Accounts

Numbers of Alkanes and Monosubstituted Alkanes. A Long-Standing Interdisciplinary Problem over 130 Years

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Enumeration of alkanes and monosubstituted alkanes with given carbon contents has been investigated by chemists and mathematicians over 130 years and solved recently by the present author in agreement with stereochemical and mathematical requirements. In the present account, the advances of the methodologies for solving the problem are discussed from an interdisciplinary point of view between chemistry and mathematics. Historical backgrounds of the interdisciplinary problem are introduced by emphasizing three epochs, i.e., the first epoch marked by Cayley, a mathematician (the 1870s), the second epoch by Pólya, a mathematician (the 1930s), and the third epoch by Fujita, an organic chemist (the first decade of this century). Among them, the accomplishments of the second epoch and those of the third epoch are compared in detail, where graphs (trees, rooted trees, or planted trees) and three-dimensional (3D) objects as mathematical terms are correlated to constitutions (two-dimensional structures) and 3D structures as chemical terms. After an introduction to terminology on isomerism and stereoisomerism, alkanes and monosubstituted alkanes are enumerated as graphs or constitutional isomers by Pólya's theorem, while they are alternatively enumerated as 3D objects or 3D-structural isomers by Fujita's proligand method. The present account of the long-standing problem would provide readers with a hint or a motivation for pursuing a concrete route to "the Heavens of Fujita," which have caricatured stereochemical and mathematical barriers lying in wait for them.

1. Introduction

1.1 How Does Chemistry Link with Mathematics? There are two interdisciplinary linkages between chemistry and mathematics. One is an indirect linkage mediated by physics, as exemplified in physical chemistry and quantum chemistry. For example, a molecule as a chemical object is regarded as a physical object governed by a Shrödinger equation, which is in turn solved as a mathematical object, as found in most textbooks on physical chemistry,[1] on quantum chemistry,[2,3] and on chemical group theory.[4] In this case, mathematics is used as a convenient tool for treating physical objects as models of chemical objects. Such physical models for representing organic molecules have continuous nature, so that they are not equal to structural formulas which exhibit discrete nature. This means that the indirect linkage has not covered some important fields of organic chemistry such as isomerism and stereoisomerism.

The other is a direct linkage, where structural formulas with atoms and bonds are treated as discrete objects (i.e., graphs) by means of chemical graph theory,[5,6] which has been recently referred to by a broader term mathematical chemistry.[7] Note that the term "graph" of the graph theory itself has originated from chemistry.[8] The direct linkage would be expected to serve as a basis of organic chemistry, because organic chemistry has heavily relied on structural formulas. In fact, expert organic chemists unconsciously adopt this linkage in handling structural formulas, especially in discussing isomerism, even though they are often unaware that their handling technique implicitly relies on the graph theory. For example, the hexagonal Kekulé structure of benzene[9] was deduced by scrutinizing the numbers of mono-, di-, and tri-substituted benzene derivatives as explained in a textbook (cf. pp. 478–481 of Ref. 10), which implicitly employed Pólya's theorem on isomer enumeration.[11–13]

However, the direct linkage has been less familiar to organic chemists than the indirect linkage to physical and quantum chemists. One of the reasons for the less familiarity of the direct linkage is that such approaches as based on graph theory have been restricted to two-dimensional (2D) structural formulas, so as not to cover stereoisomerism or stereochemistry based on three-dimensional (3D) structural formulas.

Because stereochemistry has been one of the central fields of organic chemistry, it has been necessary to develop another suitable theoretical framework for treating 3D structural formulas, i.e., mathematical stereochemistry, which is based on the direct linkage between chemistry and mathematics. Although Fujita's book on symmetry and enumeration in

Published on the web December 23, 2009; doi:10.1246/bcsj.20090008

chemistry has aimed at such mathematical stereochemistry,[14] the state-of-the-art situation of this field has not been recognized so well by organic chemists or even by chemists of other fields, as implied by the statement of a recent review (cf. page 134 of Ref. 15): "Fujita continues an immense *near single-handed* work on the development of symmetry-attentive combinatorial isomer-enumeration methodology and its application." (emphasis added by the present author) as well as by a caricature illustrating two barriers (a mathematical barrier and a stereochemical barrier) to "the Heavens of Fujita" (cf. Figure 35 of Ref. 16).

As a typical example of the direct linkage between chemistry and mathematics, the present account deals with the development of theoretical tools for solving a long-standing interdisciplinary problem over 130 years, i.e., enumeration of alkanes and monosubstituted alkanes with given carbon contents. By throwing a quick glance at the solution of this problem, the readers would realize that the direct linkage is capable of bringing about stimulating results to them. Although the processes for obtaining the solution of the problem would require some effort, their outline is traceable by the present account with historical comments on the problem. In particular, comparison between graph theory and mathematical stereochemistry provides them with a deeper insight to how chemistry links with mathematics.

1.2 Historical Backgrounds. 1.2.1 The First Epoch in Enumeration of Alkanes and Monosubstituted Alkanes: 1.2.1.1 Problem-Setting and Pioneering Solutions as Graphs or Constitutional Isomers; In the 1870s, Cayley, a mathematician investigated problems of enumerating rooted trees[17] and trees.[18,19] This was the beginning of the direct linkage between chemistry and mathematics, because Cayley himself was aware that his enumeration of trees was applicable to chemical combinatorics.[18] In his report,[17] the mathematical term trees was obviously recognized to be essentially equivalent to the chemical term isomers represented by a formula C_kH_{2k+2}, which were later specified in terms of a more systematic term alkanes. Thus, the direct linkage was far older than the indirect linkage brought about in the 1930s by the beginning of quantum physics.

Because enumeration problems have such interdisciplinary nature, they have attracted interests of many mathematicians and of a greater number of chemists. Accomplishments up to 1936 have been summarized in a book on graph theory.[20] As for a mathematical foundation for linking between rooted trees (or alcohols or monosubstituted alkanes) and trees (or alkanes), Jordan's work[21] on the dichotomy of centroidal and bicentroidal trees should be cited, because Cayley's accomplishments relied on this dichotomy. In addition, we should refer to a chemical approach conducted by Henze and Blair,[22,23] where aliphatic alcohols (rooted trees) and alkanes (trees) were enumerated after the development of recursive formulas.

1.2.2 The Second Epoch in Enumeration of Alkanes and Monosubstituted Alkanes: 1.2.2.1 Advanced Solutions as Graphs or Constitutional Isomers; In the same 1930s as the chemistry-oriented work conducted by Henze and Blair,[22,23] Pólya, a mathematician developed a versatile theorem named after him (Pólya's theorem),[24] where a permutation group governing the symmetry of molecules was used to enumerate isomers as graphs. As an application of Pólya's theorem, Pólya himself enumerated trees (as mathematical objects) or alkanes (as chemical objects), which were regarded as graphs or constitutional isomers.[24,25] Because Pólya's theorem was powerful and wide-ranging, many applications to various chemical and graph-theoretical problems have appeared in addition to the enumeration problems described above, as summarized in books[6,20,25–27] and reviews.[28–31] Among these accomplishments, mention should be made of several pioneering works for further advances, e.g., those conducted by Otter[32] and Robinson et al.[33] Moreover, there appeared several extensions,[34,35] which enhanced the versatility of Pólya's theorem.

1.2.3 Organic Stereochemistry with and without Mathematical Supports: Before we go on to the third epoch, we should describe the history of organic stereochemistry briefly and discuss how organic stereochemistry links with mathematics. This is because the third epoch will deal with alkanes as 3D structures or stereoisomers in place of alkanes as graphs (or trees) or constitutional isomers.

1.2.3.1 Organic Stereochemistry without Mathematical Supports; The 1870s, which were the first epoch made by Cayley, have been also remembered as the beginning of organic stereochemistry by van't Hoff[36] and Le Bel.[37] Although van't Hoff already obtained the number of stereoisomers having n asymmetric carbons and discussed such degenerate cases as meso compounds,[38] there have been no systematic approaches to stereoisomerism on a mathematical basis. In fact, van't Hoff's conclusion on so-called pseudoasymmetric cases[38] was erroneous from the present viewpoint at which we have arrived according to Fischer's famous work on sugars.[39–41] Organic stereochemistry regarded the degenerate cases (meso compounds and compounds with pseudoasymmetric carbons) as only exceptions, so that through the first and second epochs there had appeared no mathematical supports to systematize organic stereochemistry without excluding such exceptions.

All of these accomplishments due to the first and second epochs (except Robinson et al.[33]) were concerned with graphs or constitutional isomers, but not with 3D structures or stereoisomers, where each graph (or each constitutional isomer) was counted once. Although Pólya's theorem was also used to count steric isomers,[24,42,43] such steric isomers were counted without reflection operations, where two enantiomers of each pair were counted separately while each achiral molecule was counted just once. In other words, the contribution of an achiral molecule to the number of steric isomers is a unit, which is not differentiated from the contribution of one chiral molecule and from the contribution of another chiral molecule of the opposite handedness. Although Robinson et al. obtained the numbers of achiral alkanes and chiral ones by modifying Pólya's theorem,[33] reflection operations were not fully separated from permutation operations, so that degenerate cases having pseudoasymmetric carbons were not fully demonstrated from a stereochemical viewpoint.

1.2.3.2 Mathematical Organic Stereochemistry; Fujita's USCI Approach; In addition to Pólya's theorem, other methods based on double cosets (by Ruch et al.[44,45] and Brocas[46]) and further methods based on tables of marks (by Sheehan,[47] Kerber and Thürlings,[48] Hässelbarth,[49] and Mead[50])

were applied to enumeration problems of isomers and stereoisomers.

Later, the concept of tables of marks proposed originally by Burnside[51] was combined with the concept of coset representations by Fujita,[52] where subductions of coset representations and unit subduced cycle indices (USCIs) were proposed as new concepts for isomer enumerations. This approach is here called "Fujita's USCI approach," which has provided us with four methods for enumerating isomers:

1. The subduced-cycle-index (SCI) method[52] as a generating function method.

2. The partial-cycle-index (PCI) method[53] as another generating function method.

3. The elementary superposition method[54,55] based on the concept of elementary superposition.

4. The partially superposition method[55] based also on the concept of elementary superposition.

Their formulations and applications were summarized in Fujita's monograph.[14] Comparison of the four methods with each other and derivation of the characteristic monomial (CM) method were discussed.[56]

Fujita emphasized the importance of coset representations for point groups in order to discuss molecular symmetries.[57] In particular, he proposed the concept of sphericities to specify respective equivalence classes (orbits) governed by coset representations, which were subsidiarily generated by subduction of parent coset representations. Through the sphericity of the corresponding coset representation, a set of equivalent sites (atoms, bonds, ligands, and other objects) in a molecule was regarded as an orbit, which was classified into a homospheric, enantiospheric, or hemispheric orbit. Thereby, he developed another new concept unit subduced cycle indices with chirality fittingness (USCI-CFs), where the four methods described above were extended to agree with USCI-CFs.[55,58] They were proven to be versatile to stereoisomer enumerations.[59–61]

In addition to such quantitative applications as stereoisomer enumerations, Fujita's USCI approach enhanced by the concept of sphericities is also useful for qualitative discussions in stereochemistry, as summarized in reviews.[62,63] Several examples of its qualitative applications are as follows: systematic classification of molecular symmetry,[64] systematic investigation on local chirality and prochirality,[57,65] and characterization of anisochrony and symmetry non-equivalence.[66]

However, algebraic features of Fujita's USCI approach were criticized with respect to their popularity among organic chemists.[67] Moreover, the pictorial illustration of Figure 35 appearing in El-Basil's book[16] pointed out two barriers before arriving at "the Heavens of Fujita," i.e., a mathematical barrier and a stereochemical barrier. To face the criticism as one of synthetic organic chemists (cf. Ref. 68) and to avoid such barriers, a diagrammatical approach to Fujita's USCI approach was published recently,[69] where the concept of mandalas[70–72] was introduced. Another approach was to pursue the development of simplified methods by starting from Fujita's USCI approach, as shown in the following paragraphs.

1.2.3.3 Simplified Methods Based on Fujita's USCI Approach; Although Fujita's USCI approach is capable of enumerating isomers which are itemized with respect to given subgroups of a point group, it requires full information of subgroups contained in the point group. However, it is sometimes sufficient to obtain results without itemization of subgroups on a similar line to Pólya's theorem. Fortunately, USCIs were correlated to Pólya's cycle indices (CIs),[73] where the CIs were found to be concerned only with cyclic subgroups. This course resulted in simplified methods at the expense of the subgroup itemization. One of such simplified methods stemmed from Def. 16.1 of Fujita's monograph,[14] where subduced cycle indices (SCI) were converted into a cycle index (CI), which is identical to a CI derived by Pólya's theorem. Another method stemmed from Def. 16.5 of Fujita's monograph,[14] where PCIs were added to give an equivalent CI. Alternatively, after dominant representations and markaracter tables were defined to specify cyclic subgroups,[74] subductions of such dominant representations gave another formulation of CIs,[75] which were identical to those derived by Pólya's theorem. Moreover, subductions of Q-conjugacy representations gave an additional formulation of CIs,[76] which were identical to those derived by Pólya's theorem. The relationship between markaracter tables and Q-conjugacy character tables was discussed to characterize cyclic groups.[77] Direct subduction of Q-conjugacy representations was clarified to give characteristic monominals (CMs), which provided a further formulation of CIs.[78–80]

The above-mentioned simplified methods based on Fujita's USCI approach were extended to be capable of stereoisomer enumerations, where USCIs were replaced by USCI-CFs so as to treat chiral and achiral ligands. Various extended methods for treating chiral and achiral ligands were summarized in a review,[81] where cycle indices with chirality fittingness (CI-CFs) were derived variously. One method stemmed from Def. 19.4 of Fujita's monograph,[14] where subduced cycle indices with chirality fittingness (SCI-CFs) were converted into a CI-CF. Another method stemmed from Def. 19.7 of Fujita's monograph,[14] where partial cycle indices with chirality fittingness (PCI-CFs) were added to give a CI-CF. Characteristic monomials with chirality fittingness (CM-CFs) were proposed to give an additional formulation of CI-CFs,[82] which were identical to the CI-CFs derived from USCI-CFs.[14]

1.2.3.4 Fujita's Proligand Method; The CI-CFs used in the simplified methods based on Fujita's USCI approach were generated from the data of USCI-CFs, which required full information on subgroups of a group. To avoid this drawback, the proligand method has been developed by Fujita[83–85] to generate CI-CFs directly from respective operations of a group, where no information on subgroups is required.

For the purpose of developing Fujita's proligand method, the sphericity concept for the USCI approach, which was originally formulated as sphericities of orbits, has been modified into a new concept sphericities of cycles[83–85] through an intermediate concept sphericities of orbits for cyclic subgroups.[74,75,77,86] Note that each operation of a group is characterized by a cycle structure, where each cycle in the cycle structure is classified into a homospheric, enantiospheric, or hemispheric cycle. The modified concepts were combined with the concepts of proligands and promolecules[87] so as to develop Fujita's proligand method. An alternative formulation of Fujita's proligand method was demonstrated[88] in terms of the sphericity concept introduced directly by the concept of mandalas.[69,71]

From one point of view, Fujita's proligand method is regarded as an extension of Fujita's USCI approach by taking account of the concept of cycle indices due to Pólya's theorem. From an alternative point of view, it can be in turn regarded as an extension of Pólya's theorem by employing the concept of sphericities due to Fujita's USCI approach. Thus, Fujita's proligand method is a sublation (Aufheben) of the two methodologies, so that it succeeds to the stereochemical consistency of Fujita's USCI approach and to the succinct nature of Pólya's theorem. The merits of Fujita's proligand method have been discussed in comparison with Pólya's theorem in an article of his own.[81] Applications of Fujita's proligand method to detailed enumerations have been conducted extensively.[89–94]

1.2.4 The Third Epoch in Enumeration of Alkanes and Monosubstituted Alkanes: 1.2.4.1 Advanced Solutions as 3D Structures or 3D-Structural Isomers; The third epoch of solving the interdisciplinary problem was marked by Fujita[95,96] for the first decade of this century, where trees or alkanes were investigated as three-dimensional (3D) structures on the basis of Fujita's proligand method.[83–85] Thereby, the interdisciplinary problems of enumerating planted trees (or monosubstituted alkanes) and trees (or alkanes), which have been pending over 130 years, have been solved in agreement with both stereochemical and mathematical requirements.

To obtain basic data for enumerating trees (or alkanes), planted trees (or monosubstituted alkanes) were enumerated, where they were in turn regarded as alkyl ligands for deriving trees (or alkanes). First, Fujita's proligand method was applied to enumeration of planted 3D trees as stereochemical models of monosubstituted alkanes,[89,95] where the data of carbon content n were used recursively to evaluate the data of carbon content $n+1$. Monosubstituted alkanes were categorized as primary, secondary, and tertiary, which were respectively enumerated by Fujita's proligand method.[90] Effects of asymmetric and pseudoasymmetric centers[97] as well as of internal branching[98,99] on the numbers of achiral and chiral monosubstituted alkanes were investigated.

By starting from the data of monosubstituted alkanes (alkyl ligands), 3D trees were enumerated as stereochemical models of alkanes according to Fujita's proligand method,[91,96] where they were categorized into centroidal and bicentroidal 3D trees. After the proposal of a new dichotomy between balanced 3D trees and unbalanced ones, 3D trees (alkanes) were enumerated by combining the dichotomy with the dichotomy between centroidal 3D trees and bicentroidal ones.[92] An alternative method for enumerating 3D trees was developed on the basis of the fact that they can be regarded dually as uninuclear and as binuclear promolecules.[93] Symmetry-itemized numbers of alkanes as stereoisomers were obtained by applying Fujita's proligand method.[94] Effect of asymmetric and pseudoasymmetric centers on the numbers of achiral and chiral 3D trees (alkanes) was investigated.[100] Achiral and chiral alkanes of given carbon contents were categorized and enumerated by considering internal branching.[101]

1.3 Scope and Aims of the Present Account. Among the various advances described above, two representative approaches, i.e., graph enumeration based on Pólya's theorem of the second epoch (Subsections **3.1** and **4.2**)[24,25,27] and 3D-structure enumeration based on Fujita's proligand method of the third epoch (Subsections **3.3** and **4.4**),[95,96] are compared in detail in the following sections of the present account. This comparison will reveal the essences of the long-standing interdisciplinary problem over 130 years: enumeration of alkanes and monosubstituted alkanes with given carbon contents.

2. Terminology for Isomerism and Stereoisomerism

To begin with, we should discuss terminology for isomerism and stereoisomerism in order to categorize such isomers to be enumerated.

2.1 Constitutional Isomers and Stereoisomers in Different Levels. Because the terms concerning isomers in stereochemistry have been coined to determine isomeric relationships but not to specify molecular entities themselves, they tend to cause confusion or some ambiguity. In particular, such confusion or ambiguity becomes more troublesome in discussing quantitative aspects of stereochemistry, because stereochemistry so far has been devoted to qualitative discussions. For example, the number of constitutional isomers (per molecular formula) and the number of stereoisomers (per constitution) are different in their levels so that these two numbers of different levels cannot be compared directly.

Def. 1 (**Constitutional isomers** per molecular formula): A constitution (a structure or a 2D structure) is an object (a graphic species) that is characterized as a specific graph in which a definite number of atoms (vertices) are bounded uniquely by a definite number of bonds (edges). The term constitutional isomers (or structural isomers) is defined as a set of inequivalent constitutions which are characterized by the same molecular formula (or by the same carbon content). The number of constitutional isomers is regarded as the size of the set containing full members of inequivalent constitutions.

Def. 2 (**Stereoisomers** per constitution): The term stereoisomers is defined as a set of inequivalent 3D structures which become degenerate into a single constitution. Note that no reflection operations participate in this definition. The number of stereoisomers is regarded as the size of the set containing full members of inequivalent 3D structures per constitution. According to van't Hoff,[38] the number of stereoisomers having ℓ asymmetric carbons has been calculated to be equal to 2^{ℓ} except degenerate cases such as meso compounds and pseudoasymmetric cases.

To exemplify these definitions, let us examine monosubstituted alkanes, all of which are listed in Figure 1 (carbon content 6) and Figure 2 (carbon content 5). Each set of formulas surrounded with a broken-lined box indicates a constitution of a molecular formula $C_6H_{13}Z$ (or of carbon content 6), where Z denotes an atom (e.g., Cl). Thus, each of eight formulas **1**–**8** represents a constitution (a graph) of a molecular formula $C_6H_{13}Z$; each of eight pairs of enantiomers **9**/$\overline{\mathbf{9}}$–**16**/$\overline{\mathbf{16}}$ indicates a constitution of a molecular formula $C_6H_{13}Z$; and a quadruplet of **17**/$\overline{\mathbf{17}}$ and **18**/$\overline{\mathbf{18}}$ indicates a constitution of a molecular formula $C_6H_{13}Z$. Hence, the number of constitutional isomers (inequivalent graphs having carbon content 6) is manually determined to be 17.

2.2 Steric Isomers and 3D-Structural Isomers for Enumerating 3D Structures. In the present account, the term

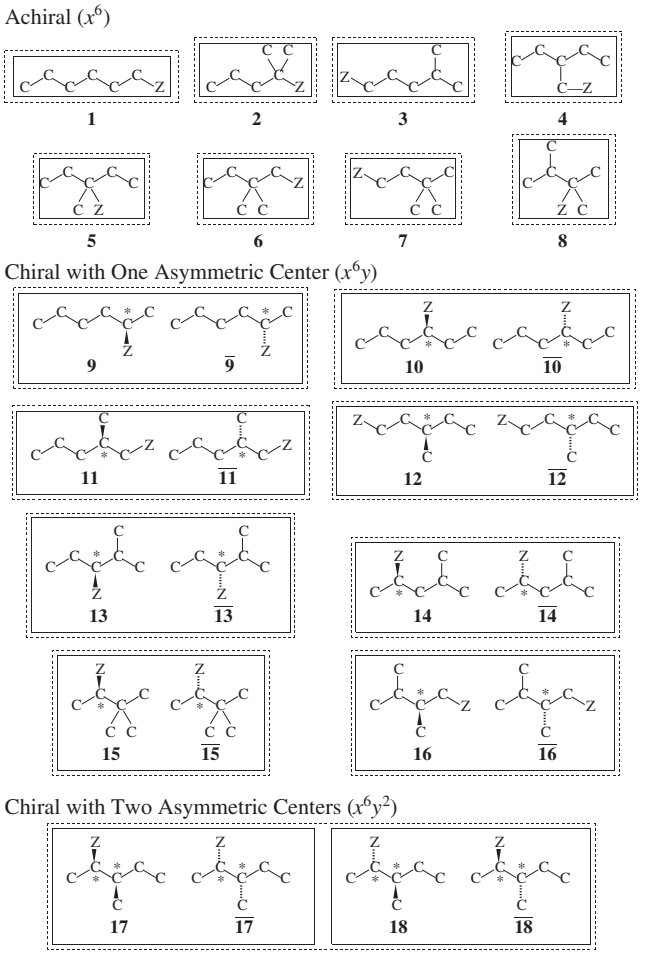
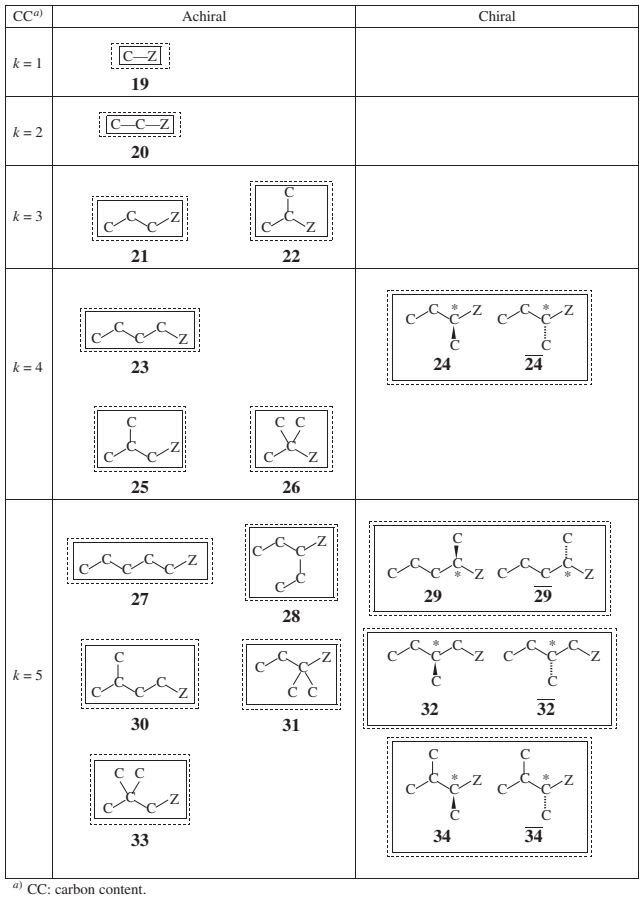


Figure 1. Monosubstituted alkanes of carbon content 6. Each of 17 constitutional isomers is surrounded by a broken-lined box; each of 18 3D-structural isomers (each achiral molecule or each pair of enantiomeric molecules) is surrounded by a straight-lined box; and each molecule represents a steric entity of 28 steric isomers. The symbol Z denotes an atom (e.g., Cl) or an achiral ligand (e.g., OH) which is regarded as a monovalent substituent. Hydrogen atoms are omitted for the sake of simplicity. Each asymmetric center is denoted by an asterisk.



[a)] CC: carbon content.

Figure 2. Monosubstituted alkanes of lower carbon contents ($k = 1$–5). Each constitutional isomer is surrounded by a broken-lined box; each 3D-structural isomers (each achiral molecule or each pair of enantiomeric molecules) is surrounded by a straight-lined box; and each molecule represents a steric isomer. The symbol Z denotes an atom (e.g., Cl) or an achiral ligand (e.g., OH) which is regarded as a monovalent substituent. Hydrogen atoms are omitted for the sake of simplicity. Each asymmetric center is denoted by an asterisk.

steric isomers is used to refer to two or more 3D structures which are related to each other by a kind of isomeric relationship described below (Def. 3). Thereby, a set of such 3D structures is regarded as being an equivalence class under the criterion (Def. 3). On the other hand, the term 3D-structural isomers is employed to denote two or more 3D structures which are related to each other by another kind of isomeric relationship (Def. 4). A set of such 3D structures is regarded as being an equivalence class due to the criterion (Def. 4). As a result, the term 3D structures (objects) should be differentiated from the term steric isomers (concerning relationships due to Def. 3) and from the term 3D-structural isomers (concerning relationships due to Def. 4) in the following discussions.

2.2.1 Steric Isomers per Molecular Formula: When 3D structures were counted per molecular formula, the resulting number can be compared with the number of constitutional isomers per molecular formula. The number obtained by this mode of counting was referred to as the number of steric isomers according to Robinson et al.[33]

Def. 3 (**Steric isomers** per molecular formula): A steric entity is an object (a molecular species) that is characterized as a 3D structure which coincides with itself under the action of rotations, where any reflection operations are not taken into consideration. If the mirror-image object does not coincide with its original steric entity under the action of rotations, they are regarded as different objects. The term steric isomers is defined as the set of inequivalent steric entities which are characterized by the same molecular formula (or by the same carbon content). The number of steric isomers is regarded as the size of the set containing full members of inequivalent 3D structures as steric entities.

According to the definition of steric isomers, each of 28 formulas (3D structures) listed in Figure 1 indicates a 3D structure as a steric entity of carbon content 6. Hence, the number of steric isomers (inequivalent 3D structures under

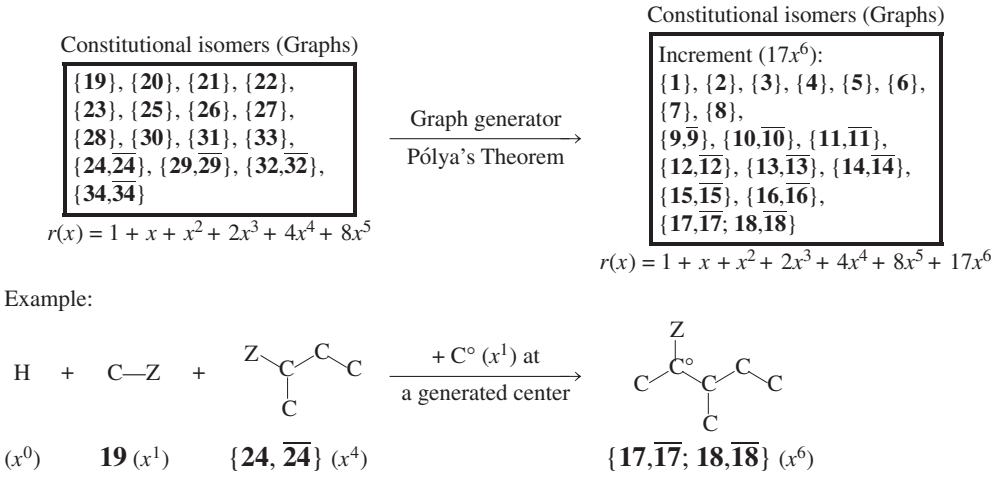


Figure 3. Graph generator based on Pólya's theorem. Monosubstituted alkanes are generated under the action of the symmetric group of degree 3 ($\mathcal{S}^{[3]}$). Each constitution which is derived by degeneration of component 3D structures involved in a pair of braces is counted just once according to Def. 1. The number of substituted alkanes of carbon content k as constitutional isomers appears as the coefficient of the term x^k.

Def. 3) is manually determined to be 28. Note that each 3D structure as a steric entity is counted just once.

The number (17) of constitutional isomers and the number (28) of steric isomers can be obtained by Pólya's theorem. This process will be discussed in the next section. It is to be emphasized that these numbers are obtained without considering reflection operations, as noted in the above-mentioned definitions. In other words, two 3D structures that must be recognized to be in an enantiomeric relationship have no connection with each other so as not to be determined to construct an enantiomeric pair. As a result, the number of steric isomers does not take account of the difference between achirality and chirality for each 3D structure counted.

2.2.2 3D-Structural Isomers per Molecular Formula: In order to discuss further aspects of stereochemistry, the number of achiral molecules and the number of enantiomeric pairs should be obtained separately. These numbers can be compared with the number of steric isomers and with the number of constitutional isomers on a common level, i.e., per molecular formula. On the same level as constitutional (structural) isomers or steric isomers per molecular formula, therefore, we coin the term 3D-structural isomers per molecular formula:

Def. 4 (3D-Structural isomers per molecular formula): A (self-)enantiomeric pair that is characterized as an achiral 3D structure or a pair of chiral 3D structures is an object which coincides with itself under an appropriate rotation and an appropriate reflection. Then, the term 3D-structural isomers is defined as a set of inequivalent (self-)enantiomeric pairs which are characterized by the same molecular formula (or by the same carbon content). The number of 3D-structural isomers is regarded as the size of the set containing full members of inequivalent (self-)enantiomeric pairs.

The term a self-enantiomeric pair is used to indicate an achiral 3D structure. Thereby, an achiral 3D structure and a pair of chiral 3D structures can be discussed as equivalence classes under the action of an achiral point group or, in other words, under the action of an appropriate rotation and an appropriate reflection.

This definition is illustrated also in Figure 1. Each set of formulas surrounded with a straight-lined box indicates a (self-)enantiomeric pair of a molecular formula $C_6H_{13}Z$ (or of carbon content 6), where Z denotes an atom (e.g., Cl). Thus, each of eight formulas **1**–**8** represents a self-enantiomeric pair (an achiral 3D structure) of a molecular formula $C_6H_{13}Z$; each of eight pairs of **9**/$\overline{\mathbf{9}}$–**16**/$\overline{\mathbf{16}}$ indicates an enantiomeric pair of a molecular formula $C_6H_{13}Z$; and each of two pairs (i.e., **17**/$\overline{\mathbf{17}}$ and **18**/$\overline{\mathbf{18}}$) indicates an enantiomeric pair of a molecular formula $C_6H_{13}Z$. Hence, the number of 3D-structural isomers (inequivalent 3D structures under Def. 4) is manually determined to be 18 (=8 + 8 + 2), as surrounded by a straight-lined box. Note that each (self-)enantiomeric pair is counted once. That is to say, each pair of enantiomeric 3D structures is counted once, just as each achiral 3D structure is counted once. The number (18) of 3D-structural isomers can be obtained by Fujita's proligand method.

The present account deals with the enumeration of 3D-structural isomers by Fujita's proligand method, which is compared with the enumerations of constitutional isomers and steric isomers by Pólya's theorem. It should be noted that the chirality or achirality of such a steric entity cannot be discussed by using the term steric isomers, while the term 3D-structural isomers is capable of discussing the chirality or achirality of such a 3D structure.

3. Enumeration of Monosubstituted Alkanes

On the basis of Def. 1, Subsection **3.1** deals with the enumeration of monosubstituted alkanes as constitutional isomers (graphs), where a graph generator (Figure 3) is introduced to visualize recursive processes due to Pólya's theorem. Subsection **3.2** is concerned with the enumeration of monosubstituted alkanes as steric isomers (Def. 3), where a steric-isomer generator (Figure 4) is introduced to demonstrate recursive processes common to Pólya's theorem and Fujita's proligand method. Subsection **3.3** deals with the enumeration of monosubstituted alkanes as 3D-structural isomers (Def. 4), where the combination of an achiral-structure generator and a

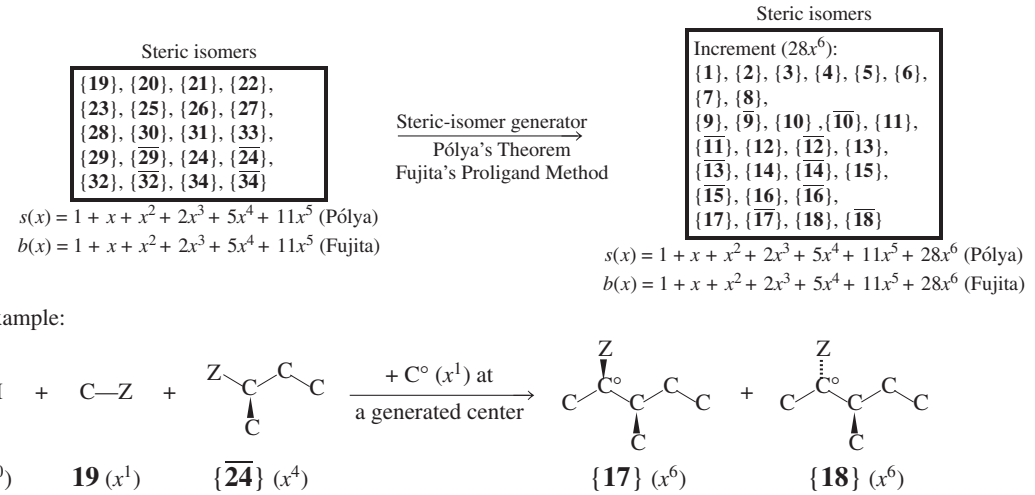


Figure 4. Steric-isomer generator based on Pólya's theorem as well as on Fujita's proligand method. Monosubstituted alkanes are generated under the action of the alternating group of degree 3 ($\mathcal{A}^{[3]}$) (Pólya) or under the action of the coset representation of the C_3 point group (Fujita). Each steric entity (3D structure) involved in a pair of braces is counted once according to Def. 3. The number of substituted alkanes of carbon content k as steric isomers appears as the coefficient of the term x^k.

diploid generator (Figure 5) is introduced to visualize recursive processes due to Fujita's proligand method.

3.1 Monosubstituted Alkanes as Graphs or Constitutional Isomers. 3.1.1 Graph Generator for Recursive Calculation: Suppose that we have enumerated monosubstituted alkanes up to carbon content 5, which are listed in Figure 2. These monosubstituted alkanes are regarded as alkyl ligands (planted trees) by omitting the substituent Z. Each of the monosubstituted alkanes of carbon content 6 listed in Figure 1 can be generated by combining an appropriate set of such alkyl ligands up to carbon content 5 (Figure 2).

If we restrict the derivation of monosubstituted alkanes to the level of constitutions (graphs, cf. Def. 1), we are able to consider a graph generator shown in Figure 3. The generator is, for example, started from the set of graphs of carbon content up to 5 (i.e., {**19**} (x); {**20**} (x^2); {**21**}, {**22**} ($2x^3$); {**23**}, {**25**}, {**26**}, {**27**} ($4x^4$); {**28**}, {**30**}, {**31**}, {**33**}, {**24**,$\overline{\mathbf{24}}$}, {**29**,$\overline{\mathbf{29}}$}, {**32**,$\overline{\mathbf{32}}$}, and {**34**,$\overline{\mathbf{34}}$} ($8x^5$)) so as to generate the increment set of 17 graphs of carbon content 6 (i.e., {**1**}, {**2**}, {**3**}, {**4**}, {**5**}, {**6**}, {**7**}, {**8**}, {**9**,$\overline{\mathbf{9}}$}, {**10**,$\overline{\mathbf{10}}$}, {**11**,$\overline{\mathbf{11}}$}, {**12**,$\overline{\mathbf{12}}$}, {**13**,$\overline{\mathbf{13}}$}, {**14**,$\overline{\mathbf{14}}$}, {**15**,$\overline{\mathbf{15}}$}, {**16**,$\overline{\mathbf{16}}$}, and {**17**,$\overline{\mathbf{17}}$; **18**,$\overline{\mathbf{18}}$} ($17x^6$)). Note that 3D structures in each pair of braces are considered to become degenerate into a single constitution (or graph) to be counted just once according to Def. 1.

For example (cf. the example of Figure 3), a starting set of a hydrogen atom, a methyl ligand derived from a graph {**19**}, and a *s*-butyl ligand derived from a graph {**24**,$\overline{\mathbf{24}}$} is placed on the three positions of a methyl skeleton (≡C°–Z) so as to generate a graph corresponding to {**17**,$\overline{\mathbf{17}}$; **18**,$\overline{\mathbf{18}}$}. Each of the 17 graphs listed in Figure 1 can be generated on a similar line by an appropriate combination of alkyl ligands selected from Figure 2 if we consider carbon centers only.

Obviously, the procedure exemplified in Figure 3 by the derivation from carbon content 5 to 6 can be repeated recursively, where an intermediate starting set of carbon content up to k is capable of generating an increment set of carbon content $k+1$. Finally, we are able to obtain a set ($\mathbf{R}_\infty$) of monosubstituted alkanes as constitutional isomers (graphs) up to infinite carbon content. Let the symbol R_k be the number of monosubstituted alkanes of carbon content k (as graphs or constitutional isomers). Then the set $\mathbf{R}_\infty$ is characterized by a generating function:

$$r(x) = \sum_{k=0}^{\infty} R_k x^k \tag{1}$$

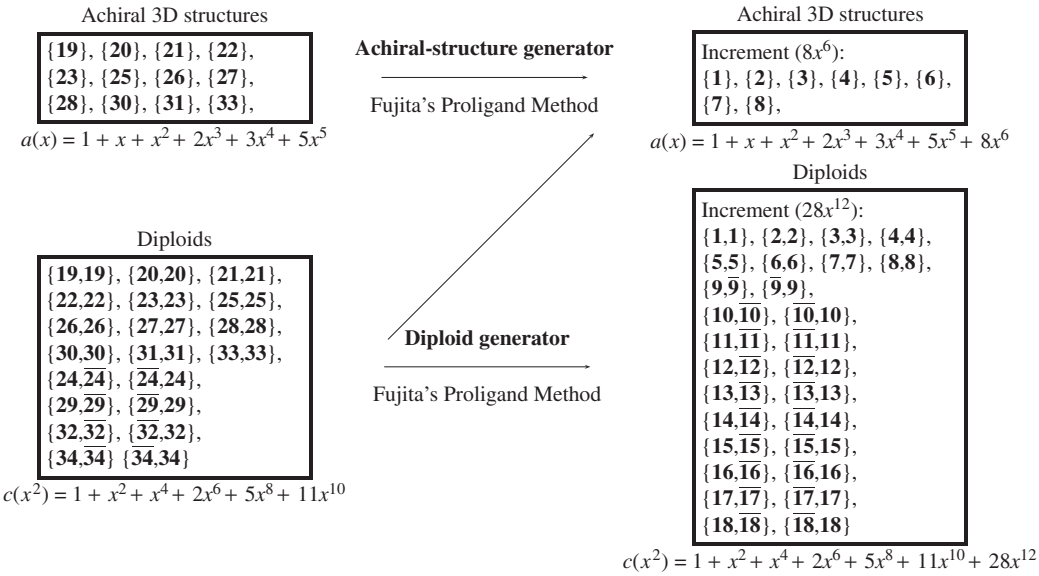
$$\begin{aligned} &= 1(=R_0) + x + x^2 + 2x^3 + 4x^4 + 8x^5 \\ &\quad + 17x^6 + 39x^7 + 89x^8 + 211x^9 + 507x^{10} \\ &\quad + 1238x^{11} + 3057x^{12} + 7639x^{13} + 19241x^{14} \\ &\quad + 48865x^{15} + 124906x^{16} + 321198x^{17} + 830219x^{18} \\ &\quad + 2156010x^{19} + 5622109x^{20} + 14715813x^{21} \\ &\quad + 38649152x^{22} + 101821927x^{23} + 269010485x^{24} \\ &\quad + 712566567x^{25} + \ldots \end{aligned} \tag{2}$$

where R_0 (=1) is an initial value for representing a hydrogen atom. To obtain each R_k according to the recursive procedure is a problem to be solved. For example, by starting from the generating function up to carbon content 5, i.e., $r(x)^{(5)} = 1 + x + x^2 + 2x^3 + 4x^4 + 8x^5$, we should evaluate the increment $17x^6$, which is added to the starting generating function to give a new generating function such as $r(x)^{(6)} = 1 + x + x^2 + 2x^3 + 4x^4 + 8x^5 + 17x^6$ for carbon content 6.

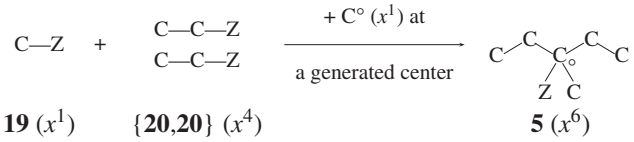
3.1.2 A Functional Equation Based on Pólya's Theorem for Enumerating Monosubstituted Alkanes as Graphs: When the three positions of a methyl skeleton (≡C°–Z) are numbered by 1, 2, and 3, they are interconverted by the following set of permutations:

$$\mathcal{S}^{[3]} = \{(1)(2)(3), (1\ 2\ 3), (1\ 3\ 2), (1)(2\ 3), (2)(1\ 3), (3)(1\ 2)\} \tag{3}$$

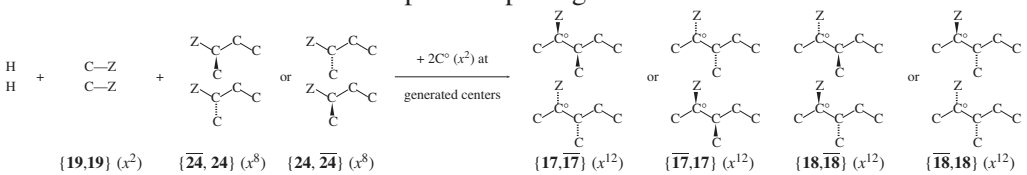
which constructs the symmetric group of degree 3 denoted by the symbol $\mathcal{S}^{[3]}$. According to Pólya's theorem, the permutation (1)(2)(3) leaves each ligand invariant so as to indicate $r(x)^3$



Example 1. Achiral-structure generator:



Example 2. Diploid generator:



Example 3. Pseudoasymmetric monosubstituted alkanes of carbon content 9:

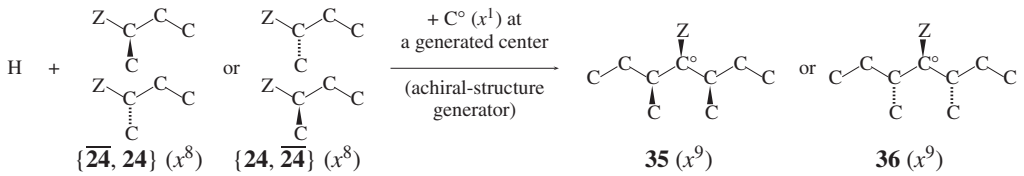


Figure 5. Achiral-structure generator and diploid generator based on Fujita's proligand method. Monosubstituted alkanes are generated under the action of the C_{3v} point group (the coset representation $C_{3v}(/C_s)$). Each constitution which is derived by degeneration of component 3D structures involved in a pair of braces is counted just once. The number of substituted alkanes of carbon content k as constitutional isomers appears as the coefficient of the term x^k.

because its cycle structure 1^3 shows the presence of three cycles of length one; the permutation (1 2 3) represents a rotation $\{1,2,3\} \rightarrow \{2,3,1\}$, which implies that three ligands at issue are identical so as to indicate $r(x^3)$ according to its cycle structure 3^1; and the permutation (1)(2 3) represents a conversion $\{1,2,3\} \rightarrow \{1,3,2\}$, which implies that one ligand is invariant and two ligands are identical so as to indicate $r(x)r(x^2)$ according to its cycle structure 1^12^1. Note that a cycle of length d is characterized by the term $r(x^d)$. Hence, the average of the six terms is calculated to give a functional equation:

$$r(x) = 1 + \frac{x}{6}\{r(x)^3 + 2r(x^3) + 3r(x)r(x^2)\} \qquad (4)$$

which is an algebraic expression for implementing the graph generator (Figure 3). This equation has been once noted by Pólya.[24,25] Note that the term 1 at the start of the right-hand side is added to take account of a hydrogen atom, and that the multiplication of x corresponds to a central carbon newly-formed. Although this equation is concerned with a generating function shown in eq 1, the multilayered structure of the set ($\mathbf{R}_\infty$) permits us to calculate the value R_{k+1} recursively from the data up to carbon content k.

The recursive calculation based on eq 4 gives the number of monosubstituted alkanes as graphs (R_k of carbon content k). For example, the introduction of $r(x)^{(5)}$ into the right-hand side of eq 4 gives the increment $17x^6$, which is added to generate

the next generating function $r(x)^{(6)}$. The resulting values are collected up to carbon content 25 in the form of a generating function (eq 2), which has been re-calculated by using the Maple programming language.[89,95]

3.2 Monosubstituted Alkanes as Steric Isomers. 3.2.1 Steric-Isomer Generator for Recursive Calculation: Suppose again that the monosubstituted alkanes up to carbon content 5, which are listed in Figure 2, are regarded as steric isomers (Def. 3). After these monosubstituted alkanes are regarded as alkyl ligands by omitting the substituent Z, an appropriate set of such alkyl ligands up to carbon content 5 (in addition to a hydrogen atom) is placed on the three positions of a methyl skeleton (≡C°–Z). Thereby each of the monosubstituted alkanes of carbon content 6 listed in Figure 1 is generated as a steric entity. If we consider the derivation of monosubstituted alkanes within the level of steric entities, we are able to consider a steric-isomer generator shown in Figure 4, where the set of 3D structures of carbon content up to 5 (i.e., {**19**} (x); {**20**} (x^2); {**21**}, {**22**} ($2x^3$); {**23**}, {**25**}, {**26**}, {**27**}, {**28**} ($5x^4$); {**30**}, {**31**}, {**33**}, {**29**}, {$\overline{\mathbf{29}}$}, {**24**}, {$\overline{\mathbf{24}}$}, {**32**}, {$\overline{\mathbf{32}}$}, {**34**}, and {$\overline{\mathbf{34}}$} ($11x^5$)) is employed to generate the increment set of twenty-eight 3D structures of carbon content 6 (i.e., {**1**}, {**2**}, {**3**}, {**4**}, {**5**}, {**6**}, {**7**}, {**8**}, {**9**}, {$\overline{\mathbf{9}}$}, {**10**}, {$\overline{\mathbf{10}}$}, {**11**}, {$\overline{\mathbf{11}}$}, {**12**}, {$\overline{\mathbf{12}}$}, {**13**}, {$\overline{\mathbf{13}}$}, {**14**}, {$\overline{\mathbf{14}}$}, {**15**}, {$\overline{\mathbf{15}}$}, {**16**}, {$\overline{\mathbf{16}}$}, {**17**}, {$\overline{\mathbf{17}}$}, {**18**}, and {$\overline{\mathbf{18}}$} ($28x^6$)). Note that each 3D structure surrounded by a pair of braces is recognized to be a steric entity to be counted just once according to Def. 3.

According to the steric-isomer generator (Figure 4), for example, a starting set of a hydrogen atom, a methyl ligand {**19**}, and a *s*-butyl ligand {$\overline{\mathbf{24}}$} is placed on the three positions of a methyl skeleton (≡C°–Z) so as to generate a steric isomer {**17**} or its diastereomer {**18**} (cf. the example of Figure 4). Each of the 28 steric isomers listed in Figure 1 can be generated on a similar line by an appropriate combination of alkyl ligands as steric isomers, which are selected from Figure 2 if we consider carbon centers only.

The procedure shown in Figure 4 can be repeated recursively, where an intermediate starting set of carbon content up to k is capable of generating an increment set of carbon content $k+1$ if monosubstituted alkanes are regarded as steric isomers. After infinite recursion if a computer capacity allows or even hypothetically, we can obtain a set ($\mathbf{S}_\infty$) of monosubstituted alkanes as steric isomers up to infinite carbon content. Let the symbol S_k be the number of monosubstituted alkanes of carbon content k, which are regarded as steric isomers. Then the set $\mathbf{S}_\infty$ is characterized by a generating function:

$$s(x) = \sum_{k=0}^{\infty} S_k x^k \tag{5}$$

$$\begin{aligned} &= 1(=S_0) + x + x^2 + 2x^3 + 5x^4 + 11x^5 + 28x^6 \\ &\quad + 74x^7 + 199x^8 + 551x^9 + 1553x^{10} \\ &\quad + 4436x^{11} + 12832x^{12} + 37496x^{13} + 110500x^{14} \\ &\quad + 328092x^{15} + 980491x^{16} + 2946889x^{17} + 8901891x^{18} \\ &\quad + 27012286x^{19} + 82300275x^{20} + 251670563x^{21} \\ &\quad + 772160922x^{22} + 2376294040x^{23} + 7333282754x^{24} \\ &\quad + 22688455980x^{25} + \ldots \end{aligned} \tag{6}$$

where S_0 (=1) is an initial value for representing a hydrogen atom.

The present problem to be solved is to evaluate S_k according to the recursive scheme due to such a steric-isomer generator. For example, by starting from the generating function up to carbon content 5, i.e., $s(x)^{(5)} = 1 + x + x^2 + 2x^3 + 5x^4 + 11x^5$, we should evaluate the increment $28x^6$ which is added to the starting generating function to give a new generating function such as $s(x)^{(6)} = 1 + x + x^2 + 2x^3 + 5x^4 + 11x^5 + 28x^6$ for carbon content 6.

3.2.2 A Functional Equation Based on Pólya's Theorem for Enumerating Monosubstituted Alkanes as Steric Isomers: For the purpose of treating steric isomers, the three positions of a methyl skeleton (≡C°–Z) are considered to be governed by the alternating group of degree 3 ($\mathcal{A}^{[3]}$) which is composed of the following set of permutations:

$$\mathcal{A}^{[3]} = \{(1)(2)(3), (1\ 2\ 3), (1\ 3\ 2)\} \tag{7}$$

According to Pólya's theorem, the following functional equation can be derived:

$$s(x) = 1 + \frac{x}{3}\{s(x)^3 + 2s(x^3)\} \tag{8}$$

which is an algebraic expression for implementing the steric-isomer generator (Figure 4) on the basis of Pólya's theorem.[24,25] Note that the term 1 at the start of the right-hand side is added to take account of a hydrogen atom, and that the multiplication of x corresponds to a central carbon newly-formed. Although this equation is concerned with a generating function shown in eq 5, the multilayered structure of the set ($\mathbf{S}_\infty$) permits us to calculate the value S_{k+1} recursively from the data up to carbon content k.

The recursive calculation based on eq 8 gives the number of monosubstituted alkanes as steric isomers (S_k of carbon content k). The resulting values are collected up to carbon content 25 in the form of a generating function (eq 6), which has been re-calculated by using the Maple programming language.[89,95]

3.3 Monosubstituted Alkanes as 3D-Structural Isomers. 3.3.1 Achiral-Structure Generator and Diploid Generator for Recursive Calculation: In order to treat monosubstituted alkanes as 3D-structural isomers on the basis of Fujita's proligand method,[83–85] two types of generators (i.e., an achiral-structure generator and a diploid generator) are taken into consideration, as shown in Figure 5.[95,96] An achiral-structure generator is not self-contained but requires the data evaluated by a diploid generator. On the other hand, the diploid generator is self-contained to be recursive in itself, as depicted in Figure 5.

Suppose that the monosubstituted alkanes up to carbon content 5 (Figure 2) are regarded as 3D-structural isomers, where each pair of enantiomeric 3D structures is counted once as a 3D-structural isomer, just as each achiral 3D structure is counted once as a 3D-structural isomer. These monosubstituted alkanes are regarded as alkyl ligands by omitting the substituent Z. Then, an appropriate set of such alkyl ligands up to carbon content 5 (in addition to a hydrogen atom) is placed on the three positions of a methyl skeleton (≡C°–Z) so as to generate monosubstituted alkanes of carbon content 6 listed in Figure 1 as 3D-structural isomers.

An achiral-structure generator shown in Figure 5 requires the data of achiral monosubstituted alkanes up to carbon content 5 as well as the data of pairs of enantiomeric monosubstituted alkanes in order to support a mechanism for constructing pseudoasymmetric monosubstituted alkanes. The generation of achiral monosubstituted alkanes of carbon content 6 does not directly require the mechanism, because two chiral *s*-butyl ligands (**24** and $\overline{\mathbf{24}}$ of carbon content 4), which are only chiral members contained in Figure 2, do not contribute together to the generation of achiral monosubstituted alkanes of carbon content 6. However, the mechanism works implicitly as shown in Example 1 of Figure 5. According to Fujita's proligand method, even an achiral ethyl ligand {**20**} constructs a pair {**20**,**20**} (a diploid) together with another ethyl ligand. Then, this pair (diploid) together with a methyl ligand **19** generates **5** of carbon content 6.

According to Fujita's proligand method, pseudoasymmetric cases can be explained by the explicit cooperation of the achiral-structure generator and the diploid generator, as exemplified in Figure 5 (Example 3). Thus, two chiral *s*-butyl ligands (**24** and $\overline{\mathbf{24}}$ of carbon content 4) construct two diploids {**24**,$\overline{\mathbf{24}}$} and {$\overline{\mathbf{24}}$,**24**}, which are regarded as ordered sets to be differentiated from each other. The two diploids along with a hydrogen atom generate two pseudoasymmetric monosubstituted alkanes of carbon content 9 (**35** and **36**), which are achiral because each of them coincides with itself under reflection. It should be emphasized that the concept of diploids is essential to characterize achiral molecules without exceptions. Note that the conventional stereochemistry has treated such pseudoasymmetric cases as more or less exceptional cases.

As shown in Example 2 of Figure 5, diploids up to carbon content 10, i.e., two hydrogen atoms (as a diploid), {**19**,**19**} (x^2), and {$\overline{\mathbf{24}}$,**24**} (x^8) or {**24**,$\overline{\mathbf{24}}$} (x^8) are combined to generate diploids of carbon content 12, i.e., {**17**,$\overline{\mathbf{17}}$} (x^{12}) or {$\overline{\mathbf{17}}$,**17**} (x^{12}); and {**18**,$\overline{\mathbf{18}}$} (x^{12}) or {$\overline{\mathbf{18}}$,**18**} (x^{12}). Thus, the diploid generator of Figure 5 is self-contained and works recursively.

3.3.2 Functional Equations Based on Fujita's Proligand Method for Enumerating Monosubstituted Alkanes as 3D-Structural Isomers: When the three positions of a methyl skeleton (≡C°–Z) are numbered by 1, 2, and 3, they are interconverted according to the coset representation of the C_{3v} point group:

$$C_{3v}(/C_s) = \{(1)(2)(3), (1\ 2\ 3), (1\ 3\ 2), \overline{(1)(2\ 3)}, \overline{(2)(1\ 3)}, \overline{(3)(1\ 2)}\} \quad (9)$$

where an overline indicates the alternation of ligand chirality. The last three operations with an overline are concerned with reflections. According to Fujita's proligand method, an achiral-structure generator is characterized by the three operations corresponding to reflections. The operation $\overline{(1)(2\ 3)}$ represents a conversion $\{1,2,3\} \rightarrow \{\overline{1},\overline{3},\overline{2}\}$, which implies that one ligand is invariant because of the homosphericity of the one-cycle, and that two chiral ligands (or achiral ligands) are interconverted into each other because of the enantiosphericity of the two-cycle. Thereby, the permutation $\overline{(1)(2\ 3)}$ is characterized by a function $a(x)c(x^2)$. Because there are three reflections, the average of the three reflections is calculated to give a functional equation:

$$a(x) = 1 + xa(x)c(x^2) \quad (10)$$

which is an algebraic expression for implementing the achiral-structure generator (Figure 5) on the basis of Fujita's proligand method. This equation has been once noted by Fujita.[95] Note that the term 1 at the start of the right-hand side is added to take account of a hydrogen atom, and that the multiplication of x corresponds to a central carbon newly-formed.

The achiral-structure generator shown in Figure 5 is applied repeatedly according to eq 10. After infinite recursion, we can obtain a set ($\mathbf{A}_\infty$) of monosubstituted alkanes as 3D-structural isomers up to infinite carbon content. Let the symbol A_k be the number of achiral monosubstituted alkanes of carbon content k which are regarded as 3D-structural isomers. Then the set $\mathbf{A}_\infty$ is characterized by a generating function:

$$a(x) = \sum_{k=0}^{\infty} A_k x^k \quad (11)$$

$$= 1(=A_0) + x + x^2 + 2x^3 + 3x^4 + 5x^5 + 8x^6 + 14x^7 + 23x^8 + 41x^9 + 69x^{10} + 122x^{11} + 208x^{12} + 370x^{13} + 636x^{14} + 1134x^{15} + 1963x^{16} + 3505x^{17} + 6099x^{18} + 10908x^{19} + 19059x^{20} + 34129x^{21} + 59836x^{22} + 107256x^{23} + 188576x^{24} + 338322x^{25} + \ldots \quad (12)$$

where A_0 (=1) is an initial value for representing a hydrogen atom.

Because each diploid is regarded as an ordered set, the number of diploids is recursively evaluated by the following functional equation:[95]

$$c(x^2) = 1 + \frac{x^2}{3}\{c(x^2)^3 + 2c(x^6)\} \quad (13)$$

which corresponds to the diploid generator based on Fujita's proligand method (Figure 5).

The diploid generator shown in Figure 5 is applied repeatedly according to eq 13. After infinite recursion, we can obtain a set (Γ_∞) of diploids of monosubstituted alkanes up to infinite carbon content. Let the symbol γ_k be the number of monosubstituted alkanes (carbon content k) which are regarded as diploids. Then the set Γ_∞ is characterized by a generating function:

$$c(x^2) = \sum_{k=0}^{\infty} \gamma_k x^{2k} \quad (14)$$

where γ_0 (=1) is an initial value for representing a hydrogen atom. Because the isomorphic relationship between the alternating group of degree 3 ($\mathcal{A}^{[3]}$) and the C_3-point group, we can obtain the relationship $\gamma_k = S_k$, although these coefficients are conceptually distinct.

The three permutations corresponding to rotations in $C_{3v}(/C_s)$ (eq 9) are governed by the coset representation $C_3(/C_1)$, which can be equalized to $\mathcal{A}^{[3]}$ (eq 7). The permutation (1)(2)(3) leaves each ligand invariant so as to indicate $b(x)^3$ because each one-cycle is characterized as being hemispheric. The permutation (1 2 3) represents a rotation $\{1,2,3\} \rightarrow \{2,3,1\}$, which implies that three ligands at issue are identical so as to indicate $b(x^3)$ in agreement of the

hemispheric nature of the three-cycle. the average of the three permutations is calculated to give a functional equation:[95]

$$b(x) = 1 + \frac{x}{3}\{b(x)^3 + 2b(x^3)\} \quad (15)$$

This equation has the same form as eq 8, but the hemisphericity for deriving eq 15 is a new matter in comparison with eq 8. This equation can be recursively used to give a generating function,

$$b(x) = \sum_{k=0}^{\infty} \beta_k x^k \quad (16)$$

which is essentially equivalent to eq 5. Because the isomorphic relationship between the alternating group of degree 3 ($\mathcal{A}^{[3]}$) and the C_3-point group, we can obtain the relationship $\beta_k = \gamma_k = S_k$, although these coefficients are conceptually distinct.

Let $C(x)$ and $B(x)$ denote generating functions to give the number of pairs of chiral monosubstituted alkanes and the total number as 3D structural isomers:

$$C(x) = \sum_{k=0}^{\infty} C_k x^k \quad (17)$$

$$= x^4 + 3x^5 + 10x^6 + 30x^7 + 88x^8 + 255x^9 + 742x^{10} + 2157x^{11} + 6312x^{12} + 18563x^{13} + 54932x^{14} + 163479x^{15} + 489264x^{16} + 1471692x^{17} + 4447896x^{18} + 13500689x^{19} + 41140608x^{20} + 125818217x^{21} + 386050543x^{22} + 1188093392x^{23} + 3666547089x^{24} + 11344058829x^{25} + \ldots \quad (18)$$

$$B(x) = \sum_{k=0}^{\infty} B_k x^k \quad (19)$$

$$= 1(=B_0) + x + x^2 + 2x^3 + 4x^4 + 8x^5 + 18x^6 + 44x^7 + 111x^8 + 296x^9 + 811x^{10} + 2279x^{11} + 6520x^{12} + 18933x^{13} + 55568x^{14} + 164613x^{15} + 491227x^{16} + 1475197x^{17} + 4453995x^{18} + 13511597x^{19} + 41159667x^{20} + 125852346x^{21} + 386110379x^{22} + 1188200648x^{23} + 3666735665x^{24} + 11344397151x^{25} + \ldots \quad (20)$$

where C_0 (=0) and B_0 (=1) is an initial value. Because $b(x) = a(x) + 2C(x)$ and $B(x) = a(x) + C(x)$, we can evaluate them by using the following equations:[95]

$$C(x) = \frac{1}{2}\{b(x) - a(x)\} = \frac{x}{6}\{b(x)^3 + 2b(x^3) - 3a(x)c(x^2)\} \quad (21)$$

$$B(x) = \frac{1}{2}\{b(x) + a(x)\} = 1 + \frac{x}{6}\{b(x)^3 + 2b(x^3) + 3a(x)c(x^2)\} \quad (22)$$

The recursive calculations based on eqs 10, 13, and 15 give the number of monosubstituted alkanes as 3D-structural isomers of various types (A_k, γ_k, and β_k of carbon content k). Thereby, the values C_k and B_k are calculated by means of eqs 21 and 22. The resulting values are collected up to carbon content 25 in the form of generating functions (eqs 12, 18, and 20).[89,95]

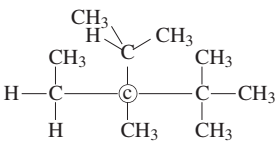
4. Enumeration of Alkanes

The data of monosubstituted alkanes, which have been obtained in Section **3**, can be regarded as the data of alkyl substituents for enumerating alkanes as graphs and 3D structures. After alkanes are categorized into centroidal and bicentroidal alkanes (Subsection **4.1**), Subsection **4.2** deals with the enumeration of centroidal and bicentroidal alkanes as constitutional isomers (Def. 1) by means of Pólya's theorem. Subsection **4.3** enumerates centroidal and bicentroidal alkanes as steric isomers (Def. 3). Subsection **4.4** deals with the enumeration of centroidal and bicentroidal alkanes as 3D-structural isomers (Def. 4) by means of Fujita's proligand method.

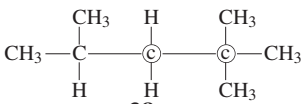
4.1 Categorization of Alkanes into Centroidal and Bicentroidal (3D-)Trees. To enumerate alkanes as trees or 3D-trees, they are categorized into centroidal trees (or 3D-trees) and bicentroidal trees (or 3D-trees), as depicted in Figure 6. For Jordan's definitions of centroidal and bicentroidal trees,[21] see Harary's book.[26] To understand the difference between centroidal and bicentroidal trees, a glance at a bicentroidal tree provides us with an easy way. That is to say, the two terminal

a) Graphs or constitutional isomers (trees)

Examples:

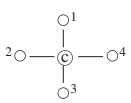


37 centroidal alkane

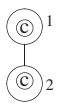


38 bicentroidal alkane

Skeletons for graphs or constitutional isomers (trees):



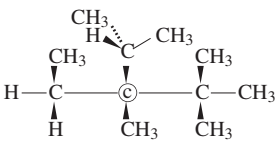
39 centroidal skeleton ($\mathcal{S}^{[4]}$)



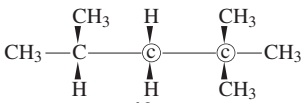
40 bicentroidal skeleton ($\mathcal{S}^{[2]}$)

b) Steric isomers or 3D-structural isomers (3D-trees)

Examples:



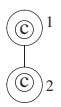
41 centroidl alkane



42 baicentroidal alkane

Skeletons for steric isomers or 3D-structural isomers (3D-trees):

43 centroidal 3D skeleton ($\mathbf{T}_d(/\mathbf{C}_{3v})$)



44 bicentroidal 3D skeleton ($\mathbf{K}(/\mathbf{K}')$)

Figure 6. Alkanes and their skeletons as centroidal and bicentroidal trees or 3D-trees. The symbol © denotes a centroid, while the symbol ©–© denotes a bicentroid.

Table 1. Numbers of Alkanes as Trees Categorized by Two Dichotomies[92,96]

k	$\hat{R}_k$ (Centroidal and unbalanced)	$\tilde{U}_k^{(G)}$ (Bicentroidal and unbalanced)	$B_k^{(G)}$ (Bicentroidal and balanced)	$R_k^{(T)}$ (Total of alkanes as graphs)	$S_k^{(T)}$ (Total of alkanes as steric isomers)
		$(\tilde{R}_k = \tilde{U}_k^{(G)} + B_k^{(G)})$		$(R_k^{(T)} = \hat{R}_k + \tilde{R}_k)$	$(S_k^{(T)} = \hat{S}_k + \tilde{S}_k)$
1	1	0	0	1	1
2	0	0	1	1	1
3	1	0	0	1	1
4	1	0	1	2	2
5	3	0	0	3	3
6	2	1	2	5	5
7	9	0	0	9	11
8	8	6	4	18	24
9	35	0	0	35	55
10	39	28	8	75	136
11	159	0	0	159	345
12	202	136	17	355	900
13	802	0	0	802	2412
14	1078	741	39	1858	6563
15	4347	0	0	4347	18127
16	6354	3916	89	10359	50699
17	24894	0	0	24894	143255
18	38157	22155	211	60523	408429
19	148284	0	0	148284	1173770
20	237541	128271	507	366319	3396844
21	910726	0	0	910726	9892302
22	1511717	765703	1238	2278658	28972080
23	5731580	0	0	5731580	85289390
24	9816092	4671096	3057	14490245	252260276
25	36797588	0	0	36797588	749329719

nodes of a bicentroid carry residues of equal carbon contents which are halves of the carbon content of the tree or 3D-tree. For example, the two terminal nodes of a bicentroid (©–©) in the tree **38** or 3D-tree **42** carry residues of carbon content 4, i.e., isobutyl and *t*-butyl. Otherwise, a tree (or 3D-tree) is determined to be centroidal, as exemplified by **37** and **41**, where each centroid (©) accommodates four ligands, i.e., methyl, ethyl, isopropyl, and *t*-butyl ligands.

4.2 Enumeration of Alkanes as Constitutional Isomers (Trees or Graphs). 4.2.1 Alkanes as Centroidal Trees: Alkanes as centroidal trees can be derived by placing four alkyl ligands (or hydrogen atoms) on the four positions of the skeleton **39** shown in Figure 6.

Because the four positions of the skeleton **39** are governed by the symmetric group of degree 4, i.e., $\mathcal{S}^{[4]}$, Pólya's theorem[24,25] teaches us that they are characterized by the following functional equation:

$$\hat{R}(x) = \frac{1}{24}\{r(x)^4 + 3r(x^2)^2 + 8r(x)r(x^3) + 6r(x)^2r(x^2) + 6r(x^4)\} \quad (23)$$

Suppose that we have evaluated the data of monosubstituted alkanes (alkyl ligands) up to m by means of eq 4 to give $r(x)^{(m)} = \sum_{k=0}^{m} R_k x^k$ (cf. eq 1). Then, the intermediate function $r(x)^{(m)}$ is introduced into the right-hand side of the functional equation represented by eq 23. The resulting function is expanded to give a generating function, where the terms of x^{2m+1} and x^{2m+2} are effective according to Jordan's criterion of centroidal trees so that their coefficients are adopted as the numbers for carbon content $k = 2m + 1$ and $2m + 2$. The evaluated values are listed in the $\hat{R}_k$ (centroidal and unbalanced) column of Table 1.

4.2.2 Alkanes as Bicentroidal Trees: Because the two positions of the skeleton **40** are governed by the symmetric group of degree 2, i.e., $\mathcal{S}^{[2]}$, they are characterized by the following functional equation:

$$\tilde{R}(x) = \frac{1}{2}\{r(x)^2 + r(x^2)\} \quad (24)$$

according to Pólya's theorem.[24,25] After we have evaluated the intermediate function (i.e., $r(x)^{(m)} = \sum_{k=0}^{m} R_k x^k$, cf. eq 1) for monosubstituted alkanes (alkyl ligands) up to m, the intermediate function $r(x)^{(m)}$ is introduced into the right-hand side of the functional equation represented by eq 24. The resulting function is expanded to give a generating function, where the term of x^{2m} is effective according to Jordan's criterion of bicentroidal trees so that the coefficient $\tilde{R}_k$ of the term is adopted as the number for carbon content $k = 2m$. The evaluated values are further categorized into balanced ($B_k^{(G)}$) and unbalanced trees ($\tilde{U}_k^{(G)}$) according to Fujita's formulation,[92] where they are listed in the respective columns of Table 1. The total numbers ($\tilde{R}_k$) of alkanes as bicentroidal trees are obtained by summing up the two columns, i.e., $\tilde{R}_k = \tilde{U}_k^{(G)} + B_k^{(G)}$.

Total numbers ($R_k^{(T)}$) of trees (centroidal plus bicentroidal trees) are calculated to be $R_k^{(T)} = \hat{R}_k + \tilde{R}_k$, which are listed in Table 1.

4.3 Enumeration of Alkanes as Steric Isomers. 4.3.1 Centroidal Steric Isomers: To enumerate centroidal alkanes as steric isomers, the four positions of the skeleton **39** are regarded as being governed by the alternating group of degree 4, i.e., $\mathcal{A}^{[4]}$, they are characterized by the following functional equation:[24,25]

$$\hat{S}(x) = \frac{1}{12}\{s(x)^4 + 3s(x^2)^2 + 8s(x)s(x^3)\} \quad (25)$$

according to Pólya's theorem.

4.3.2 Bicentroidal Steric Isomers: On the other hand, the two positions of the skeleton **40** are governed by the symmetric group of degree 2 ($\mathcal{S}^{[2]}$), they are characterized by the following functional equation:

$$\tilde{S}(x) = \frac{1}{2}\{s(x)^2 + s(x^2)\} \quad (26)$$

On similar lines to the treatments of eqs 23 and 24, the data of monosubstituted alkanes (alkyl ligands) up to m which have been obtained by means of eq 8 to be $s(x)^{(m)} = \sum_{k=0}^{m} S_k x^k$ (cf. eq 5), are introduced into the right-hand sides of the functional equations represented by eqs 25 and 26. Thereby, the coefficients ($\hat{S}_k$ for $k = 2m+1$ and $k = 2m+2$) of the terms x^{2m+1} and x^{2m+2} for eq 25 and the coefficient ($\tilde{S}_k$ for $k = 2m$) of the term x^{2m} for eq 26 are adopted as values to be calculated. The sum of them for each k, i.e., $S_k^{(\mathrm{T})} = \hat{S}_k + \tilde{S}_k$ is listed in Table 1.

4.4 Enumeration of Alkanes as 3D-Structural Isomers. 4.4.1 Centroidal 3D-Structural Isomers: To enumerate centroidal alkanes as 3D-structural isomers, we should consider a 3D-skeleton **43** shown in Figure 6, where four alkyl ligands (or hydrogen atoms) are placed on its four positions.

Because the four positions of the skeleton **43** are governed by the coset representation of $T_d(/C_{3v})$, they are characterized by the following functional equation:[92,96]

$$\hat{A}(x) = \frac{1}{2}\{a(x)^2 c(x^2) + c(x^4)\} \quad (27)$$

$$\hat{C}(x) = \frac{1}{24}\{b(x)^4 + 3b(x^2)^2 + 8b(x)b(x^3) - 6a(x)^2 c(x^2) - 6c(x^4)\} \quad (28)$$

$$\hat{B}(x) = \frac{1}{24}\{b(x)^4 + 3b(x^2)^2 + 8b(x)b(x^3) + 6a(x)^2 c(x^2) + 6c(x^4)\} \quad (29)$$

according to Fujita's proligand method,[83–85] where the symbols denote as follows: $\hat{A}(x)$ for achiral centroidal alkanes, $\hat{C}(x)$ for chiral centroidal alkanes, and $\hat{B}(x)$ for total (achiral plus chiral) centroidal alkanes.

Suppose that we have evaluated the data of $a(x)$ (eq 11 by means of eq 10), $c(x^2)$ (eq 14 by means of eq 13), and $b(x)$ (eq 16 by means of eq 15) up to the carbon content m. The intermediate functions $a(x)^{(m)}$, $c(x^2)^{(m)}$, and $b(x)^{(m)}$ are introduced into the right-hand sides of the functional equations (eqs 27–29). The resulting function is expanded to give a generating function, where the terms of x^{2m+1} and x^{2m+2} are effective so that their coefficients are adopted as the numbers for carbon content $k = 2m+1$ and $2m+2$. The evaluated values are listed in the respective columns of Table 2.[92,96]

4.4.2 Bicentroidal 3D-Structural Isomers: To enumerate bicentroidal alkanes as 3D-structural isomers, we should consider a dumbbell skeleton **44** shown in Figure 6, where two alkyl ligands (or hydrogen atoms) are placed on its two positions. The two positions of the skeleton **44** are governed by the coset representation $\mathbf{K}(/\mathbf{K}')$ of the factor group $\mathbf{K}$ according to Fujita's formulation,[92,96] where $\mathbf{K} = \mathbf{D}_{\infty h}/\mathbf{C}_{\infty}$ and $\mathbf{K}' = \mathbf{D}_{\infty h}/\mathbf{C}_{\infty v}$. Hence, they are characterized by the following functional equation:[92,96]

$$\tilde{A}(x) = \frac{1}{2}\{a(x)^2 + c(x^2)\} \quad (30)$$

$$\tilde{C}(x) = \frac{1}{4}\{b(x)^2 + b(x^2) - a(x)^2 - c(x^2)\} \quad (31)$$

$$\tilde{B}(x) = \frac{1}{4}\{b(x)^2 + b(x^2) + a(x)^2 + c(x^2)\} \quad (32)$$

according to Fujita's proligand method,[83–85] where the symbols denote as follows: $\tilde{A}(x)$ for achiral bicentroidal alkanes, $\tilde{C}(x)$ for chiral bicentroidal alkanes, and $\tilde{B}(x)$ for total (achiral plus chiral) bicentroidal alkanes.

The intermediate functions described above, i.e., $a(x)^{(m)}$, $c(x^2)^{(m)}$, and $b(x)^{(m)}$, are introduced into the right-hand sides of the functional equations (eqs 30–32). The resulting function is expanded to give a generating function, where the term of x^{2m} is effective so that its coefficient is adopted as the number for carbon content $k = 2m$. The evaluated values are listed in the respective columns of Table 2.[92,96]

For the sake of convenience, total numbers are calculated by summing the data collected in the subtotal columns in Table 2 so as to give $B_k^{(\mathrm{T})} = \hat{B}_k + \tilde{B}_k$ for total numbers, which are also listed in the last column of Table 2.

5. Comparison between Constitutional Isomers and 3D-Structural Isomers

5.1 On Monosubstituted Alkanes. The coefficients of eqs 2 and 6 (constitutional isomers and steric isomers) and those of eqs 12, 18, and 20 (3D-structural isomers) are in agreement with the numbers of structures depicted in Figure 2 up to carbon content 5. The coefficients of eqs 2 and 6 indicate $R_6 = 17$ (constitutional isomers or graphs) and $S_6 = 28$ (steric isomers), which are in agreement with the structures shown in Figure 1. Note that each constitution (or graph) is depicted in a broken-lined box. The coefficients of terms x^6 in eqs 12, 18, and 20 indicate the values for carbon content 6, i.e., $A_6 = 8$ (achiral 3D-structural isomers), $C_6 = 10$ (pairs of enantiomeric 3D-structures), $B_6 = 18$ (total 3D-structural isomers), where $B_6 = A_6 + C_6 = 8 + 10 = 18$. These values are in agreement with the structures shown in Figure 1, each of which is depicted in a straight-lined box. Note that $S_6 = A_6 + 2C_6 = 8 + 2 \times 10 = 28$.

More itemized values which take account of numbers of asymmetric carbon atoms and pseudoasymmetric carbon atoms have been obtained according to the method developed by Fujita,[97] although the detailed derivation of the method is not discussed in the present account. By introducing a dummy variable y, the following itemized values are obtained for the case of carbon content 6:[97]

$$\text{achiral} \quad A_6 = 8: \quad 8x^6 \quad (33)$$

$$\text{chiral} \quad C_6 = 10: \quad (8y + 2y^2)x^6 \quad (34)$$

$$\text{total} \quad B_6 = 18: \quad (8 + 8y + 2y^2)x^6 \quad (35)$$

Table 2. Numbers of Alkanes as 3D-Structural Isomers[92,96]

k	Centroidal alkanes			Bicentroidal alkanes			Total
	$\hat{A}_k$ (Achiral)	$\hat{C}_k$ (Chiral)	$\hat{B}_k$ (Subtotal)	$\tilde{A}_k$ (Achiral)	$\tilde{C}_k$ (Chiral)	$\tilde{B}_k$ (Subtotal)	$B_k^{(T)}$ $(=\hat{B}_k + \tilde{B}_k)$
1	1	0	1	0	0	0	1
2	0	0	0	1	0	1	1
3	1	0	1	0	0	0	1
4	1	0	1	1	0	1	2
5	3	0	3	0	0	0	3
6	2	0	2	3	0	3	5
7	7	2	9	0	0	0	9
8	7	1	8	7	4	11	19
9	21	17	38	0	0	0	38
10	22	24	46	18	24	42	88
11	61	142	203	0	0	0	203
12	72	211	283	46	180	226	509
13	186	1113	1299	0	0	0	1299
14	220	1784	2004	135	1320	1455	3459
15	567	8780	9347	0	0	0	9347
16	717	15041	15758	364	9768	10132	25890
17	1755	70750	72505	0	0	0	72505
18	2209	127072	129281	1116	75480	76596	205877
19	5454	584158	589612	0	0	0	589612
20	7149	1091507	1098656	3157	601762	604919	1703575
21	17070	4937616	4954686	0	0	0	4954686
22	22476	9554169	9576645	9660	4915803	4925463	14502108
23	53628	42617881	42671509	0	0	0	42671509
24	72656	84925546	84998202	28048	41154240	41182288	126180490
25	169175	374580272	374749447	0	0	0	374749447

$$\text{graph:}\quad R_6 = 17:\quad (8 + 8y + y^2)x^6 \tag{36}$$

where the power of each variable y indicates the number of asymmetric carbon atoms. The data of chiral monosubstituted alkanes (eq 34) show that there appear eight 3D-structural isomers with one asymmetric carbon atoms and two 3D-structural isomers with two asymmetric carbon atoms in agreement with the 3D-structures surrounded by a straight-line box in Figure 1. On the other hand, the data of graphs (eq 36) show the presence of eight graphs (constitutional isomers) with one asymmetric carbon atoms and one graph (one constitution) with two asymmetric carbon atoms, which is in agreement with the 3D-structures surrounded by a broken-lined box in Figure 1.

For the numbers of monosubstituted alkanes of carbon content 9, we find $R_9 = 211$ (eq 2) and $B_9 = 296$ (eq 20). Among them, let us examine the pseudoasymmetric cases shown in Example 3 of Figure 5. According to Fujita,[97] more detailed values can be obtained:

$$\text{achiral}\quad A_9 = 41:\quad (39 + 2y^2z)x^9 \tag{37}$$

$$\text{chiral}\quad C_9 = 255:\quad (102y + 125y^2 + 28y^3)x^9 \tag{38}$$

$$\text{total}\quad B_9 = 296:\quad \{39 + 102y + (125 + 2z)y^2 + 28y^3\}x^9 \tag{39}$$

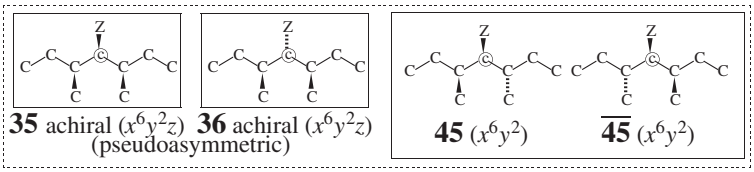
$$\text{graph:}\quad R_9 = 211:\quad (39 + 102y + 63y^2 + 7y^3)x^9 \tag{40}$$

where the number of pseudoasymmetric carbons is considered by the power of a dummy variable z, just as the number of asymmetric carbons is taken into consideration as the power of a dummy variable y.

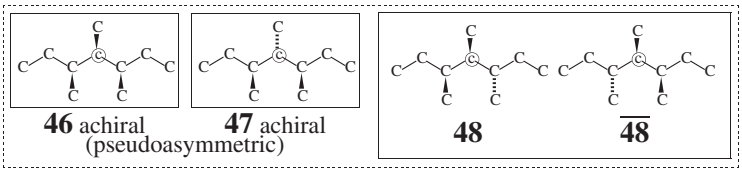
By comparison of eq 39 and eq 40, the difference between $B_9 = 296$ (eq 20) and $R_9 = 211$ (eq 2) stems from the terms $(125 + 2z)y^2$ (eq 39) and $63y^2$ (eq 40). Relevant 3D structures are listed in Figure 7a, which shows one constitution (graph) surrounded by a broken-lined box corresponding to one graph, i.e., {**35**,**36**,**45**,$\overline{\mathbf{45}}$}, among the 63 graphs ($63y^2$ of eq 40). The remaining 62 graphs (62 constitutional isomers) correspond to 248 of 3D structures, i.e., $(63 - 1) \times 2^2 = 248$ (cf. eq 40). On the other hand, the three 3D-structural isomers, each of which surrounded by a straight-lined box (i.e., {**35**}, {**36**}, and {**45**,$\overline{\mathbf{45}}$}), correspond to $(1 + 2z)y^2$ which is part of $(125 + 2z)y^2$. The remaining 124 of 3D-structural isomers (124 pairs of (self-)enantiomeric 3D structures) also correspond to 248 of 3D structures, i.e., $\{(125 + 2z) - (1 + 2z)\} \times 2^{(2-1)} = 248$ (cf. eq 39). The value 250 (i.e., 248 + **45** + $\overline{\mathbf{45}}$) has been alternatively evaluated as the number of steric isomers with two asymmetric carbons (cf. Table 4 of Ref. 97). A more systematic investigation on the fate of asymmetry and pseudoasymmetry in the enumeration of monosubstituted alkanes has been reported recently.[102]

5.2 On Alkanes. To exemplify degeneration due to pseudoasymmetry, let us examine the data of centroidal alkanes of carbon content 10, i.e., $\hat{R}_{10} = 39$ for centroidal alkanes as graphs (Table 1) and $\hat{B}_{10} = 46$ for centroidal alkanes as 3D-structural isomers (Table 2). According to the method developed by Fujita,[100] the numbers of asymmetric carbons and pseudoasymmetric carbons are taken into consideration by introducing dummy variables y and z. Thereby, the following itemized values have been obtained:

a) Monosubstituted alkanes of carbon content 9 for representing pseudoasymmetric cases.



b) Centroidal alkanes of carbon content 10 for representing pseudoasymmetric cases.



c) Bicentroidal alkanes of carbon content 10 for representing *meso* cases.

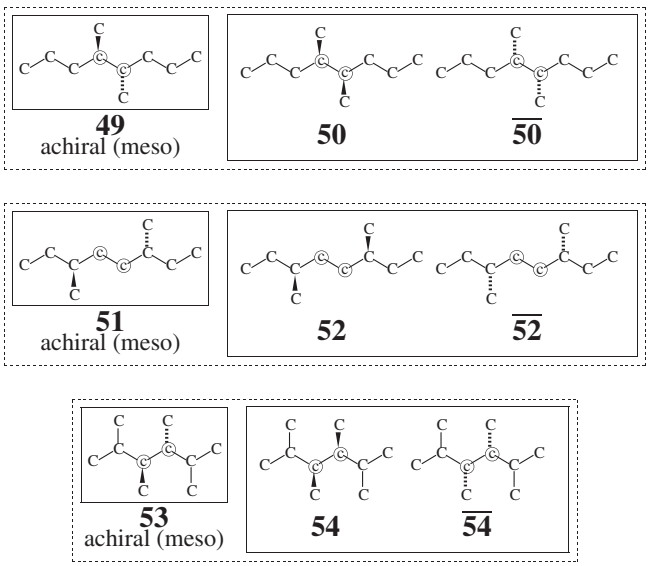


Figure 7. Monosubstituted alkanes and alkanes for exhibiting degeneration, i.e., pseudoasymmetric and meso cases. Each set of 3D structures in a broken-lined box corresponds to a single constitution, which is counted once as constitutional isomers. Each set of 3D structures in a straight-lined box corresponds to an achiral 3D-structure or a pair of enantiomeric 3D-structures, which is counted once as 3D-structural isomers. Each 3D structure is counted once as steric isomers.

$$\text{achiral} \quad \hat{A}_{10} = 22: \quad (20 + 2y^2z)x^{10} \tag{41}$$

$$\text{chiral} \quad \hat{C}_{10} = 24: \quad (13y + 11y^2)x^{10} \tag{42}$$

$$\text{total} \quad \hat{B}_{10} = 46: \quad \{20 + 13y + (11 + 2z)y^2\}x^{10} \tag{43}$$

$$\text{graph:} \quad \hat{R}_{10} = 39: \quad (20 + 13y + 6y^2)x^{10} \tag{44}$$

where the number of pseudoasymmetric carbons is considered by the power of a dummy variable z and the number of asymmetric carbons is taken into consideration as the power of a dummy variable y.

By comparison of eq 43 and eq 44, we find the difference between the term $x^{10}y^2(11 + 2z)$ for 3D-structural isomers and the term $6x^{10}y^2$ for constitutional isomers. The difference can be ascribed to pseudoasymmetry depicted in Figure 7b. Thus, the presence of two achiral 3D-structures (**46** and **47** as pseudoasymmetry) and one pair of enantiomeric 3D-structures ({**48**,$\overline{\mathbf{48}}$}) corresponds to the term $x^{10}y^2(1 + 2z)$ among $x^{10}y^2(11 + 2z)$, as illustrated by three straight-lined boxes. From an alternative viewpoint based on constitutional isomerism, the combined set {**46**,**47**,**48**,$\overline{\mathbf{48}}$} is regarded as one constitution surrounded by a broken-lined box, which is ascribed to the term $x^{10}y^2$ (one constitution) among $6x^{10}y^2$ (six constitutional isomers). The remaining $10x^{10}y^2$ (for ten 3D-structural isomers) shows the presence of 20 ($=10 \times 2^{(2-1)}$) centroidal 3D structures with two asymmetric carbons, where there occurs no degeneration. On the other hand, the remaining $5x^{10}y^2$ (for five constitutional isomers) also shows the presence of 20 ($=5 \times 2^2$) centroidal 3D structures with two asymmetric carbons.

As for degeneration due to meso cases for alkanes of carbon content 10, we find $\tilde{R}_{10} = \tilde{U}_{10}^{(G)} + B_{10}^{(G)} = 28 + 8 = 36$ (Table 1) for bicentroidal constitutional isomers and $\tilde{B}_{10} = 42$ (Table 2) for bicentroidal 3D-structural isomers. More detailed data according to the method developed by Fujita[100] have been reported as follows:

$$\text{achiral} \quad \tilde{A}_{10} = 18: \quad (15 + 3y^2)x^{10} \tag{45}$$

$$\text{chiral} \quad \tilde{C}_{10} = 24: \quad (15y + 9y^2)x^{10} \tag{46}$$

$$\text{total} \quad \tilde{B}_{10} = 42: \quad (15 + 15y + 12y^2)x^{10} \tag{47}$$

$$\text{graph:} \quad \tilde{R}_{10} = 36: \quad (15 + 15y + 6y^2)x^{10} \tag{48}$$

where the number of asymmetric carbons is taken into consideration as the power of a dummy variable y.

By the comparison between eq 47 and eq 48, we find the difference between the term $12x^{10}y^2$ for 3D-structural isomers and the term $6x^{10}y^2$ for constitutional isomers. The difference can be ascribed to pseudoasymmetry depicted in Figure 7c. The presence of three meso compounds (**49**, **51**, and **53**) is predicted by the term $3x^{10}y^2$ contained in eq 45. Recently, the fate of asymmetry and pseudoasymmetry in the enumeration of alkanes has been investigated more systematically.[103]

6. Concluding Remarks and Perspectives

6.1 To Begin with 2D Structures or with 3D Structures? That is the Question. Organic chemistry was originally founded on the basis of 2D structures, although actual organic compounds have 3D structures. As a result, organic stereochemistry as discovered afterwards by van't Hoff[36] and Le Bel[37] resulted in 2D structures being extended to 3D structures. This conventional methodology has definitely influenced the above-mentioned definitions of constitutional isomers (Def. 1) and of stereoisomers (Def. 2), which have been adopted in most textbooks on organic chemistry.[10] The conventional methodology has been effective to demonstrate qualitative aspects of stereochemistry, as found in the state-of-the-art situation of organic stereochemistry.

In contrast, the methodology employed in the present solutions of the interdisciplinary enumeration problems has the reverse direction, i.e., 3D structures to 2D structures. Thus, 3D structures are first considered as given objects, and then they are categorized into respective equivalence classes on the action of appropriate groups, e.g., symmetric groups and alternating groups for constitutional isomers and steric isomers as well as point groups for steric isomers (governed by point groups conceptually distinct from the alternating groups) and 3D-structural isomers (due to enantiomeric relationships). The present methodology is reflected in the above-mentioned definitions of steric isomers (Def. 3) and of 3D-structural isomers (Def. 4). The present account has shown that the present methodology is effective to solve quantitative problems of organic stereochemistry.

Def. 4 on 3D-structural isomers (for the present methodology) and Def. 2 on stereoisomers (for the conventional methodology) are both concerned with 3D structures but work differently to characterize the 3D structures. Obviously, one remaining task is to integrate the two methodologies, so that the resulting theoretical framework would support both qualitative and quantitative aspects of organic stereochemistry. This task open to future investigations would require the development of further theoretical tools for treating 2D and 3D structures in a common basis.

6.2 Qualitative vs. Quantitative Aspects of Stereochemistry. Stereochemistry so far has been devoted to qualitative discussions, where terms for specifying relationships are mainly employed. This feature causes some difficulties in discussing quantitative aspects of stereochemistry. In particular, the term diastereomers stems from diastereomeric relationships between inequivalent 3D-structures which coincide to give a single constitution (2D structure) but not to give a pair of enantiomers. When we use a singular term "a diastereomer" to refer to a 3D structure, it could possess a specific meaning only if an appropriate 3D structure is referred to as a counterpart. For example, we may say that the 3D structure **50** is a diastereomer of a counterpart 3D structure **49**. However, this means that we only state a diastereomeric relationship between one 3D structure **50** and the other 3D structure **49**. In other words, the 3D structure **50** itself is by no means a diastereomer. The same situation holds true more or less in the usage of a singular term "an enantiomer" or "a stereoisomer."

Such ambiguity of stereochemical terminology has been first avoided as discussed in Section **2**, before we have engaged in solving the enumerations of monosubstituted alkanes and alkanes with given carbon contents. Arriving at unambiguous terminology has required the help of Fujita's USCI approach,[14,69] which has a broader prospect as part of mathematical organic stereochemistry. Moreover, the development of such ideas as achiral-structure generators and diploid generators (Figure 5) has stemmed from direct supports provided by the concept of sphericities, which is one of the main dogmas of Fujita's USCI approach[14,69] and has been modified to develop Fujita's proligand method[83–85] as a more succinct formulation.

6.3 Oversimplified Dichotomy between Enantiomers and Diastereomers. It is worthwhile here to point out that Def. 4 is inevitable in discussions on the numbers of 3D structures in order to keep consistency with Def. 1 and Def. 3. The use of Def. 2 (according to the conventional stereochemistry) for the present enumeration problem in place of Def. 4 is unsuitable because of a drawback inherent in the conventional terminology of stereochemistry: oversimplified dichotomy between enantiomers and diastereomers.

For example, two formulas contained in each pair of **9**/$\overline{\mathbf{9}}$–**16**/$\overline{\mathbf{16}}$ (Figure 1) are determined to be stereoisomers (enantiomers) if a constitution surrounded by a broken-lined box is taken into consideration. The number of stereoisomers is determined to be 2 in each case. However, the enantiomeric relationship is not determined within the definition of stereoisomers (Def. 2), because Def. 2 involves no reflection operations. Note that there is one stereoisomeric relationship between the two stereoisomers, which is afterward determined to be one enantiomeric relationship between two enantiomers by applying reflection operations.

On the other hand, four formulas **17**/$\overline{\mathbf{17}}$ and **18**/$\overline{\mathbf{18}}$ (Figure 1) are determined to be stereoisomers if a constitution surrounded by a broken-lined box is taken into consideration. The number of stereoisomers is determined to be 4 in each case. Note that there are two enantiomeric relationships and four diastereomeric relationships if we rely on the terminology of the conventional stereochemistry. Although diastereomers are defined as stereoisomers that are not enantiomers, diastereomers cannot be counted, whereas two pairs of enantiomers and and four stereoisomers per constitution can be counted. Hence, the dichotomy between enantiomers and diastereomers is oversimplified to discuss stereoisomerism consistently.

Each of eight formulas **1**–**8** is frequently referred to by saying that there is no stereoisomer because such an achiral case is regarded as exhibiting no stereoisomerism. This means that there is no stereoisomeric (or enantiomeric) relationship. Strictly speaking, however, we should say that the number of stereoisomers is one for the achiral case, if once the number 2 or 4 is adopted for the above-mentioned chiral objects according to the above definition.

6.4 Beyond Stereochemical and Mathematical Barriers. The applicability of Fujita's USCI approach and Fujita's proligand method is not limited to the above-described enumeration problem, which has remained unsolved as an interdisciplinary problem over 130 years. The present solution of the long-standing problem would provide organic chemists with a hint or a motivation for pursuing a concrete route to "the Heavens of Fujita"[16] beyond both stereochemical and mathematical barriers.

As a remedy for the oversimplified dichotomy, the present account has adopted Defs. 1, 3, and 4 in solving the enumeration problems of alkanes and monosubstituted alkanes. However, Def. 2 should be also taken into consideration in order to give a more systematic format to stereochemistry. This task is open to further investigations.

References

1 P. W. Atkins, *Physical Chemistry*, Oxford Univ. Press, Oxford, **1998**.

2 L. Pauling, E. B. Wilson, Jr., *Introduction to Quantum Mechanics with Applications to Chemistry*, McGraw-Hill, New York, **1935**.

3 K. Fukui, *Quantum Chemistry*, Asakura Shoten, Tokyo, **1968**; Publications of Professor Kenichi Fukui: *Theor. Chem. Acc.* **1999**, *102*, 13.

4 F. A. Cotton, *Chemical Applications of Group Theory*, Wiley-International, New York, **1971**.

5 A. T. Balaban, *Chemical Applications of Graph Theory*, Academic Press, London, **1976**.

6 N. Trinajstić, *Chemical Graph Theory, Vol. I* and *II*, CRC Press, Boca Raton, **1983**.

7 N. Trinajstić, I. Gutman, *Croat. Chem. Acta* **2002**, *75*, 329.

8 J. J. Sylvester, *Nature* **1878**, *17*, 284.

9 A. Kekuié, *Justus Liebigs Ann. Chem.* **1866**, *137*, 129.

10 R. T. Morrison, R. N. Boyd, *Organic Chemistry*, 5th ed., Allyn and Bacon, Boston, **1987**.

11 G. Pólya, *Comput. Rend.* **1935**, *201*, 1167.

12 G. Pólya, *Helv. Chim. Acta* **1936**, *19*, 22.

13 G. Pólya, *Z. Kristal. (A)* **1936**, *93*, 415.

14 S. Fujita, *Symmetry and Combinatorial Enumeration in Chemistry*, Springer-Verlag, Berlin-Heidelberg, **1991**.

15 A. Milicevic, N. Trinajstic, *Chemical Modelling: Applications and Theory*, The Royal Society of Chemistry, Cambridge, **2006**, Vol. 4, pp. 405–469.

16 S. El-Basil, *Combinatorial Organic Chemistry: An Educational Approach*, Nova Science, Huntigton, New York, **2000**.

17 A. Cayley, *Philos. Mag.* **1874**, *47*, 444.

18 A. Cayley, *Rep. Brit. Assoc. Adv. Sci.* **1875**, *45*, 257.

19 A. Cayley, *Am. J. Math.* **1881**, *4*, 266.

20 N. L. Biggs, E. K. Lloyd, R. J. Wilson, *Graph Theory 1736–1936*, Oxford Univ. Press, Oxford, **1976**; Japanese Translation by S. Hitotumatu, J. Akiyama, H. Era: *Gurafu Riron he no Michi*, Chijin Shokan, Tokyo, **1986**.

21 C. Jordan, *J. Reine Angew. Math.* **1869**, *70*, 185.

22 H. R. Henze, C. M. Blair, *J. Am. Chem. Soc.* **1931**, *53*, 3042.

23 H. R. Henze, C. M. Blair, *J. Am. Chem. Soc.* **1931**, *53*, 3077.

24 G. Pólya, *Acta Math.* **1937**, *68*, 145.

25 G. Pólya, R. C. Read, *Combinatorial Enumeration of Groups, Graphs, and Chemical Compounds*, Springer-Verlag, New York, **1987**.

26 F. Harary, *Graph Theory*, Addison-Wesley, Reading, **1969**.

27 G. Pólya, R. E. Tarjan, D. R. Woods, *Notes on Introductory Combinatorics*, Birkhäuser, Boston, **1983**.

28 H. Hosoya, *Kagaku no Ryoiki*, **1972**, *26*, 989.

29 D. H. Rouvray, *Chem. Soc. Rev.* **1974**, *3*, 355.

30 O. E. Polansky, *MATCH* **1975**, *1*, 11.

31 K. Balasubramanian, *Chem. Rev.* **1985**, *85*, 599.

32 R. Otter, *Ann. Math.* **1948**, *49*, 583.

33 R. W. Robinson, F. Harry, A. T. Balaban, *Tetrahedron* **1976**, *32*, 355.

34 N. G. de Bruijn, *Indag. Math.* **1959**, *21*, 59.

35 L. Bytautas, D. J. Klein, *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 1063.

36 J. H. van't Hoff, *Arch. Néerl. Sci. Exactes Nat.* **1874**, *9*, 445.

37 J. A. Le Bel, *Bull. Soc. Chim. Fr.* **1874**, *22*, 337.

38 J. H. van't Hoff, *La Chimie Dans L'Espace*, P. M. Bazendijk, Rotterdam, **1875**.

39 E. Fischer, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 1836.

40 E. Fischer, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2683.

41 E. Fischer, *Aus meinem Leben*, Springer Verlag, Berlin, **1922**.

42 R. C. Read, in *Chemical Aplications of Graph Theory*, ed. by A. T. Balaban, Academic, London, **1976**, pp. 25–61.

43 R. E. Davies, P. J. Freyd, *J. Chem. Educ.* **1989**, *66*, 278.

44 E. Ruch, W. Hässelbarth, B. Richter, *Theor. Chim. Acta* **1970**, *19*, 288.

45 E. Ruch, D. J. Klein, *Theor. Chim. Acta* **1983**, *63*, 447.

46 J. Brocas, *J. Am. Chem. Soc.* **1986**, *108*, 1135.

47 J. Sheehan, *Can. J. Math.* **1968**, *20*, 1068.

48 A. Kerber, K.-J. Thürlings, in *Combinatorial Theory*, ed. by D. Jngnickel, K. Vedder, Springer, Berlin, **1982**, pp. 191–211.

49 W. Hässelbarth, *Theor. Chim. Acta* **1985**, *67*, 339.

50 C. A. Mead, *J. Am. Chem. Soc.* **1987**, *109*, 2130.

51 W. Burnside, *Theory of Groups of Finite Order*, 2nd ed., Cambridge University Press, Cambridge, **1911**.

52 S. Fujita, *Theor. Chim. Acta* **1989**, *76*, 247.

53 S. Fujita, *J. Math. Chem.* **1993**, *12*, 173.

54 S. Fujita, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2770.

55 S. Fujita, *Theor. Chim. Acta* **1992**, *82*, 473.

56 S. Fujita, *J. Math. Chem.* **2001**, *30*, 249.

57 S. Fujita, *J. Am. Chem. Soc.* **1990**, *112*, 3390.

58 S. Fujita, *J. Math. Chem.* **1990**, *5*, 121.

59 S. Fujita, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 203.

60 S. Fujita, *Theor. Chim. Acta* **1990**, *77*, 307.

61 S. Fujita, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2759.

62 S. Fujita, *Chem. Rec.* **2002**, *2*, 164.

63 S. Fujita, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1863.

64 S. Fujita, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 315.

65 S. Fujita, *J. Org. Chem.* **2002**, *67*, 6055.

66 S. Fujita, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 439.

67 C. A. Mead, *J. Am. Chem. Soc.* **1992**, *114*, 4018.

68 S. Fujita, *Organic Chemistry of Photography*, Springer-Verlag, Berlin-Heidelberg, **2004**.
69 S. Fujita, *Diagrammatical Approach to Molecular Symmetry and Enumeration of Stereoisomers*, University of Kragujevac, Faculty of Science, Kragujevac, **2007**.
70 S. Fujita, *MATCH* **2005**, *54*, 251.
71 S. Fujita, *MATCH* **2006**, *55*, 5.
72 S. Fujita, *J. Math. Chem.* **2007**, *42*, 481.
73 S. Fujita, *J. Math. Chem.* **1990**, *5*, 99.
74 S. Fujita, *Theor. Chim. Acta* **1995**, *91*, 291.
75 S. Fujita, *Theor. Chim. Acta* **1995**, *91*, 315.
76 S. Fujita, *Theor. Chem. Acc.* **1998**, *99*, 224.
77 S. Fujita, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1587.
78 S. Fujita, *Theor. Chem. Acc.* **1998**, *99*, 404.
79 S. Fujita, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 13.
80 S. Fujita, *Theor. Chem. Acc.* **1999**, *101*, 409.
81 S. Fujita, *Croat. Chem. Acta* **2006**, *79*, 411.
82 S. Fujita, *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1101.
83 S. Fujita, *Theor. Chem. Acc.* **2005**, *113*, 73.
84 S. Fujita, *Theor. Chem. Acc.* **2005**, *113*, 80.
85 S. Fujita, *Theor. Chem. Acc.* **2006**, *115*, 37.
86 S. Fujita, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2409.
87 S. Fujita, *Tetrahedron* **1991**, *47*, 31.
88 S. Fujita, *MATCH* **2007**, *57*, 5.
89 S. Fujita, *J. Comput. Chem., Jpn.* **2007**, *6*, 59.
90 S. Fujita, *J. Comput. Chem., Jpn.* **2007**, *6*, 73.
91 S. Fujita, *MATCH* **2007**, *57*, 265.
92 S. Fujita, *MATCH* **2007**, *57*, 299.
93 S. Fujita, *J. Math. Chem.* **2008**, *43*, 141.
94 S. Fujita, *MATCH* **2007**, *58*, 5.
95 S. Fujita, *Theor. Chem. Acc.* **2007**, *117*, 353.
96 S. Fujita, *Theor. Chem. Acc.* **2007**, *117*, 339.
97 S. Fujita, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 193. It is a great honor that this article has been selected as a BCSJ award article of *Bull. Chem. Soc. Jpn.* Vol. 81 (No. 2).
98 S. Fujita, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1078. It is a great honor that this article has been selected as a BCSJ selected paper of *Bull. Chem. Soc. Jpn.* Vol. 81 (No. 9).
99 S. Fujita, *MATCH* **2009**, *61*, 273.
100 S. Fujita, *MATCH* **2008**, *59*, 509.
101 S. Fujita, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1423.
102 S. Fujita, *MATCH* **2009**, *62*, 23.
103 S. Fujita, *MATCH* **2009**, *62*, 65.

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