Sphericities of Cycles. What Pólya's Theorem is Deficient in for Stereoisomer Enumeration

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Three methods and their extended versions for enumerating stereoisomers, which have been developed by modifying or simplifying Fujita's USCI (unit-subduced-cycle-index) approach based on the concept of sphericities of orbits in order not to take account of symmetry itemization, are applied to the enumeration problem of ethane and propane derivatives. The proligand method and its extended version based on the concept of sphericities of cycles are also applied to the same enumeration problems. These results are compared with the results based on Pólya's theorem (and Pólya's corona). Thereby, it is shown that Pólya's theorem enumerates chemical compounds as graphs, not as stereoisomers (3D chemical structures) if all of the permutations corresponding to proper and improper rotations are adopted. Moreover, if the permutations corresponding to proper rotations are adopted, Pólya's theorem enumerates chemical compounds as chiral ones, where enantiomeric relationship and achiral nature (*i.e*., self-enantiomeric relationship) are not characterized properly. The two types of applications of Pólya's theorem do not take account of improper rotations properly. Thereby, what Pólya's theorem is deficient in is concluded to be the concept of sphericity.

INTRODUCTION

Since the concepts of sphericity, sphericity indices, and unit subduced cycle indices with chirality fittingness (USCI-CFs) were proposed on the basis of orbits governed by coset representations and their subductions,[1] they have been used to discuss stereochemistry in molecules as well as to enumerate stereoisomers. The USCI approach based on the concepts is capable of enumerating isomers as 3D chemical structures (stereoisomers), where they are itemized with respect to point-group symmetries as well as to molecular formulas. However, the USCI approach requires mark tables, USCI tables, and related group theoretical tools, which are not so easily obtained, as pointed out in a recent review.[2] It should be noted that there is a trade-off between the tedeous derivation of these requisites and the capability of itemizing point-group symmetries.

On the other hand, Pólya's theorem, which has been widely used since 1930s,[3,4] is simple and convenient to calculate gross isomer numbers without taking account of symmetry-itemization. In fact, many studies on the basis of Pólya's theorem have been reported in chemical fields, as described in reviews[5,6] and books.[7,8] Various types of approaches have been reported in many articles.[9,10,11]

Before we will start our discussions on stereoisomerism and stereoisomer enumeration, the scope and limitations of Pólya's theorem should be examined from the viewpoint which the USCI approach has brought about. Strictly speaking, the term 'proligand' should be used in some cases, the term 'ligand' is used so long as such usage causes no confusion.

(i) Stereoisomers as 3D chemical structures should be described in terms of point groups, which may involve proper and improper rotations. This means that Pólya's

theorem does not directly deal with stereoisomers, because it is based on permutation groups. In particular, the permutation-group theory has disregarded the inner structures of objects to be permuted (*e.g.*, the chiralities/achiralities of ligands) so that Pólya's theorem enumerates graphs, not stereoisomers (3D chemical structures) especially in the enumeration of straight- or branched-chain organic compounds.

(ii) Even when Pólya's theorem claimed to be successful in the enumeration of stereoisomers, it failed in the characterization of enantiomeric relationship. For example, *trans*-octahedral complexes, X–ABCD–Y and Y–ABCD–X, where the plane containing four achiral ligands ABCD separates achiral ligands X and Y in a *trans* fashion, are chiral and enantiomeric to each other. Because the enumeration procedure based on Pólya's theorem employed the 24 operations corresponding to *O*-point group (*i.e.*, only the proper rotations of O_h-point group) as described in Berge's textbook,[12] the two enantiomers are not superposed so that they are counted separately. Thus the two enantiomers are not characterized as "enantiomeric" but they are recognized to have no relationship so long as the enumeration process due to Pólya's theorem is based on the *O*-point group. Although they can be characterized as being enantiomeric by employing the O_h-point group, another type of drawback appears so long as the permutations corresponding O_h-point group are used within the methodology of Pólya's theorem.

(iii) Moreover, Pólya's theorem failed in distinction between enantiomeric relationship and self-enantiomeric one (*i.e.*, achiral nature), because it took account of atoms (or at most achiral ligands) as substituents. By following the same procedure as described above,[12] *trans*-octahedral complexes, p—ABCD—p̄ and p̄—ABCD—p, where the symbols p and p̄ represent chiral ligands of opposite chirality, are also counted separately, although they are achiral. This means that the asymmetric case X–ABCD–Y/Y–ABCD–X (*i.e.*, an enantiomeric relationship) is not differentiated from the so-called pseudoasymmetric case p—ABCD—p̄/p̄—ABCD—p (*i.e.*, self-enantiomeric relationships).

There may be an *ad hoc* approach in which we mix up the enantiomeric relationship and the self-enantiomeric one (*i.e.*, achiral nature) so as to adopt the resulting mixed-up relationship (*i.e.*, the stereoisomeric relationship). Thereby, we would be permitted to say that this enumeration is concerned with stereoisomers, even though enantiomers (chiral compounds) and achiral compounds were not conceptually distinguished. Stereochemically speaking, however, this approach results in the degeneration into the stage before the foundation of the stereochemistry by van't Hoff[13] and Le Bel.[14]

(iv) To clarify enantiomeric relationship or self-enantiomeric one (*i.e.*, achiral nature) in the above-described cases, the remaining 24 operations corresponding to the improper rotations of the O_h-point group should be taken into consideration. This modification, however, causes stereochemically insufficient enumeration in the pseudoasymmetric cases. If the 48 permutations for the O_h are simply employed in applying Pólya's theorem without considering the chiralities of ligands, the enantiomeric pair of X–ABCD–Y/Y–ABCD–X and the diastereomeric pair of p—ABCD—p̄/p̄—ABCD—p exhibit the same permutation behavior. In other words, Pólya's theorem counts X–ABCD–Y/Y–ABCD–X once and, at the same time, counts p—ABCD—p̄/p̄—ABCD—p once. Obviously, this result shows that the former enantiomeric case is not distinguished from the latter diastereomeric one.

(v) So long as we rely on Pólya's theorem in the form of the conventional procedure described in Berge's textbook,[12] the use of the *O*-group (*i.e.*, the proper rotations of the O_h-group) is required rather than the use of the full O_h point group. On the other hand, stereochemical problems (*e.g.*, discrimination between enantiomeric relationship and diastereomeric one) should be solved in terms of the full O_h point group. Obviously, such undesirable switching as according to problems at issue should be avoided in order to develop an integrated approach to the stereoisomer enumeration and the solution of stereochemical problems.

(vi) As a result of disregarding the inner structures of objects, the permutation-group theory which Pólya's theorem stems from cannot properly formulate the concept of prochirality.[1] For example, the chiral ligands p and p̄ in each of the pseudoasymmetric octahedral complexes, p—ABCD—p̄ or p̄—ABCD—p, cannot be properly correlated to each other under the action of the 24 permutations corresponding to *O* so long as we obey the conventional procedure described in Berge's textbook.[12] Even if the remaining 24 permutations corresponding to the improper rotations are added to adopt O_h, the disregard of the inner structures causes failure in determining the enantiospheric orbit of p and p̄ (or equivalently the enantiospheric relationship between p and p̄).

(vii) On the same line, the p and p̄ in a pseudoasymmetric tetrahedral molecule with ABpp̄ cannot be properly correlated to each other if the 12 permutations corresponding to *T* (the proper rotations contained in the point group T_d) are taken into consideration. Even if the remaining permutations corresponding the improper rotations are added, the disregard of the inner structures causes the same failure as described above.

The longtime overlooking of the above-described failure stems from the fact that most examples reported for enumerating tetrahedral molecules have considered only achiral ligands whose inner structures are unnecessary to be taken into account. For example, *R*- and *S*-lactic acids ($CH_3CH(OH)COOH$) have been correctly enumerated with considering *T* and T_d,[2] because all of the substituents (*i.e.*, H, CH_3, OH, and COOH) are achiral in isolation.

This result, though apparently correct, cannot be extended to explain the pseudoasymmetric tetrahedral molecule (ABp$\bar{\mathrm{p}}$) within the traditional methodology based on Pólya's theorem.

It should be emphasized that the items listed above have been solved by the USCI approach.[1] In order to treat such stereochemical problems and enumeration problems as solved by the USCI approach, what is Pólya's theorem deficient in?

The deficiency of Pólya's theorem for dealing with stereoisomer enumeration as well as stereochemical problems has been now concluded to be the concept of sphericities of cycles, which is in turn a key in the proligand method developed for the enumeration of stereoisomers.[15,16] The proligand method has shown its superiority over Pólya's theorem in the enumeration of stereoisomers of tartaric acid as ethane derivatives.[17]

In this paper, the combinatorial enumeration of ethane derivatives is solved by using three methods and their extended versions that have been developed by the modification or the simplification of the USCI approach. These enumeration processes based on the concept of sphericities of orbits are discussed in comparison with the enumeration by the proligand method based on the concept of sphericities of cycles. In addition, the enumeration of propane derivatives is conducted by virtue of the proligand method in order to characterize so-called pseudoasymmetric cases. Thereby, the modification or the simplification is found to be based on a set of cyclic subgroups, which is correlated to conjugacy classes. After this comparison, Pólya's theorem is re-examined from the viewpoints of the concepts.[18]

FUJITA'S USCI APPROACH

Stereoisomers of Tartaric Acid as Ethane Derivatives

Obtaining the number of stereoisomers of tartaric acid is an old problem, which emerged at the beginning of stereochemistry. In the 1870s, van't Hoff clarified that there exist a pair of enantiomers (**4** and **$\bar{4}$**) and a *meso*-compound (**5**), although tartaric acid is constitutionally represented as one isomer (**3**, X = H, Y = OH, Z = COOH).[19] Because this solution was rather descriptive, a more quantitative approach is desirable to systematize stereochemistry. Throughout this paper, this problem will be studied as a probe for testing the versatility of the USCI approach and the proligand method in combinatorial enumeration.

To enumerate stereoisomers of ethane derivatives, the USCI approach[1] first considers a skeleton (**6**) that has two substitution positions (Figure 2).[20,21] Each of the two positions accommodates a chiral or achiral proligand to generate a promolecule such as **7**, where the inner structure of a substituent is taken into explicit consideration in
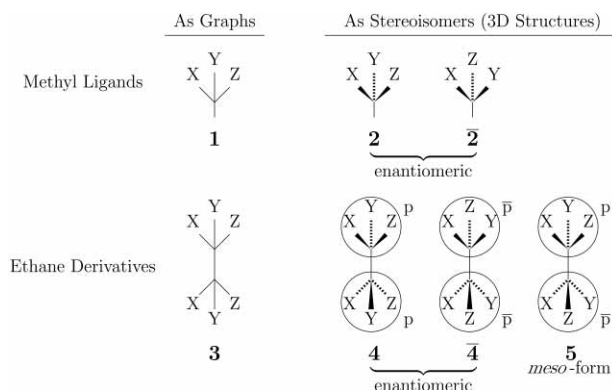

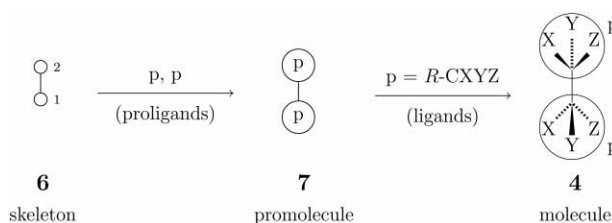Figure 1. Graphs and chemical structures for representing methyl ligands and ethane derivatives.

Figure 2. Conversion of a skeleton into a molecule through a promolecule in the enumeration of ethane derivatives. The symbol p represents a chiral proligand, which is replaced by a chiral ligand CXYZ.

terms of proligand (p). Then, each proligand is replaced by a chiral ligand (*R*-CXYZ) to produce a molecule (**4**). For naming the *R*-configuration, the priority of the atoms or achiral ligands (*i.e.*, X, Y, and Z) is presumed to be X > Y > Z; and the vacant valency of the ligand is regarded as having the lowest priority. In terms of this formulation, free rotations around respective bonds are so assured as to give the correct number of stereoisomers, although fixed conformations are illustrated in Figure 2 *etc.*

Modified Methods of Fujita's USCI Approach

Fujita's USCI approach[1] has provided four methods for stereoisomer enumeration, *i.e.*, (i) the SCI (subduced-cycle-index) method, (ii) the PCI (partial-cycle-index) method, (iii) a method based on the elementary superposition theorem, and (iv) a method based on the partial superposition theorem. As they have been compared by using enumeration problems of digraphs,[22] they can be equivalently applied to combinatorial enumeration of stereoisomers. The enumeration problem of ethane derivatives has already been studied by the SCI method[20] and by the PCI method.[21] The aim of the present subsection is to formulate modified methods by starting from the two methods of the USCI approach so that the results obtained by the modified methods are correlated to those obtained by Pólya's theorem.

– PCI Method and CI Method (Method A)

Both the SCI method and the PCI method are capable of generating cycle indices with chirality fittingness (CI-CFs), which are more informative than the CIs of Pólya's theorem. Because the PCI method provides us with a more succinct basis for correlating the USCI approach to Pólya's theorem, we start from the PCI method to formulate the CI method (Method A) based on CI-CFs and apply it to the problem of enumerating ethane derivatives.

Although the skeleton **6** (Figure 2) belongs to the point group $D_{\infty h}$, it is not easy to treat the point group because of the infinite nature. Hence, the factor group K ($= D_{\infty h} / C_{\infty}$) is taken into consideration in place of $D_{\infty h}$. The factor group K is isomorphic to the point group C_{2v}, where their inner symmetries can be treated similarly.

$$K = D_{\infty h} / C_{\infty} = \{ C_{\infty}, C_{\infty}C_2, C_{\infty}\sigma_v, C_{\infty}\sigma_h \} \quad (1)$$

$$\sim C_{2v} = \{ I, C_2, \sigma_v, \sigma_h \} \quad (2)$$

The group K has the following subgroups:

$$K_1 = \{ C_{\infty} \} \sim C_1 \quad (3)$$

$$K_2 = \{ C_{\infty}, C_{\infty}C_2 \} \sim C_2 \quad (4)$$

$$K_3 = \{ C_{\infty}, C_{\infty}\sigma_v \} \sim C_s \quad (5)$$

$$K_4 = \{ C_{\infty}, C_{\infty}\sigma_h \} \sim C'_s \quad (6)$$

$$K_5 = K = \{ C_{\infty}, C_{\infty}C_2, C_{\infty}\sigma_v, C_{\infty}\sigma_h \} \sim C_{2v} \quad (7)$$

where the corresponding subgroups of the C_{2v} are shown in the ends of respective right-hand sides.

Because the position 1 (or 2) of **6** is fixed (stabilized) by the subgroup K_3, the two positions of **6** are governed by the coset representation (CR) as follows:

$$
\begin{array}{lll}
K(/K_3): & & \\
\hline
C_{\infty} & \sim & (1)(2) \\
C_{\infty}C_2 & \sim & (1\ 2) \\
C_{\infty}\sigma_v & \sim & \overline{(1)(2)} \\
C_{\infty}\sigma_h & \sim & \overline{(1\ 2)}
\end{array} \quad (8)
$$

The concrete form of each permutation (a product of cycles) is obtained by the cosets appearing in the following coset decomposition:

$$K = K_3 + K_3C_2 = \underbrace{\{ C_{\infty}, C_{\infty}\sigma_v \}}_{1} + \underbrace{\{ C_{\infty}C_2, C_{\infty}\sigma_h \}}_{2} \quad (9)$$

The mark table of the C_{2v}-group reported in Ref. 1 (Table A.5 of Appendix A) can be used as the mark table of K:

$$
M_K =
\begin{array}{c}
 \\
K(/K_1) \\
K(/K_2) \\
K(/K_3) \\
K(/K_4) \\
K(/K_5)
\end{array}
\begin{pmatrix}
K_1 & K_2 & K_3 & K_4 & K_5 \\
4 & 0 & 0 & 0 & 0 \\
2 & 2 & 0 & 0 & 0 \\
2 & 0 & 2 & 0 & 0 \\
2 & 0 & 0 & 2 & 0 \\
1 & 1 & 1 & 1 & 1
\end{pmatrix} \quad (10)
$$

The corresponding inverse mark table (M_K^{-1}) reported in Ref. 1 (Table B.5 of Appendix B) is shown below:

$$
M_K^{-1} =
\begin{array}{c}
K_1 \\
K_2 \\
K_3 \\
K_4 \\
K_5
\end{array}
\begin{pmatrix}
\frac{1}{4} & 0 & 0 & 0 & 0 \\
-\frac{1}{4} & \frac{1}{2} & 0 & 0 & 0 \\
-\frac{1}{4} & 0 & \frac{1}{2} & 0 & 0 \\
-\frac{1}{4} & 0 & 0 & \frac{1}{2} & 0 \\
\frac{1}{2} & -\frac{1}{2} & -\frac{1}{2} & -\frac{1}{2} & 1
\end{pmatrix}
\quad
S_K =
\begin{array}{c}
K_1 \\
K_2 \\
K_3 \\
K_4 \\
K_5
\end{array}
\begin{pmatrix}
\frac{1}{4} \\
\frac{1}{4} \\
\frac{1}{4} \\
\frac{1}{4} \\
0
\end{pmatrix}
$$

with column headings $(/K_1)\ (/K_2)\ (/K_3)\ (/K_4)\ (/K_5)$ and sum.

$$(11)$$

Each row of M_K^{-1} is summed up to give a one-column matrix S_K, where the values of non-cyclic groups vanish to give zero. The USCI-CF (Unit Subduced Cycle Index with Chirality Fittingness) table of the C_{2v}-group reported in Ref. 1 (Table E.5 of Appendix E) can be used as the USCI-CF table of K, as shown in Table I.[20]

TABLE I. USCI-CF table for K

	K_1	K_2	K_3	K_4	K_5
$K(/K_1)$	b_1^4	b_2^2	c_2^2	c_2^2	c_4
$K(/K_2)$	b_1^2	b_1^2	c_2	c_2	c_2
$K(/K_3)$	b_1^2	b_2	a_1^2	c_2	a_2
$K(/K_4)$	b_1^2	b_2	c_2	a_1^2	a_2
$K(/K_5)$	b_1	b_1	a_1	a_1	a_1

Following Def. 19.6 of Fujita's book,[1] the PCI-CFs (Partial Cycle Indices with Chirality Fittingness) for this case is obtained by multiplying the $K(/K_3)$-row of Table I with M_K^{-1} (Eq. 11), i.e., $(b_1^2, b_2, a_1^2, c_2, a_2) M_K^{-1}$. Thereby, the PCI-CFs for respective symmetries are obtained as follows:

$$\text{PCI-CF}(K_1; \$_d) = \frac{1}{4}b_1^2 - \frac{1}{4}b_2 - \frac{1}{4}a_1^2 - \frac{1}{4}c_2 - \frac{1}{2}a_2 \quad (12)$$

$$\text{PCI-CF}(K_2; \$_d) = \frac{1}{2}b_2 - \frac{1}{2}a_2 \quad (13)$$

$$\text{PCI-CF}(K_3; \$_d) = \frac{1}{2}a_1^2 - \frac{1}{2}a_2 \quad (14)$$

$$\text{PCI-CF}(K_4; \$_d) = \frac{1}{2}c_2 - \frac{1}{2}a_2 \quad (15)$$

$$\text{PCI-CF}(K_5; \$_d) = a_2 \quad (16)$$

where the symbol $\$_d$ represents a_d for a homospheric orbit, b_d for a hemispheric orbit, or c_d for an enantiospheric orbit. Following Def. 19.7 of Ref. 1, the PCI-CFs (Eqs. 12–16) are summed up or the multiplication $(b_1^2, b_2, a_1^2, c_2, a_2)$ S_K is operated so as to give the CI-CF (Cycle Index with Chirality Fittingness) for this case as follows:

$$\text{CI-CF }(K; \$_d) = \frac{1}{4} b_1^2 + \frac{1}{4} b_2 + \frac{1}{4} a_1^2 + \frac{1}{4} c_2, \quad (17)$$

where the symbol $\$_d$ represents a_d, b_d, or c_d according to the sphericity of a relevant orbit.

By using the data of C_{3v} listed in Fujita's book,[1] the multiplication $(b_1^3, a_1c_2, b_3, a_3)M_{C_{3v}}^{-1}$ gives the PCI-CFs for enumerating substituted methyl ligands:

$$\text{PCI-CF}(C_1; \$_d) = \frac{1}{6} b_1^3 - \frac{1}{2} a_1 c_2 - \frac{1}{6} b_3 + \frac{1}{2} a_3 \quad (18)$$

$$\text{PCI-CF}(C_s; \$_d) = a_1 c_2 - a_3 \quad (19)$$

$$\text{PCI-CF}(C_3; \$_d) = \frac{1}{2} b_3 - \frac{1}{2} a_3 \quad (20)$$

$$\text{PCI-CF}(C_{3v}; \$_d) = a_3 \quad (21)$$

For the sake of simplicity, only achiral ligands X, Y, and Z are taken into consideration. Thereby, three ligand inventories are degenerate to give the same ligand inventory as follows:

$$a_d = c_d = b_d = X^d + Y^d + Z^d \quad (22)$$

The ligand inventory is introduced into Eqs. (18) to (21). The expansion of the resulting equations gives the following generating functions for enumerating substituted methyl ligands with respective symmetries:

$$f_{C_1} = XYZ \quad (23)$$

$$f_{C_s} = X^2Y + XY^2 + X^2Z + XZ^2 + Y^2Z + YZ^2 \quad (24)$$

$$f_{C_3} = 0 \quad (25)$$

$$f_{C_{3v}} = X^3 + Y^3 + Z^3, \quad (26)$$

where the term XYZ in the f_{C_1} represents a pair of enantiomeric ligands. From the data shown in Eqs. (23)–(26), ligand inventories for Eq. (17) are calculated as follows:

$$a_d = X^{3d} + Y^{3d} + Z^{3d} +$$
$$X^{2d}Y^d + X^dY^{2d} + X^{2d}Z^d + X^dZ^{2d} + Y^{2d}Z^d + Y^dZ^{2d} \quad (27)$$

$$c_d = X^{3d} + Y^{3d} + Z^{3d} +$$
$$X^{2d}Y^d + X^dY^{2d} + X^{2d}Z^d + X^dZ^{2d} + Y^{2d}Z^d +$$
$$Y^dZ^{2d} + 2X^dY^dZ^d \quad (28)$$

$$b_d = X^{3d} + Y^{3d} + Z^{3d} +$$
$$X^{2d}Y^d + X^dY^{2d} + X^{2d}Z^d + X^dZ^{2d} + Y^{2d}Z^d +$$
$$Y^dZ^{2d} + 2X^dY^dZ^d \quad (29)$$

Note that a_d (Eq. 27) is generated from f_{C_s} and $f_{C_{3v}}$. The last term $2X^dY^dZ^d$ in the c_d (Eq. 28) comes from $2(XYZ)^{d/2} \times (XYZ)^{d/2}$, which represents two modes of compensated chiral packing by R- and S-CXYZ ligands. On the other hand, the last term $2X^dY^dZ^d$ in the b_d (Eq. 29) comes from $(XYZ)^d + (XYZ)^d$, which represents the free packing of R- and S-CXYZ ligands. The terms other than $2X^dY^dZ^d$ in the c_d and b_d are concerned with f_{C_s} and $f_{C_{3v}}$.

Following Theorem 20.2 of the inventories (Eqs. 27–29) are introduced into Eq. (17) and expanded to give a generating function for giving the numbers of ethane derivatives as the coefficients of the respective terms:

$$f_{A+C} = (X^6 + Y^6 + Z^6) +$$
$$(X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) +$$
$$2(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) +$$
$$2(X^4YZ + XY^4Z + XYZ^4) +$$
$$3(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) +$$
$$2(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 5X^2Y^2Z^2 \quad (30)$$

The coefficient of each term $X^xY^yZ^z$ $(x + y + z = 6)$ in Eq. (30) represents the number of stereoisomers with x of X, y of Y, and z of Z, where a pair of enantiomers is counted once if chiral.

When we select the chiral ligands R- and S-CXYZ only from the ligands enumerated in Eqs. (23) – (26), we obtain the corresponding ligand inventories:

$$a_d = 0 \quad (31)$$

$$c_d = 2X^dY^dZ^d \quad (32)$$

$$b_d = 2X^dY^dZ^d \quad (33)$$

in place of Eq. (27) – (29). The inventories (Eqs. 31–33) are introduced into Eq. (17) and expanded to give a generating function for giving the numbers of ethane derivatives:

$$F = 2X^2Y^2Z^2 \quad (34)$$

– Extended PCI Method and Extended CI Method (Method A')

The extended PCI method has been described in a previous paper.[21] This method can be used to calculate an

extended CI-CF, which provides the basis of another enumeration method (Method A').

By replacing the sphericity indices $(a_k, c_k,$ and $b_k)$ by extended sphericity indices $(\psi_{(a)k}, \psi_{(c)k},$ and $\psi_{(b)k})$, the PCI-CFs (Eqs. 12–16) are converted into the corresponding extended PCI-CFs. The extended PCI-CFs are summed up to give the extended CI-CF for this case as follows:

$$\text{CI-CF}(K; \psi_{(\$)k}) = \frac{1}{4}\psi^2_{(b)1} + \frac{1}{4}\psi_{(b)2} + \frac{1}{4}\psi^2_{(a)1} + \frac{1}{4}\psi_{(c)2} \tag{35}$$

which corresponds to the CI-CF shown in Eq. (17), where the subscript ($) represents (a), (b), or (c) according to the respective sphericity. Obviously, Eq. (35) is an extended version of Eq. (17).

An enantiospheric orbit accommodate chiral ligands in a compensated chiral packing, the terms for C_1 and C_3 are represented as 2PCI-CF(C_1; $\$_{kd}$) and 2PCI-CF($C_3$; $\$_{kd}$). Hence, for the term $\psi_{(c)k}$, we can calculate as follows:

$$\text{PCI-CF}(C_s; \$_{kd}) + \text{PCI-CF}(C_{3v}; \$_{kd}) +$$

$$2\text{PCI-CF}(C_1; \$_{kd}) + 2\text{PCI-CF}(C_3; \$_{kd}) =$$

$$\frac{1}{3}b_k^3 + \frac{2}{3}b_{3k} \tag{36}$$

Then, the term b_{kd} is replaced by the term c_{kd} to give $\frac{1}{3}c_k^3 + \frac{2}{3}c_{3k}$ in accord with the compensated chiral packing. The corresponding ligand inventories are obtained:

$$\psi_{(a)k} = \text{PCI-CF}(C_s; \$_{kd}) + \text{PCI-CF}(C_{3v}; \$_{kd}) =$$

$$(a_k c_{2k} - a_{3k}) + a_{3k} = a_k c_{2k} \tag{37}$$

$$\psi_{(c)k} = \frac{1}{3}c_k^3 + \frac{2}{3}c_{3k} \tag{38}$$

$$\psi_{(b)k} = \text{PCI-CF}(C_s; \$_{kd}) + \text{PCI-CF}(C_{3v}; \$_{kd}) +$$

$$2\text{PCI-CF}(C_1; \$_{kd}) + 2\text{PCI-CF}(C_3; \$_{kd}) =$$

$$\frac{1}{3}b_k^3 + \frac{2}{3}b_{3k} \tag{39}$$

These inventories correspond to the ones shown in Eqs. (32) and (33) of Ref. 21. The three equations (Eqs. 37–39) are introduced into Eq. (35) to give the following equation:

$$\text{CI-CF}'(K[C_{3v}]; \$_d) =$$

$$\frac{1}{36}b_1^6 + \frac{1}{9}b_1^3 b_3 + \frac{1}{9}b_3^2 + \frac{1}{12}b_2^3 + \frac{1}{6}b_6 +$$

$$\frac{1}{4}a_1^2 c_2^2 + \frac{1}{12}c_2^3 + \frac{1}{6}c_6 . \tag{40}$$

This equation is called "an intermediate CI-CF". By considering atoms or achiral ligands only (X, Y, and Z), we can use identical inventories as follows:

$$a_d = b_d = c_d = X^d + Y^d + Z^d, \tag{41}$$

which are introduced into Eq. (40). Thereby, we obtain a generating function, which is identical with Eq. (30).

Simplified Enumeration

Mark tables and related ones can be reduced into simplified tables based on cyclic subgroups only. Such simplified tables are applicable to formulate further enumeration methods.

– Methods Based on Dominant Representations (Methods B and B')

Because the one-column matrix S_k (Eq. 11) contains non-zero values for cyclic subgroups and zero values for non-cyclic subgroups, the mark table (M_K) can be so restricted as to contain values cyclic subgroups only. The resulting matrix ($\tilde{M}_K$) is called a dominant markaracter table:[23,24]

$$\tilde{M}_K = \begin{array}{c} \\ K(/K_1) \\ K(/K_2) \\ K(/K_3) \\ K(/K_4) \end{array} \begin{array}{cccc} K_1 & K_2 & K_3 & K_4 \\ \left(\begin{array}{cccc} 4 & 0 & 0 & 0 \\ 2 & 2 & 0 & 0 \\ 2 & 0 & 2 & 0 \\ 2 & 0 & 0 & 2 \end{array}\right) \end{array} \tag{42}$$

The corresponding inverse of dominant markaracter table is also obtained as follows:

$$\tilde{M}_K^{-1} = \begin{array}{c} \\ K_1 \\ K_2 \\ K_3 \\ K_4 \end{array} \begin{array}{cccc} (/K_1) & (/K_2) & (/K_3) & (/K_4) \\ \left(\begin{array}{cccc} \frac{1}{4} & 0 & 0 & 0 \\ -\frac{1}{4} & \frac{1}{2} & 0 & 0 \\ -\frac{1}{4} & 0 & \frac{1}{2} & 0 \\ -\frac{1}{4} & 0 & 0 & \frac{1}{2} \end{array}\right) \end{array} \quad \tilde{S}_K = \begin{array}{c} K_1 \\ K_2 \\ K_3 \\ K_4 \end{array} \begin{array}{c} \text{sum} \\ \left(\begin{array}{c} \frac{1}{4} \\ \frac{1}{4} \\ \frac{1}{4} \\ \frac{1}{4} \end{array}\right) \end{array} \tag{43}$$

The CRs corresponding to cyclic subgroups (*i.e.*, $K(/K_1)$, $K(/K_2)$, $K(/K_3)$, and $K(/K_4)$) are called dominant representations. The subduction of dominant representations produces a dominant USCI-CF table, as shown in Table II.[24]

Theorem 5 of Ref. 24 indicates that the $K(/K_3)$-row of Table II and the one-column matrix $\tilde{S}_k$ generate the following equation:

$$\text{CI-CF}(K; \$_d) = \frac{1}{4}b_1^2 + \frac{1}{4}b_2 + \frac{1}{4}a_1^2 + \frac{1}{4}c_2 \tag{44}$$

which is identical with Eq. (17). Thus, this gives us an alternative method (Method B) for enumeration. Obviously, the extended version (Method B', *cf*. Eq. (35)) is also available.

TABLE II. Dominant USCI-CF table for K

	K_1	K_2	K_3	K_4
$K(/K_1)$	b_1^4	b_2^2	c_2^2	c_2^2
$K(/K_2)$	b_1^2	b_1^2	c_2	c_2
$K(/K_3)$	b_1^2	b_2	a_1^2	c_2
$K(/K_4)$	b_1^2	b_2	c_2	a_1^2

– Characteristic Monomial Methods (Methods C and C')

Marks (especially for dominant representations) can be regarded as characters if each mark is regarded as being specified with respect to group elements.[25] In order to discuss marks and characters in a common framework, the term 'markaracter' has been proposed.[26] Because K is isomorphic to C_{2v}, we can obtain the following character table (strictly speaking, the Q-conjugacy character table):

$$
\tilde{N}_K = \begin{array}{c} \\ A_1 \\ A_2 \\ B_1 \\ B_2 \end{array} \overset{\begin{array}{cccc} K_1 & K_2 & K_3 & K_4 \end{array}}{\begin{pmatrix} 1 & 1 & 1 & 1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & 1 & -1 \\ 1 & -1 & -1 & 1 \end{pmatrix}} \quad (45)
$$

Because the $K(/K_3)$-row of Eq. (41), *i.e.*, (2, 0, 2, 0), is represented by the sum of A_1-row and the B_1-row, we can write as follows:

$$ K(/K_3) = A_1 + B_1 \quad (46) $$

Markaracter tables and Q-conjugacy character tables have been discussed,[27,26] where subduction of Q-conjugacy representations generates characteristic monomials (CMs) as shown in Table III.

TABLE III. Characteristic monomial table for K

	K_1	K_2	K_3	K_4
A_1	b_1	b_1	a_1	a_1
A_2	b_1	b_1	$a_1^{-1}c_2$	$a_1^{-1}c_2$
B_1	b_1	$b_1^{-1}b_2$	a_1	$a_1^{-1}c_2$
B_2	b_1	$b_1^{-1}b_2$	$a_1^{-1}c_2$	a_1

In agreement of Eq. (46), the A_1-row and the B_1-row in Table III are multiplied to give (b_1^2, b_2, a_1^2, c_2). Then the application of one-column matrix (Eq. 43) gives:

$$ \text{CI-CF}(K; \$_d) = \frac{1}{4}b_1^2 + \frac{1}{4}b_2 + \frac{1}{4}a_1^2 + \frac{1}{4}c_2 \quad (47) $$

which is identical with Eqs. (17) and (44). Thus, this procedure gives us a further method (Method C) for enumeration.[28] Obviously, the extended version (Method C', *cf.* Eq. 35) is also available.

FUJITA'S PROLIGAND METHODS (METHODS D AND D')

By the inspection of Table II, one can find that the chiral cyclic groups K_1 and K_2 are correlated to hemispheric indices b_d, while the achiral cyclic groups K_3 and K_4 are correlated to homospheric indices a_d or enantiospheric indices c_d. Note that these sphericities are concerned with relevant orbits (equivalence classes). Because each row specifies an orbit governed by a CR, sphericities of orbits are taken into consideration in Method B.[15,16]

Although the Q-conjugacy character table (Eq. 45) in Method C is based on conjugate cyclic subgroups, on the other hand, it is easily linked with the usual character table of the isomorphic C_{2v}. Note that character tables are constructed in terms of conjugacy classes. This means that the conjugate subgroups of cyclic subgroups are easily correlated to the conjugacy classes of group elements. Hence, the close relationship between the Methods B and C reveals the possibility of a further method based on conjugacy classes.

According to this guideline, the data of Table II are reconstructed by means of such conjugacy classes as specified by the cycle structure of each element:

$K(/K_3)$:		product of cycles	product of sphericity indices
C_∞	~	$(1)(2)$	b_1^2
$C_\infty C_2$	~	$(1\,2)$	b_2
$C_\infty \sigma_v$	~	$\overline{(1)(2)}$	a_1^2
$C_\infty \sigma_h$	~	$\overline{(1\,2)}$	c_2

$$ (48) $$

The conjugacy class $\{C_\infty\}$ corresponds to the conjugate subgroup K_1 (= $\{C_\infty\}$). On the same line, we can compare: $\{C_\infty C_2\}$ *vs.* K_2 (= $\{C_\infty, C_\infty C_2\}$); $\{C_\infty \sigma_v\}$ *vs.* K_3 (=$\{C_\infty C_\infty \sigma_v\}$); and $\{C_\infty \sigma_h\}$ *vs.* K_4 (= $\{C_\infty, C_\infty \sigma_h\}$).

In Eq. (48), a permutation corresponding to an improper rotation is called an improper permutation and designated by an overbar. The cycles are divided into three categories and characterized by sphericities and sphericity indices. Thus, an odd-membered cycle contained in an improper permutation is called a homospheric cycle and

TABLE IV. Cycles and products of sphericity indices for enumerating methyl ligands

			Cycles	Products of sphericity indices
H	H'	proper permutation:	$(1)(2)(3)$	b_1^3
			$(1\,2\,3)$	b_3
			$(1\,2\,3)$	b_3
		improper permutation:	$\overline{(1\,2)(3)}$	$a_1 c_2$
			$\overline{(1\,3)(2)}$	$a_1 c_2$
			$\overline{(1)(2\,3)}$	$a_1 c_2$

characterized by a sphericity index a_d (d: the length of the cycle), while an even-membered cycle contained in an improper permutation is called an enantiospheric cycle and characterized by a sphericity index c_d. On the other hand, a cycle contained in a proper permutation is called a hemispheric cycle and characterized by a sphericity index b_d whether d is odd or even. Thereby, the permutations listed above are characterized by products of such sphericity indices, which are summed up to give a CI-CF (cycle index with chirality fittingness):

$$\text{CI-CF}(K; \$_d) = \frac{1}{4}(b_1^2 + b_2 + a_1^2 + c_2) \qquad (49)$$

which is identical with Eqs. (17), (44), and (47). Thus, this gives us a further method (the proligand method, Method D) for enumeration.[28]

The extended version (Method D') is also available. Thus, the extended CI-CF for this case is obtained as follows:[15,16]

$$\text{CI-CF } (K; \psi_{(\$)k}) =$$

$$\frac{1}{4}\psi_{(b)1}^2 + \frac{1}{4}\psi_{(b)2} + \frac{1}{4}\psi_{(a)1}^2 + \frac{1}{4}\psi_{(c)2}, \qquad (50)$$

which corresponds to the CI-CF shown in Eq. (49), where the subscript ($) represents ($a$), ($b$), or ($c$) according to the respective sphericity. Equation (50) is equivalent to Eq. (35), although the procedures of derivation are different from each other.

To incorporate substituted methyl ligands, let us consider two permutation groups, $H(= C_{3v}(/C_s))$ and $H'(= C_3(/C_1))$, as shown in Table IV. Sphericity indices (b_d, a_d, and c_d) for ligand enumeration can be obtained in a similar way to the sphericity indices described above. Thereby, the products of sphericity indices are obtained, as shown in Table IV. By following Eqs. (8) and (9) of Ref. 16, the data collected in Table IV give the corresponding CI-CFs as follows:

$$\text{CI-CF}(H; \$_d) = \frac{1}{6}(b_1^3 + 2b_3 + 3a_1c_2), \qquad (51)$$

$$\text{CI-CF}(H'; \$_d) = \frac{1}{3}(b_1^3 + 2b_3), \qquad (52)$$

where the symbol $ in the left-hand side represents $a, b,$ or c according to the respective sphericity. By starting from Eqs. (18) – (21), Eqs. (51) and (52) can be alternatively calculated as follows:

$$\text{CI-CF}(C_1; \$_d) + \text{CI-CF}(C_s; \$_d) +$$

$$\text{CI-CF}(C_3; \$_d) + \text{CI-CF}(C_{3v}; \$_d) = \text{CI-CF}(H; \$_d) \qquad (53)$$

$$2\text{CI-CF}(C_1; \$_d) + 2\text{CI-CF}(C_3; \$_d) +$$

$$\text{CI-CF}(C_s; \$_d) + \text{CI-CF}(C_{3v}; \$_d) = \text{CI-CF}(H'; b_d) \qquad (54)$$

Note that Eq. (52) counts enantiomeric ligands distinctly. This is the reason for the coefficients equal to 2 that appear in the left-hand side of Eq. (54).

Following Eqs. (31) – (33) of Ref. 16, we obtain the following equations:

$$\psi_{(a)k} = 2\text{CI-CF}(H; \$_{kd}) - \text{CI-CF}(H'; b_{kd}) = a_k c_{2k} , \qquad (55)$$

$$\psi_{(c)k} = \text{CI-CF}(H'; c_{kd}) = \frac{1}{3}c_k^3 + \frac{2}{3}c_{3k}, \qquad (56)$$

$$\psi_{(b)k} = \text{CI-CF}(H'; b_{kd}) = \frac{1}{3}b_k^3 + \frac{2}{3}b_{3k}. \qquad (57)$$

Obviously, Eqs. (55) – (57) are identical with Eqs. (37) – (39). This can be confirmed by the relationship shown in Eqs. (53) and (54).

Because Eq. (50) is identical with Eq. (35), the introduction of Eqs. (55) – (57) into Eq. (50) generates the same equation as Eq. (40). Hence, the same generating function as Eq. (30) takes place by the proligand method (Method D') described here.

The first proposition (Eq. 50) of Theorem 4 described in the previous paper[29] showed a procedure of enumerating achiral ligands or proligands. By the inspection of the proof for the theorem, we can find that this procedure is also applicable to any kinds of achiral objects other than ligands or proligands. Hence, the same enumeration procedure is applied to enumerate achiral stereoisomers. Note that Eq. (50) (Theorem 4) of the previous paper[29] is equivalent to a procedure in which we take the terms corresponding to all of the improper rotations contained in a CI-CF. Thus, the CI-CF$'_A$ for enumerating achiral stereoisomers is obtained by taking the terms corresponding to the improper rotations contained in Eq. (40) and by duplicating them as follows:

$$\text{CI-CF}'_A (K[C_{3v}]; \$_d) = \frac{1}{2}a_1^2 c_2^2 + \frac{1}{6}c_2^3 + \frac{1}{3}c_6, \qquad (58)$$

where the symbol $\$_d$ represents a_d for a homospheric cycle, b_d for a hemispheric cycle, or c_d for an enantiospheric cycle.

The inventories shown in Eq. (41), *i.e.*, $a_d = b_d = c_d = X^d + Y^d + Z^d$, are introduced into Eq. (58). The resulting equation is expanded to give a generating function for giving the numbers of achiral ethane derivatives as the coefficients of the respective terms:

$$f_A = (X^6 + Y^6 + Z^6) + (X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) +$$

$$2(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) +$$

$$(X^4YZ + XY^4Z + XYZ^4) +$$

$$2(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) +$$

$$2(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 4X^2Y^2Z^2. \qquad (59)$$

The coefficient of each term $X^xY^yZ^z$ $(x + y + z = 6)$ in Eq. (59) represents the number of achiral stereoisomers with x of X, y of Y and z of Z.

The second proposition (Eq. 51) of Theorem 4 described in the previous paper[29] showed a procedure for enumerating pairs of chiral ligands or proligands of opposite chiralities (*i.e.*, pairs of enantiomers). The same enumeration procedure can be adopted in the enumeration of chiral stereoisomers (strictly speaking, the enumeration of enanatiomeric pairs), if we take account of chiral compounds in place of chiral ligands or proligands. Note that Eq. (51) (Theorem 4) of the previous paper[29] is equivalent to a procedure in which we change plus signs into minus signs for the terms corresponding to all of the improper rotations contained in a CI-CF. Thus, the CI-CF$'_C$ for enumerating chiral stereoisomers (enantiomeric pairs) is obtained from Eq. (40) by changing the plus signs of terms corresponding to the improper rotations into minus signs:

$$\text{CI-CF}'_C(K[C_{3v}]; \$_d) =$$

$$\frac{1}{36}b_1^6 + \frac{1}{9}b_1^3b_3 + \frac{1}{9}b_3^2 + \frac{1}{12}b_2^3 + \frac{1}{6}b_6 -$$

$$\frac{1}{4}a_1^2c_2^2 - \frac{1}{12}c_2^3 - \frac{1}{6}c_6 . \tag{60}$$

The inventories shown in Eq. (41), *i.e.*, $a_d = b_d = c_d = X^d + Y^d + Z^d$, are introduced into Eq. (60). The resulting equation is expanded to give a generating function for giving the numbers of enantiomeric pairs of chiral ethane derivatives as the coefficients of the respective terms:

$$f_C = (X^4YZ + XY^4Z + XYZ^4) +$$

$$(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) +$$

$$X^2Y^2Z^2 . \tag{61}$$

The coefficient of each term $X^xY^yZ^z$ $(x + y + z = 6)$ in Eq. (61) represents the number of enantiomeric pairs of chiral stereoisomers with x of X, y of Y and z of Z.

Obviously, Eqs. (30), (59) and (61) are summarized into the following relationship:

$$f_{A+C} = f_A + f_C . \tag{62}$$

To testify the validity of the results of Eqs. (30), (59) and (61), Figure 3 illustrates all of the stereoisomers corresponding to the coefficients of the term $X^2Y^2Z^2$. Note that the term $X^2Y^2Z^2$ is factorized into either one of the four modes: $(XYZ)^2$, $(X^2Y)(YZ^2)$, $(X^2Y)(YZ^2)$, and $(X^2Y)(YZ^2)$. Among them, the factorized term $(XYZ)^2$ represents combinations of chiral ligands $(R\text{-}XYZ$ or $S\text{-}XYZ)$ and the remaining three represent combinations of two achiral ligands. The ligands shown in Figure 3 are encircled to
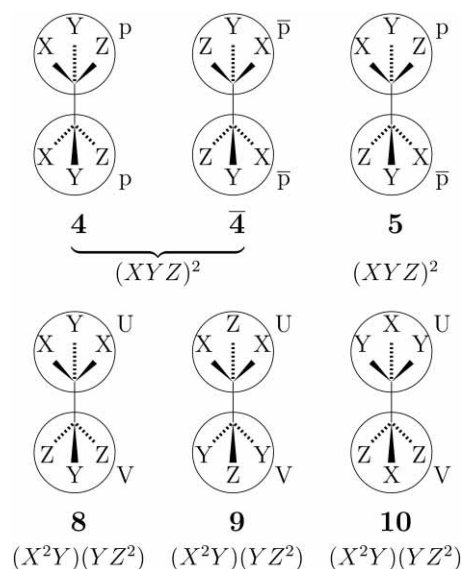

Figure 3. Enumeration of ethane derivatives. Five stereoisomers corresponding to the term $X^2Y^2Z^2$ of the generating function shown in Eq. (30). In this enumeration, a pair of enantiomers is counted once. The symbols U and V indicates achiral proligands in isolation, where the symbols p and $\overline{p}$ indicates an enantiomeric pair of chiral proligands in isolation.

show the corresponding proligands, which are designated by the symbols p or $\overline{p}$ for chiral proligands and by the symbols U and V for achiral proligands.

The coefficient of the term $X^2Y^2Z^2$ is equal to 4 in Eq. (59) (f_A) so that there exist four achiral stereoisomers, *i.e.*, **5**, **8**, **9**, and **10**. Among them, the achiral stereoisomer **5** shows a so-called *meso*-compound, in which the two ligands with opposite chiralities compensate their chiralities to give such an achiral compound.

On the other hand, the coefficient of the term $X^2Y^2Z^2$ is equal to 1 in Eq. (61) (f_C) so that there exists one enantiomeric pair of chiral stereoisomers, *i.e.*, the pair of **4** and $\overline{\mathbf{4}}$. It should be noted again that each pair of enantiomers is counted once in this enumeration.

As a result, the coefficient 4 for Eq. (59) (f_A) and the coefficient 1 for Eq. (61) (f_C) are summed up to be equal to 5, which appears as the coefficient of the term $X^2Y^2Z^2$ appearing in Eq. (30) (f_{A+C}). This result is in agreement with Eq. (62).

PSEUDOASYMMETRIC CASES TREATED BY METHODS D AND D'

In a previous paper,[29] we have reported general theorems for treating pseudoasymmetric cases. We here show the versatility of the proligand methods (Methods D and D') by using a more simplified example for characterizing such pseudoasymmetric cases.

The present example is concerned with propane derivatives (*e.g.*, **13**), which are generated from a tetrahedral skeleton (**11**) of C_s-symmetry, as shown in Figure 4. The
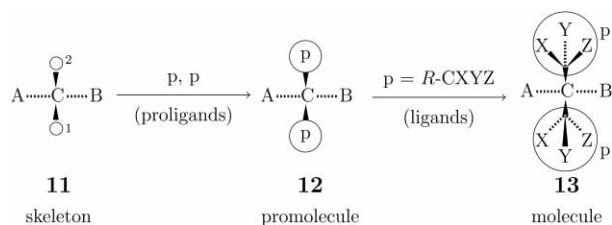
Figure 4. Conversion of a skeleton into a molecule through a promolecule in the enumeration of propane derivatives. The symbol p represents a chiral proligand, which is replaced by a chiral ligand CXYZ.

two positions of the tetrahedral skeleton (**11**) are occupied by achiral proligands A and B as fixed substituents, and the remaining two positions serve as substitution positions for generating propane derivatives. First, we consider a promolecule (**12**) by placing two chiral proligands (p) of the same kind. Then, each proligand (p) is replaced by a chiral ligand (R-CXYZ) to produce a molecule (**13**).

To put a stress on an unusual character of pseudo-asymmetric cases, we first examine the enumeration of such promolecules as **12**. Because the skeleton **11** belongs to the group:

$$C_s = \{I, \sigma\} \sim \{(1)(2), \overline{(1\ 2)}\} \qquad (63)$$

the permutations are characterized by the products of sphericity indices, b_1^2 and c_2, which are summed up to give a CI-CF:

$$\text{CI-CF}(C_s; \$_d) = \frac{1}{2}(b_1^2 + c_2) \qquad (64)$$

Suppose that substituents for the positions 1 and 2 of the skeleton **11** are selected from achiral proligands U and V; and enantiomeric pairs of chiral proligands (p/$\overline{p}$ and q/$\overline{q}$). Then, we should use such ligand inventories as follows:

$$a_d = U^d + V^d \qquad (65)$$

$$b_d = U^d + V^d + p^d + \overline{p}^d + q^d + \overline{q}^d \qquad (66)$$

$$c_d = U^d + V^d + 2p^{d/2}\overline{p}^{d/2} + 2q^{d/2}\overline{q}^{d/2} \qquad (67)$$

After introducing Eq. (66) ($d = 1$) and Eq. (67) ($d = 2$) into Eq. (64), the resulting equation is expanded to give the following generating function:

$$f^*_{A+C} = [U^2 + V^2] + UV +$$

$$\left[\frac{2}{2}(Up+U\overline{p})+\frac{2}{2}(Uq+U\overline{q})+\frac{2}{2}(Vp+V\overline{p})+\frac{2}{2}(Vq+V\overline{q})\right] +$$

$$\left[\frac{1}{2}(p^2+\overline{p}^2)+\frac{1}{2}(q^2+\overline{q}^2)\right] +$$

$$\left[\frac{2}{2}(pq+\overline{p}\overline{q})+\frac{2}{2}(p\overline{q}+\overline{p}q)\right] +$$

$$[2p\overline{p} + 2q\overline{q}]. \qquad (68)$$

In this equation, such terms as $\frac{1}{2}(Up+U\overline{p})$ represent enantiomeric pairs respectively. Thereby, the term $\frac{2}{2}(Up+U\overline{p})$, for example, should be interpreted as $2\times\frac{1}{2}(Up+U\overline{p})$ so as to represent two pairs of enantiomers. On the other hand, the term $2p\overline{p}$ indicates the presence of two achiral promolecules, which corresponds to pseudoasymmetric cases.

To enumerate achiral stereoisomers, we can use Theorem 4 (Eq. 50) of the previous paper for the enumeration of achiral ligands,[29] because the enumeration procedure is the same whether achiral stereoisomers or achiral ligands are enumerated. Thus, the CI-CF$_A$ for enumerating achiral stereoisomers is obtained by taking the terms corresponding to the improper rotations contained in Eq. (64) as follows:

$$\text{CI-CF}_A(C_s; \$_d) = c_2. \qquad (69)$$

After introducing Eq. (67) ($d = 2$) into Eq. (69), the resulting equation gives the following generating function:

$$f^*_A = [U^2 + V^2] + [2p\overline{p} + 2q\overline{q}]. \qquad (70)$$

By following Theorem 4 (Eq. 51) of the previous paper for the enumeration of chiral ligands,[29] we are able to enumerate chiral stereoisomers (enantiomeric pairs), because the enumeration procedure is the same whether chiral stereoisomers or chiral ligands are enumerated. Thus, the CI-CF$_C$ for enumerating chiral stereoisomers is obtained from Eq. (64) by changing the plus signs of terms corresponding to the improper rotations into minus signs:

$$\text{CI-CF}_C(C_s; \$_d) = \frac{1}{2}(b_1^2 - c_2). \qquad (71)$$

After introducing Eq. (66) ($d = 1$) and Eq. (67) ($d = 2$) into Eq. (71), the resulting equation is expanded to give the following generating function:

$$f^*_C = UV +$$

$$\left[\frac{2}{2}(Up+U\overline{p})+\frac{2}{2}(Uq+U\overline{q})+\frac{2}{2}(Vp+V\overline{p})+\frac{2}{2}(Vq+V\overline{q})\right] +$$

$$\left[\frac{1}{2}(p^2+\overline{p}^2)+\frac{1}{2}(q^2+\overline{q}^2)\right] +$$

$$\left[\frac{2}{2}(pq+\overline{p}\overline{q})+\frac{2}{2}(p\overline{q}+\overline{p}q)\right]. \qquad (72)$$

Obviously, Eqs. (68), (70) and (72) are summarized into the following relationship:

$$f^*_{A+C} = f^*_A + f^*_C \qquad (73)$$

To apply Method D to this case, the ligand inventories shown by Eqs. (27) – (29) are used in place of Eqs. (65) – (67). Thus, Eq. (29) ($d = 1$) and Eq. (28) ($d = 2$) are introduced into the CI-CF (Eq. 64) so as to give the following generating function:

$f^{**}_{A+C} = (X^6 + Y^6 + Z^6) +$

$(X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) +$

$2(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) +$

$3(X^4YZ + XY^4Z + XYZ^4) +$

$4(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) +$

$2(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 6X^2Y^2Z^2$.　　　　(74)

The extended version (Method D') is also available according to a general discussion described previously.[29] Thus, the extended CI-CF for this case is obtained as follows:

$$\text{CI-CF}(C_s; \psi_{(\$)k}) = \frac{1}{2} \psi^2_{(b)1} + \frac{1}{2} \psi_{(c)2}, \qquad (75)$$

which corresponds to the CI-CF shown in Eq. (64), where the subscript ($\$$) represents (*a*), (*b*), or (*c*) according to the respective sphericity.

To incorporate substituted methyl ligands, the ligand inventories shown in Eqs. (55) – (57) are introduced into the extended CI-CF shown in Eq. (75). Thus, Eq. (57) ($d = 1$) and Eq. (56) ($d = 2$) are introduced into Eq. (75) so as to give an intermediate CI-CF:

$\text{CI-CF'}(C_s[C_{3v}]; \$_d) =$

$$\frac{1}{18} b_1^6 + \frac{2}{9} b_1^3 b_3 + \frac{2}{9} b_3^2 + \frac{1}{6} c_2^3 + \frac{1}{3} c_6. \qquad (76)$$

By considering atoms or achiral ligands only (X, Y, and Z), we can use identical inventories shown in Eq. (41) (*i.e.*, $a_d = b_d = c_d = X^d + Y^d + Z^d$). After these inventories are introduced into Eq. (76), the resulting equation is expanded so as to give a generating function, which is identical with Eq. (74), *i.e.*,

$f^†_{A+C} = (X^6 + Y^6 + Z^6) +$

$(X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) +$

$2(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) +$

$3(X^4YZ + XY^4Z + XYZ^4) +$

$4(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) +$

$2(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 6X^2Y^2Z^2$.　　　　(77)

To enumerate achiral stereoisomers, we can use Theorem 4 (Eq. 50) of the previous paper[29] for the enumera-

tion of achiral ligands as shown above. Thus, the CI-CF'$_A$ for enumerating achiral stereoisomers is obtained by taking the terms corresponding to the improper rotations from Eq. (76) as follows:

$$\text{CI-CF'}_A (C_s[C_{3v}]; \$_d) = \frac{1}{3} c_2^3 + \frac{2}{3} c_6. \qquad (78)$$

By considering atoms or achiral ligands only (X, Y, and Z), we can use identical inventories shown in Eq. (41) (*i.e.*, $a_d = b_d = c_d = X^d + Y^d + Z^d$). After these inventories are introduced into Eq. (78), the resulting equation is expanded so as to give a generating function for enumerating achiral stereoisomers:

$f^†_A = (X^6 + Y^6 + Z^6) +$

$(X^4Y^4 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) +$

$2X^2Y^2Z^2$ 　　　　(79)

Theorem 4 (Eq. 51) of the previous paper[29] for the enumeration of chiral ligands is used to enumerate chiral stereoisomers (enantiomeric pairs). Thus, the CI-CF'$_C$ for enumerating chiral stereoisomers is obtained from Eq. (76) by changing the plus signs of terms corresponding to the improper rotations into minus signs:

$\text{CI-CF'}_C (C_s[C_{3v}]; \$_d) =$

$$\frac{1}{18} b_1^6 + \frac{2}{9} b_1^3 b_3 + \frac{2}{9} b_3^2 - \frac{1}{6} c_2^3 - \frac{1}{3} c_6. \qquad (80)$$

After the inventories shown in Eq. (41) (*i.e.*, $a_d = b_d = c_d = X^d + Y^d + Z^d$) are introduced into Eq. (80), the resulting equation is expanded so as to give a generating function for enumerating chiral stereoisomers:

$f^†_C = (X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) +$

$(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) +$

$3(X^4YZ + XY^4Z + XYZ^4) +$

$4(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2$
$\quad + XY^2Z^3) +$

$2(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 4X^2Y^2Z^2$ 　　　　(81)

Obviously, Eqs. (77), (79) and (81) are summarized into the following relationship:

$$f^†_{A+C} = f^†_A + f^†_C . \qquad (82)$$

To testify the validity of the results of Eqs. (77), (79) and (81), Figure 4 illustrates all of the stereoisomers corresponding to the coefficients of the term $X^2Y^2Z^2$. The ligands shown in Figure 4 are encircled to show the corresponding proligands, which are designated by the symbols
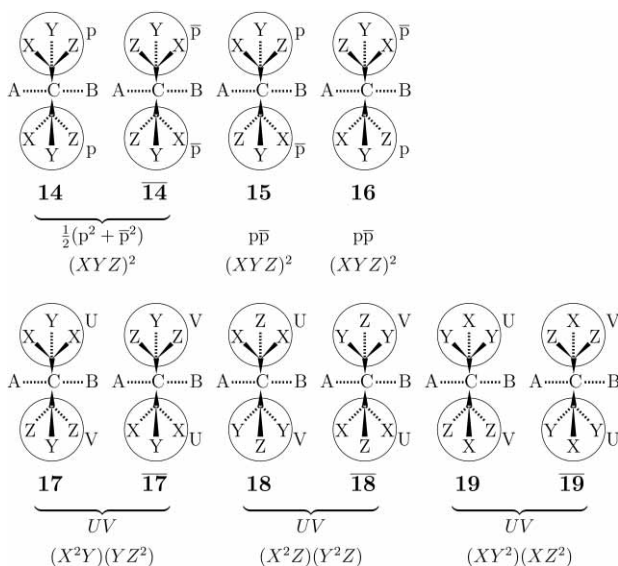
Figure 5. Enumeration of propane derivatives. Six stereoisomers corresponding to the term $X^2Y^2Z^2$ of the generating function shown in Eq. (74). In this enumeration, a pair of enantiomers is counted once.

p or $\bar{p}$ for chiral proligands and by the symbols U and V for achiral proligands.

The coefficient of the term $X^2Y^2Z^2$ is equal to 2 in Eq. (79) ($f^{\dagger}_{\mathcal{A}}$) so that there exist two achiral stereoisomers, *i.e.*, **15** and **16**. These are diastereomeric to show a so-called pseudoasymmetric case.

On the other hand, the coefficient of the term $X^2Y^2Z^2$ is equal to 4 in Eq. (81) ($f^{\dagger}_{C}$) so that there exist four enantiomeric pairs of chiral stereoisomers, *i.e.*, the four pairs represented by $14/\overline{14}$, $17/\overline{17}$, $18/\overline{18}$ and $19/\overline{19}$. It should be noted again that each pair of enantiomers is counted once in this enumeration.

As a result, the coefficient 2 for Eq. (79) ($f^{\dagger}_{\mathcal{A}}$) and the coefficient 4 for Eq. (81) ($f^{\dagger}_{C}$) are added to give 6, which appears as the coefficient of the term $X^2Y^2Z^2$ appearing in Eq. 77 ($f^{\dagger}_{\mathcal{A}+C}$). This result is in agreement with Eq. (82).

The comparison between Figure 3 and Figure 5 shows that the factorization of the term $X^2Y^2Z^2$ gives different results according to the skeletons at issue. In particular, the factorized term $(XYZ)^2$ corresponds to a *meso*-compound (**5**) in Figure 3, while it corresponds to a pseudoasymmetric case (**15** and **16**) in Figure 5. These cases are correctly treated by the present methods.

Because the $f^{\dagger}_{C}$, (Eq. 81) enumerates enantiomeric pairs (*e.g.*, **14** and $\overline{14}$), the achiral stereoisomers (**15** and **16**) counted by $f^{\dagger}_{\mathcal{A}}$ (Eq. 79) can be determined as being diastereomeric. Note that diastereomers are defined as stereoisomers that are not enantiomers in the conventional stereochemistry.

Moreover, the factorized terms $(X^2Y)(YZ^2)$, $(X^2Y)(YZ^2)$, and $(X^2Y)(YZ^2)$ correspond to achiral compounds (*i.e.*, **8**,

9, and **10**) in Figure 3, while they correspond to enantiomeric pairs of chiral derivatives, *i.e.*, $17/\overline{17}$, $18/\overline{18}$ and $19/\overline{19}$, in Figure 5. These features are in agreement with the results that the former is characterized by $f^{\dagger}_{\mathcal{A}}$ (Eq. 59) for enumerating achiral derivatives, while the latter is characterized by $f^{\dagger}_{C}$ (Eq. 81) for enumerating enantiomeric pairs.

STEREOISOMERS *vs.* GRAPHS

On Ethane Derivatives

– Enumeration of Ethane Derivatives by Pólya's Theorem

Strictly speaking, the method used here is Pólya's corona, which has been developed as an extension of Pólya's theorem in his famous article.[3,4] For the sake of convenience, "Pólya's theorem" is used here as a generic name.

To enumerate ethane derivatives, Pólya's theorem considers a permutation group of order 2 and of degree 2:

$$G = \{ (1)(2), (1\,2) \}, \qquad (83)$$

which does not take inner structures into consideration. As a result, the skeleton (**6**) is characterized by the following cycle index:

$$\mathrm{CI}(G;\ \psi_k) = \frac{1}{2}\,(\psi_1^2 + \psi_2) \qquad (84)$$

For substituted methyl ligands, the term ψ_k is represented as follows:

$$\psi_k = \frac{1}{6}\,(s_k^3 + 2s_{3k} + 3s_k s_{2k}), \qquad (85)$$

because the methyl has $\hat{H}$-symmetry:

$$\hat{H} = \{(1)(2)(3),(1\,3\,2),(1\,2\,3),(1)(2\,3),(1\,3)(2),(1\,2)(3)\}.$$

The introduction of Eq. (85) into the cycle index (Eq. 84) gives the following equation:

$$\mathrm{CI}(G[\hat{H}];\ s_d) = \frac{1}{72}\,s_1^6 + \frac{1}{18}\,s_1^3 s_3 + \frac{1}{12}\,s_1^4 s_2 + \frac{1}{18}\,s_3^2 +$$

$$\frac{1}{6}\,s_1 s_2 s_3 + \frac{1}{8}\,s_1^2 s_2^2 + \frac{1}{12}\,s_2^3 + \frac{1}{6}\,s_6 + \frac{1}{4}\,s_2 s_4 \qquad (86)$$

The dummy variable s_d in Eq. (86) is replaced by the following inventory:

$$s_d = X^d + Y^d + Z^d. \qquad (87)$$

By expanding the resulting equation, we obtain the following generating function:

$g = (X^6 + Y^6 + Z^6) +$

$(X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) +$

$2(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) +$

$2(X^4YZ + XY^4Z + XYZ^4) +$

$3(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) +$

$2(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 4X^2Y^2Z^2$ (88)

The coefficient of each term $X^xY^yZ^z$ $(x + y + z = 6)$ in Eq. (88) represents the number of isomers (as graphs) with x of X, y of Y, and z of Z.

If we consider proper rotations only, the term ψ_k is represented as follows:

$$\psi_k = \frac{1}{3}(s_k^3 + 2s_{3k})$$ (89)

because the proper rotations for the methyl ligand construct a subgroup shown by:

$$\hat{H} = \{(1)(2)(3), (1\,3\,2), (1\,2\,3)\}.$$

The introduction of Eq. (89) into the cycle index (Eq. 84) gives the following equation:

$$CI(G[\hat{H}]; s_d) = \frac{1}{18}s_1^6 + \frac{2}{9}s_1^3s_3 + \frac{2}{9}s_3^2 + \frac{1}{6}s_2^3 + \frac{1}{3}s_6$$ (90)

The dummy variable s_d in Eq. (90) is replaced by the inventory shown in Eq. (87). The resulting equation is expanded to give the following generating function:

$g' = (X^6 + Y^6 + Z^6) +$

$(X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) +$

$2(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) +$

$3(X^4YZ + XY^4Z + XYZ^4) +$

$4(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) +$

$2(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 6X^2Y^2Z^2$ (91)

The coefficient of each term $X^xY^yZ^z$ $(x + y + z = 6)$ in Eq. (91) represents the number of isomers with x of X, y of Y, and z of Z.

– *What is Polya's Theorem Deficient In?*

Methods A–D and their extended versions (A'–D') give the same generating functions as shown in Eqs. (30), (59), and (61), while Pólya's theorem (Pólya's corona) gives the generating functions shown in Eqs. (88) and (91). The comparison between these generating functions shows that they are different in the coefficients of the term $X^2Y^2Z^2$,

i.e., $5X^2Y^2Z^2$ in Eq. (30) (by Methods A/A'–D/D') *vs.* $4X^2Y^2Z^2$ in Eq. (88) and $6X^2Y^2Z^2$ in Eq. (91) (by Pólya's theorem). The factorization of each term $X^2Y^2Z^2$ into two terms representing methyl substituents demonstrates the difference more clearly:

Fujita's Methods A/A'–D/D':

$f_{A+C}:$ $5X^2Y^2Z^2 = 2(XYZ)^2 + (X^2Y)(YZ^2) +$

          $(X^2Z)(Y^2Z) + (XY^2)(XZ^2)$ (92)

$f_A:$ $4X^2Y^2Z^2 = (XYZ)^2 + (X^2Y)(YZ^2) +$

          $(X^2Z)(Y^2Z) + (XY^2)(XZ^2)$ (93)

$f_C:$ $X^2Y^2Z^2 = (XYZ)^2$ (94)

Pólya's Theorem:

$g:$ $4X^2Y^2Z^2 = (XYZ)^2 + (X^2Y)(YZ^2) +$

          $(X^2Z)(Y^2Z) + (XY^2)(XZ^2)$ (95)

$g':$ $6X^2Y^2Z^2 = 3(XYZ)^2 + (X^2Y)(YZ^2) +$

          $(X^2Z)(Y^2Z) + (XY^2)(XZ^2)$ (96)

By comparing the factorized equations, let us first discuss the difference in the term $2(XYZ)^2$ in Eq. (92) and the term $(XYZ)^2$ in Eq. (95). The coefficient 2 of the term $(XYZ)^2$ in Eq. (92) corresponds to one pair of enantiomers (**4** and **4̄**) and one achiral molecule (**5**), because Methods A/A'–D/D' count each pair of enantiomers once. The term $2(XYZ)$ directly appears in Eq. (34). The validity or consistency of Eq. (92) – (94) has been already discussed above in terms of Eqs. (30), (59), and (61). On the other hand, the coefficient 1 of the term $(XYZ)^2$ in Eq. (95) corresponds to one graph (**3**).

To show what Pólya's theorem is deficient in, it is informative to compare between Method D' (the proligand method) and Polya's theorem (Polya's corona) in terms of Eq. (86).

(i) Let us place $\psi_{(a)k} = \psi_{(c)k} = \psi_{(b)k} = \psi_k$ in Eq. (50). Thereby, Eq. (50) for Method D' (the proligand method) is converted into Eq. (84) for Pólya's theorem (Pólya's corona). It follows that Pólya's theorem (Pólya's corona) lacks the concept of sphericity. This means that Pólya's theorem (Pólya's corona) does not take account of the inner structures of ligands (especially, the chirality/achirality of ligands).

(ii) By placing $a_d = c_d = b_d = s_d$, moreover, Eq. (51) for Method D' (the proligand method) is converted into Eq. (84) for Pólya's theorem (Pólya's corona). Note that Eq. (51) counts one achiral ligand once as well as one pair of enantiomeric ligands (*cf.* **2** and **2̄**) once. Hence, Eq. (84), the results of which are apparently equal to those

based on Eq. (51) ($a_d = c_d = b_d = s_d$), turns out to take account of achiral ligands only. On the other hand, Method D' takes account both achiral and chiral ligands in the form of the ligand inventories of three kinds (Eqs. 55–57).

The above equations $\psi_{(a)k} = \psi_{(c)k} = \psi_{(b)k} = \psi_k$ and $a_d = c_d = b_d = s_d$ mean the deletion of sphericity. Hence, what Pólya's theorem is deficient in is concluded to be the concept of sphericity. The proligand method (Method D') is regarded as a substantial extension of Pólya's theorem by adding the concept of sphericity.

When we use Pólya's theorem (Pólya's corona) in terms of Eq. (90), we encounter another type of deficiency.

(i) Thus, the coefficient 6 of the term $X^2Y^2Z^2$ for g' (Eq. 91) is factorized in accord with Eq. (96) so as to correspond to the six derivatives listed in Figure 3. Stereochemically speaking, however, this enumeration regards the six derivatives (Figure 3) as being chiral ones, because this enumeration procedure lacks rotoreflection operations. In other words, each of them is counted once even if it is chiral or achiral.

(ii) As a result, it is not determined whether **4** and $\overline{\textbf{4}}$ are enantiomeric or not. The *meso*-compound (**5**) is not recognized as being achiral because of the lack of rotoreflections. On the same line, **8**–**10** are not recognized as being achiral. It should be noted that the determination of such achiralities necessitates reexamination of the enumeration results in terms of supergroups containing rotoreflections.

(iii) This type of enumeration based on Pólya's theorem fails in the determination of the achirality of so-called *meso*-compounds (*e.g.*, **5**). Hence, the enantiotopic relationship between relevant ligands (or proligands) or the enantiospheric nature of the corresponding orbit of the relevant ligands (or proligands) cannot be characterized by this type of enumeration. For example, the relationship between the ligands R-XYZ (p) and S-XYZ ($\overline{p}$) in **5** cannot be recognized as being enantiotopic, because the lack of rotoreflections in this type of enumeration results in the inconsistency that **5** is regarded as being chiral.

On Propane Derivatives

– Promolecule Enumeration by Pólya's Theorem

Let us now examine the enumeration of promolecules (*e.g.*, **12**) by applying Pólya's Theorem to the skeleton **11** in Figure 4. Because this type of enumeration disregards the inner structures of proligands, the same permutation group as shown in Eq. (83) is used on the basis of Pólya's theorem. As a result, the skeleton (**11**) is characterized by the following cycle index:

$$CI(G; s_k) = \frac{1}{2}(s_1^2 + s_2).$$ (97)

This equation is obtained by changing the sphericity indices b_1 and c_2 in Eq. (64) into the dummy variables

without sphericity, *i.e.*, s_1 and s_2. Because the inner structures of proligands are disregarded, we use here the following inventory:

$$s_d = U^d + V^d + p^d + \overline{p}^d + q^d + \overline{q}^d,$$ (98)

which is obtained by changing b_d in Eq. (66) into s_d. After introducing Eq. (98) into Eq. (97), the resulting equation is expanded to give a generating function as follows:

$$g^* = [U^2 + V^2] + UV +$$

$$[Up + U\overline{p} + Uq + U\overline{q} + Vp + V\overline{p} + Vq + V\overline{q}] +$$

$$[p^2 + \overline{p}^2 + q^2 + \overline{q}^2] +$$

$$[pq + \overline{pq} + p\overline{q} + \overline{p}q] +$$

$$[p\overline{p} + q\overline{q}].$$ (99)

If we consider proper rotations only, we should apply $G' = \{(1)(2)\}$ to characterize the skeleton (**11**). Thereby, we use the following cycle index:

$$CI(G'; s_k) = s_1^2.$$ (100)

After introducing Eq. (98) into Eq. (100), the resulting equation is expanded to give a generating function as follows:

$$g^{**} = [U^2 + V^2] + UV +$$

$$[2Up + 2U\overline{p} + 2Uq + 2U\overline{q} + 2Vp + 2V\overline{p} + 2Vq + 2V\overline{q}] +$$

$$[p^2 + \overline{p}^2 + q^2 + \overline{q}^2] +$$

$$[2pq + 2\overline{p}\overline{q} + 2p\overline{q} + 2\overline{p}q] +$$

$$[2p\overline{p} + 2q\overline{q}].$$ (101)

– Isomer Enumeration by Pólya's Theorem

When Pólya's Theorem is applied to the enumeration of propane derivatives, we can use Eq. (83) – (87), although we consider the skeleton **11** (Figure 4) in place of the one **6** (Figure 2). Thereby, the same generating function as g (Eq. 88) is obtained as follows:

$$g^\dagger = (X^6 + Y^6 + Z^6) +$$

$$(X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) +$$

$$2(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) +$$

$$2(X^4YZ + XY^4Z + XYZ^4) +$$

$$3(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) +$$

$$2(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 4X^2Y^2Z^2$$ (102)

The coefficient of each term $X^xY^yZ^z$ $(x + y + z = 6)$ in Eq. (102) represents the number of propane derivatives (as graphs) with x of X, y of Y, and z of Z.

If we consider proper rotations only, the skeleton (**11**) is characterized by the following cycle index:

$$CI(G'; \psi_k) = \psi_1^2 . \qquad (103)$$

As the term ψ_1 for substituted methyl ligands, we can use Eq. (85). The introduction of Eq. (85) into Eq. (103) give the following equation:

$$CI(G'[\hat{H}']; s_d) = \frac{1}{9} s_1^6 + \frac{4}{9} s_1^3 s_3 + \frac{4}{9} s_3^2 \qquad (104)$$

The dummy variable s_d in Eq. (104) is replaced by the inventory shown in Eq. (87). The resulting equation is expanded to give the following generating function:

$g^\dagger = (X^6 + Y^6 + Z^6) +$

$2(X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) +$

$3(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) +$

$6(X^4YZ + XY^4Z + XYZ^4) +$

$8(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) +$

$4(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 10X^2Y^2Z^2 \qquad (105)$

The coefficient of each term $X^xY^yZ^z$ $(x + y + z = 6)$ in Eq. (91) represents the number of isomers with x of X, y of Y, and z of Z.

– What is Polya's Theorem Again Deficient In?

Methods A–D give the same generating functions for enumerating promolecules described above, *i.e.*, Eqs. (68), (70), and (72). On the other hand, Pólya's theorem (Pólya's corona) gives the generating functions shown in Eqs. (99) and (101). Among the terms appearing in these equations, those composed of p and/or $\bar{p}$ are extracted as follows:

Fujita's Method D:

$f^*_{\mathcal{A}+\mathcal{C}}:$	$\frac{1}{2}(p^2+\bar{p}^2)$	$2p\bar{p}$	(106)
$f^*_{\mathcal{A}}:$	none	$2p\bar{p}$	(107)
$f^*_{\mathcal{C}}:$	$\frac{1}{2}(p^2+\bar{p}^2)$	none	(108)

Polya's Theorem:

$g^*:$	$p^2, \bar{p}^2$	$p\bar{p}$	(109)
$g^{**}:$	$p^2, \bar{p}^2$	$2p\bar{p}$	(110)

The results shown in Eqs. (106) – (108) can be confirmed by the inspection of Figure 5. Thus, a pair of enan-

tiomers (**14** and **$\overline{14}$**) is enumerated by the term $\frac{1}{2}(p^2 + \bar{p}^2)$, while two achiral stereoisomers (**15** and **16**) are enumerated by the term $2p\bar{p}$.

The treatment for deriving g^* on the basis of Pólya's theorem can be criticized from a viewpoint of stereoisomer enumeration.

(i) By the inspection of the terms p^2 and $\bar{p}^2$ appearing in g^* (Eq. 109), **14** and **$\overline{14}$** are enumerated distinctly even by considering the permutation (1 2), so that they are not recognized as a pair of enantiomers. This result stems from the fact that the treatment for g^* does not take account of inner structures. Under this condition, the term p^2 cannot be transformed into the term $\bar{p}^2$ and *vice versa*. In other words, Pólya's theorem lacks the concept of sphericity when it is applied to this type of enumerations. Thus, the enantiospheric nature of the permutation (1 2) is disregarded.

(ii) The coefficient 1 of term $p\bar{p}$ in g^* indicates that the two stereoisomers (**15** and **16**) coalesce by the action of the permutation (1 2), so that they are counted as a single stereoisomer. This result also stems from the disregard of the enantiospheric nature of (1 2) in this application of Pólya's theorem.

The treatment for deriving the generation function g^{**} on the basis of Pólya's theorem can be criticized from a viewpoint of stereoisomer enumeration.

(i) This enumeration disregards rotoreflections, as found by the lack of the permutation (1 2). Thereby, **14** and **$\overline{14}$** are enumerated distinctly to give the terms p^2 and $\bar{p}^2$, as appearing in g^{**} (Eq. 110). Although this result is apparently correct, it is inconsistent to the stereochemical viewpoint. Because of the lack of rotoreflections, the two isomers are not recognized as a pair of enantiomers.

(ii) The coefficient 2 of term $p\bar{p}$ in g^{**} indicates that the two isomers **15** and **16** are counted correctly. However, the achiral nature of **15** or **16** is not specified because of the lack of rotoreflections. Obviously, the chirality of chiral compounds (*e.g.*, **14** and **$\overline{14}$**) and the achirality of achiral ones (*e.g.*, **15** and **16**) are not differentiated conceptually in this enumeration.

Methods A–D and their extended versions (A'–D') give the same generating functions as shown in Eqs. (77), (79), and (81), whereas Pólya's theorem (Pólya's corona) gives the generating functions shown in Eqs. (102) and (105).

These generating functions are different in the coefficients of the term $X^2Y^2Z^2$, *i.e.*, $6X^2Y^2Z^2$ in Eq. (77) (by Methods A/A'–D/D') *vs.* $4X^2Y^2Z^2$ in Eq. (102) and $10X^2Y^2Z^2$ in Eq. (105) (by Pólya's theorem). Let us consider the factorization of each term $X^2Y^2Z^2$ into two terms representing methyl substituents in order to demonstrate the difference more clearly:

Fujita's Methods A/A'–D/D':

$$f^\dagger_{\mathcal{A}+C}: \qquad 6X^2Y^2Z^2 = 3(XYZ)^2 + (X^2Y)(YZ^2) +$$
$$(X^2Z)(Y^2Z) + (XY^2)(XZ^2) \qquad (111)$$

$$f^\dagger_{\mathcal{A}}: \qquad 2X^2Y^2Z^2 = 2(XYZ)^2 \qquad (112)$$

$$f^\dagger_C: \qquad 4X^2Y^2Z^2 = (XYZ)^2 + (X^2Y)(YZ^2) +$$
$$(X^2Z)(Y^2Z) + (XY^2)(XZ^2) \qquad (113)$$

Polya's Theorem:

$$g^\dagger: \qquad 4X^2Y^2Z^2 = (XYZ)^2 + (X^2Y)(YZ^2) +$$
$$(X^2Z)(Y^2Z) + (XY^2)(XZ^2) \qquad (114)$$

$$g^\ddagger: \qquad 10X^2Y^2Z^2 = 4(XYZ)^2 + 2(X^2Y)(YZ^2) +$$
$$2(X^2Z)(Y^2Z) + 2(XY^2)(XZ^2) \qquad (115)$$

Let us first discuss the difference in the term $3(XYZ)^2$ for $f^\dagger_{\mathcal{A}+C}$ in Eq. (111) and the term $(XYZ)^2$ for $g^\dagger$ in Eq. (114). The coefficient 3 of the term $(XYZ)^2$ in Eq. (111) corresponds to one pair of enantiomers (**14** and $\overline{\mathbf{14}}$) and two achiral molecules (**15** and **16**), because Methods A/A'–D/D' count each pair of enantiomers once as well as each achiral stereoisomer once. This feature assures the validity or consistency of Eqs. (111) – (113). On the other hand, the coefficient 1 of the term $(XYZ)^2$ in Eq. (114) corresponds to one graph, where one pair of enantiomers (**14** and $\overline{\mathbf{14}}$) and two achiral molecules (**15** and **16**) are regarded as being graph-theoretically the same thing.

To show what Pólya's theorem is deficient in, let us compare between Method D' (the proligand method) and Pólya's theorem (Pólya's corona) in terms of Eq. (86). By placing $\psi_{(a)k} = \psi_{(c)k} = \psi_{(b)k} = \psi_k$ in Eq. (75) and by placing $a_d = c_d = b_d = s_d$ Eq. (51) for Method D' (the proligand method), we can derive the generating function $g^\dagger$ and related equations. Such substitutions as $\psi_{(a)k} = \psi_{(c)k} = \psi_{(b)k} = \psi_k$ and $a_d = c_d = b_d = s_d$ mean the deletion of sphericity. Hence, what Pólya's theorem is deficient in is again concluded to be the concept of sphericity. The proligand method (Method D') is again regarded as a substantial extension of Polya's theorem by adding the concept of sphericity.

When we use Pólya's theorem (Pólya's corona) in terms of Eq. (104), we encounter further types of deficiency.

(i) The coefficient 10 of the term $X^2Y^2Z^2$ for $g^\ddagger$ (Eq. 105) is factorized in accord with Eq. (115) so as to correspond to the ten derivatives listed in Figure 5. Stereochemically speaking, this enumeration procedure lacks rotoreflection operations. As a result, the ten derivatives (Figure 5) is regarded as being conceptually chiral so that

each of them is counted once even if it is stereochemically determined to be chiral or achiral.

(ii) The enantiomeric pairs (*i.e.*, **14**/$\overline{\mathbf{14}}$, **17**/$\overline{\mathbf{17}}$, **18**/$\overline{\mathbf{18}}$ and **19**/$\overline{\mathbf{19}}$) are not characterized to be enantiomeric because of the lack of rotoreflections.

(iii) On the same line, **15** and **16** are not recognized as being achiral. Although they should be characterized as showing a pseudoasymmetric case, this type of enumeration based on Pólya's theorem fails in the determination of the achirality of such a case. Note that **15** and **16** of the pseudoasymmetric case are concluded to be diastereomeric by means of Method A/A'–D/D' because these methods are able to count enantiomeric pairs (Eq. 113).

(iv) The enantiotopic relationship between relevant ligands (or proligands) or the enantiospheric nature of the corresponding orbit of the relevant ligands (or proligands) cannot be characterized by this type of enumeration. For example, the relationship between the ligands *R-XYZ* (p) and *S-XYZ* ($\overline{\mathrm{p}}$) in **15** or **16** cannot be recognized as being enantiotopic, because of the lack of rotoreflections in this type of enumeration.

CONCLUSIONS

The USCI approach (Methods A–C and their extended versions) based on the concept of "sphericities of orbits" and the proligand method (Method D and Method D') based on the concept of "sphericities of cycles" are studied by using combinatorial enumeration of ethane and propane derivatives as examples. The results are compared with the ones based on Pólya's theorem (and Pólya's corona) so as to show that Pólya's theorem enumerates chemical compounds as graphs, not as stereoisomers (3D chemical structures) if all of the permutations of positions are adopted and that it enumerates chemical compounds as chiral compounds if the permutations corresponding to proper rotations are adopted. What Pólya's theorem is deficient in is concluded to be the concept of sphericity.

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SAŽETAK

Sferičnost krugova: Koncept koji čini Pólyin teorem manjkavim za prebrojavanje stereoizomera

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Preinakom Fujitinog USCI (engl. *Unit-Subduced-Cycle-Index*) pristupa, zasnovanog na konceptu sferičnosti orbita, došlo se do tri nova postupka za prebrojavanje stereoizomera, koji su u ovom radu primijenjeni na probleme prebrojavanja derivata etana i propana. Isti je problem razmatran pomoću postupka proliganada i poopćenja zasnovanog na konceptu sferičnosti krugova. Dobijeni rezultati su uspoređeni s onima postignutim primjenom Pólyinog teorema. Pokazano je da Pólyin teorem prebrojava kemijske spojeve kao grafove a ne kao stereoizomere ukoliko se uzmu u obzir sve permutacije koje odgovaraju pravim i nepravim rotacijama. Ukoliko se razmatraju samo permutacije koje odgovaraju pravim rotacijama, tada Pólyin teorem prebrojava spojeve kao kiralne i ne karakterizira prikladno enantiomeriju i akiralnost. Obje primjene Pólyinog teorema ne razmatraju na pravi način neprave rotacije, pa se u radu zaključuje da je koncept sferičnosti ono što čini Pólyin teorem manjkavim.