Mathematical Stereochemistry as the Theoretical Foundations of Organic and Inorganic Chemistry

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Mathematical stereochemistry is discussed by surveying books written on Fujita's uSCi (unit-subduced-cycle-index) approach, Fujita's proligand method, Fujita's stereoisogram approach, and related matters from a viewpoint of developing an interdisciplinary chemistry/mathematics field.

Keywords: Stereochemistry, Sphericity, Enumeration, uSCi, Stereogram

1 Introduction

In 2015, I published a book entitled "Mathematical Stereochemistry" as a milestone of my interdisciplinary research for linking chemistry and mathematics [1]. This book has aimed at comprehensive discussions on the theoretical foundations of organic and inorganic chemistry on the basis of Fujita's stereoisogram approach [2,3]. Because this book owes many fundamental ideas to a series of books I have published previously, it is a meaningful task to survey these previous books from a viewpoint of how their ideas are taken over to produce the new book. This task would provide a succinct prospect to my "Half-Century Journey from Synthetic Organic Chemistry to Mathematical Stereochemistry through Chemoinformatics" [4].

2 Serial Survey of my Books

I will here survey my books in the order of carrying out respective researches, but not in the chronological order of publication.

2.1 Organic Chemistry of Photography [5]

I published a book entitled "Organic Chemistry of Photography" (xiv + 587 pages) from Springer in 2004 [5], when film-based photography was highly expected to be replaced by digital electronic photography [6]. This book summarized the history of film-based photography from a viewpoint of synthetic organic chemistry. In particular, Chapter 19 of this book deals with the accomplishments of our research on organic compounds for instant color photography in Fuji Photo Film Co. for 25 years (1972–1997).

Through our efforts to develop dye releasers of high efficiency for instant color photography, I was deeply impressed with the importance of non-bonding stereoechemical effects. This is because a steric hindrance due to a bulky substituent (e.g., a tert-butyl group) and a stereoechemical assistance due to a six-membered transition state (e.g., a methoxyethoxy group) were key technologies introduced into dye-releasing moieties.

2.2 Computer-Oriented Representation of Organic Reactions [7]

The next target of my research in Fuji Photo Film Co. was concerned with chemoinformatics, where I aimed at the development of a reaction database. I proposed imaginary transition structures (ITSs) as the computer-oriented representation of organic reactions [8]. Figure 1 shows the construction of an imaginary transition structure (ITS) for representing an acid-catalyzed hydrolysis of ethyl acetate. The resulting ITS 1 contains three kinds of bonds, i.e., par-bonds (—), in-bonds (—o—), and
out-bonds (—||—), which are capable of representing a reaction process of the acid-catalyzed hydrolysis.

After I had changed my positions to Kyoto Institute of Technology, I summarized the versatility of ITSs in the form of a book entitled "Computer-Oriented Representation of Organic Reactions" (x + 371 pages) [7], which was published from Yoshiooka Shoten by the financial support of Japan Society for the Promotion of Science: Grant-in-aid for Publication Research Results (No. 135305, 2001).

Because ITSs were formulated as 2D structural formulas with three kinds of bonds, we were able to enumerate organic reactions by applying Pólya's theorem to ITSs in place of usual 2D structural formulas of organic compounds. This experience interested me in the application of combinatorial enumeration to organic compounds as 3D structures.

2.3 Symmetry and Combinatorial Enumeration in Chemistry [9]

Through my research on ITSs, I became aware that Pólya's theorem covered enumeration of graphs, but not 3D structures. Hence, new methods of enumerating chemical compounds as 3D structures (not as graphs) should be developed to begin with.

To enumerate both graphs and 3D structures, I developed the concept of unit subduced cycle indices (USCI) after I formulated the subduction of coset representations, which was correlated to Burnside's tables of marks. For the purpose of treating chiral ligands, I have developed the concepts of sphericities of orbits and chirality fittingness.

Under the name Fujita's USCI approach, the four methods of symmetry-itemized enumerations were developed and their versatility was testified by using various skeletons as probes [10]. In addition to these quantitative applications, Fujita's USCI approach also enables us to develop qualitative discussions on prochirality and symmetric properties of various molecules [11,12].

Fujita's USCI approach was summarized in a book entitled "Symmetry and Combinatorial Enumeration in Chemistry" (x + 368 pages), which was published from Springer in 1991.

2.4 Diagrammatical Approach to Molecular Symmetry and Enumeration of Stereoisomers [13]

Fujita's USCI approach emphasizes the concept of equivalence classes (orbits), which act intramolecularly and intermolecularly in a nested fashion. The nested features were formulated diagrammatically by the concept of mandala [14].

The diagrammatical approach based on the concept of mandala and related ideas was summarized as a book entitled "Diagrammatical Approach to Molecular Symmetry and Enumeration of Stereoisomers" (x + 206 pages) [13], which was published as Volume 4 of "Mathematical Chemistry Monographs" series in 2007.

2.5 Combinatorial Enumeration of Graphs, Three-Dimensional Structures, and Chemical Compounds [15]

Fujita's USCI approach supports both symmetry-itemized and gross enumerations of chemical compounds as 3D structures. However, a simpler method for gross enumeration of 3D structures should be developed to stand comparison with the simple procedure of Pólya's theorem.

For this purpose, I have developed Fujita's proligand method [16]. The concept of sphericities of orbits for Fujita's USCI approach has been transformed into the concept of sphericities of cycles for Fujita's proligand method, which enables us to calculate cycle indices with chirality fittingness (CI-CFs). Fujita's proligand method has been applied successfully to combinatorial enumeration of alkanes as 3D structures. This means...
that the long-standing interdisciplinary chemistry/mathematics problem over 130 years has been solved systematically [17].

Fujita's proligand method and related tools for gross enumeration have been summarized as a book entitled "Combinatorial Enumeration of Graphs, Three-Dimensional Structures, and Chemical Compounds" (xiv + 576 pages) [15], which was published in 2013 as Volume 15 of "Mathematical Chemistry Monographs" series.

2.6 Mathematical Stereochemistry [1]

My latest book entitled "Mathematical Stereochemistry" (xviii + 437 pages) [1], which was published in 2015 from De Gruyter, deals with Fujita's stereoisogram approach with various diagrammatic tools.

Fujita's stereoisogram approach provides us with methodology to clarify the roots of serious confusion in modern stereochemistry and to eliminate them systematically. I have proposed the concept of RS-stereoisomerism [2], which is an intermediate concept for mediating enantiomerism and stereoisomerism. The concept of RS-stereoisomerism is formulated algebraically by an RS-stereoisomeric group and diagrammatically by such a stereoisogram as shown in Figure 2.

The vertical direction of the stereoisogram (Figure 2) is concerned with chirality, while the horizontal direction is concerned with RS-stereogenicity. The concept of RS-stereogenicity is derived by the meaningful restriction of stereogenicity, so that we are able to determine how chirality and stereogenicity are distinct and how they interact each other. Because stereoisograms are key devices for avoiding the conceptual defects of modern stereochemistry, this way is called Fujita's stereoisogram approach.

3 Perspectives of Mathematical Stereochemistry

As conclusive remarks on my ideas for advancing mathematical stereochemistry, I here introduce my recent works which have been done during and after the publication of my new book [1].

3.1 Beyond the Situations Caricatured as "the Heavens of Fujita"

Fujita's USCI approach [9] has once been caricatured as "the Heavens of Fujita" by El-Basil (Figure 35 of [18]) at the time of 2001, when barriers to access (stereochemical and mathematical barriers) have been emphasized because of the interdisciplinary methodology of Fujita's USCI approach. El-Basil has later discussed three main stages that led to the development of a systematic study of (stereo)chemical isomer enumeration and has referred to the "Era of Fujita" as the third stage [19].

El-Basil's efforts have been focused on the elimination of a mathematical barrier (e.g., group theory) in combinatorial enumeration, because most organic chemists are unfamiliar with group theory.

As found in the survey of the preceding section, on the other hand, my efforts have aimed at systematizing so-called "Heavens of Fujita." This course means an attempt to establish mathematical stereochemistry, which would provide us with the theoretical foundations of organic and inorganic chemistry. The publication of my latest book in 2015 [1] has resulted in the demonstration of why organic and inorganic chemists should try access to mathematical stereochemistry (~"the Heavens of Fujita" systematized in terms of Fujita's stereoisogram approach). Figure 3, which is a revised version of El-Basil's caricature (Figure 35 of [18]), illustrates that my latest book [1] creates a reliable bridge for giving perspectives on so-called "Heavens of Fujita" and on "Mathematical Stereochemistry" (its title).

As new matters added to so-called "Heavens of Fujita," qualitative and diagrammatic tools derived from Fujita's USCI
approach (e.g., mandalas [13]) have been developed to discuss geometric properties of 3D structures; and discussions on stereochemistry and stereoisomerism in an integrated fashion have been conducted by means of such qualitative and diagrammatic tools as derived by Fujita's stereoisogram approach [1]. The development of these tools would reinforce the access to so-called “Heavens of Fujita” and to mathematical chemistry. Moreover, Fujita’s USCI approach for symmetry-itemized enumeration [9] has been simplified into Fujita’s proligand method for gross enumeration [15], which has become more familiar to organic and inorganic chemists.

3.2 Restructuring the System of Stereochemical Nomenclature

The CiP system [20,21] adopts chirality as a single kind of handedness, so that an absolute configuration is simply linked with chirality. I have pointed out three aspects of an absolute configuration on the basis of the stereoisogram approach [22]. Fujita’s stereoisogram approach [1] is capable of integrating the three aspects of an absolute configuration in the form of a stereoisogram. Thereby, the theoretical foundations of stereochemistry and stereoisomerism have been restructured, so as to revise the system of stereochemical nomenclature in a rational fashion [23].

For example, misleading standpoints for R/S-stereodescriptors of the CiP system [20,21] have been avoided rationally by means of Fujita’s stereoisogram approach [24]. At the same time, misleading standpoints for pro-R/pro-S-descriptors [25] have been avoided rationally by means of Fujita’s stereoisogram approach [26].

Fujita’s stereoisogram approach [1] indicates the presence of two kinds of handedness, i.e., chirality and RS-stereogenicity [27]. As a result, a stereoisogram specifies a quadruplet of RS-stereoisomers, which exhibits a net interaction between chirality and stereogenicity. One of the conceptual defects of modern stereochemistry has been concluded to be the perception of chirality as a single kind of handedness, which means the neglect of RS-stereogenicity as another kind handedness [28].

3.3 Restructuring the Scheme of Isomer Classification

The conventional stereochemistry adopts the following scheme of isomer classification:

\[
\text{enantiomerism} \subseteq \text{diastereoisomerism} \subseteq \text{stereoisomerism} \subseteq \text{constitutional isomerism} \quad (1)
\]

which suffers from the misleading subdivision of isomers into constitutional isomers (isomers different in their constitutions) and stereoisomers (isomers having the same constitution) [29] as well as from the misleading subdivision of stereoisomers into enantiomers and diastereomers. It is unfortunate for chemistry students and researchers that the misleading scheme (Eq. 1) is adopted in the form of flowcharts in textbooks on organic chemistry as well as on organic and inorganic stereochemistry.

The misleading features of the traditional scheme (Eq. 1) stem from the neglect of equivalence relationships and equivalence classes, which is recognized to be another one of the conceptual defects of modern stereochemistry. I have established the following hierarchy of isomerism [30,31] after the introduction of isoskeletomerism as an additional intermediate concept for mediating between stereoisomerism and isomerism:

\[
\text{enantiomerism} \subseteq \text{RS-stereoisomerism} \subseteq \text{stereoisomerism} \subseteq \text{isoskeletomerism} \subseteq \text{isomerism}, \quad (2)
\]

where the boldfaced stages of the hierarchy are new matters, which have been overlooked in the traditional terminology of organic chemistry. The respective stages of the hierarchy (Eq. 2) connote the corresponding equivalence relationships, i.e.,
enantiomeric relationships, RS-stereoisomeric relationships, stereoisomeric relationships, isoskeletal isomeric relationships, and isomeric relationships. Each of these equivalence relationships produces a definite set of promolecules as an equivalence class (orbit). The inclusion behavior among the resulting sets (as orbits) is demonstrated diagrammatically by an isomer-classification diagram [30, 31]. For example, Figure 4 illustrates an isomer-classification diagram for isomers having the molecular formula C$_6$H$_4$X$_2$. Note that the introduction of the concept of isoskeletons (Eq. 2) is capable of differentiating between Kekulé’s benzenes and prismanes (Ladenburg’s benzenes). And note that the traditional “positional isomerism” among 4, 5, and 6 is characterized as an inequivalence relationship within an equivalence class of isoskeletons {…}.

3.4 Systematic Enumeration under the Group Hierarchy

The hierarchy of isomerism shown by equation 2 can be transformed into the following hierarchy of groups:

\[
\begin{align*}
\text{point groups} & \subseteq \text{RS-stereoisomeric groups} \\
\text{stereoisomeric groups} & \subseteq \text{isoskeletal groups.}
\end{align*}
\]

(3)

Fujita’s USCI approach and Fujita’s proligand method, which have originally supported symmetry-itemized enumeration and gross enumeration under point groups, can be extended to be applicable to the respective groups contained in the group hierarchy (Eq. 3) [32].

3.5 Toward the Spread of Mathematical Stereochemistry

To popularize mathematical stereochemistry, organic molecules which attract interests of organic chemists should be systematically examined by a serial application of Fujita’s USCI approach [9], Fujita’s proligand method [15], and Fujita’s stereogram approach [1]. According to this guideline, I have conducted systematic enumeration of cubane derivatives and discussed their symmetries [33].

Finally, such a stereogram as Figure 2 is regarded as a unified representation of stereoisomerization as a kind of organic reaction, because the horizontal direction is recognized to show stereoisomerization (racemization, epimerization) between 2 and 3. Imagine a (real) transition state of the Walden inversion [29], i.e., Y + 2 → 3 + Y, in accord with the horizontal direction of Figure 2; and at the same time, imagine an imaginary transition structure (ITS) for this process. The unified feature of a stereogram is parallel to the unified feature of the ITS shown in Figure 1. This resemblance would be a guideline to future research on mathematical stereochemistry.
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