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Combinatorial enumeration of ethane derivatives as three-dimensional chemical structures, not as graphs. A systematic approach for enumerating and characterizing stereoisomers of tartaric acids and related compounds

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Fujita's proligand method is applied to the enumeration of ethane derivatives, where the counting of stereoisomers of tartaric acids is examined in detail as a probe for testing the versatility of the method. The cycle index with chirality fittingness (CI-CF) for enumerating ethane derivatives is obtained by Fujita's proligand method and compared with the CI-CF derived alternatively by the direct calculation of permutations of substitution positions. The two CI-CFs are identical with each other so that the methodology underlying in Fujita's method is demonstrated in a concrete fashion. The enumeration results are compared with those derived by Pólya's corona. Fujita's proligand method is shown to be capable of enumerating stereoisomers, whereas Pólya's corona is concluded to enumerate graphs, but not stereoisomers. The conceptually change from graphs to three-dimensional (3D) chemical structures is discussed, where the superiority of Fujita's proligand method is demonstrated.

KEY WORDS: organic chemistry, chirality, optical isomers, stereochemistry

1. Introduction

1.1. Conventional descriptive stereochemistry

The distinction between graphs and three-dimensional (3D) chemical structures (stereoisomers) has been one of the most crucial points in organic stereochemistry. Although the conceptual change from graphs to 3D chemical structures was exploited by Pasteur [1] and later accomplished by van't Hoff [2] and LeBel [3] during 1870s, most approaches to clarify the distinction between graphs and 3D chemical structures have still remained within descriptive (or qualitative or non-mathematical) stages.

In order to show how descriptive the distinction is, it is informative to examine the stereoisomerism of tartaric acids as a typical example, where one graph (HOOC–CH(OH)–CH(OH)COOH) was recognized to correspond to one enantiomeric pair (**1**/$\bar{\mathbf{1}}$) and one achiral stereoisomer (**2**), as shown in figure 1. Although the presence of these isomers was already pointed out by van't Hoff [2], the enumeration of these isomers was manual so that a general proof for the absence of other isomers was not taken into consideration.

Moreover, the achirality of **2** with two "asymmetric carbons", which has been referred to as "meso compounds", has been explained in several ways, all of which are descriptive. The original explanation of van't Hoff [2] considered four combinations (+−), (++), (−−), and (−+), where the symbols + and − are equivalent to *R* and *S* in the modern context of the *RS*-nomenclature. Among them, three combinations, i.e., (+−), (++), and (−−), remained because of the symmetrical equality between (+−) and (−+). After the concept of conformation was introduced, the achirality of **2** has been explained by the presence of at least one conformer (**2(a)** or **2(b)**) that is superposed onto itself by a reflection or inversion operator, as shown in figure 2. Such a conformer was once called "symmetry conformer" by Mislow [4]. Another type of meso compounds that have no "symmetry conformation" was reported and their achirality was ascribed to "transient *dl*-pair" [5], where two conformers (**3** and **4**) that are non-superposable through reflection or inversion operations are identical with each other through bond rotations [figure 3]. The different ways of explanation such as "symmetry conformation" and "transient *dl*-pair" should be replaced by a more succinct concept,

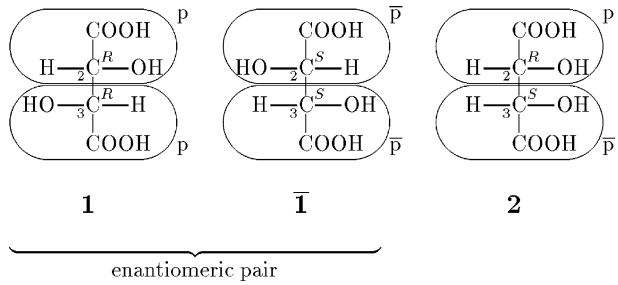

Figure 1. One pair of enantiomeric tartaric acids (**1** and $\bar{\mathbf{1}}$) and one achiral tartaric acid (**2**).

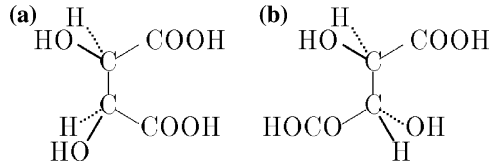

Figure 2. Examples of so-called "symmetry conformation" for the achiral tartaric acid (**2**). The left conformer (**2(a)**) has a mirror plane perpendicular to the central C–C bond, while the right conformer (**2(b)**) has an inversion center at the midpoint of the central C–C bond.

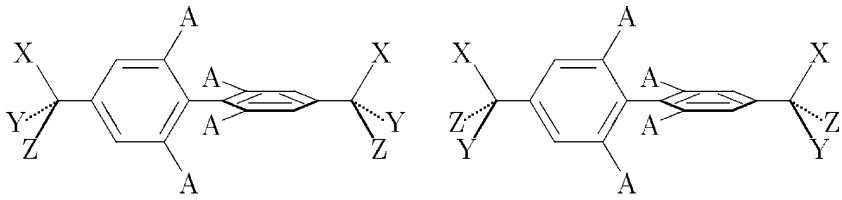

Figure 3. An example of so-called "transient *dl*-pair". The left conformer (**3**) can be converted into the right one (**4**) by the reflection with a mirror on this page. Although these two conformers are non-superposable in this projection, they becomes superposable by rotating either biphenyl unit by 90° around the biphenyl axis.

which should have a capability of serving as a basis for quantitative (or mathematical) approaches as well as for qualitative (descriptive) ones.

1.2. Conventional chemical combinatorics for graphs, but not for 3D chemical structures

On the other hand, combinatorial enumeration of isomers has been investigated as one of quantitative approaches of chemistry. In particular, Pólya's theorem [6,7] has been widely used to solve various problems in chemical fields, as found in educational articles [8–11] as well as in several reviews [12–14] and in books [15–17].

Although Pólya's theorem aimed at enumerating groups, graphs, and chemical compounds as the title of his original report indicated [6,7], the "chemical compounds" enumerated by Pólya's theorem are *graphs*, but not *3D chemical structures* from the viewpoint of stereochemistry. In other words, Pólya's theorem is incapable of treating enantiomeric relationships properly so that it is unable to enumerate stereoisomers as 3D objects. Because of this essential feature, the usage of Pólya's theorem has been restricted to give non-stereochemical solutions even if the theorem has been applied to stereochemical problems.

This feature has become more apparent when Pólya's corona [6,7] (as an extension of Pólya's theorem) is applied to enumerate stereoisomers with rotatable ligands such as substituted methyl groups. For example, Pólya's corona enumerates one graph (**5**) only in the enumeration of isomers having a ligand pattern XYZ–XYZ on an ethane skeleton, where the distinction between *R*-CXYZ and *S*-CXYZ is disregarded so that they are equalized as a graph CXYZ, as shown in figure 4. This is a general case involving the stereoisomerism of tartaric acids (figure 1). Thus, Pólya's corona (along with Pólya's theorem) is incapable of solving stereochemical problems in which such substituted methyl groups may be chiral. From the stereochemical viewpoint, in fact, there exist one pair of enantiomers (**6** and $\bar{\mathbf{6}}$) and one meso-form (**7**), as shown in figure 5.

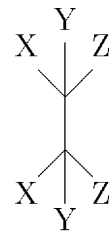

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Figure 4. Chemical graph for representing ethane derivatives of ligand pattern $X^2Y^2Z^2$ (XYZ–XYZ).

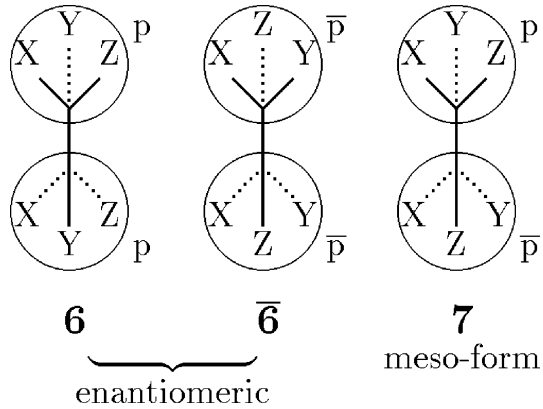


Figure 5. Chemical structures for representing ethane derivatives of ligand pattern $X^2Y^2Z^2$ (XYZ–XYZ).

1.3. Scope and aims

As clarified in the preceding sections, the two conventional approaches, i.e., the conventional descriptive stereochemistry and the conventional chemical combinatorics for graphs, should be restructured to be capable of treating 3D chemical structures. By demonstrating what they are deficient in and by introducing new concepts to avoid the deficiencies, the two approaches should be integrated and re-composed so as to give a common basis of comprehending stereochemistry.

To do this task, Fujita has proposed the concepts of *proligand* and *promolecule* [18,19], where a proligand is defined as a structureless object with chirality/achirality and a promolecule is defined as a skeleton whose substitution positions are occupied by proligands. These concepts have been used as a descriptive tool for explaining meso compounds described above [20,21]. At the same time, they have served as a mathematical tool for chemical combinatorics [22,23] under the name of the unit-subduced-cycle-index (USCI) approach [19].

Although the USCI approach is versatile to comprehend stereochemistry in detail, it requires such intimate knowledge on group theories that is not involved in a standard repertoire of combinatorics (e.g., Pólya's theorem). It is desirable to develop a new simplified method which holds the essential features of the USCI approach (i.e., sphericity, proligand, and promolecule), because there are cases in which more simplified results are sufficient. Moreover, the new simplified method should directly succeed the methodology of Pólya's theorem to accomplish the same task in a widely acceptable way. In other words, Pólya's theorem should be substantially extended in the light of the concepts of proligand and promolecules to enumerate stereoisomers, but not graphs.

According to this guideline, Fujita [24,25] has developed a new method (called the *proligand method*) based on the concept of *sphericity indices of cycles*, where both achiral and chiral ligands are taken into consideration in the light of the concepts of proligand and promolecule.

In the present paper, Fujita's proligand method will be applied to the enumeration of such stereoisomers as shown in figure 5, where its superiority over Pólya's corona as well as over Pólya's theorem will be demonstrated. This will give a quantitative solution to the problems concerning such meso compounds as the achiral tartaric acid. Thereby, such combinatorial enumeration as provided by Fujita's proligand method will be shown to enrich introductory courses as well as advanced courses in stereochemistry as a new repertoire.

2. The proligand method for enumerating chemical structures

2.1. Basic concepts

The proligand method developed by Fujita [24,25] can be applied to the enumeration of ethane derivatives as 3D chemical structures. We first consider a skeleton (**8**) that has two substitution positions. Each of the two positions accommodates a chiral or achiral proligand to generate a promolecule such as **9**, which is, for example, generated by the substitution of two chiral proligands (p). Then, the proligands are replaced by a chiral ligand (*R*-CXYZ) to produce a molecule (**10**), where 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. Thus, such stepwise processes as exemplified by figure 6 (skeleton → promolecule → molecule) are considered in the enumeration of ethane derivatives.

It should be noted that a proligand is defined as a structureless object that has chirality/achirality in isolation [18]. If a proligand is monovalent as presumed in the present article, it can be regarded as belonging to the infinite point group $\mathbf{C}_{\infty v}$ (achiral) or $\mathbf{C}_{\infty}$ (chiral) in isolation. Thus, each proligand has such an abstract meaning, whereas concrete ligands such as a methyl group

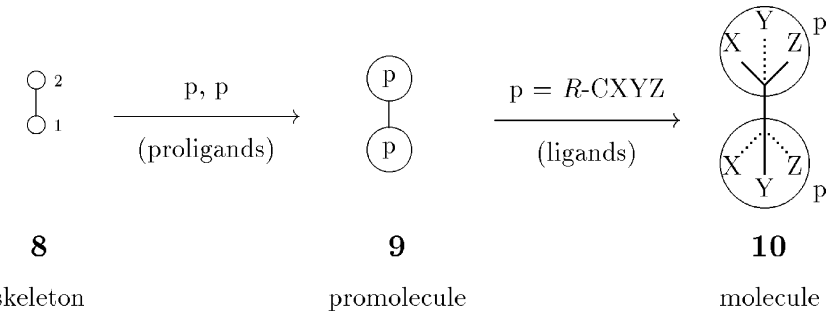


Figure 6. Process of the proligand method for converting a skeleton into a molecule through a promolecule. The symbol p represents a chiral proligand, which is replaced by a chiral ligand CXYZ.

(CH_3: $\mathbf{C}_{3v}$), a hydroxy group (OH: $\mathbf{C}_s$), and a CXYZ group ($\mathbf{C}_1$) belong to the respective point groups of finite order.

Fujita's proligand method treats stereoisomers properly in the level of *configuration* by introducing the concepts of proligand and promolecule. Without these concepts, combinatorial enumeration is forced to be carried out in the level of *conformation*, where both an eclipsed form and a staggered form (or strictly other various conformations) should be taken into consideration, as shown in figure 2. The two forms (or the other conformers) in the level of conformation should be equalized as a stereoisomer in order to accomplish the combinatorial enumeration properly in the level of configuration. This equalization is realized by Fujita's proligand method, as discussed in the following sections.

2.2. *Skeletons into promolecules*

When we sequentially number the two positions of the skeleton (**8**), we can obtain the following permutation group:

$$\widehat{\mathbf{G}} = \{(1)(2), (1\ 2), \overline{(1)(2)}, \overline{(1\ 2)}\}, \tag{1}$$

which permutes the two positions, where each overbar represents the future change of the chirality of a proligand occupying the position. It should be noted that the cycles (1 2) and $\overline{(1\ 2)}$ express the same permutation of positions but differ from each other in the action on proligand chirality. Hence, we refer to the first two permutations, i.e., (1)(2) and (1 2), as *proper permutations* in accord with the corresponding proper rotations. The second two permutations, i.e., $\overline{(1)(2)}$ and $\overline{(1\ 2)}$, are called *improper permutations* in accord with the corresponding improper rotations (rotoreflections). A cycle appearing in a proper or improper permutation is referred as a proper or improper d-cycle.

According to the sphericity of a proper or improper d-cycle appearing in each permutation, a sphericity index is assigned to the d-cycle [24]:

Table 1
Cycles and products of (extended) sphericity indices for enumerating ethane derivatives.

	Cycles	Products of sphericity indices	Products of extended sphericity indices
Proper permutation	(1)(2)	b_1^2	$\psi_{(b)1}^2$
	(1 2)	b_2	$\psi_{(b)2}$
Improper permutation	$\overline{(1)(2)}$	a_1^2	$\psi_{(a)1}^2$
	$\overline{(1\ 2)}$	c_2	$\psi_{(c)2}$

1. A proper d-cycle (odd or even) is hemispheric in general to be assigned to a sphericity index b_d.
2. An improper d-cycle (d: odd) is homospheric in general to be assigned to a sphericity index a_d.
3. An improper d-cycle (d: even) is enantiospheric in general to be assigned to a sphericity index c_d.

Thus, a sphericity index b_1 is assigned to each of one-cycles, (1) or (2), which is determined to be a hemispheric one-cycle because the one-cycle is concerned with a proper permutation. Then the product of the sphericity indices b_1^2 is assigned to the permutation represented by the product of such cycles, i.e., (1)(2). Similarly, a sphericity index b_2 is assigned to a two-cycle, (1 2), which is determined to be a hemispheric two-cycle [24] because the two-cycle is concerned with a proper permutation. Note that the letter b of the index b_d represents the hemisphericity and the subscript 1 or 2 expresses that the cycle at issue is a one-cycle or two-cycle. These results are summarized in table 1.

On the other hand, a sphericity index a_1 is assigned to each of one-cycles, $\overline{(1)}$ or $\overline{(2)}$, which is determined to be a homospheric one-cycle because the one-cycle is concerned with an improper permutation [24]. Then the product of the sphericity indices a_1^2 is assigned to the improper permutation represented by the product of such cycles, i.e., $\overline{(1)(2)}$, as shown in table 1. The letter a of the index a_d represents the homosphericity and the subscript 1 represents a one-cycle.

A sphericity index c_2 is assigned to a two-cycle, $\overline{(1\ 2)}$, which is determined to be an enantiospheric two-cycle [24] because the two-cycle is concerned with an improper permutation. The letter c of the index c_2 represents the enantiosphericity and the subscript 2 represents a two-cycle. The result is summarized in table 1.

Following equation (2) of the previous paper [24], the cycle index with chirality fittingness (CI-CF) for this case is obtained as follows:

$$\text{CI-CF}(\widehat{\mathbf{G}}; \$_d) = \tfrac{1}{4}\left(b_1^2 + b_2 + a_1^2 + c_2\right) \tag{2}$$

by using the products of sphericity indices listed in table 1, where the symbol $\$_d$ represents a sphericity index, a_d, b_d, or c_d, according to the respective sphericity.

Note that the value 4 of the fraction 1/4 of equation (2) is the order of the group $\widehat{\mathbf{G}}$.

Suppose that we select two proligands from achiral proligands (A and B) and chiral proligands (p, $\overline{\text{p}}$, q, and $\overline{\text{q}}$), where p and $\overline{\text{p}}$ (or q and $\overline{\text{q}}$) represent a pair of enantiomeric proligands in isolation. By following theorem 1 of the previous paper [24], we use the following inventories:

$$a_d = A^d + B^d, \tag{3}$$

$$c_d = A^d + B^d + 2p^{d/2}\overline{p}^{d/2} + 2q^{d/2}\overline{q}^{d/2}, \tag{4}$$

$$b_d = A^d + B^d + p^d + \overline{p}^d + q^d + \overline{q}^d. \tag{5}$$

The term "inventory" is used after the previous usage of Pólya [17], but in an extended meaning, because these equations indicate the inventory of possible achiral or chiral *proligands* as well as their *modes of accommodation*. Pólya's original usage is concerned with ligands (not proligands) and does not designate the mode of accommodation.

These inventories (equations (3)–(5)) are introduced into equation (2) and the resulting equation is expanded to give the following generating function:

$$\begin{aligned} F = {} & [A^2 + B^2] + AB \\ & + \tfrac{1}{2}[(Ap + A\overline{p}) + (Aq + A\overline{q}) + (Bp + B\overline{p}) + (Bq + B\overline{q})] \\ & + \tfrac{1}{2}[(p^2 + \overline{p}^2) + (q^2 + \overline{q}^2)] \\ & + \tfrac{1}{2}[(pq + \overline{pq}) + (p\overline{q} + \overline{p}q)] \\ & + [p\overline{p} + q\overline{q}], \end{aligned} \tag{6}$$

where the coefficient of each term represents the number of stereoisomers. Note that the present enumeration counts a pair of enantiomers once. Hence the term $(1/2)(Ap + A\overline{p})$, for example, represents one pair of enantiomers (Ap and $A\overline{p}$). When we place p = $\overline{\text{p}}$, we obtain $(1/2)(Ap + A\overline{p}) = Ap$, $(1/2)(p^2 + \overline{p}^2) = \text{p}^2$, etc. Hence, equation (6) is converted into the following form:

$$\begin{aligned} F' = {} & [A^2 + B^2] + AB + [Ap + Aq + Bp + Bq] \\ & + 2[p^2 + q^2] + 2pq. \end{aligned} \tag{7}$$

The term $2p^2$ in equation (7) comes from the terms $(1/2)(p^2 + \overline{p}^2)$ and $p\overline{p}$ appearing in equation (6). Hence, the coefficient 2 of the term $2p^2$ in equation 7 expresses the presence of one pair of enantiomers and one achiral molecule (meso-compound). This result is in agreement with figure 5, where p and $\overline{\text{p}}$ are replaced by *R*-CXYZ and *S*-CXYZ. The stereoisomers enumerated by the generating function (equation (6)) are categorized into six types, as differentiated by brackets. They are illustrated in figure 7, where an arbitrary one of enantiomers is depicted as a representative if chiral (A–p, p–p, and p–q).

Similar results to figure 7 have been obtained by employing two methods of the USCI approach proposed by Fujita [20,26]. If the reader compare between the two methods and the present proligand method, he/she would reach a deeper insight to stereochemistry,

2.3. *Promolecules into molecules*

The next step (promolecule → molecule) is the replacement of the proligands (A, B, p, $\overline{\text{p}}$, q, $\overline{\text{q}}$) by ligands derived from a methyl ligand. For this purpose, we consider extended sphericity indices ($\psi_{(\$)k}$) in place of sphericity indices ($\$_d$) described above.

2.3.1. *Extended sphericity indices*

Extended sphericity indices $\psi_{(\$)k}$ ($\$ = b, a$, or c) used in Fujita's proligand method are obtained in a similar way to sphericity indices described above for promolecules ($\$_d$: $\$ = b, a$, or c). Thus, in place of the sphericity index b_1 for a hemispheric one-cycle, we consider an extended sphericity index $\psi_{(b)1}$ is assigned to each of one-cycles, (1) or (2), which appear in equation (1) [25]. Then the product of the extended sphericity indices $\psi^2_{(b)1}$ is assigned to the permutation represented by the product of such cycles, i.e., (1)(2). Similarly, an extended sphericity index $\psi_{(b)2}$ is assigned to a two-cycle, (1 2) in place of the sphericity index b_2 for a hemispheric two-cycle [25]. Note that the subscript (b) represents the hemisphericity and the other subscript 1 or 2 expresses that the cycle at issue is a one-cycle or two-cycle. These results are summarized in table 1.

In place of the sphericity index a_1 for a homospheric one-cycle, an extended sphericity index $\psi_{(a)1}$ is assigned to each of one-cycles, $\overline{(1)}$ or $\overline{(2)}$, Then the product of the extended sphericity indices $\psi^2_{(a)1}$ is assigned to the improper permutation represented by the product of such cycles, i.e., $\overline{(1)(2)}$, as shown in table 1 [25]. The subscript (a) represents the homosphericity and the other subscript 1 represents a one-cycle.

In place of the sphericity index c_2 for an enantiospheric two-cycle, an extended sphericity index $\psi_{(c)2}$ is assigned to a two-cycle, $\overline{(1\ 2)}$ [25]. The

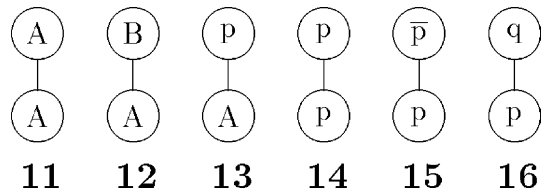


Figure 7. Promolecules based on the skeleton **8**. The molecules A–A, A–B, and p–$\overline{\text{p}}$ are achiral. The other molecules A–p, p–p, and p–q are chiral, where an appropriate enantiomer is depicted for each pair of enantiomers.

subscript (c) represents the enantiosphericity and the other subscript 2 represents a two-cycle. The result is summarized in table 1.

Following equation (34) of the previous paper [25], the CI-CF for this case is obtained as follows:

$$\text{CI-CF}(\widehat{\mathbf{G}}; \psi_{(\$)k}) = \tfrac{1}{4}(\psi_{(b)1}^2 + \psi_{(b)2} + \psi_{(a)1}^2 + \psi_{(c)2}), \tag{8}$$

by using the products of extended sphericity indices listed in table 1, where the subscript (\$) represents (a), (b), or (c) according to the respective sphericity.

2.3.2. Proligand enumeration for obtaining inventories

In order to proceed to the step converting a promolecule (e.g., **9**) into a molecule (e.g., **10**), the derivation of a methyl ligand should be examined. When we number the three positions of the methyl ligand, we obtain a permutation group $\widehat{\mathbf{H}}$ containing proper and improper rotations as well as another permutation group $\widehat{\mathbf{H}}'$ containing proper rotations only:

$$\begin{aligned}\widehat{\mathbf{H}} = \{&(1)(2)(3), (1\ 3\ 2), (1\ 2\ 3),\\ &\overline{(1\ 2)(3)}, \overline{(1\ 3)(2)}, \overline{(1)(2\ 3)}\},\\ \widehat{\mathbf{H}}' = \{&(1)(2)(3), (1\ 3\ 2), (1\ 2\ 3)\},\end{aligned}$$

where an overbar represents an improper permutation. 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 for the skeleton. Thereby, the products of sphericity indices are obtained, as shown in table 2.

By applying equations (8) and (9) of the previous paper [25] to the present case, we obtain the corresponding cycle indices with chirality fittingness (CI-CF) as follows:

$$\text{CI-CF}(\widehat{\mathbf{H}}; \$_d) = \tfrac{1}{6}\left(b_1^3 + 2b_3 + 3a_1c_2\right), \tag{9}$$

$$\text{CI-CF}(\widehat{\mathbf{H}}'; b_d) = \tfrac{1}{3}\left(b_1^3 + 2b_3\right), \tag{10}$$

Table 2
Cycles and products of sphericity indices for enumerating methyl ligands.

	Cycles	Products of sphericity indices
Proper permutation	(1)(2)(3)	b_1^3
	(1 3 2)	b_3
	(1 2 3)	b_3
Improper permutation	$\overline{(1\ 2)(3)}$	a_1c_2
	$\overline{(1\ 3)(2)}$	a_1c_2
	$\overline{(1)(2\ 3)}$	a_1c_2

where the data collected in table 2 are used. In equation (9), the symbol \$ in the left-hand side represents a, b, or c according to the respective sphericity. Note that the orders of the groups $\widehat{\mathbf{H}}$ and $\widehat{\mathbf{H}}'$ are equal to 6 and 3, respectively, which appear in the fractions of equations (9) and (10).

The former equation (equation (9)) is obtained by regarding a methyl skeleton as being achiral, because the achiral group $\widehat{\mathbf{H}}$ is used. On the other hand, the latter equation (equation (10)) is obtained by regarding a methyl skeleton as being chiral, because the achiral group $\widehat{\mathbf{H}}'$ is used.

Following equations (31)–(33) of the previous paper [25], we obtain the following equations:

$$\psi_{(a)k} = 2\text{CI-CF}(\widehat{\mathbf{H}}; \$_{kd}) - \text{CI-CF}(\widehat{\mathbf{H}}'; b_{kd}) = a_k c_{2k}, \tag{11}$$

$$\psi_{(c)k} = \text{CI-CF}(\widehat{\mathbf{H}}'; c_{kd}) = \tfrac{1}{3}c_k^3 + \tfrac{2}{3}c_{3k}, \tag{12}$$

$$\psi_{(b)k} = \text{CI-CF}(\widehat{\mathbf{H}}'; b_{kd}) = \tfrac{1}{3}b_k^3 + \tfrac{2}{3}b_{3k}, \tag{13}$$

where the subscript d in equations (9) and (10) is replaced by kd to obtain the right-hand sides. It should be noted that equation (32) for $\psi_{(c)k}$ of [25] is extended to give equation (12) so that the relevant orbit can accommodate chiral ligands as well as achiral ones.

2.3.3. Stereoisomer enumeration

The three equations (equations (11)–(13)) are introduced into equation (8) to give the following equation:

$$\begin{aligned}\text{CI-CF}'(\widehat{\mathbf{G}}[\widehat{\mathbf{H}}]; \$_d) = {} & \tfrac{1}{36}b_1^6 + \tfrac{1}{9}b_1^3 b_3 + \tfrac{1}{9}b_3^2 + \tfrac{1}{12}b_2^3 \\ & + \tfrac{1}{6}b_6 + \tfrac{1}{4}a_1^2 c_2^2 + \tfrac{1}{12}c_2^3 + \tfrac{1}{6}c_6.\end{aligned} \tag{14}$$

By considering atoms or achiral ligands only (X, Y, and Z), we can use identical inventories as follows

$$a_d = b_d = c_d = X^d + Y^d + Z^d, \tag{15}$$

which are introduced into equation (14). Thereby, we obtain a generating function for giving the numbers of ethane derivatives as the coefficients of the respective terms, which are itemized according to chemical structures:

$$\begin{aligned}f = {} & (X^6 + Y^6 + Z^6) + (X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) \\ & + 2(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) \\ & + 2(X^4YZ + XY^4Z + XYZ^4) \\ & + 3(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) \\ & + 2(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 5X^2Y^2Z^2.\end{aligned} \tag{16}$$

The coefficient of each term $X^x Y^y Z^z$ $(x + y + z = 6)$ in equation (16) 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.

To show the meanings of equations (11)–(13), the inventories (equation (15)) are introduced into these equations under the condition of $k = 1$ to give:

$$\psi_{(a)1} = X^3 + X^2Y + XY^2 + Y^3 + X^2Z + Y^2Z + XZ^2 + YZ^2 + Z^3, \tag{17}$$

$$\psi_{(c)1} = X^3 + X^2Y + XY^2 + Y^3 + X^2Z + 2XYZ + Y^2Z + XZ^2 + YZ^2 + Z^3, \tag{18}$$

$$\psi_{(b)1} = X^3 + X^2Y + XY^2 + Y^3 + X^2Z + 2XYZ + Y^2Z + XZ^2 + YZ^2 + Z^3. \tag{19}$$

The term $2XYZ$ appearing in the right-hand side of equation (18) stems from two modes of compensated pairwise packing of *R*-CXYZ and *S*-CXYZ for an enantiospheric cycle [19]. On the other hand, the term $2XYZ$ appearing in the right-hand side of equation (19) represents a respective occupation by *R*-CXYZ or *S*-CXYZ for a hemispheric cycle. The chiral ligands do not appear in equation (17) for a homospheric cycle.

2.4. *Concrete forms of permutations*

As found in the preceding derivations, Fujita's proligand method does not require the concrete forms of permutations for nonrigid molecules generated by the derivation process in which proligands in a promolecule are replaced by ligands. Instead, it only requires permutations for a promolecule (as collected in table 1 in the form of cycles for the present case) and permutations for a ligand (as collected in table 2 in the form of cycles for the present case).

To understand the total feature of the derivation process, however, it is illustrative to examine the concrete permutations for the nonrigid molecules. Suppose that the position 1 of the skeleton **17** accommodates a ligand numbered as 1–3, while the position 2 of the skeleton **17** accommodates a ligand numbered as 4–6, as depicted in figure 8.

To illustrate the concrete form of a proper permutation, let us consider (1 2) of $\widehat{\mathbf{G}}$ for **18**, where the 1 of $\widehat{\mathbf{G}}$ accommodates a ligand permuted by (1)(2)(3) of $\widehat{\mathbf{H}}$ (i.e., no rotation), while the 2 of $\widehat{\mathbf{G}}$ accommodates a ligand permuted by (4)(5)(6) of $\widehat{\mathbf{H}}$ (i.e., no rotation). Then we can obtain the following

permutation and the corresponding product of cycles:

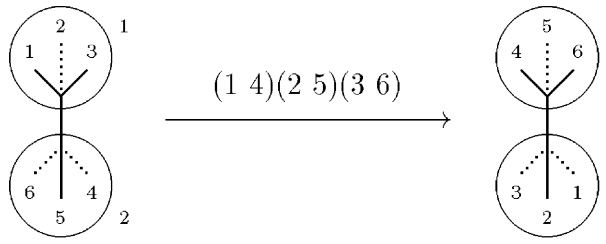
$$\left(\begin{array}{c|c} \overbrace{1\,2\,3}^{1} & \overbrace{4\,5\,6}^{2} \\ \underbrace{4\,5\,6}_{2} & \underbrace{1\,2\,3}_{1} \end{array}\right) = (1\ 4)(2\ 5)(3\ 6). \tag{20}$$

The horizontal braces over the permutation represent the original numbering of the two positions, while the horizontal braces under the permutation represent the numbering after the permutation. The product of cycles in the right-hand side of equation (20) corresponds to a product of sphericity indices (PSI), b_2^3, because all of the involved cycles are two-membered hemispheric cycles. These data are shown in the tenth data row of table 3. In similar ways, the remaining permutations (products of cycles) and PSIs for proper rotations are obtained, as collected in table 3, where each total permutation is expressed as a product of cycles.

To illustrate the concrete form of an improper permutation (figure 9), on the other hand, let us consider $\overline{(1\ 2)}$ of $\widehat{\mathbf{G}}$ for **19**, where the $\overline{1}$ of $\widehat{\mathbf{G}}$ accommodates a ligand permuted by $\overline{(1)(2\ 3)}$ of $\widehat{\mathbf{H}}$, while the $\overline{2}$ of $\widehat{\mathbf{G}}$ accommodates a ligand permuted by $\overline{(4)(5\ 6)}$ of $\widehat{\mathbf{H}}$. Then we can obtain the following permutation and the corresponding product of cycles:

$$\left(\begin{array}{c|c} \overbrace{1\,2\,3}^{1} & \overbrace{4\,5\,6}^{2} \\ \underbrace{\overline{4}\,\overline{6}\,\overline{5}}_{\overline{2}} & \underbrace{\overline{1}\,\overline{3}\,\overline{2}}_{\overline{1}} \end{array}\right) = \overline{(1\ 4)(2\ 6)(3\ 5)}. \tag{21}$$

This product of cycles corresponds to a PSI, c_2^3, because the involved cycles are two-membered enantiospheric cycles. These data are shown in the tenth data row of table 4. In similar ways, the remaining permutations (products of cycles) and



17 **18**

Figure 8. Numbering of an ethane skeleton and a proper permutation.

Table 3
Proper permutations for nonrigid ethane derivatives.

Skeleton	Ligands			
$\widehat{\mathbf{G}}$	$\widehat{\mathbf{H}}$	$\widehat{\mathbf{H}}$	Total permutation	PSI
(1)(2)	(1)(2)(3)	(4)(5)(6)	(1)(2)(3)(4)(5)(6)	b_1^6
(1)(2)	(1)(2)(3)	(4 6 5)	(1)(2)(3)(4 6 5)	$b_1^3 b_3$
(1)(2)	(1)(2)(3)	(4 5 6)	(1)(2)(3)(4 5 6)	$b_1^3 b_3$
(1)(2)	(1 3 2)	(4)(5)(6)	(1 3 2)(4)(5)(6)	$b_1^3 b_3$
(1)(2)	(1 3 2)	(4 6 5)	(1 3 2)(4 6 5)	b_3^2
(1)(2)	(1 3 2)	(4 5 6)	(1 3 2)(4 5 6)	b_3^2
(1)(2)	(1 2 3)	(4)(5)(6)	(1 2 3)(4)(5)(6)	$b_1^3 b_3$
(1)(2)	(1 2 3)	(4 6 5)	(1 2 3)(4 6 5)	b_3^2
(1)(2)	(1 2 3)	(4 5 6)	(1 2 3)(4 5 6)	b_3^2
(1 2)	(4)(5)(6)	(1)(2)(3)	(1 4)(2 5)(3 6)	b_2^3
(1 2)	(4)(5)(6)	(1 3 2)	(1 4 3 6 2 5)	b_6
(1 2)	(4)(5)(6)	(1 2 3)	(1 4 2 5 3 6)	b_6
(1 2)	(4 6 5)	(1)(2)(3)	(1 6 3 5 2 4)	b_6
(1 2)	(4 6 5)	(1 3 2)	(1 6 2 4 3 5)	b_6
(1 2)	(4 6 5)	(1 2 3)	(1 6)(2 4)(3 5)	b_2^3
(1 2)	(4 5 6)	(1)(2)(3)	(1 5 2 6 3 4)	b_6
(1 2)	(4 5 6)	(1 3 2)	(1 5)(2 6)(3 4)	b_2^3
(1 2)	(4 5 6)	(1 2 3)	(1 5 3 4 2 6)	b_6

PSIs for improper rotations are obtained, as collected in table 4, where each total permutation is expressed as a product of cycles.

By collecting the PSIs in tables 3 and 4 we obtain the CI-CF for this case as follows:

$$\text{CI-CF}''(\widehat{\mathbf{G}}[\widehat{\mathbf{H}}]; \$_d) = \tfrac{1}{36}\left(b_1^6 + 4b_1^3 b_3 + 4b_3^2 + 3b_2^3 + 6b_6 + 9a_1^2 c_2^2 + 3c_2^3 + 6c_6\right), \tag{22}$$

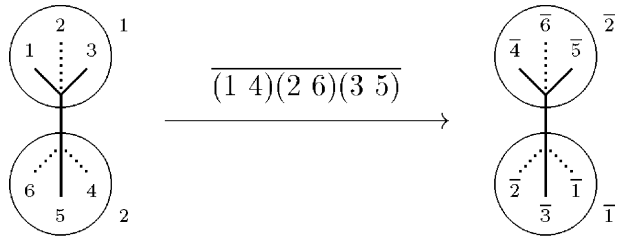
where the value 36 in the fraction 1/36 is equal to the order of the permutation group $\widehat{\mathbf{G}}[\widehat{\mathbf{H}}]$, the elements (as products of cycles) of which are listed in tables 3 and 4. This equation is identical with equation (14) which has been obtained by virtue of Fujita's proligand method.

2.5. *Achiral conformers and chiral conformers*

The staggered conformer used in figures 8 and 9 is achiral in itself (as in the fixed conformation), where an inversion operation corresponds to the permutation $\overline{(1\ 4)(2\ 6)(3\ 5)}$, as shown in figure 9. The permutations listed in

Table 4
Improper permutations for nonrigid ethane derivatives.

Skeleton	Ligands			
$\widehat{\mathbf{G}}$	$\widehat{\mathbf{H}}$	$\widehat{\mathbf{H}}$	Total permutation	PSI
$\overline{(1)(2)}$	$\overline{(1)(2\ 3)}$	$\overline{(4)(5\ 6)}$	$\overline{(1)(2\ 3)(4)(5\ 6)}$	$a_1^2c_2^2$
$\overline{(1)(2)}$	$\overline{(1)(2\ 3)}$	$\overline{(4\ 6)(5)}$	$\overline{(1)(2\ 3)(4\ 6)(5)}$	$a_1^2c_2^2$
$\overline{(1)(2)}$	$\overline{(1)(2\ 3)}$	$\overline{(4\ 5)(6)}$	$\overline{(1)(2\ 3)(4\ 5)(6)}$	$a_1^2c_2^2$
$\overline{(1)(2)}$	$\overline{(1\ 3)(2)}$	$\overline{(4)(5\ 6)}$	$\overline{(1\ 3)(2)(4)(5\ 6)}$	$a_1^2c_2^2$
$\overline{(1)(2)}$	$\overline{(1\ 3)(2)}$	$\overline{(4\ 6)(5)}$	$\overline{(1\ 3)(2)(4\ 6)(5)}$	$a_1^2c_2^2$
$\overline{(1)(2)}$	$\overline{(1\ 3)(2)}$	$\overline{(4\ 5)(6)}$	$\overline{(1\ 3)(2)(4\ 5)(6)}$	$a_1^2c_2^2$
$\overline{(1)(2)}$	$\overline{(1\ 2)(3)}$	$\overline{(4)(5\ 6)}$	$\overline{(1\ 2)(3)(4)(5\ 6)}$	$a_1^2c_2^2$
$\overline{(1)(2)}$	$\overline{(1\ 2)(3)}$	$\overline{(4\ 6)(5)}$	$\overline{(1\ 2)(3)(4\ 6)(5)}$	$a_1^2c_2^2$
$\overline{(1)(2)}$	$\overline{(1\ 2)(3)}$	$\overline{(4\ 5)(6)}$	$\overline{(1\ 2)(3)(4\ 5)(6)}$	$a_1^2c_2^2$
$\overline{(1\ 2)}$	$\overline{(4)(5\ 6)}$	$\overline{(1)(2\ 3)}$	$\overline{(1\ 4)(2\ 6)(3\ 5)}$	c_2^3
$\overline{(1\ 2)}$	$\overline{(4)(5\ 6)}$	$\overline{(1\ 3)(2)}$	$\overline{(1\ 4\ 3\ 5\ 2\ 6)}$	c_6
$\overline{(1\ 2)}$	$\overline{(4)(5\ 6)}$	$\overline{(1\ 2)(3)}$	$\overline{(1\ 4\ 2\ 6\ 3\ 5)}$	c_6
$\overline{(1\ 2)}$	$\overline{(4\ 6)(5)}$	$\overline{(1)(2\ 3)}$	$\overline{(1\ 6\ 2\ 5\ 3\ 4)}$	c_6
$\overline{(1\ 2)}$	$\overline{(4\ 6)(5)}$	$\overline{(1\ 3)(2)}$	$\overline{(1\ 6)(2\ 5)(3\ 4)}$	c_2^3
$\overline{(1\ 2)}$	$\overline{(4\ 6)(5)}$	$\overline{(1\ 2)(3)}$	$\overline{(1\ 6\ 3\ 4\ 2\ 5)}$	c_6
$\overline{(1\ 2)}$	$\overline{(4\ 5)(6)}$	$\overline{(1)(2\ 3)}$	$\overline{(1\ 5\ 3\ 6\ 2\ 4)}$	c_6
$\overline{(1\ 2)}$	$\overline{(4\ 5)(6)}$	$\overline{(1\ 3)(2)}$	$\overline{(1\ 5\ 2\ 4\ 3\ 6)}$	c_6
$\overline{(1\ 2)}$	$\overline{(4\ 5)(6)}$	$\overline{(1\ 2)(3)}$	$\overline{(1\ 5)(2\ 4)(3\ 6)}$	c_2^3



17 **19**

Figure 9. Numbering of an ethane skeleton and an improper permutation.

tables 3 and 4 corresponds to the symmetry operations of $\mathbf{D}_{3d}$ and the subsequent bond rotations of the methyl ligands in the staggered conformer (**17** or **2**). The permutations listed in tables 3 and 4 are also effective if we take account of an eclipsed conformer such as **1**.

Moreover, the permutations listed in tables 3 and 4 are effective if we select any other conformer as a basis. For example, figure 10 shows the Newman

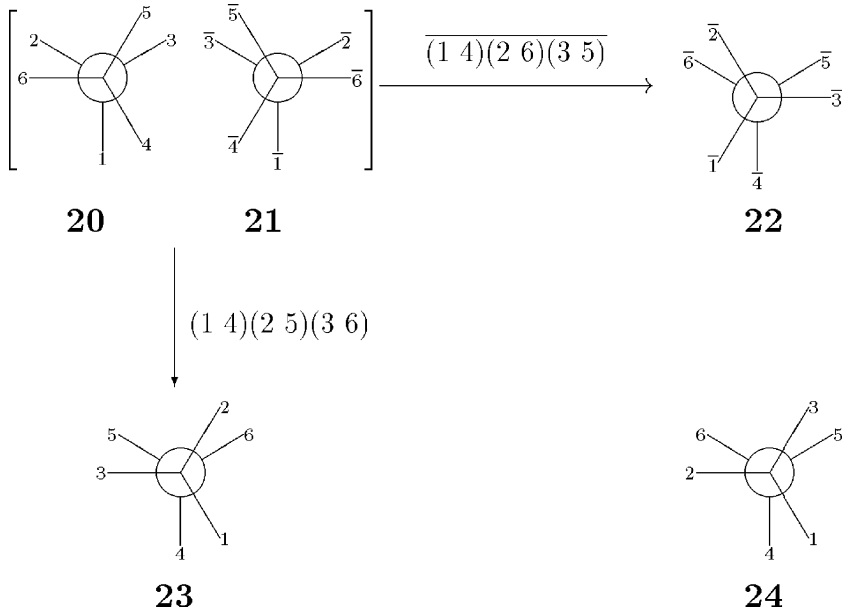


Figure 10. Permutations on a chiral conformer.

projections of a chiral conformer (**20**) of $\mathbf{D}_3$ and its enantiomeric conformer (**21**), which serves as skeletons for the permutations listed in tables 3 and 4. The action of the improper permutation $\overline{(1\ 4)(2\ 6)(3\ 5)}$ on **20** produces a conformer **22** with a different mode of numbering, where the configurations S $(1 > 2 > 3)$ and S $(4 > 5 > 6)$ in **20** are transformed into the configurations R $(\overline{1} > \overline{2} > \overline{3})$ and R $(\overline{4} > \overline{5} > \overline{6})$ in **22**. The conformer **22** can be equalized to the conformer **21** by proper rotations and bond rotations. On the other hand, the action of the proper permutation (1 4)(2 5)(3 6) on **20** produces a conformer **23** with a different mode of numbering, where the configurations S $(1 > 2 > 3)$ and S $(4 > 5 > 6)$ in **20** are the same as the configurations S $(1 > 2 > 3)$ and S $(4 > 5 > 6)$ in **23**. The conformer **23** can be equalized to the conformer **20** by proper rotations and bond rotations.

It should be noted that the action of the permutation (1 4)(2 6)(3 5) on **20** produces a conformer **24** with a different mode of numbering. However, the permutation (1 4)(2 6)(3 5) is not involved in the lists of tables 3 and 4. This means that the resulting conformer **24** cannot be equalized within the group $\widehat{\mathbf{G}}$. The conformers **22** and **24** may be equalized by bond rotations if we postulate the condition of $1 = \overline{1}$, $2 = \overline{2}$, and $3 = \overline{3}$; however, this condition is not always satisfied.

The method illustrated by figure 10 can be applied to the case shown in figure 3, where the achirality is explained in a similar way to figure 10. It should be noted that the numbering can be altered without losing generality.

The method described in this subsection must examine various conformers of a nonrigid molecule in order to comprehend the stereoisomerism and the chirality/achirality of the molecule. In contrast, Fujita's proligand method does not directly take account of such conformation, because it regards nonrigid molecules as sophisticated combinations between promolecules (with proligands) and ligands (in isolation). It should be emphasized that the sophisticated combinations are controlled by the sphericity concept.

3. Pólya's corona for enumerating graphs

In contrast to Fujita's proligand method [24,25], Pólya's corona, which has been introduced along with Pólya's theorem in his famous article [6,7], enumerates chemical compounds as graphs, not as 3D chemical structures. Thus, Pólya's corona considers the permutation group of order 2:

$$\mathbf{G} = \{(1)(2), (1\ 2)\} \tag{23}$$

to specify the skeleton (**8**), which is characterized by a cycle index represented by

$$\mathrm{CI}(\mathbf{G}; \psi_k) = \tfrac{1}{2}\left(\psi_1^2 + \psi_2\right). \tag{24}$$

When we consider methyl ligands as substituents, the term ψ_k is represented by the following equation:

$$\psi_k = \tfrac{1}{6}\left(s_k^3 + 2s_{3k} + 3s_k s_{2k}\right), \tag{25}$$

where the methyl has **H**-symmetry:

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

By introducing equation (25) into the cycle index (equation (24)), we obtain an equation having dummy variables s_d:

$$\begin{aligned}\mathrm{CI}(\mathbf{G}[\mathbf{H}]; s_d) = {} & \tfrac{1}{72}s_1^6 + \tfrac{1}{18}s_1^3 s_3 + \tfrac{1}{12}s_1^4 s_2 + \tfrac{1}{18}s_3^2 \\ & + \tfrac{1}{6}s_1 s_2 s_3 + \tfrac{1}{8}s_1^2 s_2^2 + \tfrac{1}{12}s_2^3 + \tfrac{1}{6}s_6 + \tfrac{1}{4}s_2 s_4.\end{aligned} \tag{26}$$

The dummy variables s_d in equation (26) are replaced by the following inventories:

$$s_d = X^d + Y^d + Z^d, \tag{27}$$

where each methyl ligand accommodates three atoms selected from X, Y, and Z. By expanding the resulting equation, we obtain the following generating function:

$$\begin{aligned} f' = {} & (X^6 + Y^6 + Z^6) + (X^5Y + X^5Z + XY^5 + XZ^5 + Y^5Z + YZ^5) \\ & + 2(X^4Y^2 + X^4Z^2 + Y^4Z^2 + X^2Y^4 + X^2Z^4 + Y^2Z^4) \\ & + 2(X^4YZ + XY^4Z + XYZ^4) \\ & + 3(X^3Y^2Z + X^3YZ^2 + X^2Y^3Z + X^2YZ^3 + XY^3Z^2 + XY^2Z^3) \\ & + 2(X^3Y^3 + X^3Z^3 + Y^3Z^3) + 4X^2Y^2Z^2. \end{aligned} \tag{28}$$

The coefficient of each term $X^xY^yZ^z$ $(x + y + z = 6)$ in equation (28) represents the number of isomers (as graphs) with x of X, y of Y, and z of Z. It should be noted that the coefficients collected in equation (28) have been obtained by using Pólya's corona.

The introduction of the inventory (equation 27) into the intermediate equation (equation (25)) under the condition of $k = 1$ produces the following equation:

$$\psi_1 = X^3 + X^2Y + XY^2 + Y^3 + X^2Z + XYZ + Y^2Z + XZ^2 + YZ^2 + Z^3, \tag{29}$$

where each term on the right-hand side of equation (29) shows the type of a ligand to be considered. Because the coefficient of the term XYZ in equation (29) is equal to 1, the corresponding chiral ligands R-CXYZ and S-CXYZ are equalized to be one graph.

4. 3D Structures versus graphs

Fujita's proligand approach uses a CI-CF (such as equation (8)) which is introduced by three inventories (such as equations (11)–(13)) to produce an intermediate equation (e.g., (14)). On the other hand, Pólya's corona uses a cycle index (such as equation (24)) and a single inventory (such as equation (25)) to produce an intermediate equation (e.g., (26)). This difference results in the difference of isomer numbers, which is found by comparing the coefficient of each term in the generating function (equation (16)) due to Fujita's proligand method and the corresponding one in the generating function (equation (28)) due to Pólya's corona. Thus the two generating functions are different in the coefficients of the term $X^2Y^2Z^2$.

The factorization of each term into two factors is informative, as shown for the term $X^2Y^2Z^2$ in table 5. This term can be factorized into four modes, each of which corresponds to a graph enumerated in equation (28) of Pólya's corona $(4X^2Y^2Z^2)$. The graph (**5**) shown in figure 4 is counted once to give the value 1 at the intersection between the $XYZ \times XYZ$-row an the last column in table 5.

On the other hand, Fujita's proligand method gives the coefficient 5 of $X^2Y^2Z^2$ (equation (16)), which are ascribed to the categorization of isomers collected in the third column of table 5. Table 5 (the second column) also contains

Table 5
Factorization of the term $X^2Y^2Z^2$ for ethane.

Factors	Promolecule type (figure 7)	Isomer number due to Fujita's proligand approach (equation (16))	Isomer number due to Pólya's corona (equation (28))
$X^2Y \times YZ^2$	AB	1	1
$X^2Z \times Y^2Z$	AB	1	1
$XY^2 \times XZ^2$	AB	1	1
$XYZ \times XYZ$	$p^2(\overline{p}^2)$, $p\overline{p}$	2	1
Total for $X^2Y^2Z^2$		5	4

the promolecule type of each mode of factorization. Because a pair of enantiomers is counted once in this method, a pair of p^2 and $\overline{p}^2$ is regarded as one isomer. Obviously, the meso-isomer $p\overline{p}$ is counted once. Thus, the pair of enantiomers (**6** and $\overline{\mathbf{6}}$) and the meso-isomer (**7**) shown in figure 5 are counted to give the value 2 at the $XYZ \times XYZ$-row of table 5. Note that XYZ corresponds to a chiral proligand p or $\overline{p}$.

5. Conclusion

Fujita's proligand method is applied to the enumeration of ethane derivatives, where a promolecule is regarded as a skeleton having proligands and a molecule is produced by replacing each proligand by methyl ligands. The enumeration results are compared with those derived by Pólya's corona. Fujita's proligand method is capable of stereoisomers, while Pólya's corona enumerates graphs, but not stereoisomers.

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