Set-Valued Maps as a Mathematical Basis of Computer Assistance in Stereochemistry

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Previously, the theory of the chemical identity groups, an essentially nongeometric approach to stereochemistry, has been used for the representation and interpretation of permutational isomerizations and simple chemical reactions. Presently, the extension of this treatment to complex schemes of chemical reactions, such as the highly stereoselective syntheses of chiral α-ferrocenylalkylamines from (−)-menthone, is reported. Two computer programs for the application of the above theory and of the associated set-valued maps are described, a PROLOG program and "ChemId", which is implemented in Pascal.

NONGEOMETRIC STEREOCHEMISTRY

Stereoisomerism and its observable consequences are the main topic of stereochemistry. Traditionally, stereoisomers are defined as molecules that have in common the same chemical constitution but differ in the relative spatial arrangement of their constituent atoms.

As chemistry progresses, the number of chemical compounds increases whose molecules cannot be adequately represented by geometrical models and whose stereochemical properties and behavior are not satisfactorily interpreted and predicted on the basis of purely geometric concepts, including the point group symmetries.[1]

Geometry-based approaches, such as the methods of classical stereochemistry, molecular mechanics, and modeling, as well as quantum chemistry, are suitable for, and limited to, the solution of stereochemical problems concerning single molecular individuals. When problems are encountered that involve ensembles and families of stereoisomers and permutation isomers, including molecules with time-dependent geometric features, there is a definite need for new ideas, theories, and techniques that are usable beyond the scope of customary methodology.[2-6]

In order to ensure a unified theoretical treatment of stereochemistry, some new concepts and definitions have been introduced in the past decade. Chemical identity[5] and permutational isomerism[2] are particularly important among the latter, since their combination provides the conceptual foundation for a new, unified, more abstract, and essentially nongeometric formal approach to static and dynamic stereochemistry.

Under given observation conditions, any two molecules are called chemically identical if they interconvert spontaneously and belong to the same chemical compound.[5,6]

This leads directly to a definition of stereoisomerism without explicit reference to any geometric notion: Any molecules are stereoisomeric, if they have in common the same chemical constitution but are not chemically identical.[5,6]

The (often just momentary) geometric properties and point group symmetries of stereoisomers and their essential moieties are chemically only important because they determine those operations which preserve the ultimately relevant property, the chemically observable identity of a given molecule, and which operations convert it into a distinct isomer. However, the explicitly geometry-based approach is not needed except for visualization purposes, because it is possible to rely directly on chemical identity, without going through the above translation process. Chemical identity, as a notion, justifies a unified approach that is equally valid for rigid and flexible molecules without the need for "idealized models" and "time average geometries".

PERMUTATION ISOMERS

Permutational isomerism[2,5,6] is based on the conceptual dissection of molecules into a set of ligands L and a skeleton, in a fashion that is appropriate for the problem.[3,5] The ligands are those atoms or polyatomic residues that can be interchanged; the remainder of the molecule is its skeleton.

The molecules of a pure and uniform chemical compound X are all chemically identical, although they may differ in shape at a given time. Customarily, the stereochemistry of X is described in terms of a representative momentary "molecular situation" that serves as a reference model E of X. Any considered distribution of the ligands on the skeleton can then be specified just by a permutation of the ligands of the reference model E. Each such redistribution of the ligands converts E into a model representing X, or one of its permutation isomers. The set of all distinct permutation isomers that can be thus obtained is called the family of permutation isomers of the reference isomer X relative to L and the respective skeleton.

The ligands are labeled 1, 2, ..., n according to their chemical nature (e.g., by the CIP rules[7] or by the algorithm CANON[8]), so that they are all mathematically (but not necessarily chemically) distinguishable. Let E be a reference model of X, and let $\lambda = (n_1, ..., n_k)$ be any permutation in SymL, the symmetric group on $|L|$ letters. Then λE will denote the model that results from E by the permutation $n_1 \rightarrow n_2 \rightarrow ... \rightarrow n_k \rightarrow n_1$ of the ligands (i.e., n_1 replaces n_2, ..., n_k replaces n_1), with $k \leq |L|$.

When the ligands L of X are all chemically distinguishable, those permutations of the ligands of E which generate models belonging to X form a group $S_X \subseteq$ SymL, the chemical identity group of X. The permutations of S_X maintain the chemical identity of X. Note that there is no explicit reference to any skeletal symmetry, although the skeletal symmetry rotational symmetry group may be isomorphic to S_X, or one of its subgroups. The chemical identity group represents a combination of chemistry and geometry. The left cosets λS_X of S_X in SymL represent the permutation isomers X.

If some of the ligands are chemically indistinguishable, the permutation isomers of X are represented by the double cosets $\sum \lambda S_X$ in SymL, where the so-called stabilizer group $\sum$ takes into account the chemical equivalencies of the ligands.

SET-VALUED MAPS

The set-valued map is an almost universally useful new mathematical tool for problem-solving in stereochemistry,[5,6,9] just like the equation $B + R = E$ is in constitutional chemistry.[10-16]

A set-valued map is a rule Γ, which assigns to each element

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x of a set X a subset, $\Gamma(x) \subseteq Y$ of a set Y. Hence, Γ has the functionality $\Gamma: X \rightarrow P(Y)$, with $P(Y)$ denoting a covering of Y, that is, a class of subsets of Y such that every point in Y is a member of at least one subset in that class.[9]

Stereochemical equivalence relations can generally be analyzed and expressed in terms of set-valued maps within the symmetric permutation groups, SymL, and their equivalence classes that are based on chemical identity groups, which are subgroups of SymL. Naturally, such equivalence classes do not form coverings, but partitions. Therefore only the set-valued maps between two partitions of SymL are of stereochemical interest. In mathematical terms:

For $x \in X$ the equivalence class containing x is denoted by Ξx, when Ξ is an equivalence relation in X. The set of all equivalence classes is denoted by X/Ξ.

Let $X = Y =$ SymL to be the symmetric permutation group on the alphabet L, U a subgroup of SymL, and Ξ an equivalence relation in SymL. We find for each $\mu \in$ SymL, respectively, its equivalence class $\Xi\mu$:

$$\Gamma: \text{SymL} \rightarrow P(\text{SymL})$$

$$\Gamma(\mu) = \bigcup \{\nu U \mid \nu \in \text{SymL}, \nu U \cap \Xi\mu \neq \emptyset\}$$

This means $\Gamma(\mu)$ is precisely the union of all U-left cosets that the Ξ class meets.

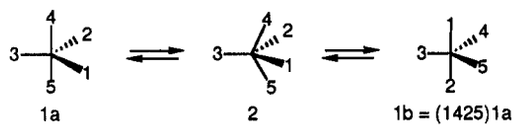
Such set-valued maps are not only useful for tracking interconversions of permutation isomers within their families, and for representing permutation isomers with some chemically indistinguishable ligands, but, as has been found recently,[6,16] the set-valued maps are a powerful and versatile device for dealing with the stereochemical aspect of chemical reactions, as is illustrated by diverse examples.

COMPUTER ASSISTANCE IN STEREOCHEMISTRY THROUGH SET-VALUED MAPS

Because of its algebraic character, the theory of chemical identity groups is ideally suited to serve as the basis of computer programs for the deductive solution of stereochemical problems. In order to work with set-valued maps on a computer, programs are needed which are at least capable of generating cosets of given chemical identity groups and of identifying their nonempty intersections. Such results can be visualized by graphs. Thus, the possible interconversions of the considered molecules within their family of permutation isomers can be traced in detail, i.e., in terms of individual models like E and its permutation isomers.

It is possible to predict the stereochemical outcome of given types of reactions, as is illustrated by the well-known Berry pseudorotation (BPR) of pentacoordinate phosphorane derivatives:[5,17]

Let the set $L = \{1, 2, 3, 4, 5\}$ be the set of ligands and let 1a ⇄ 2 ⇄ 1b be a reference reaction:



Then all interconversions of the permutation isomers in family 1 by BPR are given by set-valued maps of the transition states μS_2 in family 2. The left coset spaces of the chemical identity group S_2 of 2—which are the permutation isomers in family 2 at the same time—form the equivalence relation Ξ:

$$\Gamma(\mu) = \bigcup \{\nu S_{1a} \mid \nu \in \text{SymL}, \nu S_{1a} \cap \mu S_2 \neq \emptyset\}$$

By choosing one μ of each $\Xi\pi \in \text{SymL}/\Xi$, the BPR of the family 1 is completely obtained. To enhance the reader's understanding, the chemical identity groups of these isomers are presented:

$$S_{1a} = \{\epsilon, (123), (132), (12)(45), (13)(45), (23)(45)\}$$
$$S_2 = \{\epsilon, (1425), (12)(45), (1524)\}$$
$$S_{1b} = (1425)S_{1a}(1425)^{-1} = \{\epsilon, (345), (354), (12)(45), (12)(34), (12)(35)\}$$

The left coset spaces of the chemical identity groups S_{1a} and S_2 of the educt 1a and the transition state 2 are used as partitions of SymL. The left coset space of the chemical identity group S_2 defines an equivalence relation Ξ; the respective set-valued map is given by the union of their nonempty intersections $\lambda S_{1a} \cap \mu S_2$ (with $\lambda, \mu \in$ SymL).[18]

For example, 1a and 1b are interconverted by BPR via 2, because with $\lambda = (1425)$ the intersection $\lambda S_{1a} \cap S_2$ contains the permutations (1425) and (1524); λS_{1a} represents 1b in terms of 1a as the reference isomer, and $S_{1b} = \lambda S_{1a}\lambda^{-1}$. The set-valued map involving the transition state ϵS_2 turns out to be

$$\begin{aligned}\Gamma(\epsilon) &= \bigcup \{\nu S_{1a} \mid \nu \in \text{SymL}, \nu S_{1a} \cap \epsilon S_2 \neq \emptyset\} \\ &= \bigcup \{\nu S_{1a} \mid \nu \in \text{SymL}, \nu S_{1a} \cap S_2 \neq \emptyset\} \\ &= \epsilon S_{1a} \cup (1425)S_{1a} \cup (12)(45)S_{1a} \cup (1524)S_{1a} \\ &= S_2 \cdot S_{1a}\end{aligned}$$

Because $\epsilon S_{1a} = (12)(45)S_{1a}$ and $(1425)S_{1a} = (1524)S_{1a}$, the set-valued map of ϵ turns out to be

$$\Gamma(\epsilon) = \epsilon S_{1a} \cup (1425)S_{1a}$$

Any possible interconversions of permutation isomers of 1a are expressed by "chains" of nonempty intersections: Each transition state 2 connects two permutation isomers of 1, because $|S_2|/|S_{1a} \cap S_2| = 2$. And each permutation isomer is reachable via three distinct chiral transition states, because $|S_{1a}|/|S_{1a} \cap S_2| = 3$. The resulting graph contains not only the interconvertible permutation isomers of 1a but also the corresponding transition states, the permutation isomers of 2. Analogously, the customary graph can be directly obtained without reference to transition states of type 2 by using the left coset spaces of S_{1a} and S_{1b} as partitions of SymL.[5]

The permutation isomers of 1 into which 1a is directly converted are represented by $S_{1a} \cdot S_{1b}$, and the permutation isomers of 1 that are directly interconvertible into 1b belong to $S_{1b} \cdot S_{1a}$. Thus, $S_{1a} \cdot S_{1b} \cap S_{1b} \cdot S_{1a}$ expresses the permutation isomers that are immediately connected with the reference reaction 1a ⇄ 1b, and corresponds to a union of the BPR Musher Modes[5] of 1a and 1b.

As a preliminary study, this example was elaborated by a respective PROLOG program: The chemical identity groups S_{1a} and S_2 are considered as input parameters. In the first step, the left transversals (and thereby the left coset spaces) of both identity groups in SymL are determined. Then all nonempty interactions of the left coset spaces of S_{1a} with the left coset spaces of S_2 are identified, and this information leads to the interconversion graph of the isomers of 1a by BPR, which is the program's output. PROLOG allows the description of the aforementioned mathematical facts in a high-level declarative mode. Overall, the combination of application-oriented languages like Pascal with PROLOG seems to be promising with regard to efficiency and effectivity.

In programs dealing with groups, it is useful to employ the concept of *representation matrices*, which permits the storing of permutation groups on n symbols in an $n \times n$ triangular matrix.[19] This concept relies on the idea that a group G may be represented by a subgroup U_1 and a complete (right) transversal of U_1 in G. By reiterating this idea of representing a (sub)group, a *tower* of subgroups results:

$$\{\epsilon\} = U_m \subset U_{m-1} \subset \ldots \subset U_2 \subset U_1 \subset G$$

The knowledge of the complete right transversals of the

several U_{i+1} in U_i answers many questions about G with efficient algorithms, without explicitly dealing with its elements. By choosing a special tower of subgroups, the permutation group G on n elements may be represented by exactly n subgroups:

$$\{\epsilon\} = G^{(n)} \subset G^{(n-1)} \subset \ldots \subset G^{(1)} \subset G^{(0)} = G$$

In order to obtain this special tower of subgroups $G^{(n)}$, ..., $G^{(1)}$, the $G^{(i)}$ must be the pointwise stabilizer of the set $Y = \{1, \ldots, i\}$ in G, which is the subgroup $G_{[Y]} = \{\pi \in G | \forall x \in Y, x^\pi = x\}$. The resulting representation matrix is an $n \times n$ triangular matrix $\mathbf{M}$ with the following properties: $M_{i,i}$ is the identity permutation ϵ, and $\mathbf{M}_{i,j}$ (with $i < j$) either is undefined or is a permutation π such that π pointwise fixes the set $\{1, \ldots, i-1\}$ in G, and $i^\pi = j$. The defined entries of the ith row of the representation matrix correspond to the complete right transversal of $G^{(i)}$ in $G^{(i-1)}$.

For S_{1a} the representation matrix is

ϵ	(1 2)(4 5)	(1 3 2)	undefined	undefined
	ϵ	(2 3)(4 5)	undefined	undefined
		ϵ	undefined	undefined
			ϵ	undefined
				ϵ

Given a set of permutations of $K \subseteq$ SymL, which are the generators of a group $G = \langle K \rangle$, a representation matrix $\mathbf{M}$ for G can be constructed by using K as the input parameter. This construction of $\mathbf{M}$ takes *at most* $O(|K| \cdot n^2 + n^6)$ steps. Furthermore, using $\mathbf{M}$, in additional $O(n^2)$ steps allows a G membership test of a permutation $\pi \in$ SymL. (Recall that $n = |L|$ is the degree of the permutations in SymL, and the order of SymL is $n!$) It is easy to see that the order $|G|$ of G can be evaluated with an $O(n^2)$ complexity (where $|\mathbf{M}_i|$ is the number of defined entries in row i of $\mathbf{M}$):

$$|G| = \prod_{i=1}^{n} |\mathbf{M}_i|$$

The order of S_{1a} therefore is $3 \cdot 2 \cdot 1 \cdot 1 \cdot 1 = 6$.

Membership tests for cosets, double cosets, products of groups, and transversals can be performed on a representation matrix with an $O(n^2)$ complexity as well.

This concept is an excellent basis to extend the use of set-valued maps to a wider range of stereochemical problems as it is used in the comprehensive modular system of computer programs ChemId.[24] This system consists of three functional subunits; two of them are implemented in Pascal and one in PROLOG.

The first of them is the *functional knowledge base* which contains the main implementation of the mathematical basis of the theory of chemical identity groups. It contains algorithms for the important group-theoretic operations on permutations and sets of permutations which may be transversals or subgroups of SymL, or even cosets or products of subgroups. These sets may be conjugated or multiplied with some permutations. Algorithms for membership tests complete the power of these algorithms. Naturally, the above-introduced concept of representation matrices plays an important role in this implementation. As a mathematical raffinesse, the functional knowledge base contains such complex algorithms as set-valued maps, which is used for describing the identity of ligands, isomerization mechanisms, and Musher/Modes.

The second part, the *logic-declarative* PROLOG algorithms, collects the information (data and assumptions, as specified by the user) concerning the stereochemical system. This module also contains algorithms for tests of soundness, completeness, and redundancy of the user's data. By comparing several assumptions or combinations of assumptions, the user has the opportunity to complete a partial specified status. When the user defines tasks, algorithms find task-fitting combinations of assumptions and data. Other algorithms are generating fitting assumptions or recognize homomorphisms and isomorphisms between distinct classes of compounds by analyzing the identity, the racemate, and the constitution groups. This logic-declarative part is mainly based on search procedures but also on production systems.

The last part is a *user interface*, which controls the calling order of the functional entities. The user interface is defined by the syntax and semantics of the three formal languages CISC, ANALOG, and PRÆDLOG. The command language CISC (ChemId System Command Language) is used for the input of the considered ensemble of molecules (EM) as well as the dissection of the EM into skeleton and ligands according to the given problem. ANALOG is a highly applicative language and thereby reflects the applicative character of the functional algorithms it accesses. It primarily serves for the deductive generation of data, their chemical interpretation and presentation. PRÆDLOG programs are formulated as sets of rules with certain unknowns which the program seeks for. Their evaluation depends on algorithms implemented in the logic-declarative part. The resulting (mostly) Boolean values are chemically interpreted.

The described logical partitioning of the interface does not bother the user who is guided by a well-investigated system of windows and menus. Moreover, the description of the interface by formal languages allows any (also future) method of accessing data and algorithms and enables the user to write programs in the respective languages.

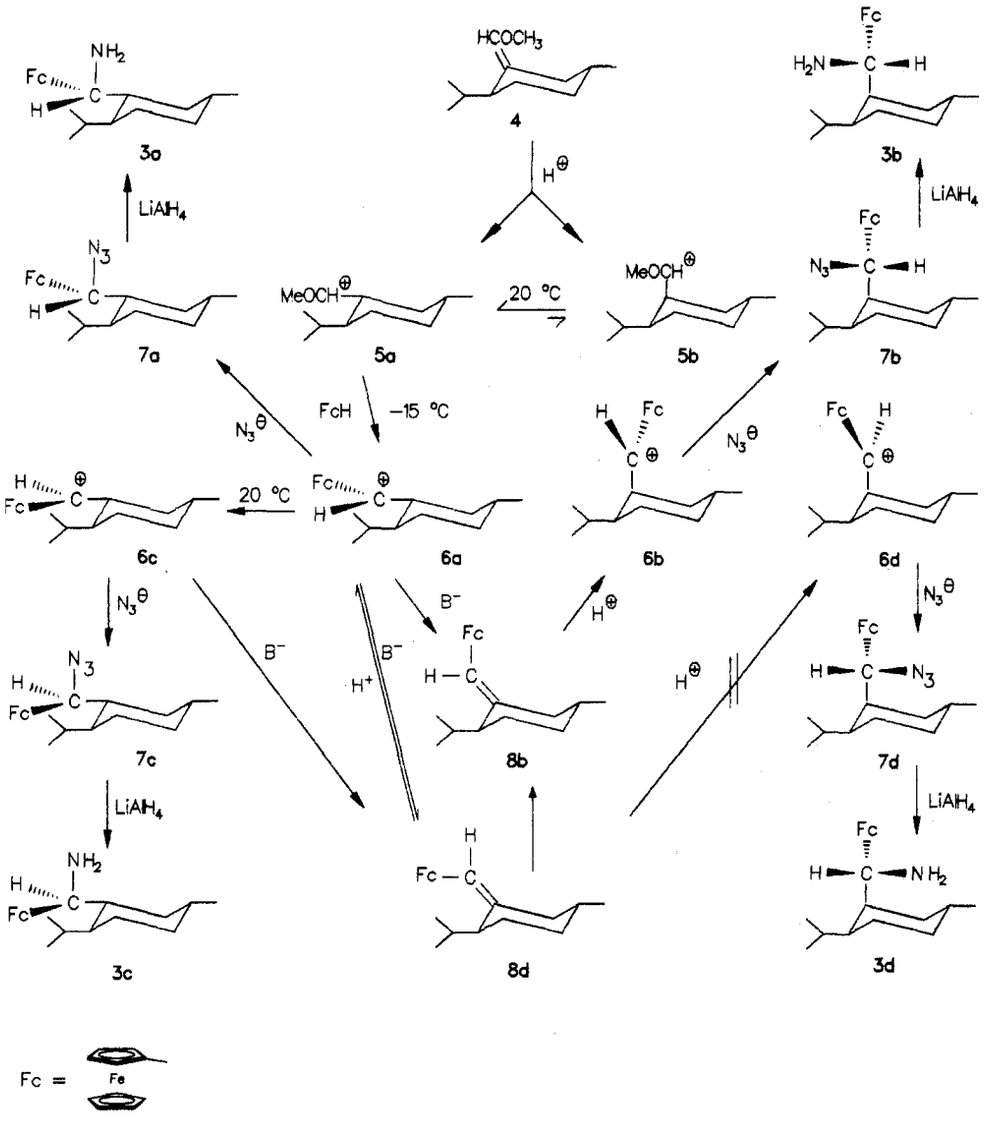
STEREOCHEMICAL ASPECT OF REACTIONS

Recently the stereochemical course of various types of Diels–Alder reactions[6] and the synthesis of cyclopentanoids[16] by cycloaddition of trimethylene methanes and ethene derivatives[20] has been analyzed by set-valued maps. The chiral α-ferrocenylalkylamines are of great interest as chiral templates for asymmetric syntheses, such as peptide syntheses by stereoselective four-component condensations.[21] Recently, some chiral α-ferrocenylalkylamines have been prepared from terpene derivatives that belong to the natural chiral pool.[22]

The three diastereomeric amines **3a–c** can be prepared from the menthone derivative **4**.[23] In this paper we report on a very detailed reinvestigation which led to improved methods for the highly stereoselective preparation of each one of the diastereomers **7a–c**. Up to now, we have not found conditions that lead to the formation of **7d**. The azides **7** are smoothly converted into the amines **3** by reduction with $LiAlH_4$; in contrast to **3c**, **3a** and **3b** crystallize well, and thus the latter are readily available in high purity. (See Scheme I.)

(−)-Menthone is readily converted into **4** by a Wittig reaction with $Ph_3P{=}CHOMe$. At a temperature of 20 °C, the kinetically controlled protonation of **4** produces the carbocations **5a** and **5b** at roughly equal rates. When the resulting solution is allowed to reach thermodynamic equilibrium at 20 °C (in ca. 3 min.), **5a** predominates strongly. Subsequently the reaction mixture is chilled to −15 °C, and ferrocene (FcH) is added. Then **6a** is formed which rearranges into **6c** at 20 °C within 6 h. Scavenging **6a** or **6c** by the azide ion yields **7a** and **7c**, respectively. The carbocations **6a** and **6c** are deprotonated by triethylamine to yield the olefins **8b** (at 20 °C; presumably the thermodynamic control) and **8d** (at −30 °C; kinetically controlled reaction). The amine **3b** is obtained from **8b** via **6b** and **7b**. The protonation of **8d** at ≤−30 °C leads to **6a** that yields **7a** on scavenging with N_3^-, and **3a** by subsequent reduction. The carbocation **6a** rearranges into **6c** at 20 °C, and this can be converted into **3c** via **7c**. We have not succeeded in protonating **8b** or **8d** to form **6d**. Thus **3d** is not available in analogy to **3a–c**.

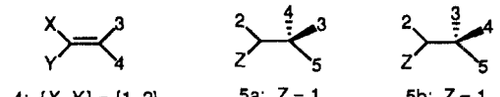
Scheme I



The above scheme of reactions can be represented in terms of set-valued maps that are useful in the computer-assisted treatment of this system of stereoselective syntheses. Here a purely geometry-based approach would be less effective.

The chemical formulas **4**–**8** correspond to the symbols 4–8 with 1 = MeO, 2 = 5 = H, 3 = CH_2, ..., 4 = CHiPr ..., 6 = Fc, and 7 = N_3.

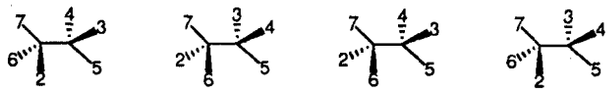
Accordingly, 4–8 are representable by the chemical identity groups S_4–S_8.



4: {X, Y} = {1, 2}
8b: X = 6; Y = 2
8d: X = 2; Y = 6

5a: Z = 1
6a: Z = 6

5b: Z = 1
6b: Z = 6



7a 7b 7c 7d

$S_4 = S_{8b} = S_{8d} = \{\epsilon, (XY)(34), (X3)(Y4), (X4)(Y3)\}$
$S_{5a} = S_{6a} = \{\epsilon, (2Z), (345), (354), (2Z)(345), (2Z)(354)\}$
$S_{5b,6b} = (34)S_{5a,6a}(34) = S_{5a,6a}$
$S_{7a} = \{\epsilon, (267), (276), (345), (354), (267)(345), (267)(354), (276)(345), (276)(354), (23)(46)(57), (24)(37)(56), (25)(36)(47), (236475), (237564), (246573), (247365), (256374), (257463)\}$

When {5, 6, 8b} → 7a is used as a reference reaction, it follows immediately that, besides 7a, also seven additional permutation isomers of 7a are formed by similar reactions, because the intersection of the chemical identity groups $S_{\{5,7,8b\}} = S_{8b} \times \{\epsilon, (57)\}$ of {5, 7, 8b} and S_{8b} contains only one element, namely the identity permutation ϵ. The resulting permutation isomers of 7a are obtained from 7a by the actions of the ligand permutations $\lambda \in S_{\{5,7,8b\}}$ and are represented by the cosets λS_{7a} of S_{7a}. We use permutations of λS_{7a} as descriptors of the conceivable products that are obtained from {5, 7, 8b}. Then:

$\epsilon \equiv$ 7a,
$(26)(34) \equiv$ 7b,
$(34) \in (23)(46)(57) \times S_{7a} \equiv$ 7c, and
$(26), \in (24)(36)(57) \times S_{7a} \equiv$ 7d,

whereas the remaining four permutation isomers, represented by the left cosets

$(57) \times S_{7a}$
$(23)(46) \times S_{7a}$
$(24)(36) \times S_{7a}$, and
$(26)(34)(57) \times S_{7a}$

describe another family of stereoisomers. For chemical reasons, all permissible products of {5, 7, 8b} must be stereoisomers of 7a. Thus the latter nonstereoisomeric products are excluded.

The stereoisomers of 7a would also have been found by determination of a set-valued map of the left coset spaces of

$S_{\{5,7,8b\}}$ and K_{7a}, the group of constitution-preserving permutations of 7a, (i.e., the ensemble identity group of 7a–d). However, this approach is more complicated than the aforementioned one.

The cardinality $|S_8 \cap D[6a,6b]| = |\{\epsilon, (26)(34)\}| = 2$ of the intersection of S_8 and the Dieter group[5] of {6a, 6b}

$$D[6a,6b] = S_{6a} \cap (34)S_{6a}(34) \cup (34)S_{6a} \cap S_{6a}(34)$$
$$= \{\epsilon, (26), (345), (354), (26)(345), (26)(354), (34), (26)(34), (35), (45), (26)(35), (26)(45)\}$$

indicates that the permutation isomers (23)(46) and (24)(36) of 6a are also available from {8a, 8b}. However, these are not stereoisomers and can thus be neglected.

The intersection $D[6a,6b] \cap S_{7a} = \{\epsilon, (345), (354)\}$ with cardinality 3 indicates that 4 (=12/3) members of the family 7 can be formed from {6a, 6b}, because $|D[6a,6b]| = 12$, and that only two isomers can be formed from 6a or 6b, respectively. The set-valued map of the left coset spaces of D[6a, 6b], S_{6a}, or S_{6b}, respectively, and S_{7a} correlates the educts and the products precisely.

The chemical identity groups of the species that belong to the reference reactions of the reaction scheme can be used to generate a cascade of set-valued maps of their left coset spaces. This cascade describes precisely the reaction scheme, representing each species that occurs in terms of permutational relation to its reference isomer.[5]

The fact that two of the ligands (2 = 5 = H) are chemically indistinguishable is irrelevant in this case, because the right coset space of their stabilizer group $\sum = \{\epsilon, (25)\}$ does not generate a chain of intersections within the left coset spaces of S_{6a} or S_{7a}.

This is the first case where a cascade of set-valued maps has been used as a representation of a complex reaction scheme.

Such cases can, of course, also be treated without the present formalism. If, however, the stereochemical aspect of complex reactions is subjected to a computer-assisted analysis, this formal approach is up to now by far the simplest, and also the most general.

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