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PROMOLECULES FOR CHARACTERIZING STEREOCHEMICAL RELATIONSHIPS IN NON-RIGID MOLECULES

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Proligands are defined as hypothetical ligands which are structureless but have chirality. A promolecule consists of a skeleton and such proligands. Promolecules based on a methane and an allene skeleton are enumerated. A molecule can be constructed by a method in which proligands on such a promolecule are replaced by ligands that have three-dimensional structures. This construction is controlled by a coset representation that governs an orbit of such proligands. Thereby, the resulting molecules are classified into matched and mismatched molecules. The matched molecules retain the symmetries of the starting promolecules; on the other hand, the mismatched molecules do not. Modes of such desymmetrizations are rationalized by subduction of coset representations. The concept of prochirality is also discussed.

1 Introduction

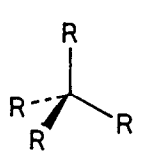
Stereochemistry of organic compounds has been discussed on the basis of three-dimensional molecular models, which vary with purposes of discussions.[1]-[3] The formulation of a molecule as an achiral or chiral skeleton with several ligands is one of dominant methodologies for discussing molecular symmetry.[4]-[6] This model directly succeeds to that of van't Hoff.[7] According to this model, Farina and Morandi[8] proposed principles for the design of high symmetry chiral molecules. This approach provided us with a useful method of determining how to realize a molecule of a desired symmetry. However, the highest attainable symmetry of a molecule is often difficult to determine, especially when the molecule contains several ligands that are mobile through bond rotations. For example, a methane molecule (**1a**) belongs to $\mathbf{T}_d$ symmetry, pentaerythitol (**1b**) have $\mathbf{D}_{2d}$ symmetry, and pentaerythitol tetra(−)-menthyloxyacetate (**1c**)[9] belongs to $\mathbf{D}_2$ symmetry. Although such highest attainable symmetries can be assigned by careful inspection, there have been no systematic methods of doing this task.

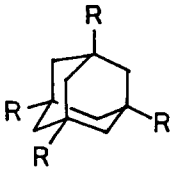
Nakazaki *et al.*[10] synthesized (−)-1,3,5,7-tetrakis[2-(1S,3S,5R,6S,8R,10R)-$\mathbf{D}_3$-trishomocubanylacetoxymethyl]adamantane (**2a**), which they once claimed to belong to **T** symmetry. Mislow[11] pointed out that the highest attainable symmetry of this compound was $\mathbf{D}_2$ in the same line as the McCasland compound (**1c**). Later, Nakazaki *et al.*[12] synthesized (+)-1,3,5,7-tetrakis[2-(1S,3S,5R,6S,8R,10R)-$\mathbf{D}_3$-trishomocubanylbuta-1,3-diynyl]adamantane (**2b**) as a true **T**-molecule.

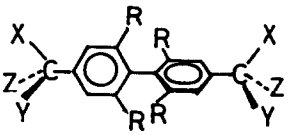
This short history indicates the importance of the effect of ligand symmetries upon the whole symmetry of such a molecule. This effect is closely related to the relationship between the global symmetry and the local symmetry in a molecule, which has been discussed by Mislow.[13]

Mislow[14] dealt with compound (**3**) as a *meso*-compound containing only $\mathbf{C}_1$-conformers. The biphenyl part of this molecule has $\mathbf{D}_{2d}$ symmetry, which is incompatible with the symmetries of terminal chiral groups. Hence, this compound (**3**) has a $\mathbf{C}_1$-conformation as the highest attainable symmetry at

any time; however, this is an achiral compound because of internal rotations. Although this phenomenon is not so strange but rather common as pointed out in a critical review,[15] it also indicates the importance of the global-local relationship in a molecule.





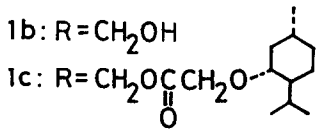


3

1a: R=H

1b: R=CH_2OH

1c: R=CH_2OCCH_2O



2a: R=CH_2OCCH_2

2b: R=C≡C-C≡C

We discussed the usefulness of coset representations (CRs) in enumerating various molecules,[16]-[21] in classifying molecular symmetry,[22] and in specifying stereochemical equivalency.[23] These applications are based on the fact that each CR governs an orbit which consists of equivalent objects (atoms, bonds faces and so on). We have recently discussed the stereochemical relationship between global symmetry and local ones in a rigid molecule.[24] This treatment affords a foundation for deciding how to obtain a molecule of a given symmetry. In a continuation of these papers, the present paper deals with such global-local relationships in non-rigid molecules, where several new concepts such as promolecules and proligands are proposed.

2 Proligands and Promolecules

In this paper, a molecule is regarded as a three-dimensional (3D) object that consists of a skeleton and ligands, where the skeleton has joint positions that are occupied by the ligands. The skeleton is considered to be a rigid 3D object belonging to **G** point group which is a supergroup of the molecular symmetry (M).[25] Each of the ligands has its own joint, which is identical with one of the joint positions if the ligand is built into the molecule. This means that ligands in a molecule are capable of internal rotation. Such a ligand-in-molecule is called a *segment*. If a ligand is assumed to be free from the symmetry environment of the molecule, it is called a *fragment*. The intrinsic symmetry (**F**) of a ligand appears in full in an isolated state (*i.e.* as a fragment), but becomes restricted when incorporated in a molecule (*i.e.* as a segmant). When the symmetry of the fragment is **F**, we call it an **F**-fragment. Such a fragment is defined as *chiral* if it cannot be superimposable onto its antipode (mirror image); and otherwise as *achiral*.

Figure 1 illustrates the present molecular model for describing molecular symmetry. Consider a molecule (**4**) that belongs to $\mathbf{C}_2$ symmetry in its highest attainable state. This molecule contains a skeleton (**6**) having four joint positions. Two methyl groups and two CXYZ groups in this molecule are regarded as segments. According to the above definition, the methyl group is a $\mathbf{C}_{3v}$-fragment (an achiral fragment) and the CXYZ group is a $\mathbf{C}_1$-fragment (or an asymmetric and chiral fragment). The skeleton (**6**) has $\mathbf{T}_d$ symmetry in isolation; but a restricted $\mathbf{C}_2$ symmetry in the molecular environment. Thus, the $\mathbf{C}_2$ symmetry is generated by replacing the four positions of **6** by the two $\mathbf{C}_{3v}$-fragments and the two $\mathbf{C}_1$-fragments.

This molecular model has several conformers becasue of internal bond rotations. Such non-rigidity can be treated by several approaches.[26]-[28] In order to discuss organic stereochemistry, however, a

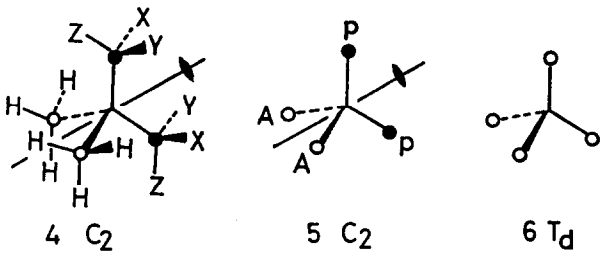


Figure 1: Molecule, promolecule and skeleton

more simplified approach is desirable. For this purpose, we introduce the concepts of proligands and promolecules. A *proligand*[29, 30] is defined as a 3D object that is structureless but has chirality. The term "having chirality" means that there are two types of proligands as fragments: achiral (A, B, C, D, $\cdots$) and chiral (p, q, r, s, $\cdots$, and their antipodes, $\overline{\mathrm{p}}$, $\overline{\mathrm{q}}$, $\overline{\mathrm{r}}$, $\overline{\mathrm{s}}$, $\cdots$). A *promolecule* is then defined as a 3D object that consists of a skeleton and such proligands. With respect to **4**, we replace the methyl group by A (achiral) and the CXYZ group by p (chiral). This replacement gives the corresponding promolecule (**5**), which retains the $\mathbf{C}_2$ symmetry. We conceptually construct a molecule by consecutive processes: (1) starting from an appropriate skeleton, (2) substituting proligands for joint positions to produce a promolecule, and (3) further replacing the proligands with ligands. In the light of this formulation, such promolecules are manipulated as hypothetically rigid 3D objects, which maintain some of the symmetrical properties of related molecules. Our targets are to enumerate such promolecules; to calrify their symmetrical properties which are perturbed by the symmetry of the skeleton and the chirality/achirality of the proligands; as well as to characterize relationships between symmetries of the promolecule and of the molecule.

3 Enumeration of Promolecules

Tetrahedral promolecules of various symmetries. Promolecules derived from the tetrahedral skeleton (**6**) can be enumerated by means of unit subduced cycle indices with chirality fittingness (USCI-CF).[18, 20] We use USCI-CFs for $\mathbf{T}_d(/\mathbf{C}_{3v})$, *i.e.*, b_1^4 for $\mathbf{C}_1$, b_2^2 for $\mathbf{C}_2$, $a_1^2c_2$ for $\mathbf{C}_s$, b_1b_3 for $\mathbf{C}_3$, c_4 for $\mathbf{S}_4$, b_4 for $\mathbf{D}_2$, a_2^2 for $\mathbf{C}_{2v}$, a_1a_3 for $\mathbf{C}_{3v}$, a_4 for $\mathbf{D}_{2d}$, b_4 for $\mathbf{T}$, and a_4 for $\mathbf{T}_d$, which themselves constitute respective subduced cycle indices with chirality fittingness (SCI-CFs). In this case, we take account of the following figure inventories:

$$a_d = A^d + B^d + C^d + D^d, \tag{1}$$

$$b_d = A^d + B^d + C^d + D^d + p^d + q^d + r^d + s^d + \overline{p}^d + \overline{q}^d + \overline{r}^d + \overline{s}^d, \tag{2}$$

and

$$c_d = A^d + B^d + C^d + D^d + 2(p\overline{p}^{d/2} + q\overline{q}^{d/2} + r\overline{r}^{d/2} + s\overline{s}^{d/2}). \tag{3}$$

These figure inventories are introduced into the SCI-CFs. We expand the resulting generating functions and collect coefficients of terms for every racemic pair. Among the terms representing equivalent proligand partitions (*e.g.* $\mathrm{A_3B}$ and $\mathrm{AB_3}$), we can select an arbitrary term as a representative without losing generality. Then, using the inverse of a mark table for $\mathbf{T}_d$, we calculate the number of isomeric promolecules (Table 1). Thus, we have one $\mathbf{T}_d$, one $\mathbf{T}$, one $\mathbf{C}_{3v}$, one $\mathbf{C}_{2v}$, one $\mathbf{S}_4$, four $\mathbf{C}_3$, four $\mathbf{C}_s$, two $\mathbf{C}_2$, and 22 $\mathbf{C}_1$ promolecules. These values are itemized with respect to the corresponding terms (proligand partitions) in the present enumeration. It should be noted that there exist no $\mathbf{D}_{2d}$ and no $\mathbf{D}_2$ promolecules in this enumeration.[32]

Table 1: Number of promolecules derived from a tetrahederal skeleton (**6**)

Proligand partition	Number of promolecules										
	C_1	C_2	C_s	C_3	S_4	D_2	C_{2v}	C_{3v}	D_{2d}	T	T_d
A^4	0	0	0	0	0	0	0	0	0	0	1
A^3B	0	0	0	0	0	0	0	1	0	0	0
A^3p	0	0	0	1	0	0	0	0	0	0	0
A^2B^2	0	0	0	0	0	0	1	0	0	0	0
A^2BC	0	0	1	0	0	0	0	0	0	0	0
A^2Bp	1	0	0	0	0	0	0	0	0	0	0
A^2p^2	0	1	0	0	0	0	0	0	0	0	0
$A^2p\overline{p}$	0	0	1	0	0	0	0	0	0	0	0
A^2pq	1	0	0	0	0	0	0	0	0	0	0
ABCD	1	0	0	0	0	0	0	0	0	0	0
ABCp	2	0	0	0	0	0	0	0	0	0	0
ABp^2	1	0	0	0	0	0	0	0	0	0	0
$ABp\overline{p}$	0	0	2	0	0	0	0	0	0	0	0
ABpq	2	0	0	0	0	0	0	0	0	0	0
Ap^3	0	0	0	1	0	0	0	0	0	0	0
$Ap^2\overline{p}$	1	0	0	0	0	0	0	0	0	0	0
Ap^2q	1	0	0	0	0	0	0	0	0	0	0
$Ap\overline{p}r$	2	0	0	0	0	0	0	0	0	0	0
Apqr	2	0	0	0	0	0	0	0	0	0	0
p^4	0	0	0	0	0	0	0	0	0	1	0
$p^3\overline{p}$	0	0	0	1	0	0	0	0	0	0	0
p^3q	0	0	0	1	0	0	0	0	0	0	0
$p^2\overline{p}^2$	0	0	0	0	1	0	0	0	0	0	0
$p^2\overline{p}r$	1	0	0	0	0	0	0	0	0	0	0
p^2q^2	0	1	0	0	0	0	0	0	0	0	0
$p^2q\overline{q}$	1	0	0	0	0	0	0	0	0	0	0
p^2qr	1	0	0	0	0	0	0	0	0	0	0
$p\overline{p}q\overline{q}$	1	0	0	0	0	0	0	0	0	0	0
$p\overline{p}qr$	2	0	0	0	0	0	0	0	0	0	0
pqrs	2	0	0	0	0	0	0	0	0	0	0

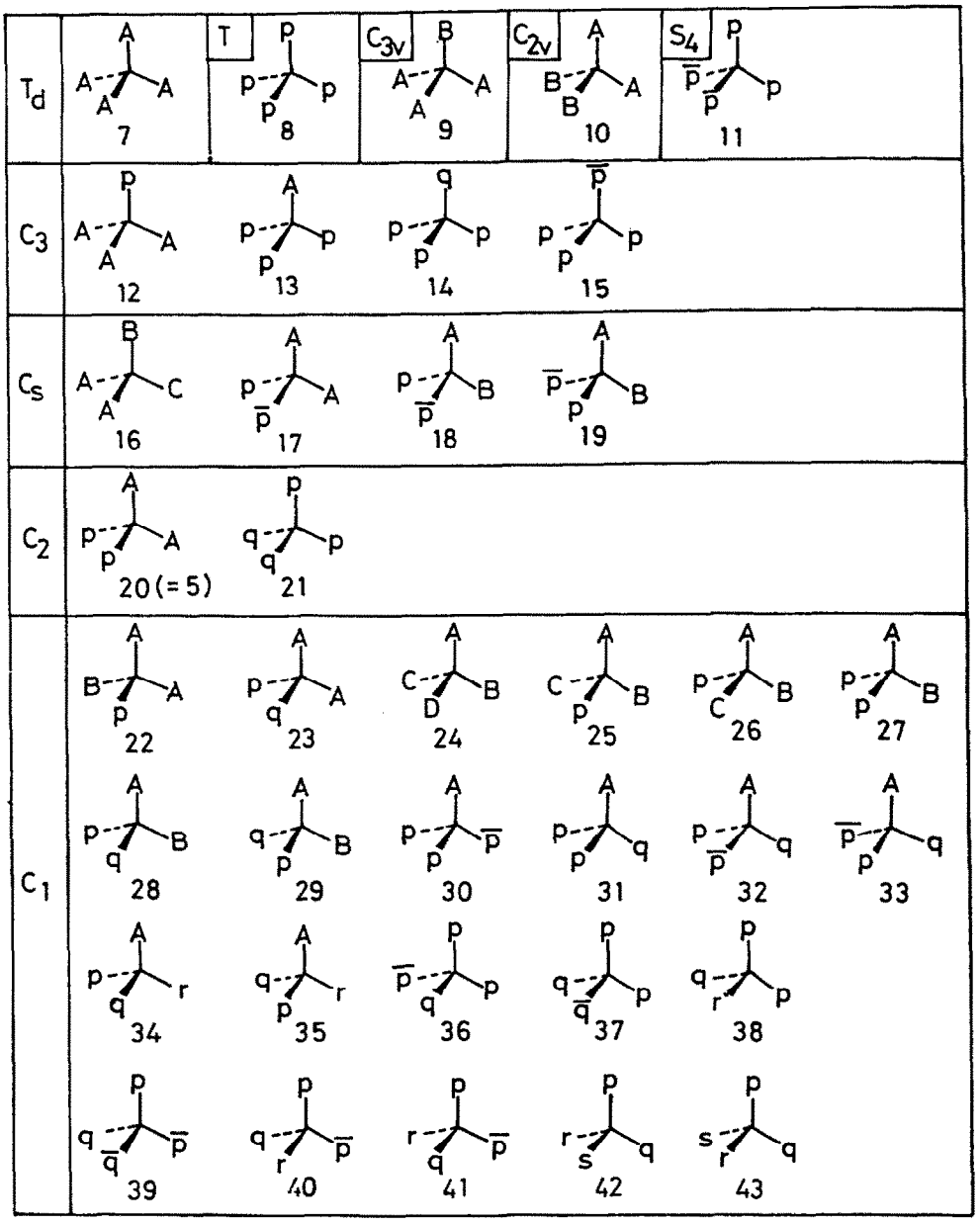


Figure 2: Tetrahedral promolecules of various symmetries

Figure 2 depicts all of these promolecules, where an arbitrary representative is selected from every racemic pair.[33]

Table 2 collects symmetrical properties of the promolecules (7 to 21). The four joint positions of the skeleton (6) construct a $\mathbf{T}_d(/\mathbf{C}_{3v})$ orbit, which remains unchanged in the promolecule (7). In the other promolecules, the orbit is divided into several orbits shown in Table 2.

Table 2: Orbits and coset representations in promolecules (7-21)

Pro-molecule	Sym-metry	Orbit	Members of an orbit	Coset representation	Chirality fittingness (Sphericity)
7	$\mathbf{T}_d$	Δ	A_4	$\mathbf{T}_d(/\mathbf{C}_{3v})$	homospheric
8	$\mathbf{T}$	Δ	p_4	$\mathbf{T}(/\mathbf{C}_3)$	hemispheric
9	$\mathbf{C}_{3v}$	Δ_1	B	$\mathbf{C}_{3v}(/\mathbf{C}_{3v})$	homospheric
		Δ_2	A_3	$\mathbf{C}_{3v}(/\mathbf{C}_s)$	homospheric
10	$\mathbf{C}_{2v}$	Δ_1	A_2	$\mathbf{C}_{2v}(/\mathbf{C}_s)$	homospheric
		Δ_2	B_2	$\mathbf{C}_{2v}(/\mathbf{C}'_s)$	homospheric
11	$\mathbf{S}_4$	Δ	$p_2\overline{p}_2$	$\mathbf{S}_4(/\mathbf{C}_1)$	enantiospheric
12	$\mathbf{C}_3$	Δ_1	p	$\mathbf{C}_3(/\mathbf{C}_3)$	homospheric
		Δ_2	A_3	$\mathbf{C}_3(/\mathbf{C}_1)$	hemispheric
13	$\mathbf{C}_3$	Δ_1	A	$\mathbf{C}_3(/\mathbf{C}_3)$	homospheric
		Δ_2	p_3	$\mathbf{C}_3(/\mathbf{C}_1)$	hemispheric
14	$\mathbf{C}_3$	Δ_1	q	$\mathbf{C}_3(/\mathbf{C}_3)$	homospheric
		Δ_2	p_3	$\mathbf{C}_3(/\mathbf{C}_1)$	hemispheric
15	$\mathbf{C}_3$	Δ_1	$\overline{p}$	$\mathbf{C}_3(/\mathbf{C}_3)$	homospheric
		Δ_2	p_3	$\mathbf{C}_3(/\mathbf{C}_1)$	hemispheric
16	$\mathbf{C}_s$	Δ_1	B	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_2	C	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_3	A_2	$\mathbf{C}_s(/\mathbf{C}_1)$	enantiospheric
17	$\mathbf{C}_s$	Δ_1	A	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_2	A	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_3	$p\overline{p}$	$\mathbf{C}_s(/\mathbf{C}_1)$	enantiospheric
18	$\mathbf{C}_s$	Δ_1	A	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_2	B	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_3	$p\overline{p}$	$\mathbf{C}_s(/\mathbf{C}_1)$	enantiospheric
19	$\mathbf{C}_s$	Δ_1	A	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_2	B	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_3	$\overline{p}p$	$\mathbf{C}_s(/\mathbf{C}_1)$	enantiospheric
20 (5)	$\mathbf{C}_2$	Δ_1	A_2	$\mathbf{C}_2(/\mathbf{C}_1)$	hemispheric
		Δ_2	p_2	$\mathbf{C}_2(/\mathbf{C}_1)$	hemispheric
21	$\mathbf{C}_2$	Δ_1	p_2	$\mathbf{C}_2(/\mathbf{C}_1)$	hemispheric
		Δ_2	q_2	$\mathbf{C}_2(/\mathbf{C}_1)$	hemispheric

These divisions are strictly controlled by a desymmetrization lattice (Fig. 3) which contains subductions of the CR $(\mathbf{T}_d(/\mathbf{C}_{3v}))$.[23] For example, the derivation of 9 from 6 is represented by

$$\mathbf{T}_d(/\mathbf{C}_{3v}) \downarrow \mathbf{C}_{3v} = \mathbf{C}_{3v}(/\mathbf{C}_{3v}) + \mathbf{C}_{3v}(/\mathbf{C}_s), \tag{4}$$

which is found in Fig. 3. Equation 4 is schematically represented by

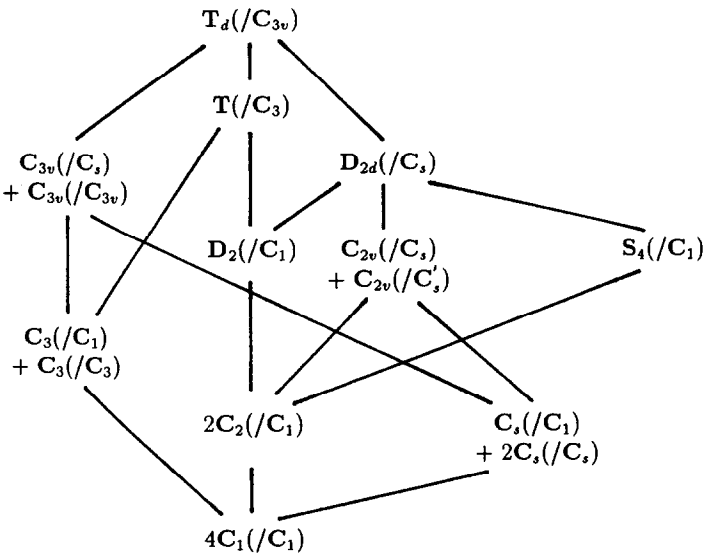
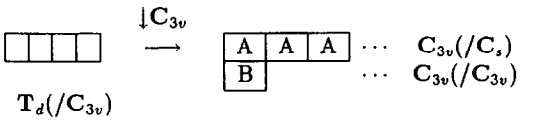


Figure 3: Desymmetralization lattice for $T_d(/C_{3v})$



Each CR has its chirality fittingness, which determines a mode of substitution of proligands. Thus, a homospheric orbit takes only achiral proligands of the same kind. An enantiospheric orbit takes (1) achiral proligands of the same kind or (2) one half of chiral proligands and the other half of their antipodes. A hemispheric orbit permits (1) achiral proligands of the same kind and (2) chiral proligands of the same chirality. These criteria hold true in the data of Table 2. For example, two orbits generated by eq. 4 are both homospheric; in addition, the length of the $C_{3v}(/C_{3v})$ orbit is equal to 1 and that of $C_{3v}(/C_s)$ orbit is euqal to 3. Hence, we have an A_3B-promolecule (**9**).

Examination of the C_s promolecules (**16** to **19**) is instructive, since there emerge several modes of occupation. The above criteria indicate that, in anyone of these promolecules, the two $C_s(/C_s)$ orbits require distinct achiral proligands. In addition, the $C_s(/C_1)$ orbit takes two achiral proligands or a pair of antipodal chiral proligands. Thus, **16** is an example of the former occupation of the $C_s(/C_1)$ orbit; and **18** and **19** are examples of the latter. The promolecule (**17**) shows that the two $C_s(/C_s)$ can take proligands of the same kind; however, these two proligands belong to distinct orbits.

It is worthwhile comparing the present enumeration with Prelog's one[4] as well as with our previous one.[6] Prelog used Young's diagrams which designate ligand partitions. His method takes no account of symmetrical properties in the process of enumeration; there is hence no systematic itemization concerning molecular symmetries. As a result, the symmetry of a resulting molecule is determined by finding symmetry elements. Our previous method adopted an analogous procedure.

On the other hand, we use such a term as $A_2p\overline{p}$ for denoting ligand partitions; and a symbol of a CR or a Young's diagram for designating a site partition (*i.e.* division of an orbit into suborbits). Our method first determined a symmetry at issue, into which a given orbit is subduced. We then fill the resulting suborbits in the light of their chirality fittingnesses. This process is closely related to enumeration by USCI-CFs, which algebraically provides the numbers of promolecules in an itemized form concerning

proligand partitions and symmetries.

Prelog's and our previous enumeration may afford some confusions in specifying stereochemical equivalency. For example, compare promolecule **44** (equivalent to **17**) with **16** (Fig. 4). By means of these treatments, one may take no account of the difference between the As of **16** and those of **44**. Thus, they may be errouneously considered to be placed in the same symmetrical environment, although this mistake can be, of course, avoided by careful inspection. On the other hand, the present method discriminates them in terms of orbits. Thus, the two As of **16** construct an $C_s(/C_1)$ orbit, whereas the two As of **44** construct two distinct $C_s(/C_s)$ orbits.

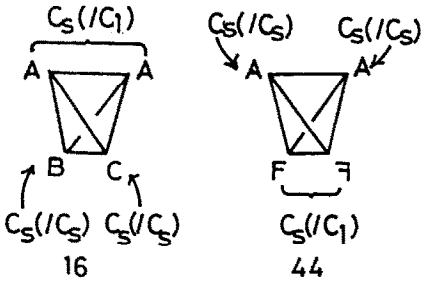
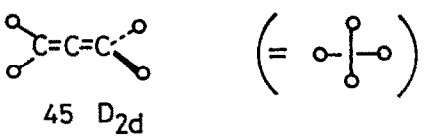


Figure 4: Orbits of C_s promolecules (**16** and **44**)

Promolecules derived from an allene skeleton. Consider an allene skeleton (**45**). The four joint positions of the skeleton (**45**) construct a $D_{2d}(/C_s)$ orbit.



Promolecules derived from an allene skeleton (**45**) are enumerated by means of USCI-CFs. SCI-CFs used are equal to the USCI-CFs. Equations 1-3 are used as figure inventories. The promolecules are depicted in Figure 5, which contains an arbitrary representative selected from every racemic pair. Comparison of Fig. 2 with Fig. 5 are useful to understand the fiffernce between the skeletons **6** and **45**. For example, the ligand partition (A^2B^2) produces one molecule (**10**) of C_{2v} symmetry (Fig. 2). On the other hand, it produces **48** (C_{2v}) and **57** (C_2') by starting from **45** (Fig. 5). The ligand partition (A^2p^2) produces one promolecule (**20**) in the series of **6**, whereas it produces three promolecules (**55**, **58**, and **59**) on the basis of **45**.

Table 3 collects symmetrical properties of the promolecules (**46** to **62**). The $D_{2d}(/C_s)$ orbit of **45** is divided into several orbits according to a desymmetrization lattice (Fig. 6), which contains subductions of the CR ($D_{2d}(/C_s)$).

4 Molecules Based on Promolecules

Matched molecules. Suppose that a set of equivalent proligands in a promolecule belong to an $H(/H_i)$ orbit, where **H** is the point group of the promolecule and H_i is its subgroup indicating the local symmetry of the orbit.[34] Any proligand agrees with the local symmetry (H_i), because it is considered

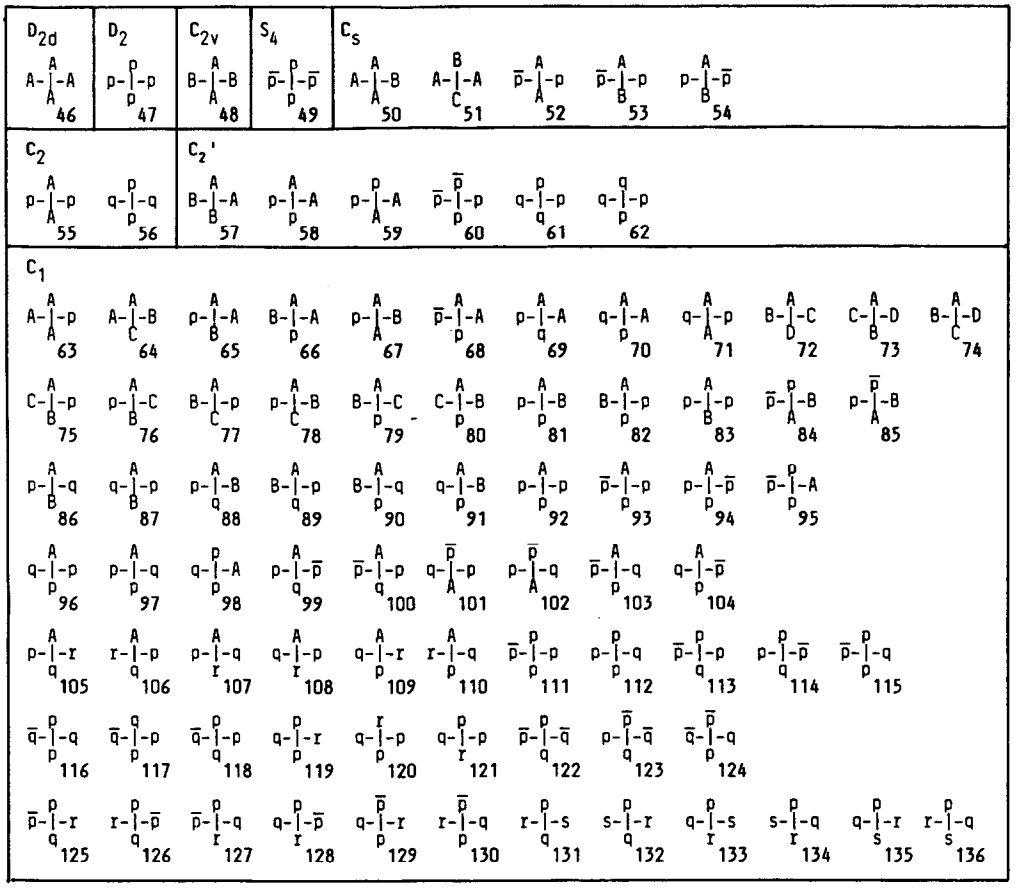


Figure 5: Promolecules derived from an allene skeleton (**45**)

Table 3: Orbits and coset representations in promolecules (**46-62**)

Pro-molecule	Sym-metry	Orbit	Members of an orbit	Coset representation	Chirality fittingness (Sphericity)
46	$\mathbf{D}_{2d}$	Δ	A_4	$\mathbf{D}_{2d}(/\mathbf{C}_s)$	homospheric
47	$\mathbf{D}_2$	Δ	p_4	$\mathbf{D}_2(/\mathbf{C}_1)$	hemispheric
48	$\mathbf{C}_{2v}$	Δ_1	A_2	$\mathbf{C}_{2v}(/\mathbf{C}_s)$	homospheric
		Δ_2	B_2	$\mathbf{C}_{2v}(/\mathbf{C}_s')$	homospheric
49	$\mathbf{S}_4$	Δ	$p_2\overline{p}_2$	$\mathbf{S}_4(/\mathbf{C}_1)$	enantiospheric
50	$\mathbf{C}_s$	Δ_1	A	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_2	B	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_3	A_2	$\mathbf{C}_s(/\mathbf{C}_1)$	enantiospheric
51	$\mathbf{C}_s$	Δ_1	B	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_2	C	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_3	A_2	$\mathbf{C}_s(/\mathbf{C}_1)$	enantiospheric
52	$\mathbf{C}_s$	Δ_1	A	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_2	A	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_3	$p\overline{p}$	$\mathbf{C}_s(/\mathbf{C}_1)$	enantiospheric
53	$\mathbf{C}_s$	Δ_1	A	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_2	B	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_3	$p\overline{p}$	$\mathbf{C}_s(/\mathbf{C}_1)$	enantiospheric
54	$\mathbf{C}_s$	Δ_1	A	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_2	B	$\mathbf{C}_s(/\mathbf{C}_s)$	homospheric
		Δ_3	$\overline{p}p$	$\mathbf{C}_s(/\mathbf{C}_1)$	enantiospheric
55	$\mathbf{C}_2$	Δ_1	A_2	$\mathbf{C}_2(/\mathbf{C}_1)$	hemispheric
		Δ_2	p_2	$\mathbf{C}_2(/\mathbf{C}_1)$	hemispheric
56	$\mathbf{C}_2$	Δ_1	p_2	$\mathbf{C}_2(/\mathbf{C}_1)$	hemispheric
		Δ_2	q_2	$\mathbf{C}_2(/\mathbf{C}_1)$	hemispheric
57	$\mathbf{C}_2'$	Δ_1	A_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
		Δ_2	B_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
58	$\mathbf{C}_2'$	Δ_1	A_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
		Δ_2	p_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
59	$\mathbf{C}_2'$	Δ_1	A_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
		Δ_2	p_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
60	$\mathbf{C}_2'$	Δ_1	p_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
		Δ_2	$\overline{p}_2$	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
61	$\mathbf{C}_2'$	Δ_1	p_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
		Δ_2	q_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
62	$\mathbf{C}_2'$	Δ_1	p_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric
		Δ_2	q_2	$\mathbf{C}_2'(/\mathbf{C}_1)$	hemispheric

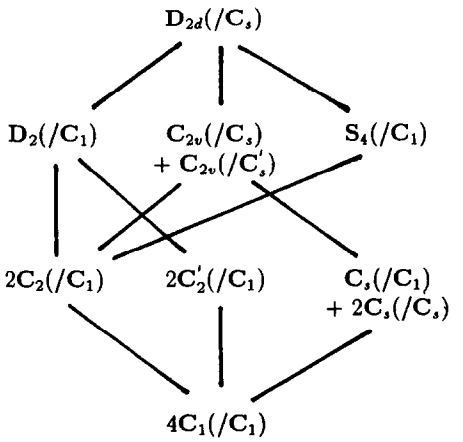


Figure 6: Desymmetralization lattice for $D_{2d}(/C_s)$

to be structureless. However, a ligands that has a 3D structure is not always compatible with such local symmetry.

Consider that a proligand in a promolecule is replaced by a ligand, where their achiral/chiral characters are presumed to be equal. If the symmetry (**F**) of the ligand as a fragment is a supergroup of the local symmetry ($\mathbf{H}_i$), in other words, if the ligand matches the local symmetry of the promolecule, the symmetry of the promolecule remains unchanged in the resulting molecule. We call the resulting molecule a *matched molecule*.[29]

Such matched molecules can be classified into two categories ($\mathbf{F} = \mathbf{H}_i$ and $\mathbf{F} > \mathbf{H}_i$). The first case is that **F** is equal to $\mathbf{H}_i$. There appears no restriction in this type of construction of mactched molecules. For example, the promolecule (**7**) can be converted into neopentane and like, when each A is replaced by a methyl group. The methyl group as a fragment has C_{3v} symmetry, which is compatible with the local symmetry of the $T_d(/C_{3v})$ orbit of **7**. Hence, this molecule ideally has the same T_d symmetry as **7**, where the global symmetry of **7** retains in the resulting neopentane.[35] Moreover, there emerges no restriction concerning the C_{3v}-fragment. The Nakazaki compound (**2b**) is another example of this case. Obviously, the D_3-trishomocubanyl group belongs to C_3, which is compatible with the $T(/C_3)$ orbit of an adamantane promolecule (analogous to **8** collected in Table 2).

If $\mathbf{F} > \mathbf{H}_i$, the symmetry (**F**) of a ligand is restricted to $\mathbf{H}_i$ as a segment, whereas global symmetry is not affected. Consider the case of **46** derived from the allene skeleton (**45**). Since the four joints of **46** construct a $D_{2d}(/C_s)$ orbit, this orbit has C_s local symmetry. A methyl group (a C_{3v}-fragment) matches this local symmetry. This means that the resulting tetramethylallene retains the same D_{2d} symmetry as the promolecule (**46**). However, the C_{3v} symmetry of the methyl fragment is restricted to C_s according to the following expression:

$$C_{3v}(/C_s) \downarrow C_s = C_s(/C_1) + C_s(/C_s) \text{ for three hydrogens} \quad (5)$$

and

$$C_{3v}(/C_{3v}) \downarrow C_s = C_s(/C_s) \text{ for the joint carbon.} \quad (6)$$

Equation 5 indicates that the three hydrogens are split into a $C_s(/C_1)$ orbit (two hydrogens) and a $C_s(/C_s)$ orbit (one hydrogen), if there appears an appropriate energy barrier.

Figure 1 illustrates an example that involves the two cases, *i.e.*, $\mathbf{F} = \mathbf{H}_i$ for the CXYZ groups and $\mathbf{F} \geq \mathbf{H}_i$ for the methyl groups, becasue $\mathbf{H}_i$ is equal to C_1 in **5** (= **20**). Obviously, if $\mathbf{H}_i$ is equal to C_1

(an identity group), the corresponding orbit (governed by an RR) accepts any ligands, since the relation $\mathbf{F} \geq \mathbf{H}_i$ ($= \mathbf{C}_1$) holds for and $\mathbf{F}$.

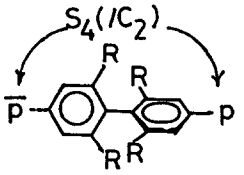
Mismatched molecules. Suppose that $\mathbf{F} < \mathbf{H}_i$. Then, the symmetry ($\mathbf{F}$) of a ligand is incompatible with the local symmetry ($\mathbf{H}_i$) of an $\mathbf{H}(/\mathbf{H}_i)$ orbit of a promolecule. The resulting molecule (called a *mismatched molecule*) no longer retains the original symmetry ($\mathbf{H}$) of the promolecule.

Let $\mathbf{M}$ be the symmetry of the molecule ($\mathbf{M} < \mathbf{H} \leq \mathbf{G}$). If $\mathbf{H}$ is chiral, $\mathbf{M}$ can be selected as chiral; if $\mathbf{H}$ is achiral, $\mathbf{M}$ can be selected as achiral. If $\mathbf{F}$ is a subgroup of $\mathbf{M}$ and if $| \mathbf{M} | / | \mathbf{F} |$ is equal to $| \mathbf{H} | / | \mathbf{H}_i |$, the $\mathbf{H}(/\mathbf{H}_i)$ orbit in the promolecule restricted into an $\mathbf{M}(/\mathbf{F})$ orbit in the resulting molecule. Such an $\mathbf{M}$ group can be obtained by the inspection of a desymmetrization lattice for $\mathbf{H}$.

Consider the promolecule (**7**), in which the four As are replaced by four hydroxymethyl ligands (CH_2OH). This ligand in isolation has $\mathbf{C}_s$ symmetry, which is incompatible with the $\mathbf{C}_{3v}$ local symmetry. When we examine the desymmetrization lattice (Fig. 3), we find $\mathbf{D}_{2d}(/\mathbf{C}_s)$, where $| \mathbf{T}_d | / | \mathbf{C}_{3v} | = | \mathbf{D}_{2d} | / | \mathbf{C}_s | = 2$. Hence, the resulting pentaerythritol belongs to $\mathbf{D}_{2d}$ symmetry; and the four CH_2OH ligands construct a $\mathbf{D}_{2d}(/\mathbf{C}_s)$ orbit.

The McCasland $\mathbf{D}_2$ molecule (**1c**) is a mismatched molecule derived from the promolecule (**8**); *i.e.*, $\mathbf{T}(/\mathbf{C}_3) \rightarrow \mathbf{D}_2(/\mathbf{C}_1)$. This desymmetrization is rationalized by Fig. 3. That is to say, the symmetry ($\mathbf{C}_1$) of the ligand mismatches the $\mathbf{C}_3$ local symmetry of $\mathbf{T}(/\mathbf{C}_3)$ and lowers the symmetry of the molecule (**1c**) to have $\mathbf{D}_2$. Thereby, the $\mathbf{C}_1$ symmetry becomes compatible to the CR ($\mathbf{D}_2(/\mathbf{C}_1)$). The Nakazaki $\mathbf{D}_2$ molecule (**2a**) can be explained in the same line.

The Mislow molecule (**3**) can be derived from a promolecule (**137**), where $p\bar{p}$ proligands construct an $\mathbf{S}_4(/\mathbf{C}_2)$ orbit. Since CXYZ ligands ($\mathbf{C}_1$) are incompatible with this CR, the resulting molecule (**3**) no longer belongs to $\mathbf{S}_4$ but to $\mathbf{C}_1$. It should be noted that *the chirality/achirality of such a molecule is determined by the chirality/achirality of the corresponding promolecule.*



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There is another type of mismatched molecules. Suppose that the symmetry $\mathbf{F}'$ of a ligand is neither a subgroup nor a supergroup of $\mathbf{H}_i$. If $\mathbf{F}$ is selected as being equal to $\mathbf{F}' \cap \mathbf{H}_i$, the above treatment holds for this case. There exists such an $\mathbf{F}$ group; in the lowest cases, $\mathbf{F}$ may be $\mathbf{C}_s$ for an achiral $\mathbf{F}'$ and $\mathbf{C}_1$ for a chiral $\mathbf{F}'$.

Let us examine the promolecule (**7**), in which As are replaced by phenyl groups. The symmetry of the phenyl group is $\mathbf{C}_{2v}$, whereas the local symmetry is $\mathbf{C}_{3v}$. Hence, we select $\mathbf{F} = \mathbf{C}_{2v} \cap \mathbf{C}_{3v} = \mathbf{C}_s$. We look up a $(/\mathbf{C}_s)$ term in Fig. 3; in a similar way as pentaerythritol, we are able to find $\mathbf{D}_{2d}(/\mathbf{C}_s)$. Hence, we conclude that the resulting tetraphenylmethane has $\mathbf{D}_{2d}$ symmetry.

Highest attainable symmetry. The above discussions provide us with a general approach to the judgement of the highest attainable symmetry of a given molecule. The procedure is summarized as follows. (1) The molecule is converted into the corresponding promolecule by replacing ligands by proligands. (2) The symmetry and orbits (CRs) of the promolecule are determined. (3) The chirality/achirality of the molecule is determined by the symmetry of the promolecule. (4) From each CR, we have a local symmetry for each proligand. (5) We examine whether the symmetry of a ligand is compatible with such a local symmetry or not. (6) A matched (compatible) molecule retains the symmetry of the promolecule in the highest attainable state. (7) A mismatched (incompatible) molecule lower the symmetry of the promolecule. The resulting symmetry is judged in terms of a desymmetrization lattice.

5 Prochiralities of Promolecules and Molecules

In a previous paper,[23] we have proposed a novel definition of *prochirality*. Although this definition can be applied to all types of molecules, the previous discussion mainly took rigid molecules into consideration. We here extend this definition in order to treat promolecules as well as non-rigid molecules.

Definition of prochirality. The concept of prochirality is ascribed to the presence of an enantiospheric orbit. This is based on a theorem:[23] *an enantiospheric orbit is capable of separating into two hemispheric orbits of the same length under a chiral environment, whether the change is reversible or irreversible.* As exemplified in Fig. 1, a promolecule (*e.g.* **5**) has joint positions which are occupied by proligands. A set of equivalent proligands (as segments) constructs an orbit, which corresponds to an orbit of the joints in one-to-one fashion. Hence, we can regard the chirality fittingness (sphericity) for the orbit of proligands as being the same as that for the orbit of joints. A *prochiral promolecule* is then defined as a promolecule that has at least one enantiospheric orbit of proligands.[37]

Tables 2 and 3 contain such chirality fittingnesses for promolecules. Among them, enantiospheric orbits are concerned with prochirality. For example, the promolecule (**11**) has four prolignds that are the members of an enantiospheric ($\mathbf{S}_4(/\mathbf{C}_1)$) orbit. Under a chiral environment, the orbit is split into two hemispheric orbits (p_2 and $\overline{p}_2$ perturbed), which are energetically different. In other words, the original enantiospheric orbit is degenerated under an achiral environment.

The prochiralities of the $\mathbf{C}_s$-promolecules (**16**-**19**) come from their respective enantiospheric orbits (Δ_3) governed by $\mathbf{C}_s(/\mathbf{C}_1)$. The $\mathbf{C}_s(/\mathbf{C}_1)$ orbit (Δ_3) of **16** takes two achiral proligands (A_2); on the other hand, the Δ_3 orbit of **17**, **18**, or **19** is occupied by a pair of antipodal proligands ($p\overline{p}$). These two modes of occupation are characteristic of such enantiospheric orbits.

It should be noted that p and $\overline{p}$ of an enantiospheric orbit (*e.g.* in **17**) are equivalent to each other as segments. This fact may be strange to organic chemists, since their convention discriminates a chiral moiety from its mirror image. On the other hand, it is natural for organic chemists to recognize that the two A's of an enantiospheric orbit (*e.g.* in **16**) are equivalent. In spite of such opposite recognitions, the relationship between p and $\overline{p}$ has the same effects as does the relationship between the two A's. Mathematically speaking, such an enantiospheric orbit is an equivalence class, the two halves of which are equivalent in the sense that they coincide with each other by an improper rotation, but not by a proper rotation. Thus, the two A's coincide with each other by an improper rotation only in the same manner as does the $p\overline{p}$. That is to say, each of the two A's is ristricted to $\mathbf{C}_1$ (asymmetric) in such a promolecule as **16**. In addition, the one A is the mirror image of the other A under the ristricted condition (as segments). Misunderstanding regarding these facts has created a vast number of confusions concerning prochirality and related concepts, as discussed in the following section.

Matched molecules can be treated in the same line as promolecules. Fig. 1 shows that a matched molecule (*e.g.* **4**) has joint positions which are occupied by ligands. A set of equivalent ligands (as segments) constructs an orbit which is equivalent to that of proligands. This corresponds to an orbit of the joints in one-to-one fashion. Hence, we regard the chirality fittingness (sphericity) for the orbit of ligands as being the same as that for the orbit of joints. A *prochiral matched molecule* is then defined as a matched molecule that has at least one enantiospheric orbit of ligands.

Orbits of ligands in mismatched molecules are also considered to be orbits of such joints. Since the symmetry of such a mismatched molecule differs from that of the corresponding promolecule, two types of prochiralities should be taken into account. The one is concerned with such a mismatched molecule and the other with a parent promolecule. A *prochiral mismatched molecule* in the former sense (*i.e.*, as an appropriate conformer of the highest attainable symmetry) is defined as a mismatched molecule that has at least one enantiospheric orbit of ligands, where the symmetry at issue is that of the mismatched molecule. A *prochiral mismatched molecule* in the latter sense (*i.e.*, as an average conformation) is defined as a mismatched molecule that corresponds to a prochiral promolecule. Which prochiralities are effective would be variable and should be determined experimentally. For example, the Mislow molecule (**3**) is chiral in the highest attainable symmetry; but prochiral in the latter sense, because the corresponding

promolecule (**137**) has an enantiospheric orbit $\mathbf{S}_4(/\mathbf{C}_2)$. As a result, the replacement of p or $\bar{p}$ by an appropriate achiral ligand can produce a chiral molecule.

Comments on conventional definitions. In connection with the preceding analysis, we should reexamine previous definitions of the term "prochirality". The original version of Hanson[31] was as follows: "If a chiral assembly is obtained when a point ligand is a finite nonchiral assembly of point ligands is replaced by a new point ligand, the original assembly is prochiral." This definition is obviously a special case of the present one if the terms "assembly" and "point ligand" are replaced by the terms *promolecule* and *achiral proligand*. The original definition was revised by Hirschmann and Hanson so that "prochirality" was used with reference to prostereoisomerism[38] and further with reference to the terms "graphochiral" and "pherochiral".[39] This revision, however, changed the meanings of the original terms so as to aim at preparing sequence rules in a formal fashion. In the light of this revision, Cg^+g^-hi (equivalent to **18**) and $Cg^+g^-h^+i^-$ (equivalent to **40** or **41**) are "achiral" centers of stereoisomerism with a chiral configuration; and $Cg^+g^-h^+h^-$ (equivalent to **39**) is a "chiral" center of setereoisomerism with a chiral configuration. Contrary to this, **18** is achiral; and **40** (or **41**) and **39** are chiral in the present criterion. Since the achiral **18** (Cg^+g^-hi) can produce the chiral **22** (Cg^+jhi), it seems hard to understand why **18** (Cg^+g^-hi) should not be called "prochiral".

Prelog and Helmchen[5] differentiated centers of "prochirality" (*e.g.*, for **16**), those of "pseudoasymmetry" (*e.g.*, for **18** and **19**) and those of "propseudoasymmetry" (*e.g.*, for **17** or **44**) from each other. The term "propseudoasymmetry" would produce a serious confusion, even though their statament on stereochemistry is to the point. Using this term, they focussed their attention on the two A's of **17** (equivalently **44** in Fig. 4). The propseudoasymmetry indicates that one of the two A's is replaced by B producing a *meso* promolecule (**18** or **19**) having a pseudoasymmetric center. However, this process is chemoselective and by no means stereoselective.[23] There exists a stereoselective process for the promolecule (**17**), which is the replacement of either one of $p\bar{p}$ to create a chiral promolecule (*e.g.* **22**). Thus, the term "propseudoasymmetry" contradicts itself, because a promolecule with a center of propseudoasymmetry can produce a chiral promolecule in addition to a promolecule having a center of pseudoasymmetry.

The latter example also indicates that the term "centers" of prochirality *etc.* has no sound basis. Thus, the conversion of **17** into **22** does not stem from the handedness of such an center, but from a stereoselective distinction regarding the halves of the enantiospheric orbit (Δ_3) of **17**. Such an orbit by no means depends upon any of such centers. Hence, stereochemical phenomena must be discussed on the basis of orbits governed by coset representations. They should not be ascribed to such "centers", as pointed out by Mislow and Siegel.[13]

The Mislow-Siegel defintion of prochirality[13] can give results equivalent to ours by careful examination, although it does not contain the present concepts such as sphericities of orbits. We have recently discussed their concept of $(\text{pro})^r$-chirality.[23]

The preceding analysis implies that there are two types of representations for stereochemistry: (1) a representation for reproducing or rewriting a stereostructure and (2) a representation for discussing streochemical relationships. In the begining and as for rather simple molecules, the two representations were identical with each other in all of the proposed rules.[40, 31, 41] However, every revision for aiming at a more complicated cases has more and more separated the two representations and has attached greater importance to (1) than to (2). Conventional confusions stem from such approaches that substitute (1) for (2) without recognizing this fact. The present change of viewpoints thinks much of (2) and thereby provides us with a deeper insight on stereochemistry.

6 Conclusion

In order to characterize symmetrical properties of a non-rigid molecule, several concepts are introduced, where the non-rigidity stems from internal bond rotations. One of such concepts is proligands, which are defined as hypothetical ligands being structureless but having chirality. A promolecule is an abstract three-dimensional object that consists of a skeleton and such proligands. According to this formulation,

promolecules can be manipulated as rigid objects. Thus, promolecules based on a methane and an allene skeleton are enumerated systematically by using unit subduced cycle indices with chirality fittingness. By starting from one of these promolecules, a molecule can be constructed, where proligands contained are replaced by approriate ligands that have three-dimensional structures. This construction is controlled by a coset representation that governs an orbit of such proligands or equivalently by the corresponding local symmetry. The resulting molecules are classified into matched molecule of which symmetries retain the symmetries of the starting promolecules; or into mismatched molecules of which symmetries lower. Modes of such desymmetrizations are explained by a desymmetrization lattice indicating subduction of coset representations. Prochirality concerning promolecules and non-rigid molecules are discussed.

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