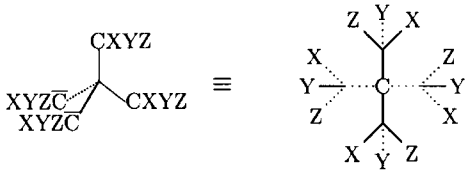
Let us next consider the desymmetrization of the $\mathbf{C}_{2v}(/\mathbf{C}_s)$-orbit in **2**. From the subduction table of $\mathbf{C}_{2v}$,[22] we select size-invariant subductions as follows:

$$\mathbf{C}_{2v}(/\mathbf{C}_s) \downarrow \mathbf{C}_2 = \mathbf{C}_2(/\mathbf{C}_1) \tag{9}$$

$$\mathbf{C}_{2v}(/\mathbf{C}_s) \downarrow \mathbf{C}'_s = \mathbf{C}'_s(/\mathbf{C}_1) \tag{10}$$

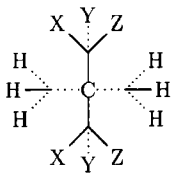
among which the orbit corresponding to $\mathbf{C}'_s(/\mathbf{C}_1)$ is enantiospheric, giving the $\mathbf{C}_s$-derivative (**5**) as a prochiral promolecule. When we select methyl ligands as ligands A's (i.e. A = CH_3) along with a trisubsituted methyl ligand and its enantiomer as ligands of $\mathbf{C}_1$-symmetry (i.e. Q = CXYZ and $\overline{\mathrm{Q}}$ = $\overline{\mathrm{C}}$XYZ), we obtain **10** (Fig. 7) as a $\mathbf{C}'_s$-molecule, in which the orbit of Q and $\overline{\mathrm{Q}}$ is governed by $\mathbf{C}'_s(/\mathbf{C}_1)$. Note that the prime symbol in $\mathbf{C}'_s$ indicates either of the two conjugate subgroups ($\mathbf{C}_s$ and $\mathbf{C}'_s$) within $\mathbf{C}_{2v}$, since the conjugation vanishes after the subduction into $\mathbf{C}'_s$.

3.3 Allene Derivatives. The four hydrogens of allene construct a four-membered homospheric orbit, which corresponds to the coset representation $\mathbf{D}_{2d}(/\mathbf{C}_s)$. From the



8 **9** ($\mathbf{S}_4$)

Fig. 6. Prochiral methane derivative as an extrinsic *meso* compound.



10 ($\mathbf{C}_s$)

Fig. 7. Prochiral methane derivative as an extrinsic *meso* compound.

subduction table of $\mathbf{D}_{2d}$,[22] we can select size-invariant subductions as follows:

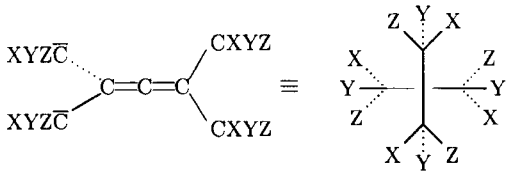
$$\mathbf{D}_{2d}(/\mathbf{C}_s) \downarrow \mathbf{S}_4 = \mathbf{S}_4(/\mathbf{C}_1), \tag{11}$$

$$\mathbf{D}_{2d}(/\mathbf{C}_s) \downarrow \mathbf{D}_2 = \mathbf{D}_2(/\mathbf{C}_1), \tag{12}$$

among which the $\mathbf{S}_4(/\mathbf{C}_1)$-orbit is enantiospheric so as to produce a prochiral $\mathbf{S}_4$-derivative. When we select Q = CXYZ and its enantiomer $\overline{\mathrm{Q}}$ = $\overline{\mathrm{C}}$XYZ as ligands of $\mathbf{C}_1$-symmetry, we obtain **11**, which is schematically represented by the diagram **12** (Fig. 8).

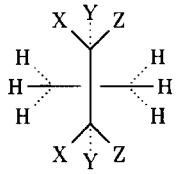
The two sets of methylene hydrogens in allene are replaced by AA and BB to give a promolecule of $\mathbf{C}_{2v}$-symmetry. The resulting promolecule is regarded as a starting skeleton, where the AA and the BB each construct $\mathbf{C}_{2v}(/\mathbf{C}_s)$-orbits. Let us select the orbit of BB for desymmetrization in agreement of a size-invariant subduction shown in Eq. 10. This subduction is executed by replacing BB by a set of chiral ligands of opposite chiralities (Q and $\overline{\mathrm{Q}}$) to give an allene promolecule AAQ$\overline{\mathrm{Q}}$ of $\mathbf{C}_s$-symmetry. Then, the resuting $\mathbf{C}_s(/\mathbf{C}_1)$-orbit of Q$\overline{\mathrm{Q}}$ is regarded as an origin of prochirality because of its enantiosphericity. When we select Q = CXYZ and its enantiomer $\overline{\mathrm{Q}}$ = $\overline{\mathrm{C}}$XYZ as ligands of $\mathbf{C}_1$-symmetry along with methyl ligands as ligands A's, we obtain **13** (Fig. 9) as an extrinsic *meso* compound.

3.4 Adamantane Derivatives. Adamantane itself has $\mathbf{T}_d$-symmetry, where its bridge-head hydrogens construct a



11 **12** ($\mathbf{S}_4$)

Fig. 8. Prochiral allene derivative as an extrinsic *meso* compound.



13 ($\mathbf{C}_s$)

Fig. 9. Prochiral tetramethylallene derivative as an extrinsic *meso* compound.

four-membered orbit ascribed to $\mathbf{T}_d(/\mathbf{C}_{2v})$. On the other hand, adamantane-2,6-dione belongs to $\mathbf{D}_{2d}$, where the set of four bridgehead hydrogens gives a four-membered orbit ascribed to $\mathbf{D}_{2d}(/\mathbf{C}_s)$. The conversion from adamantane to adamantane-2,6-dione is regarded as a desymmetrization from a $\mathbf{T}_d$-skeleton to a $\mathbf{D}_{2d}$-skeleton. The process of the desymmetrization is described by the following subductions:[22]

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{D}_{2d} = \mathbf{D}_{2d}(/\mathbf{C}_s), \quad \text{(bridgeheads)} \quad (13)$$

$$\mathbf{T}_d(/\mathbf{C}_s) \downarrow \mathbf{D}_{2d} = \mathbf{D}_{2d}(/\mathbf{C}_1) + \mathbf{D}_{2d}(/\mathbf{C}_s), \quad \text{(bridges)} \quad (14)$$

$$\mathbf{T}_d(/\mathbf{C}_{2v}) \downarrow \mathbf{D}_{2d} = \mathbf{D}_{2d}(/\mathbf{C}_2') + \mathbf{D}_{2d}(/\mathbf{C}_{2v}). \quad \text{(carbons)} \quad (15)$$

The four bridgehead hydrogens ascirbed to $\mathbf{T}_d(/\mathbf{C}_{3v})$ in adamantane remain equivalent in adamantane-2,6-dione so as to give $\mathbf{D}_{2d}(/\mathbf{C}_s)$, as shown by Eq. 13. Although this subduction is a size-invariant subduction, the sphericity does not change during the desymmetrization process. On the other hand, the twelve bridge hydrogens ascribed to $\mathbf{T}_d(/\mathbf{C}_s)$ in adamantane are desymmetrized according to Eq. 14. Thus, the resulting $\mathbf{D}_{2d}(/\mathbf{C}_1)$-orbit corresponds to the eight bridge hydrogens in adamantane-2,6-dione, while the $\mathbf{D}_{2d}(/\mathbf{C}_s)$ has no correspondence since the four hydrogens (two methylenes) are reduced into the carbonyl groups.

The four bridgehead carbons are desymmetrized in the same way as the bridgehead hydrogens. On the other hand, the six carbons ascirbed to $\mathbf{T}_d(/\mathbf{C}_{2v})$ in adamantane are divided into two equivalence classes according to Eq. 15, where the two carbonyl carbons in adamantane-2,6-dione are governed by $\mathbf{D}_{2d}(/\mathbf{C}_{2v})$ and the four carbons by $\mathbf{D}_{2d}(/\mathbf{C}_2')$.

Let us now consider the orbits of the bridgehead ligands (A's) in an adamantane (**14**) and an adamantane-2,6-dione (**15**), as shown in Fig. 10. When we select A = CH_3 ($\mathbf{C}_{3v}$), the promolecules (**14** and **15**) are changed into molecules, of which the highest attainable symmetries are $\mathbf{T}_d$ and $\mathbf{D}_{2d}$, respectively.

The size-invariant subduction for the four A's in the adamantane derivative (**14**) is represented by Eq. 5 to give a four-membered $\mathbf{S}_4(/\mathbf{C}_1)$-orbit. The resulting enantiospheric orbit is packed with two proligands (Q) and two enantiomeric proligands ($\overline{\text{Q}}$), giving a prochiral promolecule (**16**). Since the local symmetry is $\mathbf{C}_1$ as found in the symbol $\mathbf{S}_4(/\mathbf{C}_1)$, we can select Q = CXYZ and $\overline{\text{Q}}$ = $\overline{\text{C}}$XYZ in order to obtain the corresponding molecule. The resulting molecule (**16**) is an extrinsic meso compound.

In a similar way, an $\mathbf{S}_4(/\mathbf{C}_1)$-orbit is generated by the size-invariant subduction of the orbit for the four A's in the adamantane-2,6-dione derivative (**15**), as shown in Eq. 11. The resulting $\mathbf{S}_4(/\mathbf{C}_1)$-orbit is enantiospheric so that it is packed with two proligands (Q) and two enantiomeric proligands ($\overline{\text{Q}}$). The resulting promolecule (**17**) is prochiral according to the criterion shown in Theorem 1. Since the local symmetry is $\mathbf{C}_1$, the proligands Q and $\overline{\text{Q}}$ can be replaced by such chiral ligands as Q = CXYZ and $\overline{\text{Q}}$ = $\overline{\text{C}}$XYZ to give the corresponding molecule of $\mathbf{S}_4$-symmetry. The resulting molecule (**17**) is an extrinsic meso compound.

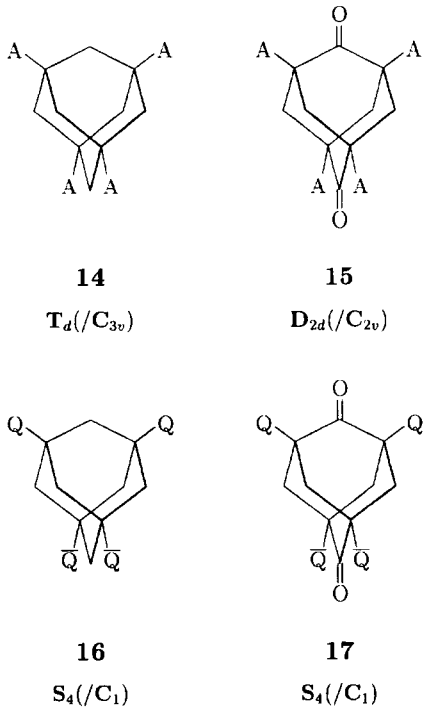


Fig. 10. Prochiral derivatives of adamantane and adamantane-2,6-dione as extrinsic *meso* compounds.

3.5 Biphenyl Derivatives. Biphenyl derivatives may have stereoisomers coming from restricted rotation. For example, a biphenyl derivative **18** with achiral ligands (A) has $\mathbf{D}_{2d}$-symmetry. The set of the achiral ligands (A) constructs a two-membered orbit governed by the coset representation $\mathbf{D}_{2d}(/\mathbf{C}_{2v})$, which is determined to be homospheric. Hence, the orbit can be desymmetrized according to a size-invariant subduction (Theorem 1), as shown by the following equation:[22]

$$\mathbf{D}_{2d}(/\mathbf{C}_{2v}) \downarrow \mathbf{S}_4 = \mathbf{S}_4(/\mathbf{C}_2). \quad (16)$$

The resulting two-membered $\mathbf{S}_4(/\mathbf{C}_2)$-orbit is enantiospheric so that it is packed with one proligand (Q) and its enantiomeric proligand ($\overline{\text{Q}}$), giving a promolecule (**19**).

The local symmetry of the $\mathbf{D}_{2d}(/\mathbf{C}_{2v})$-orbit in the promolecule **18** is $\mathbf{C}_{2v}$, each ligand A can be replaced by a three-membered cyclic ligand of $\mathbf{C}_{2v}$-symmetry without desymmetrization. Thereby, we obtain the corresponding molecule **20**. On the other hand, the local symmetry of the $\mathbf{S}_4(/\mathbf{C}_2)$-orbit in **19** is $\mathbf{C}_2$, the chiral ligand Q (and $\overline{\text{Q}}$) can be replaced by a three-membered cyclic ligand of $\mathbf{C}_2$-symmetry (and its enantiomeric ligand) without desymmetrization. The resulting molecule **21** has $\mathbf{S}_4$-symmetry and is prochiral as an extrinsic meso compound. It should be noted that **20** and **21** are drawn in arbitrary conformations and should be tested as to whether they are isolable or not. When chiral ligands of $\mathbf{C}_1$-symmetry (e.g. Q = CXYZ and $\overline{\text{Q}}$ = $\overline{\text{C}}$XYZ) are selected for **19**, the resulting molecule no longer belongs to $\mathbf{S}_4$, as reported once by Mislow.[25,26] The prochirality of such a mismatched case has been discussed by us.[17]

4 Intrinsic *Meso* Compounds. 4.1 General Treatment. The intrinsic cases (from **3** to **6** and **7**) as general

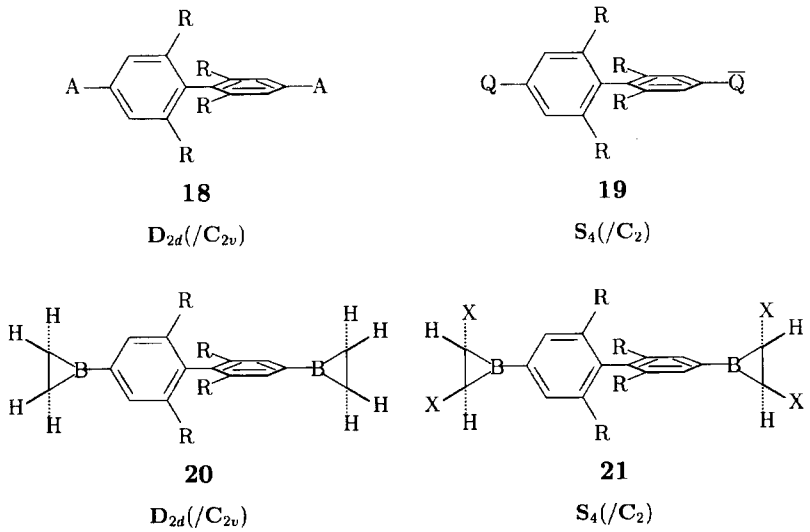


Fig. 11. Prochirality in biphenyl derivatives.

cases have been discussed in Chapter 8 of our book[22] in terms of a compensated chiral packing. The conclusion is that the compensated chiral packing of an enantiospheric orbit produces two diastereomeric (pro)molecules, which are called intrinsic meso compounds in the present paper. The following examples show some intrinsic meso compounds to clarify their characteristics as compared with extrinsic ones described above (Fig. 11).

4.2 Methane Derivatives. A diastereomeric pair of intrinsic meso compounds (**22** and **23**) of C_s-symmetry are shown in Fig. 12. They are obtained according to the scheme shown in Fig. 3 (**3**→**6** and **7**), where we select A = CH_3 and B = CF_3 as the original achiral ligands, and Q = CXYZ and its enantiomer $\overline{Q}$ = $\overline{C}$XYZ as ligands of C_1-symmetry. It should be noted that the orbit of hydrogens ($H^{(a)}$ and $H^{(b)}$) in **3** is governed by the coset representation $C_s(/C_1)$ and that the set of the chiral ligands in **22** or **23** is governed by the same coset representation $C_s(/C_1)$.

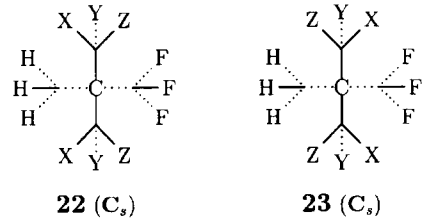


Fig. 12. Prochiral methane derivatives as intrinsic *meso*-compounds.

4.3 Allene Derivatives. Another diastereomeric pair for illustrating intrinsic *meso* compounds is shown in Fig. 13. They are obtained as a promolecule with ABQ$\overline{Q}$ by starting from an allene skeleton, where we select CH_3 and CF_3 as achiral ligands, and Q = CXYZ and its enantiomer $\overline{Q}$ = $\overline{C}$XYZ as ligands of C_1-symmetry. The resulting pair (**24** and **25**) illustrates diastereomeric isomers categorized into intrinsic *meso* compounds. It should be noted the orbit of two hydrogens in an allene promolecule with ABHH is governed by the coset representation $C_s(/C_1)$ and that the set of the chiral ligands in such a promolecule with ABQ$\overline{Q}$ as **24** or **25** is governed by the same coset representation $C_s(/C_1)$.

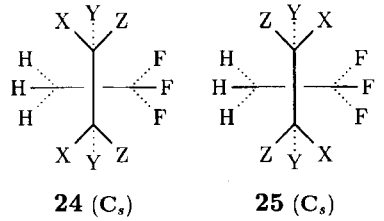


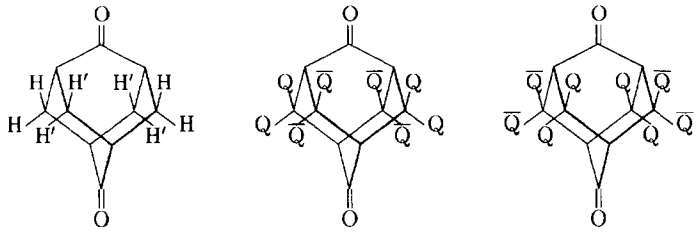
Fig. 13. Prochiral allene derivatives as intrinsic *meso*-compounds.

4.4 Adamantane Derivatives. A more complicated example is shown in Fig. 14. The eight bridge hydrogens in adamantane-2,6-dione (**26**) construct an enentiospheric orbit governed by $D_{2d}(/C_1)$. Suppose that the one half (H) and the other half (H′) are replaced by Q and $\overline{Q}$. Then we obtain a diastereomeric pair of two prochiral promolecules (**27** and **28**), which are intrinsic *meso* compounds in the present criterion. The set of the Q's and the $\overline{Q}$'s is also governed by $D_{2d}(/C_1)$.

Discussion

1 Equivalence for Extrinsic and Intrinsic *Meso* Compounds. It is worth comparing between extrinsic cases and intrinsic ones by using relevant skeletons. A size-invariant subduction represented by Eq. 9 explains the process of the desymmetrization from a methane with AAHH to a derivative with AAQ$\overline{Q}$, which is an example of extrinsic *meso* compounds, as shown by **10** in Fig. 7. In this case, a homospheric orbit $C_{2v}(/C_s)$ is desymmetrized into an enantiospheric orbit $C_s(/C_1)$. The resulting derivative with AAQ$\overline{Q}$ is the same molecule as the alternatively packed AA$\overline{Q}$Q.

On the other hand, there occurs no desymmetrization in the process from a methane with ABHH to derivatives with ABQ$\overline{Q}$ and AB$\overline{Q}$Q, where the point group C_s is unchanged before and after such derivation, as found in Fig. 12 (**22** and **23**). This type of derivative is called an intrinsic *meso* com-



26 **27** **28**

$D_{2d}(/C_1)$ $D_{2d}(/C_1)$ $D_{2d}(/C_1)$

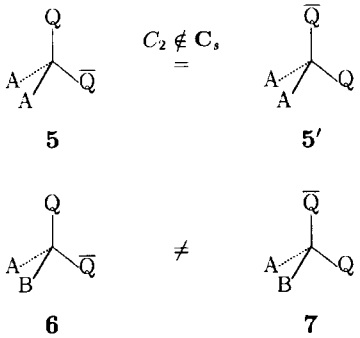
Fig. 14. Prochiral adamantane-2,6-diones as intrinsic *meso*-compounds

pound; such derivatives are characterized by the appearance of a diastereomeric pair. Thus the resulting derivative with ABQ$\overline{\text{Q}}$ (e.g. **22**) is diastereomeric to the alternatively packed AB$\overline{\text{Q}}$Q (e.g. **23**). The coset representation $\mathbf{C}_s(/\mathbf{C}_1)$ governing the two hydrogens of ABHH remains unchanged so as to give $\mathbf{C}_s(/\mathbf{C}_1)$ governing the set of Q and $\overline{\text{Q}}$.

The absence and presence of diastereomeric pairs are rationalized by the schemes shown in Fig. 15. Two promolecules **5** and **5′** due to size-invariant subductions followed by alternative pairwise packings of chiral ligands are identical with each other, since **5** is superimposed on **5′** by the C_2-operation involved in $\mathbf{C}_{2v}$ (i.e., the symmetry of AAHH). Hence, the extrinsic case can be concluded to have no diastereomeric pair. This has already been indicated in general in the proof of Theorem 1. Note that the C_2-operation is an element of the symmetry $\mathbf{C}_{2v}$ of the corresponding mother skeleton AAHH, but not an element of $\mathbf{C}_s$ that is the symmetry of AAQ$\overline{\text{Q}}$. This situation is akin to the one encountered in combinatorial enumeration of isomers (see Chapter 13 of our book[22]).

On the other hand, **6** and **7** produced by a pairwise packing are not identical with each other, since no proper operations exist to superimpose them. Hence, each intrinsic case is concluded to give a diastereomeric pair. This has been already indicated in general in Chapter 8 of our book.[22]

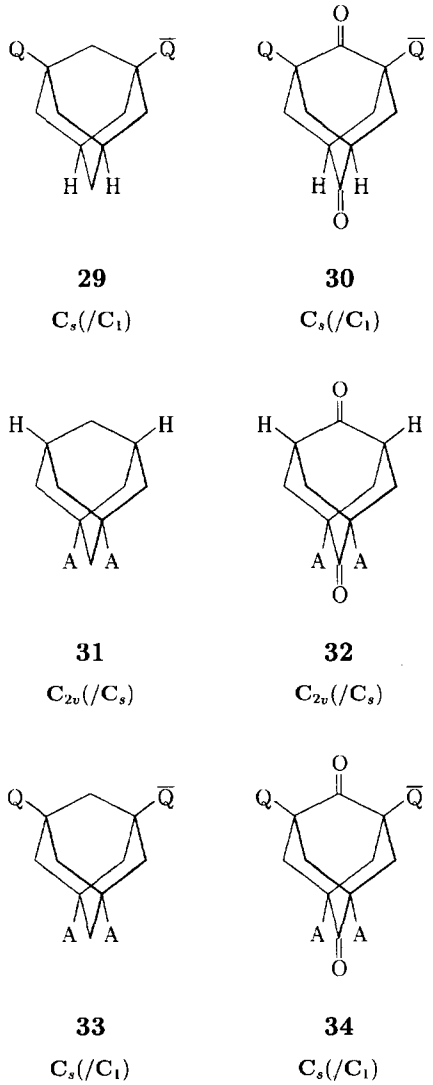
2 Selection of Mother Skeletons. As found in the preceding sections, desymmetrization of a mother skeleton is a key concept of discussing stereochemical phenomena. We here point out the importance of the selection of such a mother skeleton. Thus, there are several ways to generate prochiral (pro)molecules by starting from adamantane and adamantane-2,6-dione, as shown in Fig. 16. The processes of the desymmetrizations are described by the following subductions:[22]



5 **5′**

6 **7**

Fig. 15. Equivalence for extrinsic and intrinsic *meso*-compounds.



29 **30**

$\mathbf{C}_s(/\mathbf{C}_1)$ $\mathbf{C}_s(/\mathbf{C}_1)$

31 **32**

$\mathbf{C}_{2v}(/\mathbf{C}_s)$ $\mathbf{C}_{2v}(/\mathbf{C}_s)$

33 **34**

$\mathbf{C}_s(/\mathbf{C}_1)$ $\mathbf{C}_s(/\mathbf{C}_1)$

Fig. 16. Another prochirality in adamantane and adamantane-2,6-dione.

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{C}_s = \mathbf{C}_s(/\mathbf{C}_1) + 2\mathbf{C}_s(/\mathbf{C}_s), \quad (17)$$

$$\mathbf{D}_{2d}(/\mathbf{C}_s) \downarrow \mathbf{C}_s = \mathbf{C}_s(/\mathbf{C}_1) + 2\mathbf{C}_s(/\mathbf{C}_s), \quad (18)$$

where a set of Q and $\overline{\text{Q}}$ occupies a two-membered $\mathbf{C}_s(/\mathbf{C}_1)$-

orbit in each of the cases producing **29** and **30**.

The processes of the desymmetrizations producing **29** and **30** can be rationalized alternatively by size-invariant subductions. Thus, the adamantanes (**14** and **15**) are desymmetrized into $\mathbf{C}_{2v}$-promolecules (**31** and **32**) according to the following subductions:[22]

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{C}_{2v} = \mathbf{C}_{2v}(/\mathbf{C}_s) + \mathbf{C}_{2v}(/\mathbf{C}'_s), \quad (19)$$

$$\mathbf{D}_{2d}(/\mathbf{C}_s) \downarrow \mathbf{C}_{2v} = \mathbf{C}_{2v}(/\mathbf{C}_s) + \mathbf{C}_{2v}(/\mathbf{C}'_s). \quad (20)$$

Then, the homospheric $\mathbf{C}_{2v}(/\mathbf{C}_s)$-orbit of the two hydrogens in each promolecule (**31** or **32**) is subduced in a size-invariant way (Eq. 10) so as to produce a prochiral promolecule (**33** or **34**). The resulting promolecule is essentially equivalent to the promolecule (**29** or **30**) derived directly (A = H).

Finally, we emphasize that no topic terms have been used throughout the results and the discussion described in the present paper. Since the sphericity terms are based on the concept of coset representations and their subductions,[22] they are effective to discuss stereochemical phenomena in a more straightfoward fashion than the topic terms.

Conclusion

An even-membered homospheric orbit can be desymmetrized into an enantiospheric orbit, where the sizes of the relevant orbits remain invariant. This has been proved in general so as to give a theorem concerning the concept of size-invariant subductions. Thereby, prochiral molecules can be classified into extrinsic or intrinsic meso cases. Thus, prochiral molecules due to size-invariant subductions followed by a pairwise packing of chiral ligands are named extrinsic *meso* compounds, which are characterized as having no diastereomeric isomers. On the other hand, prochiral molecules due to a pairwise packing of chiral ligands without desymmetrization are named intrinsic *meso* compounds, which are shown to have diastereomeric isomers. The concept and the resulting classification method have been applied to the design and characterization of prochiral molecules derived from methane, allene, adamantane, and biphenyl.

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