

# Algebraic Chirality Criteria and Their Application to Chirality Classification in Rigid Molecular Systems<sup>†</sup>

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The “configurational” approach is shown to shift several stereochemical problems to the analysis of combinatorial rather than geometrical objects. On the basis of this approach, algebraic chirality criteria for point 3D configurations and their superpositions (labeled, graph, and molecular configurations) are deduced. The application of the suggested criteria makes it possible to elaborate a new classification system which is directly applied to rigid chiral objects (i.e., to fixed spatial realizations of complete and hydrogen-depleted molecular graphs and to skeleton, framework, and core graphs as well). Several examples of rigid F-, G-, N-, P-, and S-chiral molecules are briefly considered; the simple designation system for nonrigid molecular entities is also outlined.

## 1. INTRODUCTION

During the last two decades, an increasing interest in applications of discrete mathematics to qualitative description of molecular shapes has resulted in several formal approaches to stereochemical problems. Among them, at least three independent approaches were based on just the same idea which was used however for different purposes. In the first approach,<sup>1</sup> which was described by A. S. Dreiding and K. Wirth in 1980, the spatial features of molecules were characterized by  $(n,d)$ -multiplexes, each of them representing an equivalence class of figures formed by  $n$  points (corresponding to atoms) in  $d$ -dimensional space. Although mathematical objects (i.e., tournaments, arrangements, and chirotops) relating to  $(n,d)$ -multiplexes were thoroughly studied<sup>2</sup> by A. W. M. Dress, in both papers no special attention was paid to generation problems for these objects and to their interrelations with other objects describing commonly adopted molecular characteristics (i.e., molecular composition and connectivity).

In the second approach,<sup>3</sup> initiated by the present authors in 1987, the central point was just to rigorously describe the interrelation between mathematical objects corresponding to molecular composition, connectivity, and configuration and to derive an exact formulation of the related generation problems. The introduced notions of (global) 1D, 2D, and 3D configurations were, in fact, analogs of Dreiding and Wirth's  $(n,d)$ -multiplexes, but their applications to stereochemical problems were completely different (see below).

The main purpose of the third approach, M. Johnson's approach,<sup>4</sup> published in 1991, was to construct chemical stereographs which were suggested in order unambiguously to describe the essential features of molecular geometry. The “handedness” was one of characteristics assigned in Johnson's approach to any tetrad (i.e., to four-atomic chain of a molecular graph); this characteristic closely corresponds to the ones suggested in two other approaches. The second characteristic, that of “clincity”, was associated with a sine

of the dihedral angle formed by four-atomic chain; the authors of the present paper hope that the account of clincity can lead to improved methods which will make it possible to generate and unambiguously classify stereoisomers of organic compounds.

The fundamentals as well as applications of the second, “configurational” approach were considered mainly in the Russian publications;<sup>3,5–8</sup> the only exceptions are ref 5b (an introduction to the notion of point 2D configuration) and ref 7b (the rigorous description of stereoisomerism in triangulane molecules; this paper was written in collaboration with synthetic chemists). In addition to the starting idea,<sup>3</sup> which consists in application of the *Ladder of Combinatorial Objects* to the description of generation problems for molecular, constitutional, and stereoformulas, several other topics related to the suggested notions have been studied up to the present. The investigated topics are as follows:

- (1) two kinds of directed graphs which uniquely correspond to planar point configurations,<sup>5</sup>
- (2) several numerical characteristics—namely, configurational and configuration-topological indices—for planar 2D as well as spatial 3D configurations,<sup>6</sup>
- (3) general enumeration formulas for 2D and 3D configurations corresponding to unbranched chains,<sup>7</sup> and
- (4) algebraic criteria making possible to suggest a novel classification scheme for chiral rigid molecules.<sup>8</sup>

Keeping in mind that chirality criteria are of special interest for organic chemists but were only briefly considered in the above cited publications, we present here the material of two preliminary communications<sup>8a</sup> in a complete form and support it with examples and illustrations. Some chemical applications of group theory are firstly discussed (in section 2) in order to introduce the needed mathematical formalism and to demonstrate the simplest applications of this formalism. The terminology and designations correspond to those of the dissertation,<sup>8b</sup> which summarizes the main results obtained up to the present.

## 2. PRELIMINARY NOTES

In this preliminary section, chemical applications of several powerful group-theoretical tools are briefly mentioned; an

<sup>†</sup> This material was a major topic of the summarizing report “Combinatorial Approach to Stereochemical Problems: A Brief Survey”, presented by the first author at the 6th International Conference on Mathematical Chemistry, Pitlochry, June 10–14, 1995.

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examination of modern textbooks (e.g., refs 9–11) undoubtedly shows that groups play the dominant role in many stereochemical problems, especially those related to classification, enumeration, and generation of (chiral or achiral) molecular entities. The fact that certain groups are extremely useful for the description of chirality phenomena may be illustrated by the development of chirality algebra<sup>12</sup> and by the appearance of numerous new groups recently suggested by chemists (only selected references are cited below). Several types of local symmetry groups,<sup>13</sup> framework<sup>14</sup> and topological symmetry<sup>15</sup> groups, pseudochirality<sup>16a</sup> and configuration symmetry<sup>16b</sup> groups, nonrigid symmetry groups<sup>17,18</sup> and groups of chemical identity<sup>10b</sup> may serve as convincing examples. It is important that in most cases the chirality of particular molecular object arises if some “larger” group does not contain specific elements (typically associated with inversion or reflection operations) which do not belong to the “smaller” group, namely to subgroup of index 2 in the “large” group. Thus, in the case of any rigid spatial object, the classical chirality criterion states that its rotation-reflection (“large”) group must not contain improper symmetry elements (i.e., reflection planes, rotation-reflection axes, and inversion center) which do not belong to the rotation (“small”) group of the object under discussion.

The significant feature of the above cited groups is that their elements can be treated either as operations which interconvert all points of some (typically 3D) space or as permutations which interconvert elements of some finite set. In the last case, the symmetry of the molecular object is characterized by some *permutation group* which, in turn, can be treated (see e.g., ref 19b) as an ordered pair  $(G, X)$  with  $G$  being an abstract group and  $X$  being the finite set on which  $G$  acts. It is important that  $G$  and  $X$  are typically group-theoretical and set-theoretical constructions; this means that they can be formed from simpler groups and sets by some well-defined rules.

From the chemist's point of view, it is important that many permutation groups are related to problems of permutational isomerism. This type of stereoisomerism arises if achiral or chiral ligands can be distributed between predefined skeleton sites in different ways. Classification, enumeration, and generation problems corresponding to chiral as well as achiral permutational and other substitution isomers are well-investigated; textbooks,<sup>9b,10b,c,11</sup> reviews,<sup>20</sup> and original papers<sup>21</sup> can serve as key references. On the other hand, many groups used in theoretical stereochemistry are not based on the (more or less artificial) differentiation between skeletal atoms and ligands. These permutation groups are typically associated either with molecular geometry (e.g., point symmetry and site symmetry groups, framework groups, nonrigid symmetry groups) or with local configurations of predefined stereocenters in an organic structure (e.g., J.G. Nourse's Configuration Symmetry Groups<sup>16b</sup>).

In the present approach, several finite permutation groups are also used in order to describe specific types of molecular symmetry and to rigorously formulate corresponding generation problems for molecular entities taken as a whole (i.e., with no differentiation between skeletal atoms and ligands). Unlike the above permutation groups, new groups however do not require exact molecular geometry or specific stereocenters to be explicitly known. Some novel, “configurational” characteristics must be known instead, and for this reason, the new permutation groups may be said to represent

configurational symmetries of molecular entities. The notion of 3D point configuration is formally introduced in section 3; here we only stress that 3D configurations should not be confused with local stereochemical configurations<sup>22a</sup> being associated with some stereogenic units (such as asymmetric atoms or double bonds).

The essential feature of the “configurational” approach to stereochemical problems is that all three main molecular characteristics—namely, composition, connectivity, and configuration—are treated in a very similar manner. In order to completely understand the corresponding mathematical models, the reader need be acquainted only with the following discrete-mathematical notions:

- (1) functions between finite sets (i.e., mappings from one set into another),
- (2) orbits of induced permutation groups on the sets of functions (and the corresponding partitions of these sets into equivalence classes), and
- (3) automorphism groups of particular functions.

It should be noted that very similar mathematical models are elaborated by the present authors in order to formalize some problems of reaction design<sup>23a</sup> and nonempirical computer-assisted synthesis.<sup>23b</sup>

The detailed description of all needed mathematical concepts may be easily found in specialized literature of different levels of complexity: a popular textbook,<sup>19a</sup> an advanced manual,<sup>19b</sup> and a special monograph<sup>19c</sup> can serve as examples. For the sake of brevity, almost all notions related to orbits of induced permutation groups (or, in other words, to corresponding partitions of the sets of functions) are considered here only on an intuitive level; the needed mathematical comments are typically represented as notes. On the other hand, automorphism groups of particular functions play the dominant role in the formulation of suggested chirality criteria and hence are supplied by numerous examples.

The general formal model appears as follows. *The composition, connectivity, and global point configuration of atom sets uniquely correspond to orbits of the induced permutation groups acting on the sets of functions (mappings) from  $m$ th Cartesian powers of atom sets  $W$  into some label sets  $M$ . In this representation, the symmetry of any function—and hence the symmetry associated with composition, connectivity, or point configuration of any molecule—is characterized by its automorphism group, i.e., by a subgroup of the symmetric group  $S_{|W|}$  which converts a given function into itself.* It should be noted that the present formulation is combinatorial<sup>24</sup> in essence, and for this reason, the symmetries associated with permutations of automorphism groups (and corresponding chirality criteria, see section 3) may be also said to be combinatorial.

Two trivial applications are first examined. Thus, the function  $\varphi$  from the  $n$ -atomic set  $W$  (that is  $|W| = n$  and  $m = 1$ ) into the set  $M_1$  of suitable chemical elements—organogens represents molecular formula with the atoms being sequentially numbered by integers 1, 2, ...,  $n$ ; the equivalence class of such functions (corresponding to just the same molecular entity but with different numberings of atoms) correctly defines the *molecular composition*. For any function  $\varphi$ , its automorphism group<sup>25</sup>

$$\text{Aut}(\varphi) = \{s \in S_{|W|} : \varphi s^{-1} = \varphi\}$$

is the subgroup of  $S_{|W|}$  which describes the symmetry associated with the molecular formula under discussion.

Similarly, the function  $\chi$  from the set  $W^{(2)}$  (which consists of  $n(n-1)/2$  unordered pairs of different atoms; that is  $m = 2$ ) into the set  $M_2$  of possible bond multiplicities (normally, 0, 1, 2, 3) uniquely describes the molecular graph with unlabeled but sequentially numbered<sup>26</sup> vertices. The equivalence class of these functions corresponds to the graph with unnumbered vertices and correctly defines the *molecular connectivity*. For each function  $\chi$ , its automorphism group

$$\text{Aut}(\chi) = \{s \in S_{|W|} : \chi s^{-1} = \chi\}$$

describes the symmetry of the corresponding unlabeled graph.

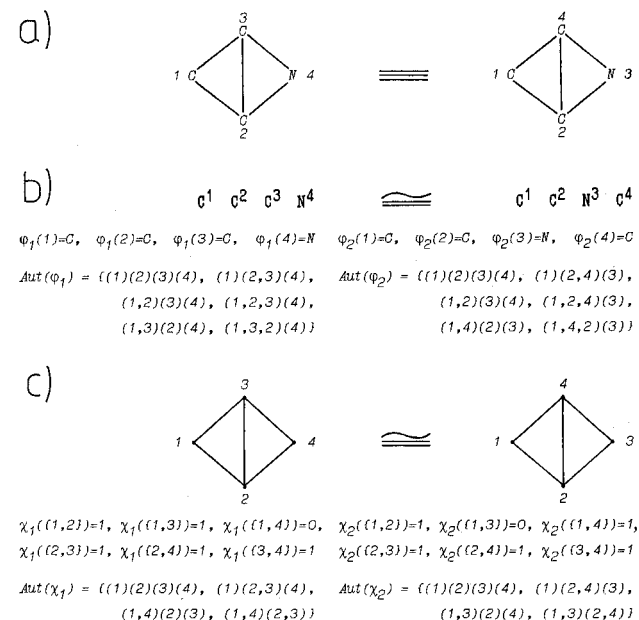
**Example 1.** In Chart 1b, two functions  $\varphi_1$  and  $\varphi_2$  correspond to different numberings of the 2-azabicyclobutane skeleton (cf. Chart 1a); this small and highly strained skeleton is used only for the sake of brevity. It is easy to see that  $\varphi_1$  and  $\varphi_2$  are interconverted by an induced action of the permutation (1)(2)(3,4). For this reason,  $\varphi_1$  and  $\varphi_2$  belong to the same equivalence class, or in other words, to the same orbit of certain induced group acting on the set of functions  $\varphi$  from the set  $W = \{1,2,3,4\}$  into the set  $M_1 = \{C^I, C^{III}, N^II, \dots\}$  (roman numbers indicate formal valencies of carbon and nitrogen atoms in azabicyclobutane skeleton). The automorphism groups  $\text{Aut}(\varphi_1)$  and  $\text{Aut}(\varphi_2)$  also presented in Chart 1b, are really conjugate subgroups<sup>27</sup> of the symmetric group  $S_4$ .

Similarly, in Chart 1c two functions  $\chi_1$  and  $\chi_2$  are associated with different numberings of the corresponding (isomorphic) unlabeled skeleton graphs and hence describe the connectivity of the azabicyclobutane skeleton. These functions are also interconverted by the induced action of the permutation (1)(2)(3,4) and therefore are equivalent with respect to the doubly induced group<sup>28</sup> acting on the set of functions  $\chi$  from the set  $W^{(2)}$  of six unordered pairs  $\{1,2\}, \{1,3\}, \{1,4\}, \{2,3\}, \{2,4\}, \{3,4\}$  into the set  $M_2 = \{0,1,2,3\}$  of possible bond orders. In this case, the groups  $\text{Aut}(\chi_1)$  and  $\text{Aut}(\chi_2)$  (conjugate Klein four-groups) consist of four automorphisms of corresponding unlabeled graphs (cf. Chart 1c).

The above consideration clearly shows that molecular graphs and multigraphs with unnumbered vertices are typical combinatorial objects. This fact is in accordance with the commonly adopted<sup>29</sup> definition of graph by finite nonempty set of its vertices together with the edge set consisting of unordered pairs of (pairwise different) vertices. In many modern papers on topological stereochemistry (see e.g., ref 30), the graphs are however treated as topological objects;<sup>31</sup> for that purpose, graph edges are assumed to be completely elastic in 3D (or 2D) space. In this case, the dimensionless object (graph) is, in fact, replaced by its spatial realization in which metric characteristics—distances, angles between edges, etc.—are not taken into account.

The present authors' opinion is that there can exist at least three levels in the spatial realization of graphs. In the first—topological—level, the edges are allowed to be stretchable but all metric characteristics are ignored, while in the third—geometrical—level, all distances, angles, and dihedral angles are viewed to be explicitly known. This standpoint

**Chart 1.** Two Differently Numbered 2-Azabicyclobutane Skeletons (a) Together with Equivalent Functions Which Characterize the Composition (b) and Connectivity (c) of These Skeletons<sup>a</sup>



<sup>a</sup> The symmetries associated with numbered skeletons are explicitly represented by automorphism groups of functions  $\varphi$  and  $\chi$ .

is shared by N. J. Turro<sup>32</sup> who also differentiates between graphs (dimensionless objects), forms (elastic topological objects), and figures (rigid geometrical objects). The notions presented in this paper (those of graph and molecular configurations, see section 5) represent the second level, intermediate between topological and geometrical ones. In this, "configurational" level, all quantitative metric characteristics are ignored, graph edges are thought to be straight lines, and the shape of any graph in 3D, 2D, or 1D space (similarly to composition and connectivity) is described by combinatorial tools, i.e., by functions between finite sets.

### 3. CHIRALITY CRITERION FOR POINT 3D CONFIGURATIONS

In the configurational approach, the functions between finite sets are used for *qualitative* description of point systems formed by  $n$  atoms of any molecule in 3D, 2D, or 1D space. The equivalence classes of these functions define *3D*, *2D*, and *1D configurations* which are similar to molecular composition and connectivity in that sense that they are *global* characteristics of the molecule (in contrast to commonly adopted local configurations being associated with possible dispositions of ligands around tetrahedral carbon atoms, double bonds, etc.). In this paper, only the global 3D configurations and the criteria of their chirality are discussed.

In order to describe the relative disposition of the point system formed by  $n$  atoms in 3D space, the functions  $\psi$  from the set  $W^{(4)}$  (consisting of all  $n(n-1)(n-2)(n-3)$  ordered quadruples  $[i,j,k,l]$  of numbered points; that is  $m = 4$ ) into the set  $M_3 = \{-1, 0, +1\}$  should be considered. In this case, the value of  $\psi([i,j,k,l])$  is thought to be equal to +1 (or -1) if the point  $l$  is located before (or behind) the plane in which other points  $i, j, k$  are ordered clockwise;  $\psi([i,j,k,l]) = 0$  if all four points are situated in a plane. An examination of possible four-point systems shows however that the sign of

$\psi$  really depends on the sequential order of point numbers in any ordered quadruple. More explicitly, any odd permutation<sup>33</sup> of arguments  $i, j, k, l$  in a quadruple changes the sign of  $\psi$ , that is

$$\psi([i,j,k,l]) = -\psi([j,i,k,l]) = \psi([j,k,i,l]) = -\psi([k,l,i,j])$$

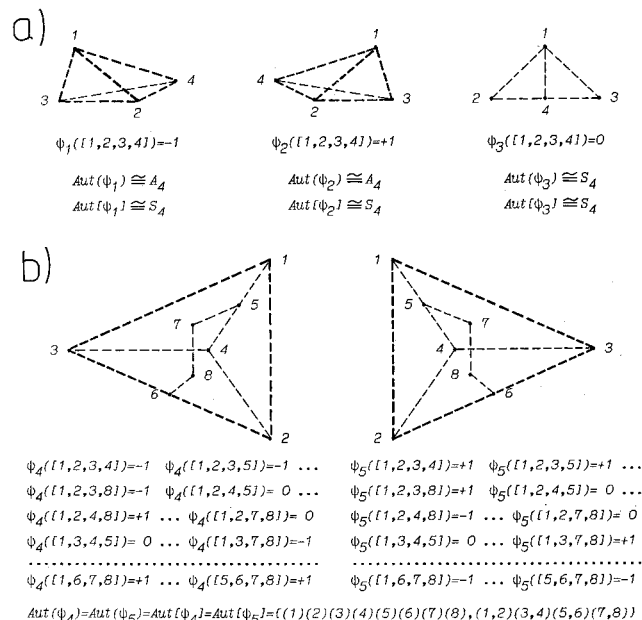
etc. This means that only *alternating* functions  $\psi$ , satisfying this condition, need to be used for characterization of real point systems in 3D space. On the other hand, the values of  $\psi$  for all  $4! = 24$  possible ordered quadruples (corresponding to any given four-subset  $\{i,j,k,l\}$ ) are interdependent, and hence only one of them is really needed to unambiguously describe the function  $\psi$ . For representation purposes, the values of all “standard” quadruples  $[i,j,k,l]$ ,  $i < j < k < l$ , are chosen in the present approach; just these values are depicted in Chart 2.

Thus, the alternating functions  $\psi$  from the sets  $W^{[4]}$  into the set  $M_3 = \{-1, 0, +1\}$  and equivalence classes of these functions (also defined by orbits of corresponding doubly induced groups<sup>34</sup>) are used as configurational characteristics of point systems formed by  $n$  atoms of any molecule in 3D space. Both the functions  $\psi$  (related to numbered point systems) and their equivalence classes are denoted here as *point 3D configurations* (3D-PCs); the words “numbered” and “abstract” will be added if necessary to actually differentiate between individual functions and corresponding equivalence classes.

An additional specific feature of the functions  $\psi$  is significant for the following discussion. Contrary to functions  $\varphi$  and  $\chi$ , for any function  $\psi$  (except that with all zero values of  $\psi([i,j,k,l])$ ) a unique *antipode* function  $\bar{\psi}$  with the values  $\bar{\psi}([i,j,k,l]) = -\psi([i,j,k,l])$  necessarily exists. It is important that  $\psi$  and  $\bar{\psi}$  can belong either to the same or to different equivalence classes. In the former case, the functions  $\psi$  and  $\bar{\psi}$  are *isomorphic*; the corresponding abstract point 3D configuration (i.e., equivalence class to which  $\psi$  and  $\bar{\psi}$  belong) is said to be *achiral*. In the latter case, two equivalence classes, to which *nonisomorphic* functions  $\psi$  and  $\bar{\psi}$  belong, do not intersect and form an *enantiomorphic pair of chiral point configurations*.<sup>35</sup> The fact that chiral 3D-PCs appear as equivalence classes of functions between finite sets means that chirality here under discussion is of combinatorial nature.

To characterize the symmetry associated with any given numbered 3D-PC (i.e., with the function  $\psi$ ) two permutation groups must be introduced. The first of them,  $Aut(\psi) = \{s \in S_{|W|}: \psi \tilde{s}^{-1} = \psi\}$ , consists of all permutations, called *(+)-automorphisms*, which convert a given function  $\psi$  into itself. The second group, the *expanded automorphism group*  $Aut[\psi] = \{s \in S_{|W|}: \psi \tilde{s}^{-1} = \psi \text{ or } \psi \tilde{s}^{-1} = \bar{\psi}\}$ , can contain additional permutations—*(-)-automorphisms*<sup>36</sup>—which convert  $\psi$  into its antipode function  $\bar{\psi}$ . It is easy to see that the “normal” automorphism group  $Aut(\psi)$  is sufficient to reveal all symmetries associated with any chiral 3D-PC. In this case, both functions  $\psi$  and  $\bar{\psi}$  belong to different equivalence classes, and hence the group  $Aut[\psi]$  contains no *(-)-automorphisms* and is identical to  $Aut(\psi)$ . In the case of achiral 3D-PCs, the group  $Aut(\psi)$  consists only of *(+)-automorphisms* and is a subgroup of index 2 in the group  $Aut[\psi]$ . For this reason, just the expanded group  $Aut[\psi]$  is a group which describes all symmetries associated with a function  $\psi$  and corresponding achiral 3D-PC.

**Chart 2.** Examples of Achiral (a) and Chiral (b) Numbered Point 3D Configurations Together with Their “Normal” and Expanded Automorphism Groups<sup>a</sup>



<sup>a</sup> The dashed lines in pictorial representations are used with the sole purpose of visualizing relative spatial arrangements of points in 3D space.

The above consideration shows that there exists a very simple criterion making it possible to recognize the “combinatorial” chirality of any point 3D configuration except that with all zero values of  $\psi([i,j,k,l])$ . This algebraic criterion may be written in the form

$$Aut[\psi] = Aut(\psi)$$

Thus, if the groups  $Aut[\psi]$  and  $Aut(\psi)$  coincide, then the function  $\psi$  belongs to one of two enantiomorphic abstract 3D-PCs and is therefore chiral. In the case of achiral numbered 3D-PCs, the groups  $Aut[\psi]$  and  $Aut(\psi)$  can never be identical due to existence of *(-)-automorphisms* in  $Aut[\psi]$ .

The suggested chirality criterion is formally very similar to that commonly used for spatial objects which are said to be chiral if their point symmetry groups contain no improper symmetry elements (i.e., mirror planes, rotation-reflection axes, and inversion center). In order to underline this similarity, the classical chirality criterion should be reformulated as follows: “the spatial object is chiral if and only if its rotation-reflection group coincides with its rotation group”.

**Example 2.** Three possible four-point 3D configurations  $\psi_1$ – $\psi_3$  are represented in Chart 2a. Although two tetrahedra corresponding to antipode functions  $\psi_1, \psi_2$  are thought to be irregular, the numbered configurations  $\psi_1$  and  $\psi_2$  are achiral and belong to just the same equivalence class. In order to prove it, two points—e.g., 3 and 4—must be renumbered; the formal transformation (corresponding to doubly induced action of the permutation (1)(2)(3,4)) takes into account that  $\psi$  is an alternating function

$$\psi_1([1,2,4,3]) = -\psi_1([1,2,3,4]) = \psi_2([1,2,3,4])$$

The comparison of the both “normal” automorphism groups (isomorphic to alternating group  $A_4$ ) with corresponding

expanded groups (isomorphic to symmetric group  $S_4$ ) also shows that the abstract 3D-PC, to which  $\psi_1$  and  $\psi_2$  belong, is achiral. The third function of Chart 2a,  $\psi_3$ , cannot be however converted into  $\psi_1$  or  $\psi_2$  by renumbering of points, and hence belongs to a separate, also achiral,<sup>37</sup> abstract 3D-PC.

The chirality of point 3D configurations is exemplified in Chart 2b by antipode functions  $\psi_4$  and  $\psi_5 \equiv \bar{\psi}_4$  and corresponding regular tetrahedra with the points 7 and 8 being located in the centers of regular triangles. The detailed examination reveals that all possible renumberings of points and corresponding doubly induced actions of permutations from the symmetric group  $S_8$  do not interconvert tetrahedra and functions  $\psi_4$  and  $\psi_5$ . Thus,  $\psi_4$  and  $\psi_5$  are not only antipodes but represent the enantiomorphic pair of the chiral eight-point 3D configuration. The suggested chirality criterion also proves that both functions  $\psi_4$ ,  $\psi_5$  are chiral (because their normal as well as expanded automorphism groups consist of just the same permutations; cf. Chart 2b).

#### 4. SYMMETRY PROPERTIES OF GEOMETRICALLY REALIZABLE POINT 3D CONFIGURATIONS

The propositions of the preceding section show that to any (numbered)  $n$ -point system in 3D space there corresponds a unique function  $\psi$ . The reverse statement is not necessarily true: there exist many functions  $\psi$  to which *no spatial arrangement of  $n$  points can correspond*. Such functions (and corresponding abstract 3D-PCs) are called *geometrically nonrealizable in 3D-space*, and, in the general case, it can be quite difficult to recognize whether a given function  $\psi$  is geometrically realizable or not. However, the solution of realizability problems is typically needed only if one wants to sequentially generate all or some part of the nonisomorphic  $n$ -point 3D configurations. This generation problem is, in fact, quite similar to that for molecular graphs and multigraphs (the rigorous mathematical statement of graph generation problems may be found e.g. in ref. 29b).

Turning to interrelations between realizable 3D-PCs and their *geometrical realizations* (i.e., arrangements of real points in 3D space), it should be once more stressed that each function  $\psi$  is, in fact, *a combinatorial but not geometric characteristic* of the corresponding point system. This means that any 3D-PC contains no information about interpoint distances, angles, dihedral angles etc., but characterizes *the types of all polyhedral figures formed by 4-, 5-, ..., and  $n$ -point (sub)systems in 3D space*. In this sense, 3D-PCs are closely related to (molecular) topological forms which were introduced<sup>22b</sup> in order to formulate the topology-based approach to the description of configurations. The modern interpretation of this notion<sup>5b</sup> shows however that topological forms are, in fact, systems of several convex hulls (corresponding to possibly intersecting polyhedral figures) which are not well suited for numerical manipulations with point as well as molecular systems.

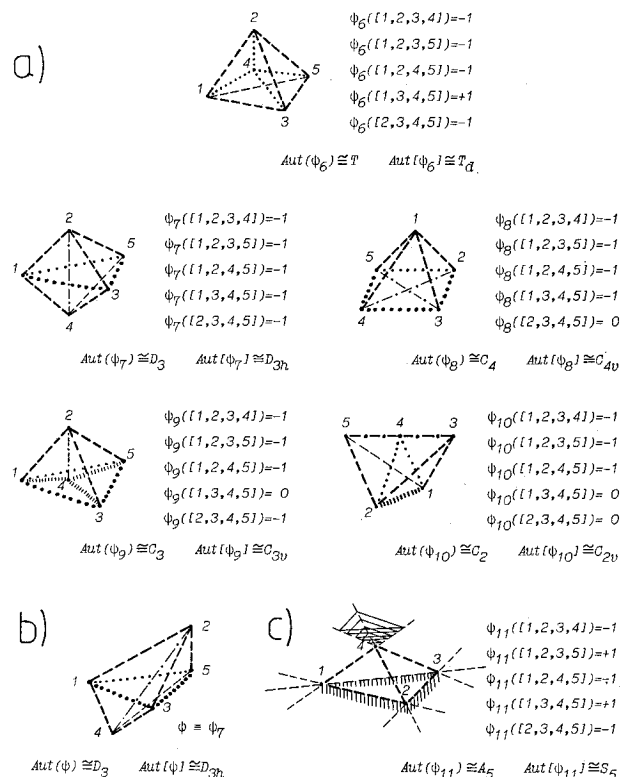
For the purposes of this paper, it is important to note that 3D-PCs are not very sensitive to exact geometries of point systems; any geometry violation making the "shape" of the point system unchanged (i.e., conserving the types of all polyhedral figures formed by 4-, 5-, ...,  $n$ -point (sub)systems in 3D space) do not affect functions  $\psi$ . The simplest convincing example may be found in Chart 2a: the same functions  $\psi_1$  and  $\psi_2$  correspond to a regular tetrahedron and

to all possible irregular tetrahedra with  $D_{2d}$ ,  $C_{3v}$ ,  $C_{2v}$ ,  $D_2$ ,  $C_2$ ,  $C_s$ , and  $C_1$  point symmetry groups. It is also evident that small shifts of one or several points in chiral tetrahedra of Chart 2b cannot alter eight-point configurations  $\psi_4$  and  $\psi_5$ . The above examples show that any realizable 3D configuration may be also associated with the whole equivalence class of its geometrical realizations; this class consists of an infinite number of "snapshots" which correspond to geometrically nonidentical arrangements of points in 3D space.

It should be stressed here that for arbitrary geometrical realizations of a given 3D-PC, its rotation and rotation-reflection (= point symmetry) groups do not necessarily coincide with automorphism groups  $Aut(\psi)$  and  $Aut[\psi]$ , respectively. On the other hand, to any proper (or improper) symmetry element of the point group, there necessarily corresponds a unique (+)-automorphism (or (-)-automorphism). The formal proof looks as follows: if  $s$  corresponds to a symmetry element, then the geometric distance  $\rho_{ij}$  is evidently equal to  $\rho_{s(i),s(j)}$  for all pairs  $i, j \in \{1, 2, \dots, n\}$ . This leads to a conclusion that for each pair of ordered quadruples  $[i, j, k, l]$  and  $[s(i), s(j), s(k), s(l)]$  either two superposable (if  $s$  is a proper symmetry element) or two antipodal (if  $s$  is an improper symmetry element) tetrahedra correspond. In the first case,  $s$  is a (+)-automorphism of the function  $\psi$ , while in the second case,  $s$  is a (-)-automorphism which belongs to an expanded group  $Aut[\psi]$  but not to "normal" group  $Aut(\psi)$ .

The above consideration shows that for each realizable point 3D configuration, at least one<sup>38</sup> "ideal" geometrical realization with rotation and rotation-reflection groups being isomorphic to groups  $Aut(\psi)$  and  $Aut[\psi]$  must exist. It is evident that "ideal" geometrical realizations are the most symmetrical ones; in these realizations the values  $\rho_{ij}$ ,  $\alpha_{i,j,k}$ , and  $\beta_{i,j,k,l}$  (corresponding to all distances for pairs of points  $[i, j]$ , to all angles for ordered triples of points  $[i, j, k]$ , and to all dihedral angles for ordered quadruples of points  $[i, j, k, l]$ ) must be necessarily equal to the values  $\rho_{s(i),s(j)}$ ,  $\alpha_{s(i),s(j),s(k)}$ , and  $\beta_{s(i),s(j),s(k),s(l)}$ , respectively. For this reason, "ideal" geometrical realizations are constantly used here instead of functions  $\psi$  in order to visualize spatial configurations under discussion. The represented polyhedral figures should be imagined to be as regular as it is needed to reflect all automorphisms of corresponding functions  $\psi$ .

**Example 3.** In the case of  $n = 5$ ,  $3^{5 \cdot 4 \cdot 3 \cdot 2 \cdot 1} = 243$  possible alternating functions  $\psi$  form 12 equivalence classes; six of them (consisting of 10, 20, 30, 40, 60, and 1 function,<sup>39</sup> respectively) are geometrically realizable. The representatives of five realizable 3D-PCs (functions  $\psi_6 - \psi_{10}$ ) are shown in Chart 3a together with corresponding "ideal" polyhedral figures. These figures are differentiated not only by their convex hulls (trigonal bipyramids, tetragonal pyramids and three distinct types of tetrahedra) but also by types and relative dispositions of four-point subfigures (i.e., tetrahedra, planar quadrangle, face-centrated and edge-centrated triangles). In order to visualize geometrical, and hence combinatorial, symmetries associated with "ideal" realizations, several sorts of dashed and dotted lines are used in Chart 3a; lines of the same sort indicate the distances between corresponding points to be necessarily equal. One of many possible "nonideal" realizations is exemplified (for 3D-PC  $\psi_7$ ) in Chart 3b. Although the irregular trigonal bipyramid of Chart 3b belongs to  $C_s$  point group, it represents 3D-PC

**Chart 3.** Geometrical Realizability and Symmetry of Five-Point 3D Configurations<sup>a</sup>

<sup>a</sup> "Ideal" (a) and "nonideal" (b) numbered polyhedral figures are characterized by functions  $\psi_6$ – $\psi_{10}$  and corresponding automorphism groups. The nonrealizability of the function  $\psi_{11}$  makes it impossible to localize point 5 in 3D space (c).

$\psi_7$  (with the "normal" and expanded automorphism groups being isomorphic to  $D_3$  and  $D_{3h}$ —but not to  $C_1$  and  $C_s$ —point symmetry groups).

The last part of Chart 3 demonstrates that for the function  $\psi_{11}$  (representing one of six nonrealizable abstract 3D-PCs) no polyhedral figures can be constructed in 3D-space. From Chart 3c it is evident that point 5 is required to be localized below the plane 123 (due to the value of  $\psi_{11}$  for quadruple [1,2,3,5]) but within the trigonal sector indicated (due to the values of  $\psi_{11}([1,2,4,5])$ ,  $\psi_{11}([1,3,4,5])$ , and  $\psi_{11}([2,3,4,5])$ ). However, these two regions of 3D space do not intersect at all.

One of the above examples, namely that of the "centrated tetrahedron", is closely related to the classical notion of "asymmetric carbon atom" which, in turn, is traditionally associated with the symmetry group  $T_d$  of the regular tetrahedron. The application of the "geometry-based" group  $T_d$  for the explanation of enantiomerism in tetrasubstituted methane derivatives *Cabde* was however criticized by several authors. For instance, I. Ugi et al. underline<sup>10b</sup> that "... although the asymmetric carbon atoms behave as if they had an idealized  $T_d$  skeleton, they in fact never have that idealized  $T_d$  skeletal symmetry". The decreased symmetry of *Cabde* framework is undoubtedly caused by deviations from idealized regular geometry due to unequal bond angles and bond lengths of the central atom *C* with four distinct ligands. These deviations cannot however violate the type of polyhedral figure ("centrated tetrahedron") and hence the corresponding five-point 3D configuration  $\psi_6$  as well. For this reason, in the authors' opinion, just the groups  $Aut[\psi_6]$  and  $Aut(\psi_6)$  characterizing "combinatorial" rather than "geometrical"

symmetries of the concentrated tetrahedron are really associated to the stereochemical behavior of the asymmetric carbon atom. In order to completely describe the corresponding enantiomeric phenomena, the groups associated with molecular composition and connectivity must be additionally taken into account.

## 5. SUPERPOSITIONS OF FUNCTIONS AND CHIRALITY CRITERIA FOR LABELED, GRAPH, AND MOLECULAR CONFIGURATIONS

Up to this moment, the discussion was restricted to point systems formed by atoms of a molecule in 3D space. The introduced functions  $\psi$ , characterizing point 3D configurations, are however very similar to the functions  $\varphi$  and  $\chi$  which were shown in section 2 to be associated with molecular composition and connectivity. The formal similarity of functions  $\varphi$ ,  $\chi$ , and  $\psi$  leads to a conclusion that combinations of two or three functions may be used for a more detailed characterization of molecules.

One such combination, that of functions  $\varphi$  and  $\chi$ , simultaneously reflects the composition and connectivity of any given molecule and hence is unequivocally associated with the constitution of the molecule under discussion. From the mathematical point of view, this combination, denoted by  $\kappa = (\varphi, \chi)$ , is simply a pair of functions with domain sets  $W$  and  $W^{(2)}$ , respectively. In order to pictorially represent a given superposition  $\kappa$ , the unlabeled graph (corresponding to a function  $\chi$ ) with numbered vertices must be superposed with the labels of all its vertices in accordance with the values of a function  $\varphi$ . For this reason, the name *superposition* is used here for  $\kappa$  (and similar combinations of functions); it is evident that any superposition  $\kappa = (\varphi, \chi)$  uniquely corresponds to the labeled molecular graph or, in other words, to the constitutional formula with the atoms sequentially numbered by integers 1, 2, ..., *n*.

Every equivalence class of superpositions  $\kappa$  (consisting of pairs  $(\varphi, \chi)$  with both functions  $\varphi$  and  $\chi$  being interconverted by induced actions of all permutations of the symmetric group  $S_{|W|}$ ) evidently corresponds to commonly adopted constitutional formula, and hence is a proper mathematical characteristic of the *molecular constitution*. On the other hand, for any particular superposition  $\kappa = (\varphi, \chi)$ , its automorphism group  $Aut(\kappa)$  is a subgroup of  $S_{|W|}$  consisting only of those permutations *s* which convert both constituent functions  $\varphi$  and  $\chi$  into themselves:

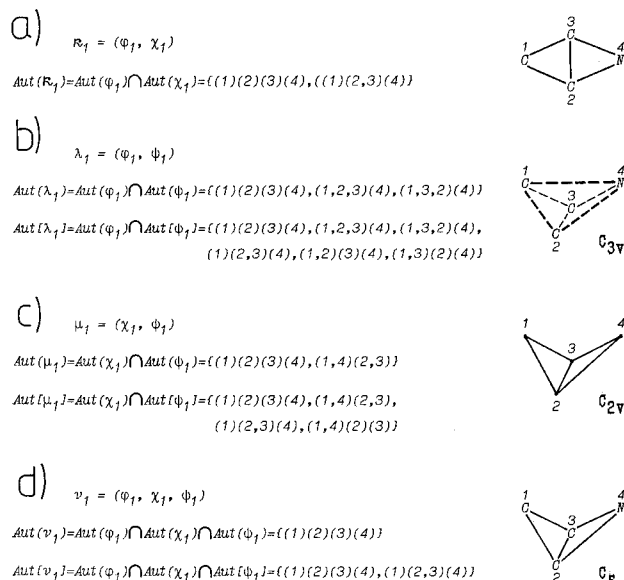
$$Aut(\kappa) = \{s \in S_{|W|} : \varphi s^{-1} = \varphi \text{ and } \chi s^{-1} = \chi\}$$

This permutation group describes the symmetry associated with the labeled molecular graph (or constitutional formula) and is evidently an intersection<sup>40</sup> of the automorphism groups  $Aut(\varphi)$  and  $Aut(\chi)$

$$Aut(\kappa) = Aut(\varphi) \cap Aut(\chi)$$

Three other possible superpositions— $\lambda = (\varphi, \psi)$  ("composition" + "3D point configuration"),  $\mu = (\chi, \psi)$  ("connectivity" + "3D point configuration"), and  $\nu = (\varphi, \chi, \psi)$  ("composition" + "connectivity" + "3D point configuration")—are introduced in just the same manner. Thus, the numbered *labeled 3D configuration* (3D-LC)  $\lambda$  is defined by a pair  $(\varphi, \psi)$ ; in order to pictorially represent this superposition, the "ideal" polyhedral figure (corresponding to geometrically realizable 3D-PC  $\psi$ ) needs to be superposed

**Chart 4.** Description of the Chemical Constitution (a) and of the Labeled (b), Graph (c), and Molecular (d) Configurations by Superpositions of Functions  $\varphi$ ,  $\chi$ , and  $\psi^a$



<sup>a</sup> The symmetries of (numbered) 2-azabicyclobutane skeleton graph and of corresponding 3D-LC, 3D-GC, and 3D-MC are characterized by automorphism groups of superpositions  $\kappa_1$ ,  $\lambda_1$ ,  $\mu_1$ , and  $\nu_1$ .

with the labels of all its numbered points in accordance with the values of  $\varphi$ . Similarly, the numbered graph 3D configuration (3D-GC)  $\mu$  is defined by a pair  $(\chi, \psi)$ . In this case, the “ideal” polyhedral figure (corresponding to the function  $\psi$ ) is superposed with the unlabeled graph; this means that any pair of numbered points in the geometrical realization of  $\psi$  must be connected by an edge of multiplicity 0, 1, 2, or 3 in accordance with the corresponding value of the function  $\chi$ . Finally, the numbered molecular 3D configuration (3D-MC)  $\nu$  is defined by a single possible triple  $(\varphi, \chi, \psi)$ ; this superposition can also be represented by pairs  $(\kappa, \psi)$  (“constitution” + “3D point configuration”),  $(\lambda, \chi)$  (“3D labeled configuration” + “connectivity”), and  $(\mu, \varphi)$  (“3D graph configuration” + “composition”). The molecular 3D configuration is evidently the most detailed combinatorial characteristic of the molecule; in corresponding pictorial representations not only “ideal” polyhedral figures formed by numbered atoms but also atom symbols and bond multiplicities are explicitly shown. It should be noted that all the above superpositions  $(\lambda, \mu, \nu)$  are similar to function  $\psi$  and contain no information about numerical characteristics—distances, angles, dihedral angles, etc.—of the systems formed by labeled points, graph vertices, or atoms in 3D space.

It is important that all kinds of superpositions under discussion also form equivalence classes (abstract 3D-LCs, 3D-GCs, 3D-MCs) consisting of those superpositions  $\lambda = (\varphi, \psi)$ ,  $\mu = (\chi, \psi)$ ,  $\nu = (\varphi, \chi, \psi)$  for which two or three constituent functions are interconverted by induced actions of all permutations  $s \in S_{|W|}$ ; these permutations evidently correspond to  $n! = |W|!$  possible renumberings of  $n$  labeled points, graph vertices, or atoms, respectively. The notion of chirality may be also applied to abstract 3D-LCs, 3D-GCs, and 3D-MCs as well as to individual superpositions  $\lambda$ ,  $\mu$ , and  $\nu$ . Thus, the equivalence class to which a given superposition  $\lambda$  ( $\mu$  or  $\nu$ ) and its antipode  $\bar{\lambda} = (\varphi, \bar{\psi})$  ( $\bar{\mu} = (\chi, \bar{\psi})$ , or  $\bar{\nu} = (\varphi, \chi, \bar{\psi})$  simultaneously belong represents

achiral 3D-LC (3D-GC or 3D-MC). In the case of chiral 3D-LCs (3D-GCs or 3D-MCs), two disjoint classes to which superpositions  $\lambda$  and  $\bar{\lambda}$  ( $\mu$  and  $\bar{\mu}$ ,  $\nu$  and  $\bar{\nu}$ ) belong, form an enantiomeric pair.<sup>41</sup> It is also evident that every achiral (chiral) numbered superposition is isomorphic (not isomorphic) to its antipode counterpart.

The description of the symmetry associated with any numbered labeled, graph, or molecular 3D configuration involves appropriate “normal” and expanded automorphism groups. The first of these groups consists of those permutations  $s \in S_{|W|}$ , called (+)-automorphisms, which convert two or three constituent functions and hence the corresponding superposition  $\lambda$ ,  $\mu$ , or  $\nu$  into itself. The second, expanded automorphism group, can contain additional permutations which convert functions  $\varphi$  and/or  $\chi$  into itself but  $\psi$  into its antipode function  $\bar{\psi}$ . These permutations, called (−)-automorphisms, evidently convert superpositions  $\lambda$ ,  $\mu$ , and  $\nu$  into their antipodes  $\bar{\lambda} = (\varphi, \bar{\psi})$ ,  $\bar{\mu} = (\chi, \bar{\psi})$ ,  $\bar{\nu} = (\varphi, \chi, \bar{\psi})$ , respectively. In all cases, normal as well as expanded automorphism groups are intersections of appropriate groups of constituent functions:

$$Aut(\lambda) = Aut(\varphi) \cap Aut(\psi); \quad Aut[\lambda] = Aut(\varphi) \cap Aut[\psi]$$

$$Aut(\mu) = Aut(\chi) \cap Aut(\psi); \quad Aut[\mu] = Aut(\chi) \cap Aut[\psi]$$

$$Aut(\nu) = Aut(\varphi) \cap Aut(\chi) \cap Aut(\psi)$$

$$Aut[\nu] = Aut(\varphi) \cap Aut(\chi) \cap Aut[\psi]$$

The above formulas show that “ideal” geometrical realizations (i.e., polyhedral figures) corresponding to labeled, graph, and molecular configurations can be less symmetric in comparison with “ideal” figures corresponding to point 3D configurations. This means that (+)-automorphisms and (−)-automorphisms (and, certainly, corresponding proper and improper symmetry elements) can disappear if they do not belong to groups  $Aut(\varphi)$  and/or  $Aut(\chi)$ . This fact, in turn, leads to a conclusion that 3D-LCs, 3D-GCs, and 3D-MCs are combinatorially chiral if and only if their expanded groups do not contain (−)-automorphisms. For this reason, the chirality criteria for superpositions  $\lambda = (\varphi, \psi)$ ,  $\mu = (\chi, \psi)$ , and  $\nu = (\varphi, \chi, \psi)$  must be written in the form

$$Aut[\lambda] = Aut(\lambda)$$

$$Aut[\mu] = Aut(\mu)$$

$$Aut[\nu] = Aut(\nu)$$

**Example 4.** From the functions  $\varphi_1$ ,  $\chi_1$ , and  $\psi_1$  (cf. Charts 1 (parts b and c) and 2a) four possible superpositions  $\kappa_1$ ,  $\lambda_1$ ,  $\mu_1$ , and  $\nu_1$  are constructed and represented in Chart 4a–d. As for the constituent functions, all superpositions correspond to numbered 2-azabicyclobutane skeletons. Superpositions  $\kappa_1$ ,  $\lambda_1$ ,  $\mu_1$ , and  $\nu_1$  are, in fact, representatives of equivalence classes consisting of  $4!/|Aut(\kappa_1)| = 12$ ,  $4!/|Aut(\lambda_1)| = 8$ ,  $4!/|Aut(\mu_1)| = 12$ , and  $4!/|Aut(\nu_1)| = 24$  individual superpositions (cf. note 39); these classes unambiguously describe chemical constitution as well as the (abstract) labeled, graph, and molecular configurations of bicyclobutane skeleton. The fact that all permutation groups explicitly presented in Chart 4a–d are really intersections may be easily checked by comparison of permutations forming automorphism groups of functions  $\varphi_1$ ,  $\chi_1$ , and  $\psi_1$  (cf. Chart 1 (parts b and c) and 2a, respectively).

It should be noted that although "ideal" geometrical realizations of superpositions  $\lambda_1 = (\varphi_1, \psi_1)$ ,  $\mu_1 = (\chi_1, \psi_1)$ ,  $\nu_1 = (\varphi_1, \chi_1, \psi_1)$  are not thought to be regular tetrahedra, the permutations of their rotation and rotation-reflection groups ( $C_3$  and  $C_{3v}$ ,  $C_2$  and  $C_{2v}$ ,  $C_1$  and  $C_s$ ; cf. tetrahedra of Chart 4b–d) evidently correspond to those of "normal" and expanded automorphism groups. The examination of the groups  $Aut[\lambda_1]$ ,  $Aut[\mu_1]$ , and  $Aut[\nu_1]$  makes it possible to detect 3, 2, and 1 (–)-automorphisms (corresponding to 3, 2, and 1 mirror planes in tetrahedral figures of Chart 4b–d). According to the suggested chirality criteria, this means that numbered 3D-LC  $\lambda_1$ , 3D-GC  $\mu_1$ , and 3D-MC  $\nu_1$  (and hence their "ideal" geometrical realizations of Chart 4b–d) are actually achiral.

### 6. THREE ADDITIONAL EXAMPLES

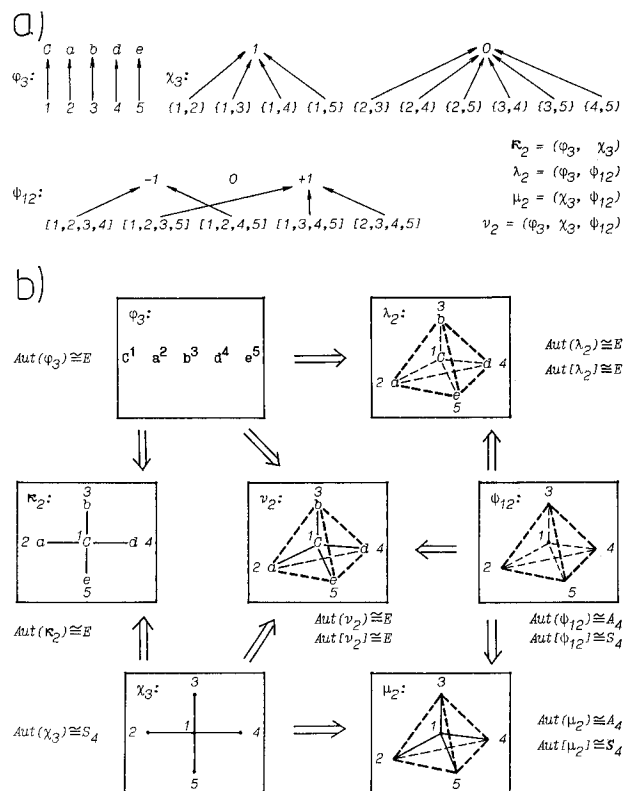
In this section, the applications of the suggested chirality criteria to several chemical problems are briefly discussed. In examples 5 and 6, the chirality of the asymmetric carbon atom *Cabde* and two imaginary enantiomerization modes for chirally tetrasubstituted methane derivatives are analyzed from combinatorial point of view. Example 7 goes back to V. A. Nikanorov, who has systematically examined possible types of regular and irregular tetrahedra with colored vertices and edges. V. A. Nikanorov has observed<sup>42</sup> that among 11 possible graphs with four vertices and ordinary edges, the "chain" graph  $P_4$  is a single graph with all nonplanar geometrical realizations being chiral, and this fact is easily explained by means of the chirality criterion for graph 3D configurations.

**Example 5.** In order to explain the chirality of simple molecules *Cabde*, the functions  $\varphi_3$  and  $\chi_3$  describing composition and connectivity of these molecules, and the function  $\psi_{12}$  associated with their point 3D configuration, are represented in Chart 5a by arrow schemes. The functions  $\varphi_3$ ,  $\chi_3$ , and  $\psi_{12}$  and four possible superpositions ( $\kappa_2$ ,  $\lambda_2$ ,  $\mu_2$ , and  $\nu_2$ ) are visualized in Chart 5b together with corresponding automorphism groups.

The application of the chirality criteria to three "superposed" centrated tetrahedra of Chart 5b (which are not thought to be necessarily regular) shows superposition  $\mu_2 = (\chi_3, \psi_{12})$  to be achiral but superpositions  $\lambda_2 = (\varphi_3, \psi_{12})$  and  $\nu_2 = (\varphi_3, \chi_3, \psi_{12})$  to be combinatorially chiral. This means that the chirality of labeled 3D configuration  $\lambda_2$  and of molecular 3D configuration  $\nu_2$  arises due to the intersection of the identity group  $Aut(\varphi_3) \cong E$  with the alternating ( $A_4$ ) and symmetric ( $S_4$ ) automorphism groups of the function  $\psi_{12}$ . Thus, the chirality of the asymmetric carbon atom is completely independent of connectivity ( $Aut(\chi_3) = Aut[\mu_2]$ ) and of the exact geometry of the centrated tetrahedron figure but is of combinatorial nature, i.e., due to the absence of (–)-automorphisms in the intersection group  $Aut(\varphi_3) \cap Aut[\psi_{12}] = E \cap S_4 = E$ .

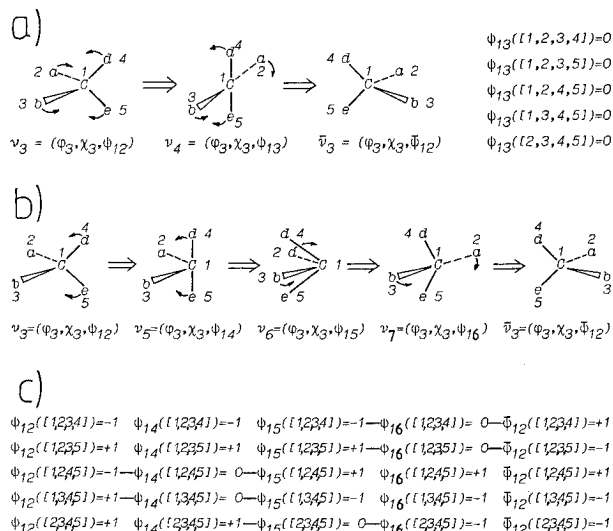
**Example 6.** One of many possible modes of intramolecular motions, that of *tetrahedral decompression*, was theoretically investigated<sup>22b,c</sup> in connection with enantiomerization processes in chiral tetrasubstituted methanes. Thus, two synchronous decompressions (i.e., intramolecular motions resulting in a gradual increase of bond angles  $aCb$  and  $dCe$ ; cf. Chart 6a) lead to an achiral planar molecule *Cabde*, while the similar decompression process for a single bond angle  $dCe$  in Chart 6b leads to chiral disphenoid-like and

**Chart 5.** Formal Description (a) and Pictorial Representation (b) of the Functions  $\varphi_3$ ,  $\chi_3$ , and  $\psi_{12}$  and Their Superpositions  $\kappa_2$ ,  $\lambda_2$ ,  $\mu_2$ , and  $\nu_2$  Needed for the Explanation of Chirality in Tetrasubstituted Methane Derivatives *Cabde*<sup>a</sup>



<sup>a</sup> Note that functions  $\psi_{12}$  and  $\psi_6$  (cf. Chart 3a) are isomorphic; one of them can be converted into another by appropriate renumbering of points.

**Chart 6.** Two Enantiomerization Modes (a and b) for Chiral Tetrasubstituted Methane Derivatives<sup>a</sup>



<sup>a</sup> The lines in Chart 6c correspond to quadruples which sequentially change their values in the course of transformation  $\psi_{12} \rightarrow \psi_{14} \rightarrow \psi_{15} \rightarrow \psi_{16} \rightarrow \psi_{12}$ .

then pyramidal<sup>43a</sup> structures. Surely, the reverse processes (with the same bond angles in the case of Chart 6a, and with bond angle  $aCb$  in the case of Chart 6b being involved) can lead to the enantiomer of the starting molecule, thus making it possible to classify both overall results as enantiomerization processes. From the chemical point of view, the enantiomerization mode of Chart 6a is very natural (because



chirality disappears in a planar intermediate), while the second enantiomerization mode, that of Chart 6b, seems to be somewhat unusual.

In order to explain how the local configuration of asymmetric carbon atoms can be altered without passing through an achiral intermediate, the values of the functions  $\psi$  for all "standard" quadruples must be analyzed. The comparison between the values represented in Chart 6c for functions  $\psi_{12}$  and  $\psi_{12}$  (corresponding to tetrahedral point figures), for functions  $\psi_{14}$  and  $\psi_{16}$  (corresponding to disphenoid-like point figures) and for the function  $\psi_{15}$  (corresponding to the tetragonal-pyramidal point figure) evidently shows that all quadruples really pass through their own "achiral intermediates" being characterized by zero values of  $\psi$ . Thus, the main difference between enantiomerization modes of Chart 6a,b arises from the fact that all four-point subfigures are "enantiomerized" simultaneously in the first case (cf. values of  $\psi_{13}$  in Chart 6a) but not simultaneously in the second case.<sup>43b</sup>

It should be noted here that chirality properties of molecular entities depend upon their molecular 3D configurations (i.e., superpositions  $\nu_3, \bar{\nu}_3, \nu_4, \nu_5, \nu_6$ , and  $\nu_7$  of Chart 6a,b) but not on individual functions  $\psi_{12}-\psi_{16}$ . The suggested chirality criterion may be applied to all 3D-MCs except that characterized by superposition  $\nu_4$  (because this superposition is identical to its antipode  $\bar{\nu}_4 = (\varphi_3, \chi_3, \psi_{13})$ ). All other diastereomeric<sup>44</sup> 3D-MCs (contrary to corresponding point 3D configurations) are evidently chiral—their expanded automorphism groups  $Aut[\nu] = Aut(\varphi_3) \cap Aut(\chi_3) \cap Aut[\psi_i]$  are identical to "normal" groups  $Aut(\nu) = Aut(\varphi_3) \cap Aut(\chi_3) \cap Aut(\psi_i)$ ,  $i = 12, 14-16$ . The fact that all  $(-)$ -automorphisms of expanded groups  $Aut[\psi_{12}]$ ,  $Aut[\psi_{14}] \cong Aut[\psi_{16}]$ ,  $Aut[\psi_{15}]$  (isomorphic to point groups  $T_d$ ,  $C_{2v}$ , and  $C_{4v}$ , respectively) disappear due to intersection with the same identity group  $Aut(\varphi_3) \cong E$  (cf. Chart 5) clearly shows that the chirality of tetrahedral, disphenoid-like, and pyramidal *Cabde* molecules is of just the same type.

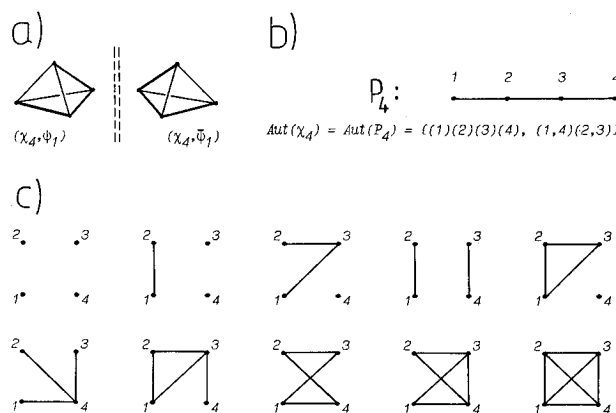
**Example 7.** Let all possible regular tetrahedra with unlabeled vertices and labeled edges be considered. Each type of these tetrahedra is evidently characterized by (abstract) graph 3D configurations or by superpositions  $\mu = (\chi, \psi)$  with the function  $\chi$  corresponding to unlabeled graphs (with 0–6 ordinary edges) and with the function  $\psi = \psi_1$  representing a tetrahedral geometry of four-point systems. V. A. Nikanorov's observation that only regular tetrahedra of Chart 7a with a "spiral" disposition of labeled edges are chiral may be now reformulated as follows. A "chain" graph  $P_4$  (Chart 7b) is a single graph of order 4 with all nonplanar geometrical realizations of its 3D-GC  $\mu = (\chi_4, \psi_1)$  being chiral. To rigorously prove this proposition, the chirality criterion for 3D-GCs must be rewritten as

$$Aut(\chi) \cap S_4 = Aut(\chi) \cap A_4$$

In this notation,  $Aut(\chi)$  designates the automorphism group of any graph with four vertices, while  $S_4$  and  $A_4$  are expanded and "normal" groups of four-point 3D configuration  $\psi \equiv \psi_1$  (cf. Chart 2a).

The well-known (see, e.g., ref 19) fact that  $A_4$  is a subgroup of  $S_4$  consisting of all even permutations<sup>33</sup> leads to a trivial conclusion that the above equation holds *if and only if* the group  $Aut(\chi)$  contains no odd permutations. On the other hand, it is easy to check that the automorphism group of the

**Chart 7.** Edge-Labeled Regular Tetrahedra (a) and Corresponding Graph (b) with No Odd Permutations in Its Automorphism Group<sup>a</sup>



<sup>a</sup> Chart 7c demonstrates that renumbering of vertices in accordance with the odd permutation (1,2)(3,4) does not violate connectivity of any other numbered graph with four vertices.

graph  $P_4$  consists of two even permutations (explicitly shown in Chart 7b), while the groups of other graphs with four vertices necessarily contain at least one odd permutation. This fact is visualized in Chart 7c by 10 (numbered) graphs containing just the same permutation (1,2)(3,4) in their automorphism groups. Thus, the odd permutation (1,2)(3,4) guarantees all 3D-GCs and hence all regular tetrahedra with edge labelings corresponding to graphs of Chart 7c to be achiral. The irregular tetrahedra (representing "nonideal" geometrical realizations of 3D-GCs) can obviously be either chiral or achiral.

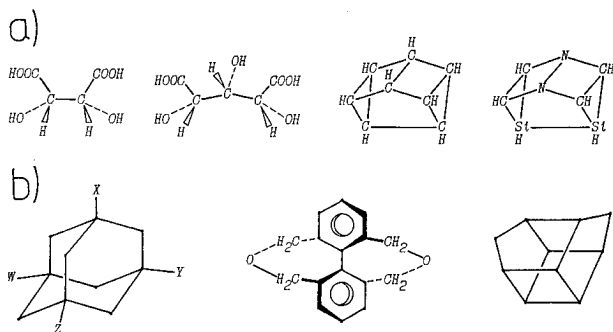
The above examples convincingly show that achiral point figures can be transformed into chiral ones if their points and/or edges are approximately labeled. These labelings can result in a disappearance of all  $(-)$ -automorphisms from corresponding expanded groups, thus making labeled figures "combinatorially" chiral. This fact leads to a new classification principle which takes into account the "source" of chirality being associated with spatial disposition of points, with geometric violations, or with labels reflecting composition and connectivity of an organic molecule.

## 7. GENERAL CLASSIFICATION SCHEME FOR CHIRAL RIGID MOLECULES

Traditionally, the classification of chiral molecules is based on "elements of chirality". One of these elements, that of *chirality center*, is well-suited for the description of relatively simple (especially acyclic) molecules; this notion is really a background of the commonly accepted CIP nomenclature rules.<sup>45</sup> The other elements, *chirality axes and planes*, although less clearly defined, have been successfully applied to relatively broad classes of chiral organic molecules (e.g., allenes, spiranes, biaryls,  $\pi$ -complexes, etc.). The classification based on elements of chirality is sometimes ambiguous and includes many special cases, perhaps, the most severe criticism of its backgrounds was made by K. Mislow and J. Siegel<sup>13b</sup> who stated that "elements of chirality" are not directly related to chirality itself but are, in fact, *stereogenic units*. In the present paper, only several drawbacks of the traditional classification are summarized in example 8.

**Example 8.** The well-known fact that many organic molecules with two or more asymmetric carbon atoms can be achiral due to the existence of a symmetry plane may be

**Chart 8.** Achiral Molecules with Two, Three, and Four Asymmetric Carbon Atoms (**a**) and Chiral Molecules with Poorly Defined Elements of Chirality (**b**)<sup>a</sup>



<sup>a</sup> The last hypothetical structure of Chart 8a is used to visualize four "hidden" chirality centers of a parent structure (cuneane).

often explained by compensation effect of two chiral centers of opposite configuration. The typical examples (meso-tartaric acid and one of two diastereomers of "pseudochiral" 2,3,4-trihydroxyglutaric acid) are represented in Chart 8a together with polycyclic structures—cuneane and its hypothetical heteroanalog. The last two examples convincingly show that not the pairwise "interaction" between chirality centers but the global geometry of the molecule results in the disappearance of chirality associated with each of four asymmetric carbon atoms.

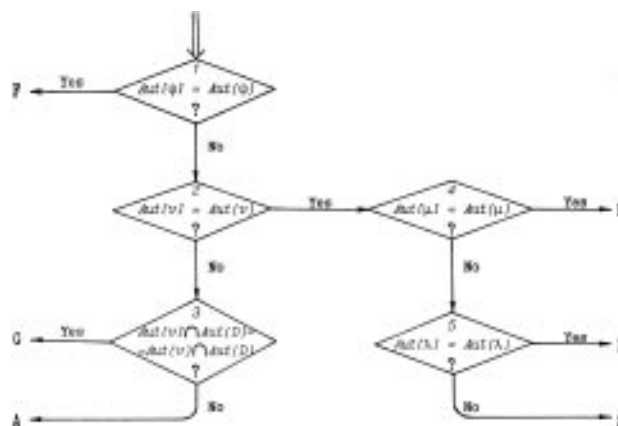
Chart 8b demonstrates that the selection of chirality centers and axes depends neither on real symmetry elements nor on the type of molecular chirality. Thus, in asymmetrically substituted adamantane, its chirality center lies in the geometrical center of the molecule though it is not occupied by an atom. In a very similar situation, the geometrical center of a doubly bridged biphenyl derivative is not considered as a chirality center; in this case, one of three real  $C_2$ -axes (namely that passing through the central bond of biphenyl) is chosen to represent axial chirality. Finally, a single nontrivial symmetry element ( $C_2$ -axis) of 1,3-bishomocubane molecule is not considered as a chirality axis in this polycyclic structure.

The above examples show that some global characteristics of the whole structure rather than local elements of chirality should be used for rational classification of the chirality of organic molecules. In the authors' opinion, just the chirality criteria for 3D-PCs, 3D-MCs, 3D-GCs, and 3D-LCs can serve as simple algebraic tools for unambiguous classification of chirality in rigid molecular systems. This classification is however applicable not only for actually rigid molecules (with the geometries being practically unaffected by intramolecular motions) but also for fixed conformations<sup>46</sup> of flexible molecules as well.

The main idea of the suggested classification principle is as follows. The "ideal" geometric figure formed from points (corresponding to atoms of any nonplanar molecular species) can be either chiral or achiral. In the first case, the molecule under discussion is said to be *F-chiral* ("conFigurationally" chiral); this means that the corresponding point 3D configuration  $\psi$  behaves alone as the source of chirality.

In the second case, the "ideal" figure with labeled points (atom symbols) and, probably, multiple lines must be analyzed. This figure evidently represents a molecular 3D configuration (i.e., superposition  $\nu = (\varphi, \chi, \psi)$ ); if it is chiral, then the chirality of the corresponding molecule can be

**Chart 9.** Determination of Chirality Type for Rigid Molecules<sup>a</sup>



<sup>a</sup> Symbols *F*, *G*, *N*, *P*, *S* correspond to *F*-, *G*-, *N*-, *P*-, and *S*-chiral, while *A*—to achiral molecular systems.

caused by disposition of atom symbols, ordinary and multiple bonds, or both factors simultaneously. In these cases, the molecule is said to be *P-chiral* ("comPositionally" chiral, because atom symbols define molecular composition), *N-chiral* ("conNectively" chiral, because ordinary and multiple bonds define molecular connectivity), or *S-chiral* ("conStitutionally" chiral, because atom symbols and chemical bonds define molecular constitution).

Finally, if molecular 3D configuration, i.e., the superposition  $\nu$ , is combinatorially achiral, then the molecule under discussion is either achiral or its chirality appears due to deviations of molecular geometry from "ideal" geometrical realization of corresponding 3D-MC. In this case, the molecule is said to be *geometrically* or *G-chiral*; it is necessary to note that *G-chirality* is typically caused by the disappearance of improper symmetry elements in asymmetrical rotamers of flexible molecules. Other factors, such as steric hindrances, hydrogen bonds, donor–acceptor or other specific intra- or inter-molecular interactions, can also lead to *G-chirality* of nonrigid as well as rigid molecules.

The above consideration evidently shifts classification problems to analysis of combinatorial rather than geometrical objects thus making it possible to use suggested chirality criteria for 3D-PCs, 3D-MCs, 3D-GCs, and 3D-LCs instead of searching for improper symmetry elements in corresponding "ideal" geometrical realizations. The geometric information is really needed to be known only in the single classification step, i.e., in the step making it possible to differentiate between *G-chiral* and achiral molecules. In this case, we assume the square matrix  $D = (d_{ij})$  with off-diagonal entries  $d_{ij}$  being interatomic geometric distances is explicitly known. If  $Aut(D)$  is a subgroup of the symmetric group consisting of those permutations  $s$  for which the matrix equation  $SDS^{-1} = D$  holds,<sup>47</sup> then the criterion of *G-chirality* can be written as

$$Aut[\nu] \cap Aut(D) = Aut(\nu) \cap Aut(D)$$

The last equation evidently shows that all (–)-automorphisms of the expanded group  $Aut[\nu]$  (and hence all improper symmetry elements of an "ideal" geometrical realization) do not belong to the point symmetry group  $Aut(D)$  thus making this group identical to the rotation group  $Aut(\nu) \cap Aut(D)$  of the molecule under discussion.

One of several possible<sup>48</sup> procedures for the determination of chirality type is visualized in Chart 9. In step 1 of the

presented procedure, the absence of  $(-)$ -automorphisms in the expanded group of the point 3D configuration makes it possible to immediately detect configurational or  $F$ -chirality. If  $(-)$ -automorphisms are really found in  $Aut[\psi]$  and also in the expanded group of the molecular 3D configuration (see answers "No" in steps 1 and 2), then the additional checking step 3 makes it possible to detect geometrical or  $G$ -chirality, which arises due to the disappearance of all  $(-)$ -automorphisms in the "geometric" symmetry group  $Aut(D)$ . If all  $(-)$ -automorphisms of  $Aut[\psi]$  do not belong to the expanded group  $Aut[v]$  (see answer "Yes" in step 2), then the factors which result in their disappearance should be analyzed. In step 4 of the classification procedure, the absence of  $(-)$ -automorphisms in the expanded group of the graph 3D configuration makes it possible to detect  $N$ -chirality (note that groups associated with 3D-LCs are completely ignored in this case). If all  $(-)$ -automorphisms of the group  $Aut[\psi]$  do not belong to the expanded group of the labeled 3D configuration (see answer "Yes" in step 5), then compositional or  $P$ -chirality is observed. The last of the formally possible cases takes place if some part of the  $(-)$ -automorphisms from the group  $Aut[\psi]$  do not belong to the group  $Aut[\mu]$ , while all others do not belong to the group  $Aut[\lambda]$ ; constitutional or  $S$ -chirality is found in such (quite rare) situations.

It should be noted that the above classification procedure can be applied not only to complete molecules but to some well-defined parts of molecules as well. For example, hydrogen depleted molecules and molecular skeletons can be also found to be  $F$ -,  $G$ -,  $N$ -,  $P$ -,  $S$ -chiral, or achiral. The main problem arises however from the fact that practically significant parts of molecules (e.g., molecular skeleton, framework, or core) are often not rigorously defined. Thus, the notion of "molecular skeleton" is unambiguously defined for all hydrocarbons but not for complex molecules which contain di- and polyvalent heteroatoms in cycles, side chains, and functional groups. For this reason, we suggest here the simple formal rules which make it possible easily to find four practically significant parts of molecular structures starting from conventional structural formulas.

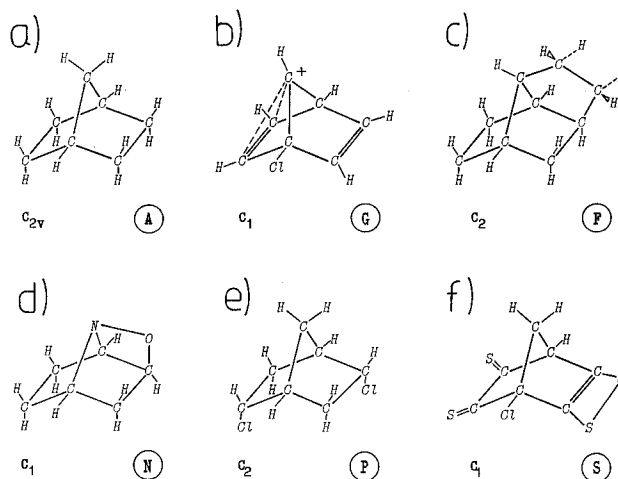
(1) *Hydrogen-depleted molecule* is defined traditionally; in order to obtain the corresponding hydrogen-depleted molecular graph all hydrogen vertices should be deleted from a given structural formula.

(2) *Molecular skeleton* is recursively defined to consist of all carbon atoms together with those heteroatoms which are connected with two or more skeletal atoms; in order to obtain the skeleton graph starting from the hydrogen-depleted molecular graph, all noncarbon vertices of degree 1 (i.e., connected with a single neighbour by a classical ordinary, double, or triple bond) should be sequentially deleted.

(3) *Molecular framework* is recursively defined to consist of all carbon and noncarbon atoms being connected with two or more framework atoms; in order to obtain the framework graph starting from the skeleton graph, all carbon and noncarbon vertices of degree 1 should be sequentially deleted.

(4) *Molecular core* is recursively defined to consist of all atoms which are connected with three or more core atoms; in order to obtain the core graph from the corresponding framework graph, all chains consisting of vertices of degree 2 should be sequentially deleted. The ends of all these chains

**Chart 10.**  $G$ -,  $F$ -,  $N$ -,  $P$ -, and  $S$ -Chiral Derivatives (b–f) of Achiral Nonbornane Structure (a)



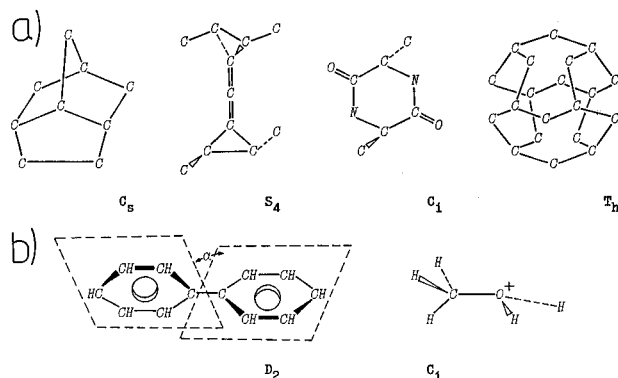
must be connected by additional "fictive" bonds (unless these ends coincide or are yet connected by a "normal" chemical bond).

The construction of several hydrogen-depleted, skeleton, framework, and core graphs and the application of the suggested classification procedure to corresponding parts of molecules are exemplified in section 9.

## 8. ILLUSTRATING EXAMPLES OF $F$ -, $G$ -, $N$ -, $P$ -, $S$ -CHIRAL AND ACHIRAL MOLECULAR OBJECTS

In this section, the examples of chiral as well as achiral rigid molecular entities are visualized by their (mainly "ideal") geometrical realizations. For the sake of brevity, no functions  $\psi$  and superpositions  $\lambda = (\varphi, \psi)$ ,  $\mu = (\chi, \psi)$ , and  $\nu = (\varphi, \chi, \psi)$  are explicitly shown; the corresponding "normal" and expanded automorphism groups are also thought to be immediately observed from pictorial representations. Most examples of this (and the following) section are selected from monographs<sup>10a,49</sup> and reviews.<sup>20b,50</sup>

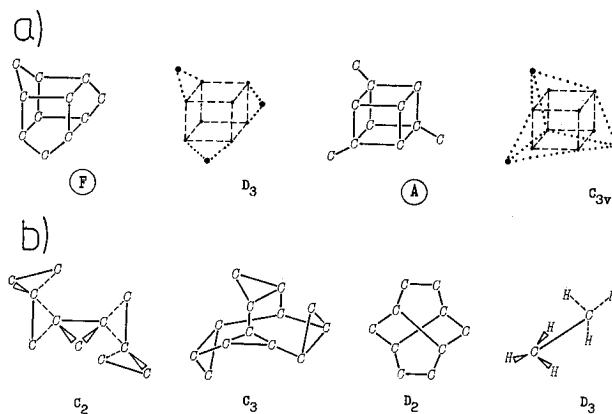
**Example 9.** The classification procedure of the preceding section will be first illustrated for five chiral derivatives of an achiral rigid norbornane structure. Two  $(-)$ -automorphisms of the groups  $Aut[\psi] \equiv Aut[v]$  (characterizing symmetries of point and molecular 3D configurations for unsubstituted norbornane molecule) evidently correspond to symmetry planes of  $C_{2v}$  spatial realization of Chart 10a. Only one of these  $(-)$ -automorphisms belongs to the group  $Aut[v] \subset Aut[\psi]$  characterizing the less symmetrical but "combinatorially" achiral 1-chloronorbornadien-7-yl cation of Chart 10b. This  $(-)$ -automorphism does not belong however to the group  $Aut(D)$  because nonclassical interaction (although being ignored in the graph structure) appreciably shifts the charged carbon atom toward one double bond. For this reason, the answers "No", "No", and "Yes" in steps 1, 2, and 3 of the classification procedure clearly show the nonclassical cation of Chart 10b to be geometrically chiral. In the next example, that of Chart 10c, the brexane structure consists of two norbornane moieties which are interconverted by a symmetry element ( $C_2$  axis). The visual examination shows that not only the group  $Aut[v]$  but also the group  $Aut[\psi]$  (which characterizes the point 3D configuration of brexane molecule) contains no  $(-)$ -automorphisms. Thus, the answer "Yes" in step 1 of the classification procedure

**Chart 11.** Achiral Hydrogen-Depleted Graphs (a) and Examples of *G*-Chiral Conformations in Nonrigid Molecular Entities (b)

immediately shows that the brexane molecule is configurationally chiral.

In three other examples of Chart 10, the molecular geometries are quite similar to that of unsubstituted norbornane thus making two symmetry planes (and corresponding  $(-)$ -automorphisms) to be conserved in “ideal” point figures and in expanded groups  $Aut[\psi]$  of corresponding 3D-PCs. These  $(-)$ -automorphisms do not belong however to groups  $Aut[\nu]$  due to unsymmetrical dispositions of atom symbols and/or chemical bonds; this fact requires (after answers “No” and “Yes” in steps 1 and 2) the automorphism groups of graph and labeled 3D configurations to be examined. In the case of Chart 10d, the examination of the spatial graph with unlabeled vertices clearly shows it to be unsymmetrical. This means that no  $(-)$ -automorphisms can be detected in a group  $Aut[\mu]$  (in step 4 of the classification procedure) thus making the corresponding 1-aza-8-oxatricyclo[3.3.0.0<sup>2,7</sup>]octane structure connectively chiral. In the case of *endo,endo*-2,5-dichloronorbornane molecule (cf. Chart 10e), both the  $(-)$ -automorphisms and corresponding symmetry planes are conserved in the group  $Aut[\mu]$  and in corresponding unlabeled spatial graph. However, these  $(-)$ -automorphisms do not belong to the expanded group  $Aut[\lambda]$  because the “ideal” spatial figure formed out of disconnected but labeled points contains no symmetry planes. For this reason, the answer in step 5 of the classification procedure is “Yes”, and the dichloronorbornane molecule is compositionally chiral. The last pictorial representation of Chart 10 visualizes the hypothetical tricyclic isomer of norbornane-2,3,5,6-tetrathione; in this molecule, one of the symmetry planes disappears due to an unsymmetrical disposition of atom symbols (*Cl* and *H* at  $C_1$  and  $C_4$ ), while the other disappears due to an unsymmetrical disposition of chemical bonds in *SCCS*-fragments. This means that both the expanded groups  $Aut[\mu]$  and  $Aut[\lambda]$  contain a single  $(-)$ -automorphism, and the answers “No” in steps 4 and 5 of the classification procedure show that this molecule is constitutionally chiral.

Several specific features of *F*-, *G*-, *N*-, *P*-, *S*-chiral and achiral molecular entities are additionally considered. First of all, the symbol *A*, designating achirality, is not associated with real type of improper symmetry element(s) corresponding to  $(-)$ -automorphism(s) of the group  $Aut[\nu]$ . For this reason, the first three hydrogen-depleted graphs of Chart 11a (possessing a single symmetry plane, rotation-reflection axis, and inversion center, respectively) and the hypothetical perhomocubane skeleton (possessing these three types of improper symmetry at the same time) are not differentiated in the suggested classification scheme.

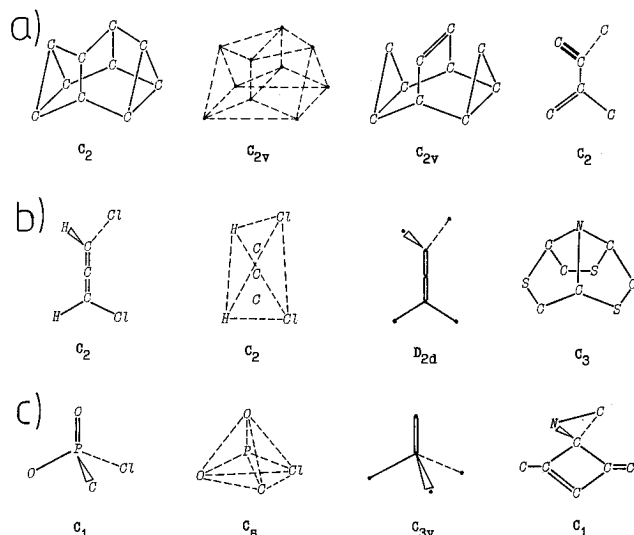
**Chart 12.** *F*-Chiral and Achiral Cubane Derivatives (a) and Additional Examples of *F*-Chirality (b)

The general comment on *G*-chirality is associated with physical reasons which result in this type of chirality. Not only specific interactions (such as formation of nonclassical bonds; cf. Chart 10b) but also all types of intramolecular motions can lead to *G*-chirality if these motions violate achiral molecular geometry but leave the corresponding molecular configuration unchanged. Thus, in the first example of Chart 11b, the represented “intermediate” biphenyl rotamer with  $\alpha < 90^\circ$  and the most symmetrical  $D_{2d}$  rotamer with  $\alpha = 90^\circ$  are characterized by the same (achiral) 3D-MC; for this reason, the less symmetrical  $D_2$  rotamer of the nonrigid biphenyl skeleton is undoubtedly *G*-chiral. The second example of Chart 11b demonstrates that the presence of elongated (or shortened) chemical bonds can also result in *G*-chirality; in the case of methyloxonium cation, the elongation of one *O*–*H* bond must not be considered however as a step of dissociation process.

The main feature of configurational chirality is that point figures corresponding to *F*-chiral molecular entities are always chiral, and this fact does not depend on the relative disposition of point labels (atom symbols) and/or bond orders (ordinary or multiple) until the corresponding point 3D-configuration  $\psi$  is unchanged. Thus, not only  $D_3$ -trishomocubane itself but also all its heteroanalogs or other structures with geometries similar to the left polyhedral figure of Chart 12a are also *F*-chiral. On the other hand, significant shifts of three heavy points in this polyhedral figure can alter the function  $\psi$  thus resulting in new 3D-PC which need not necessarily be *F*-chiral. An example of such a polyhedral figure together with achiral trimethylcubane skeleton is shown on the right of Chart 12a.

Numerous *F*-chiral rigid polycyclic hydrocarbons, e.g., triangulanes, twistanes, trishomobullvalenes (visualized in Chart 12b by their skeleton graphs), and helicenes, have been synthesized to date. Many fixed conformations of flexible molecular entities (such as “intermediate” ethane rotamer of Chart 12b) may be also considered as typical examples of *F*-chirality.

The examples of *N*-chirality are not so numerous; in general, the molecular entities, in which improper symmetry elements of their “ideal” polyhedral figures disappear due to the unsymmetrical disposition of chemical bonds, are said to be connectively chiral. It is important that this type of chirality is always retained for all heteroanalogs of any *N*-chiral structure but must not be retained if the relative

**Chart 13.** Specific Features of *N*-Chiral (a), *P*-Chiral (b), and *S*-Chiral (c) Molecular Entities<sup>a</sup>

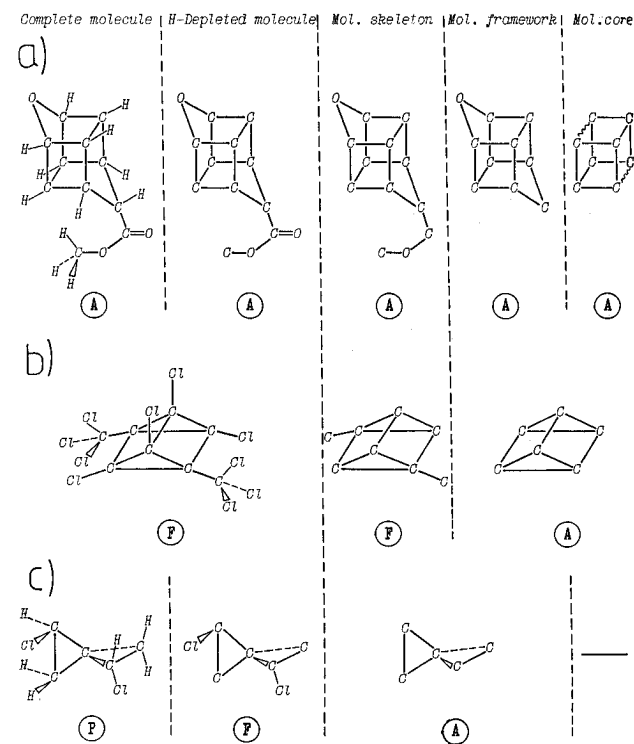
<sup>a</sup> The unlabeled and labeled polyhedral figures are visualized in the second column of this chart.

disposition of chemical bonds is changed. In Chart 13a, the *N*-chiral barettane skeleton graph together with its achiral "ideal" figure and geometrically very similar achiral tetracyclo-[3.3.2.0<sup>2,4</sup>.0<sup>6,8</sup>]dec-9,10-ene skeleton are pictorially represented. The conformations of flexible molecular entities may be also found to be *N*-chiral; the nonplanar *n*-butane skeleton graph (cf. Chart 7a) and the nonplanar rotamer of 2,3-dimethylbuta-1,3-diene skeleton graph of Chart 13a may serve as examples.

The next type of chirality, that of compositional chirality, is no doubt the most frequently encountered in practice. Many simple tetrasubstituted methane derivatives (see Example 5) as well as various heteroanalogs of achiral structures are typically *P*-chiral. The specific feature of this type of chirality consists in the fact that labeled polyhedral figures (with labels being represented by atom symbols) are necessarily chiral, although corresponding point figures and unlabeled spatial graphs are always achiral. In Chart 13b, the chirally labeled polyhedral figure and achiral spatial graph corresponding to *P*-chiral dichloroallene molecule are pictorially shown; the example on the right of Chart 13b demonstrates that trithiasubstituted derivative of an achiral structure hexahydro-6*b*-azacyclopenta[*cd*]pentalene) is compositionally chiral.

The main remark on constitutional or *S*-chirality is that this type of chirality is quite rare and may be considered as exotic. In this case, the labeled polyhedral figure and unlabeled spatial graph can be both achiral, and a single chiral spatial object is associated with labeled spatial graph (and corresponding molecular 3D-configuration). This type of chirality is exemplified in Chart 13c by the hydrogen-depleted graph of methylphosphonous chloride; the *S*-chiral skeleton of a hypothetical spirobicyclic structure is used as an additional example.

Summarizing the above results, we can state that introduced chirality types do not necessarily correspond to such notions as "molecular chirality", "conformational chirality", or "topological chirality".<sup>51</sup> The mentioned discrepancy can be easily understood if one takes into account that the suggested classification principle is really based on "com-

**Chart 14.** Formation of Hydrogen-Depleted, Skeleton, Framework, and Core Graphs for Selected 1,4-Bishomocubane (a), Prismane (b), and Spiropentane (c) Derivatives<sup>a</sup>

<sup>a</sup> The chirality types are indicated by symbols A, F, and P.

binatorial" symmetries of polyhedral figures rather than on any more detailed nature of corresponding molecular entities.

## 9. CONCLUDING REMARKS

In the final section of this paper, two particular topics are briefly discussed. These topics may be regarded as a complement to the suggested classification scheme for rigid molecular systems. The first of the considered problems is associated with formal rules which make it possible sequentially to construct four essential parts of organic structures; some specific features of the construction procedure and possible interrelations between chirality types (assigned to parts of molecules) are illustrated by several examples. The second topic deals with nonrigid molecular systems; the suggested simple rules make it possible to identify the chirality type for the whole family of interconverting molecular entities if particular conformations of nonrigid systems are properly selected.

Let us turn to the formal rules of section 7; the application of these rules to the construction of hydrogen-depleted structures, molecular skeletons, frameworks, and cores is illustrated in Example 10. Note that the suggested rules are formulated for molecular graphs (i.e., conventional constitutional formulas) but not for their spatial realizations. For this reason, the designations of some chirality types shown in Chart 14 are valid only for selected conformations of corresponding molecular entities.

**Example 10.** In Chart 14a, the four steps resulting in hydrogen-depleted molecule, molecular skeleton, framework, and core are visualized for the methyl oxabishomocubancarboxylate molecule; 12 hydrogen atoms, 1 carbonyl oxygen atom, 1 acyclic  $-C-O-C-$  chain, and 2 homological modules ( $-O-$  and  $-C-$ ) are sequentially deleted in

this example. It is important to note that three types of oxygen atoms are deleted in different steps:

- (1) the carbonyl oxygen is connected with a single neighbor and hence does not belong to the molecular skeleton,
- (2) the second, "acyclic" oxygen atom can be deleted only in the course of the iteration process (i.e. after univalent carbon was initially deleted from the skeleton graph); this atom is evidently absent in the molecular framework, and
- (3) the last, "bridge" oxygen atom necessarily belongs to the molecular framework but not to the molecular core.

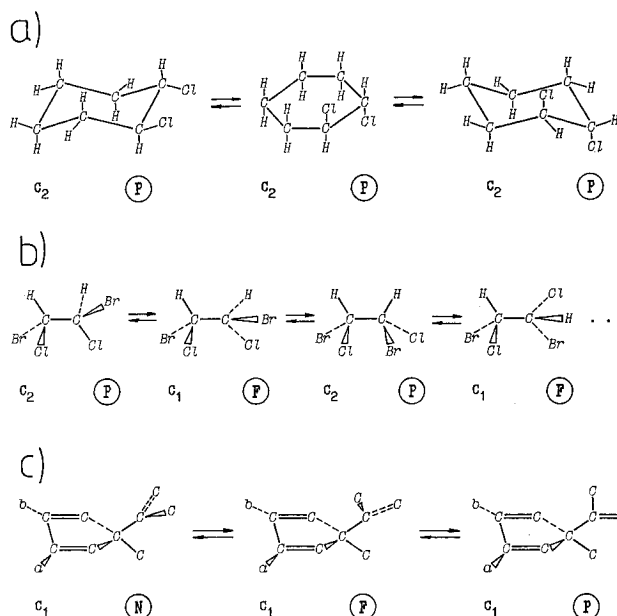
Note that in a core graph, both the deleted atoms ( $-O-$  and  $-C-$ ) are substituted by "fictive" wiggly bonds; just the same wiggly bond should correspond to any chain consisting of arbitrary number of carbon or non-carbon atoms.

The examples of Chart 14b,c convincingly demonstrate that four essential parts of molecular graph must not be necessarily different. Thus, in the case of perchlorodimethylprismane (cf. Chart 14b), the hydrogen-depleted graph is identical to the "complete" molecular graph (due to the absence of hydrogens), and the core graph is identical to the framework graph (because there are no vertices connected with two neighbors in the framework graph). Similar reasons lead to the conclusion that skeleton and framework graphs necessarily coincide for all cyclic and polycyclic structures which do not contain acyclic side chains (cf. Chart 14c). An additional feature of the suggested rules is that in some cases "empty" graphs can be produced. Thus, if all vertices of degree 2 are deleted from a framework graph corresponding to any monocyclic or bicyclic structure, then two vertices of degree 1 are formed. These vertices must be, in turn, deleted thus resulting in the "empty" core graph; a typical example of "core-free" structures is exemplified by the spirobicyclopentane framework of Chart 14c. For similar reasons, all acyclic molecules are characterized by "empty" framework graphs, and all inorganic structures containing no cycles—with "empty" skeleton graphs.

The simple consideration shows that chirality types assigned to objects of the higher level (e.g., molecular skeleton) must not be necessarily conserved for objects of lower level(s) (e.g., framework and core). Achirality is an evident exception; this fact is exemplified in Chart 14a for the achiral conformation of methyl oxabishomocubane carboxylate and for the corresponding also achiral objects of lower levels (i.e., hydrogen-depleted, skeleton, framework, and core graphs). On the other hand, chirality types assigned to chiral objects can be either identical (cf. the particular conformation of perchlorodimethylprismane and its skeleton graph in Chart 14b) or nonidentical (cf. dichlorospiropentane structure and its hydrogen-depleted graph in Chart 14c). It is evident that formal comparison of symbols assigned to essential parts of molecules (starting from molecular core) makes it possible easily to detect the level in which chirality arises. Thus, the formal (computerizable) treatment of the string *AAFFFF*, corresponding to Chart 14b, clearly shows that the chirality of dimethylprismane and all its derivatives is caused by an asymmetrical disposition of acyclic carbon atoms in the achiral molecular framework.

Up to this moment, only individual conformations of molecular entities were analyzed. Surely, any approach

**Chart 15.** Examples of (*P*)-Chirality (a), (*FP*)-Chirality (b), and (*FNP*)-Chirality (c) in Nonrigid Systems



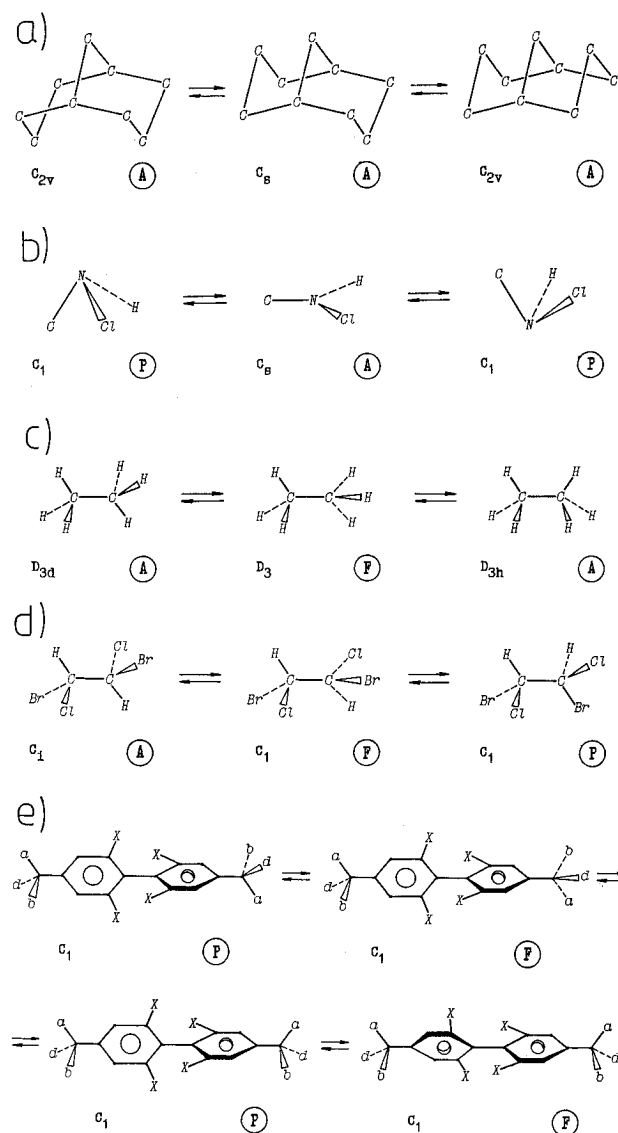
based on combinatorics rather than physics cannot answer two fundamental questions: "What types of intramolecular motions (i.e., rotations around single bonds, inversions at nitrogen atoms, inversions of cyclohexane or other cycles, oscillations of some atoms or atomic groups) are really allowed for a given molecule?" and "What conformations are (relatively) more stable and hence must be taken into account?". On the other hand, if these questions are answered, i.e., if appropriate conformations are selected, then chirality properties of any flexible molecule can be easily described in terms of initially assigned chirality types of particular conformations. For this purpose, the simple combinations of symbols *F*, *G*, *N*, *P*, and *S* (and also *A*) can evidently be used.

In order to designate chirality types of chiral nonrigid molecular entities, the sequences of alphabetically ordered symbols *F*, *G*, *N*, *P*, *S* in brackets are suggested. Note that although the number of conformations can be infinite, the length of any sequence does not exceed 5 in any case. For this reason, the number of possible "nonrigid chirality types" cannot exceed  $2^5 - 1 = 31$ .

**Example 11.** Three typical situations are pictorially represented in Chart 15. The first example, that of Chart 15a, demonstrates that just the same chirality type can be assigned to all selected conformations. Thus, if only proper chair (i.e., with symmetry  $D_{3d}$ ) and planar (i.e., with symmetry  $D_{6h}$ ) forms of the cyclohexane ring are taken into account, then *P*-chirality of diequatorial, planar, and diaxial conformations leads to a conclusion that nonrigid *trans*-1,2-dichlorocyclohexane must be classified as (*P*)-chiral molecule. The examination of Chart 15b shows that staggered and eclipsed rotamers of chiral 1,2-dibromo-1,2-dichloroethane molecule are *P*-chiral, while all intermediate rotamers are *F*-chiral; for this reason, the presented stereoisomer of  $C_2H_2Br_2Cl_2$  (and its enantiomer, too) is said to be (*FP*)-chiral.

In some cases, three or more different chirality symbols can be assigned to interconverted conformations. Thus, the examination of various rotated conformations of the isopropenyl unit in substituted cyclopenta-1,3-diene skeleton of Chart 15c (with *a* and *b*,  $a \neq b$ , being simple substituents

**Chart 16.** Designations for Achiral Nonrigid Systems: Bicyclo[3.3.1]nonane (a) and *N*-Chloromethylamine (b), Ethane (c) and *meso*-1,2-Dichloro-1,2-dibromoethane (d) Rotamers, and Conformations of 2,2',4,4',6,6'-Hexasubstituted Diphenyl with Bulky Groups *X* and Chiral Substituents *Cabd* (e)



such as *Cl* and *Br*) reveals *N*-, *F*-, and *P*-chiral rotamers; as a result this nonrigid molecular skeleton is said to be (*FNP*)-chiral.

It is interesting that the suggested designation system may also be used for achiral molecular entities which correspond to families of interconverted (a) achiral, (b) achiral and chiral, or (c) only chiral conformations. In the last case, the real chirality disappears due to the fact that equal amounts of both enantiomers simultaneously exist for any chiral conformation; the most widely known example of such "achiral molecules with no achiral conformation" is Mislow's ester.<sup>52</sup> The suggested designations for flexible achiral molecules are very similar to those for chiral molecules but with symbols *f*, *g*, *n*, *p*, *s* (and also *a*<sup>53</sup>) standing instead of *F*, *G*, *N*, *P*, *S* (and *A*).

**Example 12.** The interconverted chair-chair, chair-boat, and boat-boat forms of the bicyclo[3.3.1]nonane skeleton (cf. Chart 16a) may serve as typical example of an (*a*)-achiral nonrigid molecular entity; all intermediate conformations can be also thought to be achiral in this case. The example of Chart 16b visualizes the two-step inversion of the *P*-chiral

tetrahedral *N*-chloromethylamine skeleton *via* a planar structure. The fact that the enantiomerization process is rapid under normal conditions leads to the conclusion that *N*-chloromethylamine skeleton is (*ap*)-achiral. In Chart 16c, an example of (*af*)-achirality is given; the staggered and eclipsed ethane rotamers are evidently both achiral, while all intermediate rotamers are *F*-chiral in this case. Unlike unsubstituted ethane, achiral, *F*-chiral, and *P*-chiral conformations of *meso*-1,2-dibromo-1,2-dichloroethane can be observed in the course of the internal rotation process (cf. Chart 16d). For this reason, the nonrigid *meso*-1,2-dibromo-1,2-dichloroethane molecule is said to be (*afp*)-achiral.

In the last example, a somewhat simplified spatial model of Mislow's mixed ester<sup>52</sup> of (+)- and (−)-menthol with 2,2',6,6'-tetranitro-4,4'-diphenic acid is visualized. The substitution of two menthyl groups in this ester for *Cabd* fragments (cf. ref 17c) makes it possible to detect *P*-chiral and *F*-chiral rotamers;<sup>54</sup> some of them are shown in Chart 16e. The fact that each *P*- and *F*-chiral conformation can be converted into its enantiomer by a feasible 90° rotation of diphenyl moiety leads to a conclusion that (*fp*)-achirality is observed in this case. A similar examination of Mislow's ester itself shows this "achiral molecule with no achiral conformation" to be classified as (*f*)-achiral.

Ending this paper, the authors note that examination of complex molecular entities (such as Mislow's ester) by means of the suggested chirality criteria is typically quite sophisticated *if molecular 3D configurations are represented pictorially*. On the other hand, the computer implementation of classification procedures would make it possible simultaneously to assign chirality types to "complete", hydrogen-depleted, skeleton, framework, and core graphs *if molecular geometries are explicitly known*. For this purpose, we are planning to work out (in collaboration with Dr. Th. Wieland, Universität Bayreuth) a special "classification" subprogram. The main features of this subprogram, and the results obtained will be published elsewhere.

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**Note Added in Proof.** The mentioned computer program is elaborated up to date and its application shows that in nontrivial cases, the visual examination of spatial models cannot guarantee correct recognition and treatment of all symmetries. Thus, the computer investigation reveals *S*-chirality (but not *P*-chirality) in tetrahedral figures of Chart 16b; this fact leads to the conclusion that flexible *N*-chloromethylamine skeleton is, in fact, (*as*)-achiral.

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  - (22) (a) The notion of configuration is not unambiguously formulated in organic chemistry; several suggested definitions are discussed in ref 22b. In the present approach, the word “configuration” is understood in a broad sense, i.e., as a qualitative characteristic of relative spatial disposition of some parts, namely points, graph vertices, or atoms, of the whole point system, spatial graph, or molecule, respectively. (b) Drozd, V. N.; Zefirov, N. S.; Sokolov, V. I.; Stankevitch, I. V. *Zh. Organ. Khimii* **1979**, 15, 1785–1793 [in Russian]. (c) Kuz'min, V. E.; Stel'makh, I. B. *Zh. Strukt. Khimii* **1987**, 28, 45–49 [in Russian].
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  - (25) This brief notation means that  $\varphi(s^{-1}(w)) = \varphi(w)$  for all  $w \in W$ . The expression for  $Aut(\chi)$  should be understood similarly; in this case the induced permutation  $\bar{s}$  is thought to act on the set of unordered pairs  $W^{(2)}$  of different atoms.
  - (26) The consideration of molecular graphs needs vertex labels and numbers to be differentiated. Vertex labels (or colors) are associated with atom names, while sequential numbers (integers 1,2,...,n) unambiguously identify graph vertices.
  - (27) These subgroups are constructed of two smaller symmetric groups ( $S_1$  and  $S_3$ ), each of them acting on its own subset ( $W'$  and  $W''$ ,  $W' \cap W'' = \emptyset$ ,  $W' \cup W'' = W$ ). In the example of Chart 1b,  $W'$  corresponds to a single nitrogen atom while  $W''$ —to three carbon atoms.
  - (28) For each permutation  $s$  of a symmetric group  $S_{|W|}$ , its “ordinary” induced action permutes unordered pairs of  $W^{(2)}$ , while the corresponding “doubly” induced action converts all functions  $\chi$  one into another. The detailed description of the doubly induced groups (in fact, power groups, cf. Harary, F.; Palmer, E. *J. Combin. Theory* **1966**, 1, 157–173) will be a subject of further papers in which various generation problems for molecular objects are rigorously formulated.
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  - (31) This treatment leads however to some inconsistencies in the definition of topological chirality. Thus, the nonplanar graph  $K_{3,3}$  (as well as the complete graph  $K_5$ ) is considered<sup>30a</sup> as the source of topological chirality. It does not mean however that all nonplanar realizations of this graph are necessarily chiral; K. Mislow has recently proved (cf. note 3 in ref 30b) that two nonadjacent edges of  $K_{3,3}$  must be colored for this purpose. But many edge-colored planar graphs, such as the graph of the trigonal prism with two colored edges belonging to different triangles and quadrangles, are also chiral in 3D space.
  - (32) Turro, N. J. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 882–901.
  - (33) The permutation is even (odd) if it contains an even (odd) number of even cycles in its cycle decomposition. All even permutations of the symmetric group  $S_n = S_{|W|}$  form an alternating group  $A_n = A_{|W|}$  of order  $n!/2$ .
  - (34) The “ordinary” induced action of a permutation  $s \in S_{|W|}$  can convert standard quadruple  $[i,j,k,l]$ ,  $i < j < k < l$ , into nonstandard one, and this is a reason why the functions  $\psi$  from the set  $W^{(4)}$  (but not  $W^{(4)}$ ) are really used in the definition of point 3D configuration.
  - (35) The special kind of doubly induced group may be, in fact, constructed for interconversion of enantiomorphic 3D-PCs (ref 8b). For the purposes of this paper, it is significant only that the functions belonging to enantiomorphic point 3D configurations cannot be interconverted by simple renumbering of point systems.
  - (36) Several names were proposed by mathematicians to differentiate between two kinds of automorphisms. These are “(+1)-automorphisms” and “(−1)-automorphisms”,<sup>2</sup> “proper automorphisms” and “improper automorphisms”,<sup>18a</sup> and “automorphisms” and “enantiomorphisms”.<sup>18b</sup> Although in our preceding publications,<sup>8a,b</sup> the terms “automorphisms” and “antiautomorphisms” were used, we prefer here the names which are similar to those of A. W. M. Dress.<sup>3</sup>
  - (37) It should be noted that planar systems with the same number of points (e.g., planar “quadrangle”, “centrated triangle”, and four-point system of Chart 2a) are characterized by the same functions with all zero values of  $\psi([i,j,k,l])$  and hence can be differentiated only by corresponding 2D configurations (cf. ref 5b). Such planar systems are certainly achiral in 3D space but cannot be analyzed by means of suggested chirality criterion; the obvious reason is that any “zero” function  $\psi$  coincides with its antipode function  $\bar{\psi}$  in this exceptional case.
  - (38) In the case of point configurations, an infinite number of “ideal” geometries really exists. One of the reasons is that any scaling (i.e., simultaneous increase or decrease of all distances in the geometrical realization) alters neither the symmetry of the point system nor corresponding 3D configuration  $\psi$ .
  - (39) Each equivalence class consists of  $n!/|Aut(\psi)|$  numbered 3D-PCs; the values of  $|Aut(\psi)|$  coincide with orders of rotation groups ( $T$ ,  $D_3$ ,  $C_4$ ,  $C_3$ , and  $C_2$ ) for “ideal” polyhedral figures of Chart 3a.
  - (40) It is well-known that any intersection of two or more finite permutation groups (of the same degree) is also a group.
  - (41) The term “enantiomeric” may be also applied to individual superpositions  $\lambda$  and  $\lambda'$  ( $\mu$  and  $\mu'$ ,  $\nu$  and  $\nu'$ ) if these superpositions cannot be interconverted by renumbering of labeled points (graph vertices or atoms) and  $\bar{\lambda}$  is isomorphic to  $\lambda'$  ( $\bar{\mu}$  is isomorphic to  $\mu'$ ,  $\bar{\nu}$  is isomorphic to  $\nu'$ ).



- (42) Nikanorov, V. A., unpublished results reported on scientific colloquium of the Chemical Department, Moscow State University.
- (43) (a) Strictly speaking, two sorts of pyramidal structures can be observed in the process under discussion. The trigonal-bipyramidal intermediate (to which a separate function  $\psi$  corresponds) is omitted for the sake of brevity. (b) For other explanation of enantiomerization phenomena, see: Ruch, E. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 65–72.
- (44) Nonisomorphic 3D-MCs (3D-LCs or 3D-GCs) may be said to be *diastereomeric* if corresponding constituent functions  $\varphi$  and  $\chi$  ( $\varphi$  or  $\chi$ ) are isomorphic, i.e., relate to the same chemical constitution (composition or connectivity).
- (45) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385–415. Prelog, V.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 567–583.
- (46) The notion of conformation is not unambiguously defined in chemical literature; several suggested definitions were discussed in ref 22b. In this paper, following D.H.R. Barton and R.C. Cookson (see: *Quart. Revs.* **1956**, *10*, 44–82) we associate conformations of molecules with their geometries, i.e., with those spatial dispositions of atoms which are not superposable upon each other. On the other hand, the conformations which can be interconverted by rotations around single bonds only are denoted here as rotamers.
- (47) In the matrix equation,  $S$  denotes the unique permutation matrix corresponding to a given permutation  $s$ . The permutation matrix is a special kind of matrix which contains a single unit entry in every row and column (all other matrix entries are equated to zeros).
- (48) In the simple procedures (similar to that of Chart 9), the permutations of all groups are viewed to be explicitly known. This fact makes it possible for the procedure of Chart 9 to be directly applied to “ideal” and “nonideal” geometrical realizations of 3D-PCs, 3D-MCs, 3D-GCs, and 3D-LCs (because  $(-)$ -automorphisms of all expanded groups and symmetry elements of the point group  $Aut(D)$  can be visually detected in this case). The computer implementation of the classification procedure is somewhat more complicated, because the key step of the corresponding combinatorial algorithm includes the time-consuming back-track search for  $(-)$ -automorphisms of the group  $Aut[\psi]$ . On the other hand, the computer implementation of steps 2–5 in Chart 9 needs only quite trivial checks if several data structures (lists of atom symbols, graph adjacency matrices, and distance matrices  $D$ ) are converted into themselves by action of already found  $(-)$ -automorphisms.
- (49) Hochstrasser, R. M. *Molecular Aspects of Symmetry*; W. A. Benjamin: New York, 1966.
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- (51) Topologically chiral structures are not specially discussed in this paper; the main reason is that topological stereoisomers can be treated in just the same way as other organic structures. For example, catenanes may be in principle found to be  $F$ -,  $G$ -,  $N$ -,  $P$ -,  $S$ -chiral or achiral, and the result should depend on geometries and relative disposition of two (or more) disconnected components.
- (52) Mislow, K.; Bolstad, R. *J. Am. Chem. Soc.* **1955**, *77*, 6712–6713.
- (53) Surely, the symbol  $a$  is not associated with specific type of chirality. This symbol cannot be however omitted—it indicates that achiral conformations do really exist for a given flexible molecule.
- (54) The restricted rotation around a central  $C-C$  bond is taken into account, but a coplanar disposition of benzene rings is thought to be disallowed (due to presence of four bulky  $X = NO_2$  groups).

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