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Graphs to chemical structures 1. Sphericity indices of cycles for stereochemical extension of Pólya’s theorem

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Abstract. Pólya’s theorem has been concluded to be concerned with graphs, but not with chemical structures, where it is incapable of treating chiral ligands properly. In order to take account of chiral ligands along with achiral ones, coset representations (CRs) for cyclic subgroups have been examined to classify permutations of the CRs into proper and improper elements. As a result, a *k*-cycle contained in each permutation has been classified into an enantiospheric, homospheric, or hemispheric one. Thereby, sphericity indices of *k*-cycles have been defined according to the enantiospheric, homospheric, or hemispheric nature of each *k*-cycle. On the basis of the sphericity indices, cycle indices with chirality fittingness (CIs-CF) have been defined in place of Pólya’s cycle indices. The CIs-CF have been proved to be capable of enumerating of stereoisomers with chiral and achiral ligands. Their capabilities have been confirmed by using allene derivatives as examples.

Keywords: Cycle index—Chirality fittingness—Sphericity index—Pólya’s theorem

1. Introduction

As found in the title of Pólya’s original paper “Kombinatorische Anzahlbestimmungen für Gruppen, Graphen und chemische Verbindungen” [1] (translated later into English as “Combinatorial enumeration of groups, graphs, and chemical compounds” [2]), combinatorial enumeration for chemistry has been based on a presumption that chemical compounds can be regarded as kinds of graphs. Many graph-theoretical studies have been conducted according to this presumption, where each atom or ligand occupying a vertex (node) of a graph has been implicitly considered to be structureless, as implicated in books [3, 4, 5] and reviews [6, 7, 8]. Although the presumption has not been explicitly discussed in such graph-theoretical studies, its involvement can be exemplified if ligands with inner structure (e.g., chiral/achiral ligands) are taken into consideration. If we rely on Pólya’s theorem, for example, an enantiomeric relationship between tetrahedral molecules with achiral ligands A, B, C, and D cannot be discriminated from a diastereomeric relationship between tetrahedral molecules with $\mathrm{ABp\overline{p}}$, where ligands A and B are achiral and p and $\overline{\mathrm{p}}$ are enantiomeric in isolation. As a result, the two isomers (enantiomers) with ABCD are counted once and the isomers (diastereomers) with $\mathrm{ABp\overline{p}}$ are also counted once on the action of the symmetric group of degree 4. Obviously, the latter should be counted twice from a stereochemical point of view, as they are well known to be a pseudo-asymmetric case. Thus, Pólya’s theorem based on the graph-theoretical approach has turned out to disregard such inner structures as the chirality/achirality of ligands.

In order to treat the chirality/achirality of ligands, several approaches have been reported. One approach has been based on double cosets of permutation groups [9], which have been extended to be applied to further elaborate cases [10, 11].

An alternative approach which we have reported as the unit-subduced-cycle-index approach (USCI) [12] was based on the subduction of coset representations. In this approach, we clarified that the sphericity of an orbit is important to stereochemical discussions when taking account of the chirality/achirality of ligands [13, 14] and that the chirality fittingness (CF) due to the sphericity produces the USCIs with CF, which can be applied to combinatorial enumerations [15]. As an extension of the USCI approach, we have reported the subduction of dominant representations [16], which has been clarified to produce cycle indices (CIs) equivalent to those genereated by Pólya’s theorem. A further approach reported by us [17, 18] was based on the subduction of **Q**-conjugacy representations, which has generated characteristic monomials (CMs) for combinatorial enumeration. The CIs derived from the USCIs and the CMs derived from the the subduction of **Q**-conjugacy representations

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can be combined with the sphericity concept so as to produce CIs with CF (CIs-CF) and CMs with CF [19]. Thereby, we have been able to conduct combinatorial enumeration of isomers with chiral and achiral ligands.

The approaches described in the preceding paragraph have an apparent disadvantage that they use conjugate subgroups in their formulations. Such conjugate subgroups can be derived from group–subgroup relationships, which are usually difficult to obtain. On the other hand, a merit of Pólya's theorem is ascribed to the fact that it uses conjugacy classes but not conjugate subgroups in its formulation. The specification of conjugacy classes is generally easier than that of conjugate subgroups. This merit should be taken into consideration in cases of brief calculations of isomer numbers, even though the enumerations due to Pólya's theorem are only concerned with molecular formulas but not with point-group symmetries.

In this paper, the original definition of the sphericity concept will be reexamined in terms of conjugacy classes so that Pólya's theorem will be extended substantially by combining it with the sphericity concept. This new formulation will provides us with a revolution in our stereochemical viewpoints, i.e., from graphs to chemical structures.

2. Mathematical formalism

2.1. *Conjugacy classes and cyclic subgroups*

Let $\mathbf{G}(/\mathbf{G}_i)$ be a coset representation of a point group $\mathbf{G}$, where $\mathbf{G}_i$ is a subgroup of $\mathbf{G}$. The coset representation $\mathbf{G}(/\mathbf{G}_i)$ can be regarded as a permutation group $\mathbf{P}$ of degree $n = |\mathbf{G}|/|\mathbf{G}_i|$, if the coset representation is faithful[1]. In this paper, we will mainly consider such faithful cases. But the discussions in this paper hold true for unfaithful cases in which the order of $\mathbf{P}$ is not always equal to the order of $\mathbf{G}$. Moreover, the following discussions do not lose generality for cases in which the $\mathbf{P}$ corresponds to a sum of such coset representations, although the present approach takes account of one coset representation.

An element P of $\mathbf{P}$ is a permutation of degree n, which is represented by a cycle decomposition involving the number $v_k(P)$ of k-cycles. Note that Pólya's theorem puts $z(P) = s_1^{v_1(P)} s_2^{v_2(P)} \cdots s_n^{v_n(P)}$, where $s_1, s_2, \ldots, s_n$ are dummy variables. It should be emphasized that Pólya's theorem does not discriminate whether the element P corresponds to a proper rotation or an improper one. In other words, Pólya's theorem does not take chiral ligands into consideration.

On the other hand, because the present approach equalizes $\mathbf{P}$ to the coset representation $\mathbf{G}(/\mathbf{G}_i)$, each element P of $\mathbf{P}$ corresponds to a proper or an improper rotation of the point group $\mathbf{G}$ through $\mathbf{G}(/\mathbf{G}_i)$. The element P is called a *proper element* if it corresponds to a proper rotation of $\mathbf{G}$, and called an *improper element* if it corresponds to an improper rotation of $\mathbf{G}$. Such an improper element is represented by a product of cycles with overlines, which emphasize the change of the chirality of each ligand to the opposite chirality.

Let the cycle decomposition of an improper element P of $\mathbf{P}$ be represented by the number $v_k(P)$ of k-cycles, where we place $k = 1, 2, \ldots, n$ and $n = |\mathbf{G}|/|\mathbf{G}_i|$. When the order of the element P is equal to ℓ, the element P generates a cyclic subgroup:

$$\mathbf{P}_\ell = \{P^1, P^2, \ldots P^\ell\}. \tag{1}$$

Because the element of P corresponds to an improper rotation, P^j corresponds to an improper rotation if the integer j is odd, while it corresponds to a proper rotation if the integer j is even. Because the resuting cyclic subgroup $\mathbf{P}_\ell$ corresponds to an achiral cyclic subgroup $\mathbf{S}_\ell$ of $\mathbf{G}$, it contains $\ell/2$ proper elements and the same number of improper elements; hence, the integer ℓ is concluded to be even.

The achiral cyclic subgroup $\mathbf{S}_\ell$ contains the maximum chiral subgroup $\mathbf{C}_{\ell/2}$, the order of which is half of $\mathbf{S}_\ell$. Let us place $\ell = 2\ell_1\ell_2$, where the integer ℓ_1 is odd or even ($\ell_1 \geq 1$) and the integer ℓ_2 is odd ($\ell_2 \geq 1$). The ℓ_1 can be further represented by $\ell_1 = 2^m\ell_3$, where $m(\geq 0)$ is an integer and ℓ_3 is an odd number ($\ell_3 \geq 1$). Note that the power m is selected so that 2^m is the largest divisor of ℓ_1 to leave the odd number ℓ_3 as a divisor. Thereby, we can place $\ell = 2 \times 2^m\ell_3\ell_2$, where ℓ_3 and ℓ_2 are odd integers. There are only two cases as follows:

1. Let us consider ℓ' that is a divisor of $\ell/2$ $(= 2^m\ell_3\ell_2)$. Then ℓ/ℓ' is an even number. Since the order of the maximum chiral subgroup $\mathbf{C}_{\ell/2}$ is $\ell/2$ $(= 2^m\ell_3\ell_2)$, the resulting cyclic group $\mathbf{C}_{\ell'}$ is a subgroup of $\mathbf{C}_{\ell/2}$. Because $\mathbf{C}_{\ell/2}$ is chiral, its subgroup $\mathbf{C}_{\ell'}$ is also chiral. It follows that the corresponding coset representation $\mathbf{S}_\ell(/\mathbf{C}_{\ell'})$ is enantiospheric, where the degree $|\mathbf{S}_\ell|/|\mathbf{C}_{\ell'}|$ is equal to the even number ℓ/ℓ'.
2. Let us place $\ell'' = 2\ell_1 = 2 \times 2^m\ell_3$. Since we have placed $\ell = 2\ell_1\ell_2 = 2 \times 2^m\ell_3\ell_2$, the number ℓ'' is not a divisor of $\ell/2$ $(= 2^m\ell_3\ell_2)$. It follows that a cyclic subgroup of order ℓ'' ($\mathbf{S}_{\ell''}$) is not a subgroup of the maximum chiral subgroup $\mathbf{C}_{\ell/2}$. This means that $\mathbf{S}_{\ell''}$ is an achiral group. Hence, the corresponding coset representation $\mathbf{S}_\ell(/\mathbf{S}_{\ell''})$ is homospheric, where the degree $|\mathbf{S}_\ell|/|\mathbf{S}_{\ell''}|$ is equal to an odd number $\ell/\ell''(= \ell_2)$.

2.2. *Sphericities of k-cycles*

Let us next examine a k-cycle contained in the improper element P. In general, the k-cycle generates a cyclic subgroup $\mathbf{C}_k$ of order k, where k is equal to ℓ or to a divisor of ℓ. Since the cylic group $\mathbf{C}_k$ is homomorphic to the cyclic group P, the identity element of $\mathbf{C}_k$ corresponds to the kernel of homomorphism $\mathbf{N}$ in $\mathbf{P}_\ell$ $(= \mathbf{S}_\ell)$. The kernel $\mathbf{N}$ is a normal subgroup of $\mathbf{P}_\ell$, where the order of $\mathbf{N}$ is equal to $\ell' = |\mathbf{P}_\ell|/|\mathbf{C}_k| = \ell/k$, as shown in

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[1] For example, a square-planar complex of $\mathbf{D}_{4h}$ symmetry is controlled by a permutation group isomorphic to $\mathbf{D}_4$, if no chiral ligands are taken into consideration. This is an apparent unfaithful case. If chiral and achiral ligands are taken into consideration, however, the four-positions of the square-planar complex are governed by the coset representation $\mathbf{D}_{4h}(/\mathbf{C}''_{2v})$. For a more detailed discussion, see Ref. [20]. Such a symbol as $|\mathbf{G}|$ represents the order of the group $\mathbf{G}$.

theorem 13.2 of Ref. [12]. Note that $\mathbf{N}$ is also a cyclic subgroup of $\mathbf{P}_\ell$.

Lemma 1 If k is an even number, the k-cycle in an improper element P corresponds to an enantiospheric coset representation. Such a k-cycle as contained in an improper element is here called *enantiospheric k-cycle*, if k is even.

Proof If k is an even number, we can consider the cyclic subgroup $\mathbf{C}_{\ell'}(=\mathbf{N})$ described previously, where we place $\ell' = \ell/k$. Then, the k-cycle corresponds to the coset representation $\mathbf{S}_\ell(/\mathbf{C}_{\ell'})$, where its degree is calculated to be $|\mathbf{S}_\ell|/|\mathbf{C}_{\ell'}| = \ell/\ell' = \ell/(\ell/k) = k$. Since k is an even number, the coset representation $\mathbf{S}_\ell(/\mathbf{C}_{\ell'})$ is enantiospheric.

Lemma 2 If k is an odd number, the k-cycle in an improper element P corresponds to a homospheric coset representation. Such a k-cycle as contained in an improper element is here called *homospheric k-cycle*, if k is odd.

Proof If k is an odd number, we can consider the cyclic subgroup $\mathbf{S}_{\ell''}(=\mathbf{N})$ described previously, where we place $\ell'' = \ell/k$. Then, the k-cycle corresponds to the coset representation $\mathbf{S}_\ell(/\mathbf{S}_{\ell''})$, where its degree is calculated to be $|\mathbf{S}_\ell|/|\mathbf{S}_{\ell''}| = \ell/\ell'' = \ell/(\ell/k) = k$. Since k is an odd number, the coset representation $\mathbf{S}_\ell(/\mathbf{S}_{\ell''})$ is homospheric.

Obviously, a k-cycle in a proper element of $\mathbf{P}$ always corresponds to a hemispheric coset representation, whether k is even or odd. Such a k-cycle as contained in a proper element is here called a *hemispheric k-cycle*.

2.3. CF and sphericity indices

According to lemmas 1 and 2, one of the sphericity indices is ascribed to each of the cases described earlier:

1. An enantiospheric k-cycle in an improper element (i.e., k is even) is ascribed to a sphericity index c_k. Such an enantiospheric k-cycle can act on a set of k achiral ligands of the same kind to maintain the symmetry of the ligand set. Moreover, it can act on a set of $k/2$ chiral ligands (p) of the same kind and $k/2$ of their enantiomeric ligands ($\overline{\mathrm{p}}$), where the following two ways of packing maintain the symmetry of the ligand set to be invariant, as shown in Fig. 1.
2. A homospheric k-cycle in an improper element (i.e., k is odd) is ascribed to a sphericity index a_k. Such a homospheric k-cycle can act on a set of k achiral ligands of the same kind to maintain the symmetry of the ligand set to be invariant. It is incapable of acting on a set of chiral ligands.
3. A hemispheric k-cycle is ascribed to a sphericity index b_k, whether k is even or odd. Such a hemispheric k-cycle can act on a set of k achiral ligands as well as a set of k chiral ligands to maintain the symmetry of the ligand set to be invariant.

$$\underbrace{\begin{array}{|c|c|c|c|}\hline \mathrm{p} & \mathrm{p} & \cdots & \mathrm{p} \\ \hline \overline{\mathrm{p}} & \overline{\mathrm{p}} & \cdots & \overline{\mathrm{p}} \\ \hline \end{array}}_{k/2} \qquad \underbrace{\begin{array}{|c|c|c|c|}\hline \overline{\mathrm{p}} & \overline{\mathrm{p}} & \cdots & \overline{\mathrm{p}} \\ \hline \mathrm{p} & \mathrm{p} & \cdots & \mathrm{p} \\ \hline \end{array}}_{k/2}$$

Fig. 1. Two modes of ligand packing for an enantiospheric k-cycle

Thus, the sphericity indices a_k, c_k, and b_k control modes of ligand packing, which are equivalent to those due to CF proposed previously [12,13]. Thereby, we define a CI-CF by using the sphericity indices a_k, c_k, and b_k.

2.4. CIs-CF for combinatorial enumeration

Let $\mathbf{P}$ be a coset representation of a point group, as described earlier. An element P of $\mathbf{P}$ is a permutation of degree n, which is represented by a cycle decomposition involving the number $\nu_k(P)$ of k-cycles ($\sum_{k=1}^{n} k\nu_k(P)$). Each of the k-cycles corresponds to a sphericity index $\$_k$, where $\$_k$ is a_k if P is an improper element and k is odd, $\$_k$ is c_k if P is an improper element and k is even, and $\$_k$ is b_k if P is a proper element. Hence, the element P corresponds to a product of sphericity indices $\$_1^{\nu_1(P)}\$_2^{\nu_2(P)}\cdots\$_n^{\nu_n(P)}$. Thereby, a CI-CF for the present case is defined as follows:

$$\mathrm{CI-CF}(\mathbf{P};\$_\mathrm{d}) = \frac{1}{|\mathbf{P}|}\sum_{\mathrm{P}\in\mathbf{P}} \$_1^{\nu_1(\mathrm{P})}\$_2^{\nu_2(\mathrm{P})}\cdots\$_\mathrm{n}^{\nu_\mathrm{n}(\mathrm{P})}, \tag{2}$$

where $\$_d$ is a_d if P is an improper element and d is odd, $\$_d$ is c_d if P is an improper element and d is even, and $\$_d$ is b_d if P is a proper element.

The discussions described in Chap. 13 of Ref. [12] hold true for the present case except that the sphericity indices are taken into consideration. Theorem 13.8 of Ref. [12] can be rewritten as an extended theorem for treating substitution with chiral ligands as well as achiral ones:

Theorem 1 *Let* $\mathbf{P}$ *be a coset representation of a point group, which governs a set* Δ *of n positions. Suppose that the cycle structure of* $P(\in\mathbf{P})$ *is represented by* $(1^{\nu_1(P)}2^{\nu_2(P)}\cdots n^{\nu_n(P)})$, *where* $\sum_{k=1}^{n} k\nu_k(P)$. *Each position of* Δ *is occupied by an achiral or a chiral ligand selected from a set of ligands,*

$$\mathbf{X} = \{\mathrm{x}_1, \mathrm{x}_2, \ldots, \mathrm{x}_n; \mathrm{p}_1, \mathrm{p}_2, \ldots, \mathrm{p}_n; \overline{\mathrm{p}}_1, \overline{\mathrm{p}}_2, \ldots, \overline{\mathrm{p}}_n\},$$

where each x_j *represents an achiral ligand and each pair of* p_j *and* $\overline{\mathrm{p}}_j$ *represents an enantiomeric pair of chiral ligands. Consider isomers having* θ_1 *of* x_1, θ_2 *of* $\mathrm{x}_2, \ldots, \theta_n$ *of* x_n; θ'_1 of p_1, θ'_2 *of* $\mathrm{p}_2, \ldots, \theta'_n$ of p_n; *and* θ''_1 *of* $\overline{\mathrm{p}}_1$, θ''_2 *of* $\overline{\mathrm{p}}_2, \ldots$ θ''_n *of* $\overline{\mathrm{p}}_n$, *where*

$$\begin{aligned}[\theta] :&\theta_1 + \theta_2 + \cdots + \theta_n + \\ &\theta'_1 + \theta'_2 + \cdots + \theta'_n + \\ &\theta''_1 + \theta''_2 + \cdots + \theta''_n = n.\end{aligned} \tag{3}$$

Let the symbol B_θ *denote the number of isomers of such isomers as having* $[\theta]$. *A generating function for calculating* B_θ *is represented by*

$$\begin{aligned}&\sum_{[\theta]} B_\theta \mathrm{x}_1^{\theta_1}\mathrm{x}_2^{\theta_2}\cdots\mathrm{x}_n^{\theta_n}\mathrm{p}_1^{\theta'_1}\mathrm{p}_2^{\theta'_2}\cdots\mathrm{p}_n^{\theta'_n}\overline{\mathrm{p}}_1^{\theta''_1}\overline{\mathrm{p}}_2^{\theta''_2}\cdots\overline{\mathrm{p}}_n^{\theta''_n} \\ &= \mathrm{CI-CF}(\mathbf{P}; \$\_\mathrm{d}),\end{aligned} \tag{4}$$

where the summation is concerned with all of the partitions ($[\theta]$) *shown in Eq. (3). The sphericity indices* $\$_d$ *in the CI-CF are ligand inventories replaced by*

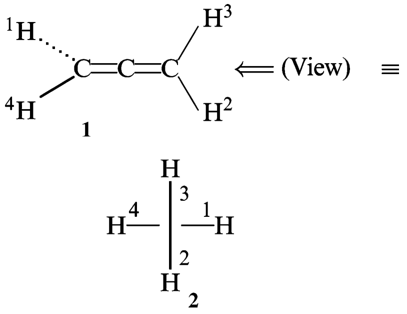

Fig. 2. Convention for drawing allene derivatives

$$a_d = x_1^d + x_2^d + \cdots + x_n^d, \tag{5}$$

$$c_d = x_1^d + x_2^d + \cdots + x_n^d + 2p_1^{d/2}\overline{p}_1^{d/2} + 2p_2^{d/2}\overline{p}_2^{d/2} + \cdots + 2p_n^{d/2}\overline{p}_n^{d/2}, \tag{6}$$

$$b_d = x_1^d + x_2^d + \cdots + x_n^d + p_1^d + p_2^d + \cdots + p_n^d + \overline{p}_1^d + \overline{p}_2^d + \cdots + \overline{p}_n^d. \tag{7}$$

3. Results of combinatorial enumeration

3.1. Enumeration based on theorem 1

As an example for showing the usefulness of this theorem, let us consider an allene skeleton belonging to a $\mathbf{D}_{2d}$ point group,

$$\{I, C_{2(3)}, C_{2(1)}, C_{2(2)}, \sigma_{d(1)}, \sigma_{d(2)}, S_4, S_4^3\},$$

where the four vertices are numbered from 1 to 4, as shown Fig. 2. For the sake of simplicity, the right diagram **(2)** is used in place of the right formula **(1)**.

Each element of the $\mathbf{D}_{2d}$ point group permutes the numbered positions and produces a permutation (cycles) shown in Table 1. The resulting set of permutations for all of the elements is identical with a coset representation $\mathbf{D}_{2d}(/\mathbf{C}_s)$, which has been described previously [12].

Lemmas 1 and 2 determine the sphericities of every k-cycles, which produce a product of sphericity indices, as summarized in Table 1. By applying Eq. (2) to this case, the corresponding CI-CF is obtained as follows:

$$\mathrm{CI-CF}(\mathbf{D}_{2d}; a_d, b_d, c_d) = \frac{1}{8}b_1^4 + \frac{3}{8}b_2^2 + \frac{1}{4}a_1^2c_2 + \frac{1}{4}c_4. \tag{8}$$

Note that $|\mathbf{D}_{2d}|$ is equal to 8. This CI-CF is identical with the ones obtained alternatively by the USCI approach (theorem 19.5 of Ref. [12]) and by the CM method [19][2].

Suppose that the four positions of the allene skeleton (**1** or **2**) are substituted by a set of four atoms selected from a set of achiral ligands:

$$L_a = \{\ \mathrm{A},\ \mathrm{B},\ \mathrm{X},\ \mathrm{Y}\} \tag{9}$$

and a set of chiral ligands:

$$L_c = \{\ p,\ \overline{p},\ q,\ \overline{q},\ r,\ \overline{r},\ s,\ \overline{s},\ \}, \tag{10}$$

Table 1. Product of sphericity indices for allene

Element		Permutation (cycles), $\mathbf{D}_{2d}(/\mathbf{C}_s)$	Type of rotation	Product of sphericity indices
I	~	(1)(2)(3)(4)	Proper	b_1^4
$C_{2(3)}$	~	(1 4)(2 3)	Proper	b_2^2
$C_{2(1)}$	~	(1 2)(3 4)	Proper	b_2^2
$C_{2(2)}$	~	(1 3)(2 4)	Proper	b_2^2
$\sigma_{d(1)}$	~	$\overline{(1)(2\ 3)(4)}$	Improper	$a_1^2c_2$
$\sigma_{d(2)}$	~	$\overline{(1\ 4)(2)(3)}$	Improper	$a_1^2c_2$
S_4	~	$\overline{(1\ 2\ 4\ 3)}$	Improper	c_4
S_4^3	~	$\overline{(1\ 3\ 4\ 2)}$	Improper	c_4

where the symbols with and without an overline represent a pair of enantiomeric ligands.

According to Eqs. (5), (6), and (7), the ligand inventories for this case are obtained to be

$$a_d = \mathrm{A}^d + \mathrm{B}^d + \mathrm{X}^d + \mathrm{Y}^d, \tag{11}$$

$$c_d = \mathrm{A}^d + \mathrm{B}^d + \mathrm{X}^d + \mathrm{Y}^d + 2p^{d/2}\overline{p}^{d/2} + 2q^{d/2}\overline{q}^{d/2} + 2r^{d/2}\overline{r}^{d/2} + 2s^{d/2}\overline{s}^{d/2}, \tag{12}$$

$$b_d = \mathrm{A}^d + \mathrm{B}^d + \mathrm{X}^d + \mathrm{Y}^d + p^d + \overline{p}^d + q^d + \overline{q}^d + r^d + \overline{r}^d + s^d + \overline{s}^d. \tag{13}$$

The inventories (Eqs. 11, 12, 13) are introduced into the CI-CF (Eq. 8) and the resulting equation is expanded to give a generating function:

$$\begin{aligned}
f =& \mathrm{CI-CF}(\mathbf{D}_{2d}; a_d, b_d, c_d) \\
=& (\mathrm{A}^4 + \mathrm{B}^4 + \cdots) + (\mathrm{A}^3\mathrm{B} + \mathrm{A}^3\mathrm{X} + \cdots) \\
&+ \frac{1}{2}[(\mathrm{A}^3p + \mathrm{A}^3\overline{p}) + (\mathrm{A}^3q + \mathrm{A}^3\overline{q}) + \cdots] \\
&+ 2(\mathrm{A}^2\mathrm{B}^2 + \mathrm{A}^2\mathrm{X}^2 + \cdots) \\
&+ 2(\mathrm{A}^2\mathrm{BX} + \mathrm{A}^2\mathrm{BY} + \cdots) \\
&+ \frac{3}{2}[(\mathrm{A}^2\mathrm{B}p + \mathrm{A}^2\mathrm{B}\overline{p}) + (\mathrm{A}^2\mathrm{B}q + \mathrm{A}^2\mathrm{B}\overline{q}) + \cdots] \\
&+ \frac{3}{2}[(\mathrm{A}^2p^2 + \mathrm{A}^2\overline{p}^2) + (\mathrm{A}^2q^2 + \mathrm{A}^2\overline{q}^2) + \cdots] \\
&+ 2(\mathrm{A}^2p\overline{p} + \mathrm{A}^2q\overline{q} + \cdots) \\
&+ \frac{3}{2}[(\mathrm{A}^2pq + \mathrm{A}^2\overline{pq}) + (\mathrm{B}^2pq + \mathrm{B}^2\overline{pq}) + \cdots] \\
&+ 3\mathrm{ABXY} \\
&+ \frac{6}{2}[(\mathrm{ABX}p + \mathrm{ABX}\overline{p}) + (\mathrm{ABX}q + \mathrm{ABX}\overline{q}) + \cdots] \\
&+ \frac{3}{2}[(\mathrm{AB}p^2 + \mathrm{AB}\overline{p}^2) + (\mathrm{AB}q^2 + \mathrm{AB}\overline{q}^2) + \cdots] \\
&+ 4(\mathrm{AB}p\overline{p} + \mathrm{AB}q\overline{q} + \cdots) \\
&+ \frac{6}{2}[(\mathrm{AB}pq + \mathrm{AB}\overline{pq}) + (\mathrm{AX}pq + \mathrm{AX}\overline{pq}) + \cdots] \\
&+ \frac{1}{2}[(\mathrm{A}p^3 + \mathrm{A}\overline{p}^3) + (\mathrm{A}q^3 + \mathrm{A}\overline{q}^3) + \cdots] \\
&+ \frac{3}{2}[(\mathrm{A}p^2\overline{p} + \mathrm{A}p\overline{p}^2) + (\mathrm{A}q^2\overline{q} + \mathrm{A}q\overline{q}^2) + \cdots] \\
&+ \frac{3}{2}[(\mathrm{A}p^2q + \mathrm{A}\overline{p}^2\overline{q}) + (\mathrm{B}p^2q + \mathrm{B}\overline{p}^2\overline{q}) + \cdots] \\
&+ \frac{6}{2}[(\mathrm{A}p\overline{p}q + \mathrm{A}p\overline{pq}) + (\mathrm{B}p\overline{p}q + \mathrm{B}p\overline{pq}) + \cdots] \\
&+ \frac{6}{2}[(\mathrm{A}pqr + \mathrm{A}\overline{pqr}) + (\mathrm{B}pqr + \mathrm{B}\overline{pqr}) + \cdots] \\
&\cdots.
\end{aligned} \tag{14}$$

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[2] The term $(1/4)b_4$ in Eq. (44) of Ref. [19] should read $(1/4)c_4$, as shown in Eq. (8) of the present article

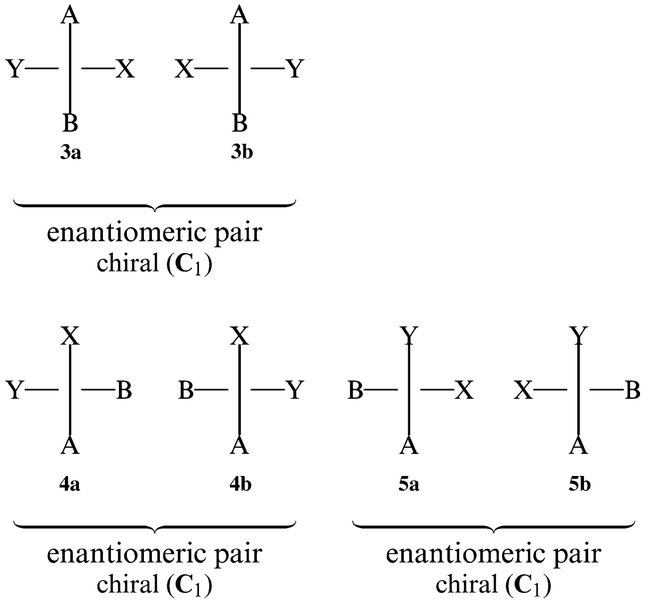

Fig. 3. Allene derivatives with the formula ABXY

Note that each coefficient indicates the number of isomers for achiral derivatives or the number of enantiomeric pairs for chiral derivatives. For example, the term $\frac{1}{2}(A^3p + A^3\overline{p})$ shows one pair of enantiomers (A^3p and $A^3\overline{p}$). These values are consistent with those derived by an alternative method, which were reported in Chapt. 21 of Ref. [12][3].

3.2. Enumerated isomers for testing the present approach

3.2.1. Isomers with achiral ligands only

As an example of isomers having achiral ligands only, let us examine the term ABXY in Eq. (14), where the coefficient of the term ABXY is equal to 3. According to this result, we can depict three isomers shown in Fig. 3, i.e., **3a** (paired with **3b**), **4a** (paired with **4b**), and **5a** (paired with **5b**). Stereochemically speaking **3a** (paired with **3b**) is a constitutional isomer with **4a** (paired with **4b**) and **5a** (paired with **5b**). The isomers **4a** (paired with **4b**) and **5a** (paired with **5b**) are in diastereomeric relationship with each other.

3.2.2. Isomers with chiral and achiral ligands

On the other hand, we encounter more complicated cases if we take account of chiral ligands along with achial ligands. For example, the coefficient of the term $ABp\overline{p}$ is equal to 4 in Eq. (14). Thus, we can depict four isomers, as shown in Fig. 4, i.e., **6**, **7**, **8a** (paired with **8b**), and **9a** (paired with **9b**).

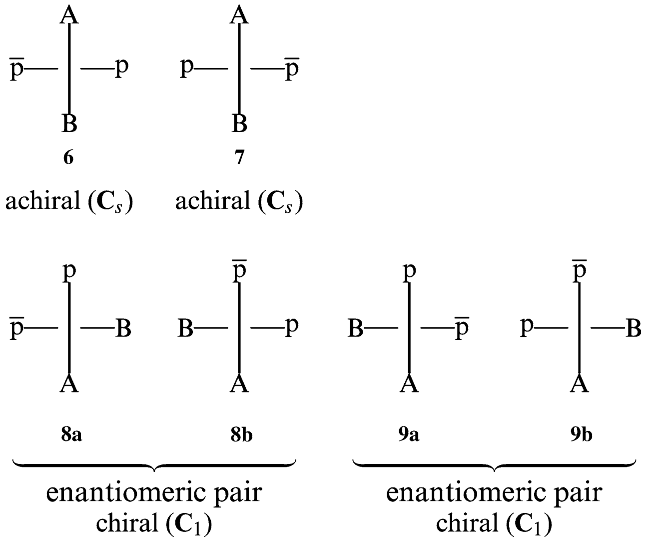

Fig. 4. Allene derivatives with the formula $ABp\overline{p}$

The two isomers **6** and **7** in the top row of Fig. 4 are achiral so that they are converted into themselves (or homomers) by all of the elements of $\mathbf{D}_{2d}$ (Table 1). As found easily, they are so-called "pseudo-asymmetric commpounds", since they are determined to be diastereomeric to each other, where the improper elements of $\mathbf{D}_{2d}$ (Table 1) invert the skeleton chirality as well as the ligand chirality. Note that **6** is converted into **7** and vice versa, if the inversion of the ligand chirality is not taken into consideration.

The isomers **8a** (paired with **8b**) and **9a** (paired with**9b**) in the bottom row of Fig. 4 are respectively chiral, where the improper elements of $\mathbf{D}_{2d}$ (Table 1) cause the reflection between **8a** and **8b** or between **9a** and **9b**. The relationship between **8a** (paired with **8b**) and **9a** (paired with **9b**) in the bottom row is determined to be diastereomeric. The relationship between the top row and the bottom row is determined to be constitutionally isomeric.

4. Comparison of Pólya's theorem with theorem 1

4.1. Pólya's theoerm as a special case of theorem 1

As found in the formulation described previously, Pólya's theorem is a special case of theorem 1, where it takes account of achiral ligands only. Thus, the sphericity indices of three kinds (a_d, c_d, and b_d) in Eq. (2) are neglected to generate a dummy variable of a single kind (s_d) so that Eq. (2) is converted into the following Pólya's CI:

$$\mathrm{CI}(\mathbf{P}; \mathrm{s_d}) = \frac{1}{|\mathbf{P}|} \sum_{\mathrm{P} \in \mathbf{P}} \mathrm{s}_1^{\nu_1(\mathrm{P})} \mathrm{s}_2^{\nu_2(\mathrm{P})} \cdots \mathrm{s}_n^{\nu_n(\mathrm{P})}, \tag{15}$$

where **P** represents a permutation group that comprises usual permutations. where **P** represents a permutation

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[3] The value listed at the intersection between the $ABp\overline{p}$ row and the $\mathbf{C}_s$ column of Table 21.3 (Ref. [12]) should read 2. The corresponding structural formulas have been correctly depicted as structures **53** and **54**. Equation (48) of Ref. [19] contains erroneous terms. The term $(1/2)(Ap^2q\cdots)$ should read $(3/2)(Ap^2q\cdots)$ and the term $A^2q\overline{p}$ should read $A^2q\overline{q}$, as shown in Eq. (14) of the present article.

group that comprises usual permutations. Note that no rotoreflections are taken into consideration. Moreover, the three ligand inventories (Eqs. 5, 6, 7) are replaced by a single ligand inventory as follows:

$$s_d = \mathrm{x}_1^d + \mathrm{x}_2^d + \cdots + \mathrm{x}_n^d. \tag{16}$$

The comparison of the present formulation (based on Eqs. 2, 5, 6, 7) with Pólya's theorem (based on eq. 15 and eq. 16) indicates the scope and limitations of graph-thereoretical approaches [2, 4] and of permutation-group approaches [21, 22], where ligands on vertices or nodes of a graph are regarded as points or structureless objects. In other words, chiral ligands (or other objects having structure) are not taken into consideration. Hence, these approaches are insufficient to discuss stereochemistry that is concerned with compounds having both achiral and chiral ligands.

This point can directly be confirmed by the fact that Eq. (16) for Pólya's theorem has the same form as Eq. (5) for the present formulation.

4.2. Formal application of Pólya's theoerm to isomer counting by considering both achiral and chiral ligands

4.2.1. Other ligand inventories and generating functions

If the framework based on Pólya's theorem is formally applied to cases in which chiral ligands are involved, the following inventory may be used in place of Eq. (16).

$$\begin{aligned} s_d =& \mathrm{x}_1^d + \mathrm{x}_2^d + \cdots + \mathrm{x}_n^d + \\ & \mathrm{p}_1^d + \mathrm{p}_2^d + \cdots + \mathrm{p}_n^d + \overline{\mathrm{p}}_1^d + \overline{\mathrm{p}}_2^d + \cdots + \overline{\mathrm{p}}_n^d. \end{aligned} \tag{17}$$

However, this type of calculation results in the violation of CF, which has been discussed in our previous papers [14, 23].

To exemplify such violation of CF, we examine allene derivatives having chiral ligands by using Pólya's theorem. The permutation group **P** that is isomorphic to the point group $\mathbf{D}_{2d}$ of the allene skeleton is represented as follows:

$$\begin{aligned} \mathbf{P} =& \{(1)(2)(3)(4), (1\ 4)(2\ 3), (1\ 2)(3\ 4), (1\ 3)(2\ 4), \\ & (1)(2\ 3)(4), (1\ 4)(2)(3), (1\ 2\ 4\ 3), (1\ 3\ 4\ 2)\}. \end{aligned} \tag{18}$$

which are the same permutations but different in the absence of overlines (see Table 1).

By applying Eq. (15) to this case, the corresponding CI is obtained as follows:

$$\mathrm{CI}(\mathbf{P}; \mathrm{s_d}) = \frac{1}{8}s_1^4 + \frac{3}{8}s_2^2 + \frac{1}{4}s_1^2 s_2 + \frac{1}{4}s_4, \tag{19}$$

which is obtained by converting a_d, b_d, and c_d into s_d in Eq. (8). According to Eq. (17), the ligand inventory for this case is obtained to be

$$\begin{aligned} s_d =& \mathrm{A}^d + \mathrm{B}^d + \mathrm{X}^d + \mathrm{Y}^d + \\ & \mathrm{p}^d + \overline{\mathrm{p}}^d + \mathrm{q}^d + \overline{\mathrm{q}}^d + \mathrm{r}^d + \overline{\mathrm{r}}^d + \mathrm{s}^d + \overline{\mathrm{s}}^d. \end{aligned} \tag{20}$$

This inventory (Eq. 20) is introduced into the CI (Eq. 19) and the resulting equation is expanded to give a generating function:

$$\begin{aligned} f' =& \mathrm{CI}(\mathbf{P}; \mathrm{s_d}) \\ =& (\mathrm{A}^4 + \mathrm{B}^4 + \cdots) + (\mathrm{A}^3\mathrm{B} + \mathrm{A}^3\mathrm{X} + \cdots) \\ & + (\mathrm{A}^3\mathrm{p} + \mathrm{A}^3\overline{\mathrm{p}} + \mathrm{A}^3\mathrm{q} + \mathrm{A}^3\overline{\mathrm{q}} + \cdots) \\ & + 2(\mathrm{A}^2\mathrm{B}^2 + \mathrm{A}^2\mathrm{X}^2 + \cdots) \\ & + 2(\mathrm{A}^2\mathrm{BX} + \mathrm{A}^2\mathrm{BY} + \cdots) \\ & + 2(\mathrm{A}^2\mathrm{Bp} + \mathrm{A}^2\mathrm{B}\overline{\mathrm{p}} + \mathrm{A}^2\mathrm{Bq} + \mathrm{A}^2\mathrm{B}\overline{\mathrm{q}} + \cdots) \\ & + 2(\mathrm{A}^2\mathrm{p}^2 + \mathrm{A}^2\overline{\mathrm{p}}^2 + \mathrm{A}^2\mathrm{q}^2 + \mathrm{A}^2\overline{\mathrm{q}}^2 + \cdots) \\ & + 2(\mathrm{A}^2\mathrm{p}\overline{\mathrm{p}} + \mathrm{A}^2\mathrm{q}\overline{\mathrm{q}} + \cdots) \\ & + 2(\mathrm{A}^2\mathrm{pq} + \mathrm{A}^2\overline{\mathrm{pq}} + \mathrm{B}^2\mathrm{pq} + \mathrm{B}^2\overline{\mathrm{pq}} + \cdots) \\ & + 3\mathrm{ABXY} \\ & + 3(\mathrm{ABXp} + \mathrm{ABX}\overline{\mathrm{p}} + \mathrm{ABXq} + \mathrm{ABX}\overline{\mathrm{q}} + \cdots) \\ & + 2(\mathrm{ABp}^2 + \mathrm{AB}\overline{\mathrm{p}}^2 + \mathrm{ABq}^2 + \mathrm{AB}\overline{\mathrm{q}}^2 + \cdots) \\ & + 3(\mathrm{ABp}\overline{\mathrm{p}} + \mathrm{ABq}\overline{\mathrm{q}} + \cdots) \\ & + 3(\mathrm{ABpq} + \mathrm{AB}\overline{\mathrm{pq}} + \mathrm{AXpq} + \mathrm{AX}\overline{\mathrm{pq}} + \cdots) \\ & + (\mathrm{Ap}^3 + \mathrm{A}\overline{\mathrm{p}}^3 + \mathrm{Aq}^3 + \mathrm{A}\overline{\mathrm{q}}^3 + \cdots) \\ & + 2(\mathrm{Ap}^2\overline{\mathrm{p}} + \mathrm{Ap}\overline{\mathrm{p}}^2 + \mathrm{Aq}^2\overline{\mathrm{q}} + \mathrm{Aq}\overline{\mathrm{q}}^2 + \cdots) \\ & + 2(\mathrm{Ap}^2\mathrm{q} + \mathrm{A}\overline{\mathrm{p}}^2\overline{\mathrm{q}} + \mathrm{Bp}^2\mathrm{q} + \mathrm{B}\overline{\mathrm{p}}^2\overline{\mathrm{q}} + \cdots) \\ & + 3(\mathrm{Ap}\overline{\mathrm{p}}\mathrm{q} + \mathrm{Ap}\overline{\mathrm{pq}} + \mathrm{Bp}\overline{\mathrm{p}}\mathrm{q} + \mathrm{Bp}\overline{\mathrm{pq}} + \cdots) \\ & + 3(\mathrm{Apqr} + \mathrm{A}\overline{\mathrm{pqr}} + \mathrm{Bpqr} + \mathrm{B}\overline{\mathrm{pqr}} + \cdots) \cdots. \end{aligned} \tag{21}$$

4.2.2. Isomer equivalency

Let us now compare Eqs. (14) and (21) with respect to several representative cases.

1. Chiral isomers with achiral ligands only. As an example of isomers having achiral ligands only, let us compare the term ABXY in Eq. (21) with that in Eq. (14). The coefficient of the term ABXY is equal to 3 in Eq. (14) as well as in Eq. (21). This result based on Pólya's theorem is identical with the one based on theorem 1, since isomers with achiral ligands only are enumerated by Pólya's theorem. The three isomers have already been shown in Fig. 3, i.e., **3a** (paired with **3b**), **4a** (paired with **4b**), and **5a** (paired with **5b**).
2. Achiral isomers with achiral and chiral ligands. The coefficient of the term $\mathrm{ABp\overline{p}}$ is equal to 3 in Eq. (21), whereas the corresponding value is equal to 4 in Eq. (14). This is because the two isomers **6** and **7** among the isomers depicted in Fig. 4 are equalized to be counted as one isomer. Thus, **6** and **7** are interchangeable by the permutation (1 4)(2)(3), which was involved in the derivation of the CI (Eq. 15). Note that this permulation does not take a reflection of ligand chirality into consideration.
3. Chiral isomers with achiral and chiral ligands. In Eq. (14), the number of isomeric pairs of enantiomers is given by the coefficient of such a composite term as $(1/2)(\mathrm{ABp}^2 + \mathrm{AB}\overline{\mathrm{p}}^2)$. Hence the term $(3/2)(\mathrm{ABp}^2 + \mathrm{AB}\overline{\mathrm{p}}^2)$ in Eq. (14) means that there exist three pairs of enantiomers, as depicted in Fig. 5. Thus, we can find **10a** (paired with **10b**), **11a** (paired with **11b**), and **12a** (paired with **12b**). The two enantiomers of each

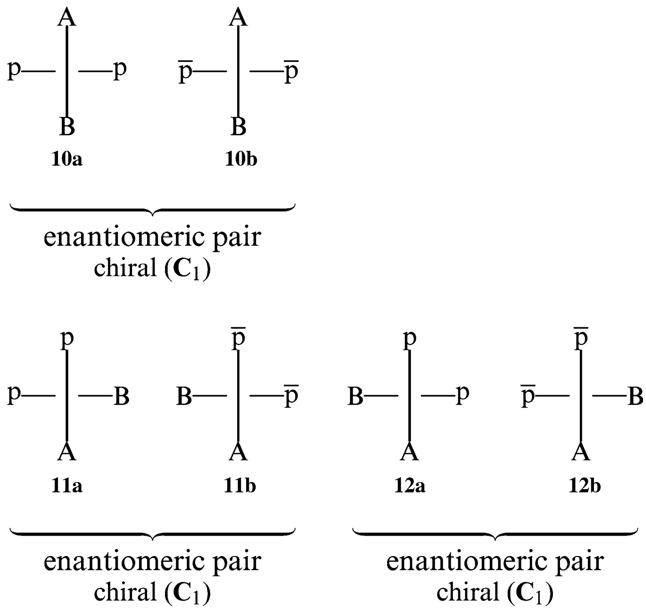

Fig. 5. Allene derivatives with the formula ABp^2 and $AB\overline{p}^2$

enantiomeric pair are interchangeable by the improper permutation $\overline{(1\;4)(2)(3)}$. The three pairs of enantiomers cannot be equalized by all of the permutations $[\mathbf{D}_{2d}(/\mathbf{C}_s)]$ listed in Table 1 so that they do not coincide with each other on the action of $\mathbf{D}_{2d}(/\mathbf{C}_s)$ but they are correlated to each other by the same composite term $(1/2)(ABp^2 + AB\overline{p}^2)$.

On the other hand, the coefficient of the term ABp^2 in Eq. (21) shows the presence of two molecules, which corresponds to **10a** as one molecule and a pair of diastereomers (**11a** and **12a**) as one molecule. In a similar way, the coefficient of the term $AB\overline{p}^2$ in Eq. (21) indicates the presence of two molecules, which corresponds to **10b** as one molecule and a pair of diastereomers (**11b** and **12b**). It should be noted that the two diastereomers of the pair (**11a/12a**) or of the pair (**11b/12b**) are equalized by the permutation $(1\;4)(2)(3)$. It follows that the action of **P** (Eq. 18) forces us to regard them as one molecule under the assumption of Pólya's theorem. Moreover, the pair (**11a/12a** for ABp^2) and the pair (**11b/12b** for $AB\overline{p}^2$) cannot be correlated to each other on the action of **P** (Eq. 18), although the two pairs are enantiomeric to each other.

4.3. Conceptual revolution from graphs to chemical structures

As shown in the preceding discussions, theorem 1 of the present approach is based on models in which a skeleton can take chiral and achiral ligands. Thus, theorem 1 regards a coset representation of a point group as a homomorphic permutation group so that each permutation of the coset representation is classified into a proper or improper element. Thereby, chiral ligands along with achiral ligands can be properly treated as substituents for a skeleton.

On the other hand, Pólya's theorem is based on models in which a skeleton takes achiral ligands only. Thus, Pólya's theorem uses a permutation group directly, so it is incapable of classifying proper and improper elements. As a result, Pólya's theorem cannot treat the substitution of chiral ligands properly.

In summary, theorem 1 is capable of enumerating chemical structures, whereas Pólya's theorem is incapable of enumerating chemical structures but is only concerned with graphs. It follows that the conceptual change from Pólya's theorem to theorem 1 has provided us with a revolution in our stereochemical viewpoints, i.e., from graphs to chemical structures.

5. Conclusion

The detailed discussions of the present paper have shown that Pólya's theorem is concerned with graphs, but not with chemical structures, where it is incapable of treating chiral ligands properly. In order to take account of chiral ligands along with achiral ones, sphericity indices of *k*-cycles have been defined according to the enantiospheric, homospheric, or hemispheric nature of each *k*-cycle. Thereby, CIs-CF have been defined so as to enumerate stereoisomers with chiral and achiral ligands.

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