

A PROPOSAL FOR A MODIFICATION OF THE CAHN, INGOLD AND PRELOG CLASSIFICATION OF CHIRALITY ¹

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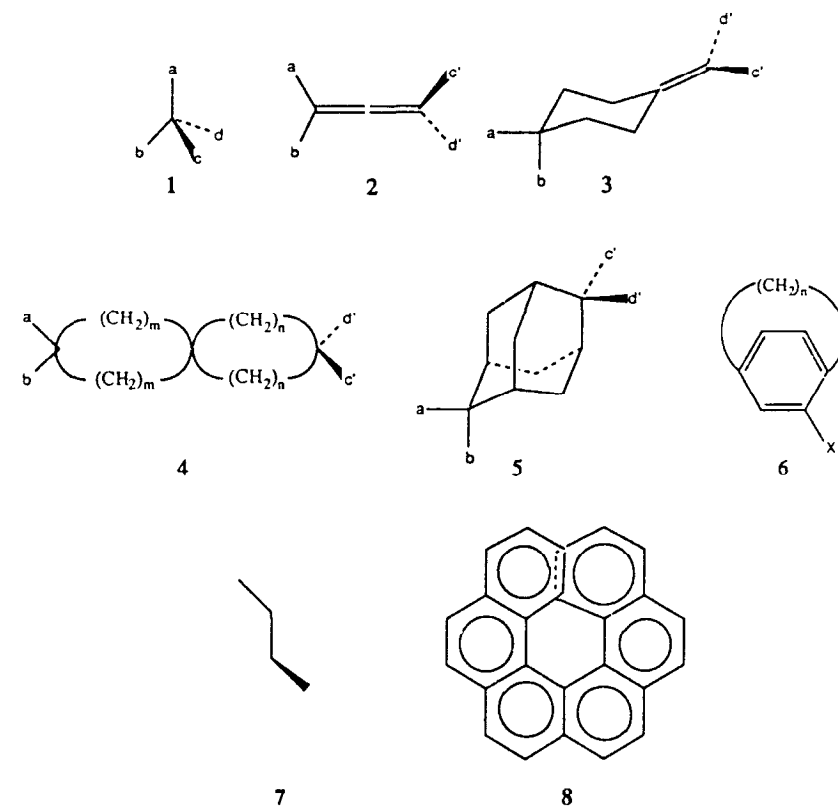
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Abstract : In spite of its wide usage the Cahn, Ingold and Prelog (CIP) classification of chirality has some deficiencies. In particular, there is no uniform generally accepted system of designation of chirality sense and some descriptors used can be interpreted in contradictory ways, as it happens in the cyclophanes case. Therefore, a modification of the classification is proposed here with the purpose to remove the deficiencies of the CIP classification changing as little as possible in existing practice. The importance of so called conformational chirality underestimated both in the classification and in chemical practice is stressed.

A Short Review of the Creation and Development of the CIP Classification

In spite of a great amount of collected experimental data the domain of chirality is still *in statu nascendi*. The formulation of a general symmetry based condition of chirality took about a hundred years since the Pasteur idea on the interrelation between molecular chirality and symmetry (2) have been forgotten after the introduction of the concept of an asymmetric carbon atom by van't Hoff (3) and Le Bel (4). Thus, the condition of chirality started from the idea of an asymmetric carbon atom and was completed with a lack of improper S_n axis in a molecule as a general condition of chirality. On the basis of their former papers (5) Cahn, Ingold and Prelog published their famous classification of chirality (6) more than 20 years ago. In the classification the authors named three elements of chirality : a centre, an axis and a plane of chirality and gave helicity, *i. e.* chirality of helicenes and DNA spirals, and the conformational chirality of the *gauche* butane type as additional kinds of chirality. These elements have been exemplified rather than precisely defined (7 - 9). Thus, an asymmetric carbon atom 1 served as an example of the centre of chirality, tetrasubstituted allenes 2, alkylicyclohexanes 3, spiranes 4, adamantanes 5 and biphenyls 9 were given as possessing axes of chirality and substituted bridged aryls 6 as the molecules exhibiting a plane of chirality. In the early papers by Cahn, Ingold and Prelog (5) the elements of chirality have been interpreted as the results of dissymmetrization of a regular tetrahedron possessing T_d symmetry, of a S_4 symmetry axis and of a symmetry plane C_s , respectively. Although a centre of chirality has

been discussed almost exclusively in terms of an asymmetric carbon atom, a possibility of the centre not coinciding with any atom was mentioned. Two systems of chirality descriptors, R/S and P/M, have been proposed which should be equivalent and interchangeable for molecules possessing axes or planes of chirality such as tetrasubstituted biphenyls **9** for which both could be applied. The R/S system of the preference of substituents on an asymmetric centre was created which is widely used and proved to be extremely efficient in the classification of configuration. On the other hand, the P/M system of chirality designation has found less approval



(see below). The P/M designators showing the sense of the screw formed by three consecutive vectors visualized in Fig. 1 were applied in two different ways in Ref. 6: They describe mutual orientation of substituents around central bond of the *gauche* butane type or they could refer to overall chirality of secondary helical or propeller-like structures such as hexahelicene **8**, [4.4.4]propellane **19** (called 9, 10-tetramethylene-*cis*-decaline in Ref. 6), *etc.*. Although molecules consisting of atoms with coordination number less or equal to four were the main target

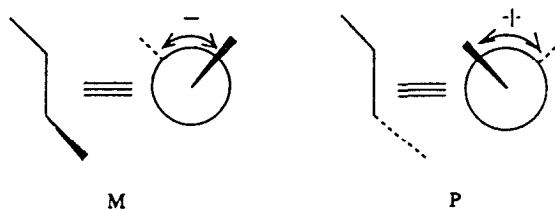


Fig. 1. The P and M chirality descriptors

of the CIP classification some rules concerning complexes with the numbers equal to 5 and 6 have also been given. The CIP classification of chirality has been briefly summarized in the IUPAC recommendations for nomenclature in organic chemistry (10).

In a subsequent revision Prelog and Helmchen (14a) analyzed chirality of a molecule in terms of chiral arrangements of atoms in its molecular model. In particular, chirality of three-point arrangements in two-dimensional space as well as that of four-point arrangements in three-dimensional space was discussed. Two different chiral nonplanar arrangements shown at Fig. 2 are possible in the latter case, the one corresponding to four different substituents (on which a simplex can be built) around an asymmetric carbon atom and the second one corresponding to three consecutive vectors forming a screw. Prelog and Helmchen defined the elements of chirality as stereogenic units consisting of an achiral skeleton and a set of substituents, a simple constitution-preserving permutation of which produces a stereomorphic figure (14b) and they described the way in which four-point simplexes corresponding to the centre, axis and plane of chirality can be found. A representation of a molecule in form of a molecular digraph was described enabling factorization of the molecule into centres of chirality. Then, chiral descriptors and the priority rules for substituents were summarized with minor modifications of some previous rules. For molecules **23** and **24** possessing stereogenic atoms lying on a symmetry axis topological differences between the ligands were invoked to determine the sense of chirality of this group of atoms. The authors also formulated a recommendation prescribing the use of the R/S symbols exclusively for description of the sense of chirality of centres of chirality and the P/M ones solely for the description of the sense of axes and planes of chirality.

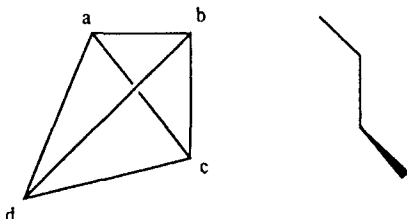


Fig. 2. Two chiral nonplanar four-points arrangements

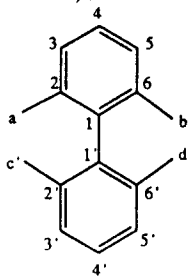
Another attempt to solve the problem of the CIP elements of chirality has been carried out by Sokolov (32) who claims that "introduction of chirality means the introduction of elements of metrics, namely, the distinction between equal distances (that corresponding to achirality) and unequal distances (that correspond to chirality)". According to Sokolov "the n -dimensional isotropic space R^n can be filled with a $(n-1)$ -dimensional chiral figure, and this process requires the obligatory presence of a singular $(n-2)$ -dimensional achiral figure which the filling figure is whirling" and the centre of chirality is associated with two-dimensional figure, *i. e.* Archimedean spiral, filling R^2 , while the axis of chirality is associated with cylindrical helicoide filling in R^3 , and a two-dimensional plane of chirality should be the singular element of the chiral filling of hyperspace R^4 with a chiral (helical) three-dimensional space.

A well-known rule for diastereoisomer count states that for a molecule possessing n asymmetric atoms the maximum number of stereoisomers due to existence of these atoms is equal to 2^n . This rule is of great practical importance because it states that there are at most two diastereomeric pairs of enantiomers for two asymmetric atoms in a molecule, *etc.* Eliel (21) suggested that this rule should be extended so that n would include what was later called other elements of chirality. Some authors used the rule later in this sense (9) but it seems that it has not found its way into textbooks (19c, 22). As will be shown below the rule can be generalized for molecules exhibiting both asymmetric atoms and conformational chirality.

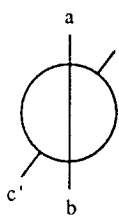
The most important literary critique of the classification

In spite of its wide usage the CIP classification has been sharply criticized. A very important argument disfavours the classification raised by several groups (7 - 9) was the lack of the definitions of the elements of chirality in the original CIP paper. The most important and general critiques were expressed by Mislow and Siegel (11) and Hirschmann and Hanson (7, 13a, 13b). In a series of papers (13a) summarized in a review article "On factoring chirality and stereoisomerism" (13b) the last authors pointed out that the elements of chirality are not

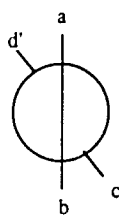
symmetry-related, thus, they cannot be unequivocally derived by dissymetrization of a symmetry element as was done at the early stage of the development of the CIP classification. Hirschmann and Hanson have also shown that the CIP elements of chirality are not introduced and cannot be applied in a consequent way. In particular, they said that the axis and plane of chirality were very similar and for atoms without coordination number bigger than four they could be replaced by a single element (7). The authors also noticed that the neglect of conformational chirality and helicity by Prelog and Helmchen (14a) was a serious restriction limiting substantially the applicability of the CIP classification. As a remedy, instead of the elements of chirality, more general steric units have been proposed imposing no limitations on the coordination numbers of the atoms involved. A centre, a line and a plane of stereoisomerism (13c) have been defined (13d) but a factorization of a molecule into independent steric elements was recognized to be a very difficult problem which, similar to the factorization of a molecule into elements of



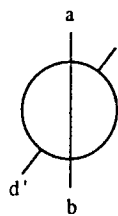
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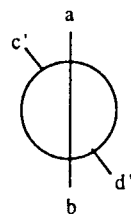
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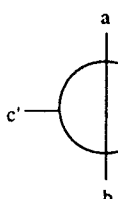
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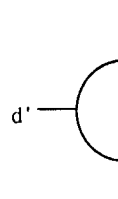
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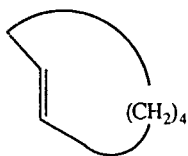
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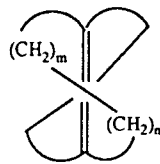
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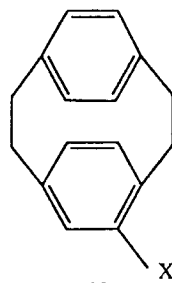
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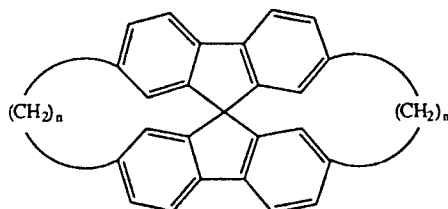
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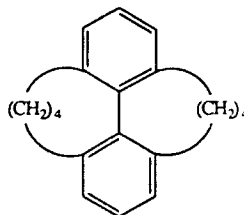


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13a n = 6 - 8,

13b n ≠ 6 - 8



14

chirality, could not be fully formalized. The authors expressed some criticism on the CIP and Prelog and Helmchen notation of configuration but no system of isomer description was proposed instead to denote stereoisomers on the basis of their steric elements. In their approach Hirschmann and Hanson have also intentionally given up the interrelation between the number of steric elements in a molecule, or that of the elements of chirality present in it, and the maximum number of stereoisomers due to their existence.

The CIP classification has also been strongly criticized by Mislow and Siegel (11) in their famous article on "Stereoisomerism and local chirality". Similarly to the Hirschmann and Hanson observation, the authors noticed that the CIP elements of chirality are not symmetry-related, *e. g.* unsubstituted vespirenes 13a and bridged biphenyls 14 of the same D_2 symmetry have different elements of chirality according to the CIP classification; a chirality axis in the latter molecule and a centre of chirality in the former one. They have also formulated "classical chemical purposes served by the concept of the 'asymmetric carbon atom', *i. e.* enumeration, classification and description of stereoisomers" which will be used in the subsequent discussion in a generalized form. Mislow and Siegel were first to recognize an essential difference between stereogenicity and chirotopicity and their examples of the molecules possessing "chiral methyl groups" and "pseudoasymmetric carbon atoms" clearly show the distinction between the properties since in the former ones they are chirotopic and nonstereogenic while the opposite is true for the latter ones. The authors also stated that "elements of chirality" are purely related to stereogenicity" and concluded stating that "it is advisable to abandon expressions such as 'centre of chirality', 'axial chirality' and the like".

The authors' opinion on the classification and its critiques

A short reminder of the purposes, for which the elements of chirality should serve, seems of value for the following discussion. As stated above, Mislow and Siegel (11) cited enumeration, classification and description of stereoisomers as the classical chemical purposes served by the concept of an asymmetric carbon atom. The same is applicable to elements of chirality if we limit ourselves to stereoisomers due to the existence of the elements in a molecule under investigation. In the discussion below the CIP classification and its critiques as well as steric elements introduced by Hirschmann and Hanson (7, 13a, 13b) will be analyzed for consistency and fulfillment of the above purposes.

Also, as stated above, there are no definitions of the elements of chirality in the original CIP paper. The Prelog and Helmchen definitions do not solve the problem since they define the elements in terms of stereogenic units formed by an achiral skeleton with substituents an odd permutation of which yields a stereomorphic figure. This definition is based on the McCasland definition (12) extended by Mislow and Siegel (11). The problem of the stereogenic unit definition will be addressed elsewhere (20), here we would like only to mention that the Prelog and Helmchen definitions cannot be applied to molecules possessing chiral skeletons, thus, they have left helicity and some cases of conformational chirality out of the scope of the classification. Chirality of bridged twisted ethylenes and aryls such as *trans*-cyclooctene 10, betweenanes 11 and cyclophanes 12 which are usually considered as having a plane of chirality (16, 18, 19a) also cannot be classified in terms of the Prelog and Helmchen definitions (14b) since the molecules do not have achiral skeletons and/or they do not transform to their stereoisomers under odd permutations of substituents (14b). Therefore, it seems that in Ref. 14a similarly to the original CIP paper (6) and the following usage, analogies rather than definitions form a basis of the chirality classification. In general, we believe that the Mislow and Siegel observation on the essential difference between stereogenicity and chirotopicity (11) precludes defining the elements of chirality in terms of stereogenic units (see discussion below). It seems also that the imprecise treatment of conformationally flexible molecules such as spiranes 4 for $n = m = 2$, alkylidenecyclohexanes 3 and biphenyls 9 (6, 18, 19b) (which also do not conform to the Prelog and Helmchen definition for frozen conformations, see discussion below) contributed to the unclear situation in the domain of chirality. For instance, 2,2',6,6'-tetrasubstituted biphenyl 9 has been treated under an unformulated assumption on rapid internal rotation around the central bond. Then according to (6, 14a) the molecule possesses an axis of chirality for which the R/S or P/M systems of designation of chirality can be used interchangeably (6) or only the P/M system should be used according to (14a). The former recommendation leads to a discrepancy in case of the molecule with frozen rotation and torsional angle ϕ different from 0° and 90° since a permutation of a and b substituents changes designation of the sense of chirality, let us say from R to S, while the sense of the screw, *e. g.* the P (or M) descriptor remains unchanged. On the other hand, the Prelog and Helmchen recommendations on the exclusive use of the P/M system for the description of the sense of chirality axes has not always been followed in practice (16, 17, 27). We also believe that the Sokolov interpretation of the elements of chirality (32) is insignificant since the elements of chirality, which according to CIP intentions refer to four-points figures isomorphic with molecular fragments in three-dimensional space, are associated with spaces of

different dimensionality by Sokolov and the interrelation between the Sokolov ($n - 1$)-dimensional chiral figures and chiral three-dimensional molecules is unclear.

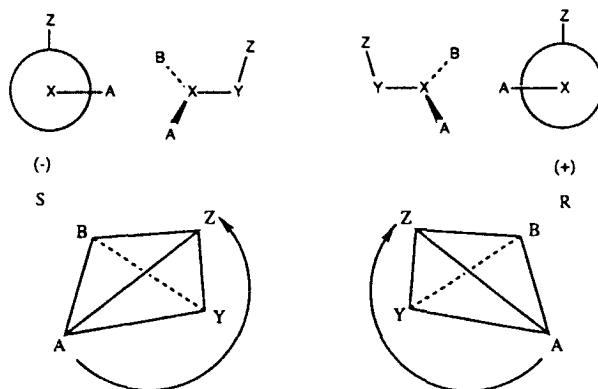
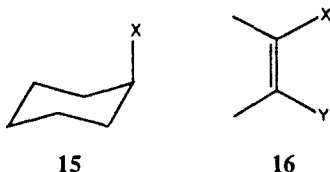


Fig. 3. The notation used for planar chirality : sign of the torsional angle $AXYZ$ is denoted by the R/S symbols which for certain substituents have the opposite meaning to the CIP one determined on the basis of the $ABYZ$ tetrahedron.

The lack of precise definitions of the elements of chirality in the CIP classification has sometimes resulted in an unclear or even contradictory description of stereoisomers due to existence of elements of chirality in a molecule under investigation. Different systems of chirality and stereoisomer designations are sometimes coined for specific molecules. These systems, although mostly reported as examples of the CIP classification, are not always consistent with the R/S and P/M systems developed by Cahn, Ingold and Prelog (6) and recommended by the IUPAC (10). Two examples of the inconsistencies are especially striking. The first one is discussed in detail by Schloegel in his review on cyclophanes (17). For the molecules 6, 10 - 12 and similar ones the signs of torsional angles used to denote chirality of cyclophanes (17), which should be described in terms of the P/M symbols, are usually artificially denoted by the R/S symbols (sometimes with the subscript p for planar), which for certain substituents give a reversed R/S notation of the sense of chirality as compared to that determined on the basis of the CIP rules of preference of substituents (Fig. 3). The second example of an appropriate creation of new symbols for isomers description is provided by the Crowder analysis of the conformational equilibrium of chain hydrocarbons (24) where completely new symbols are coined instead of the generally accepted g^+ and g^- ones or instead of the IUPAC recommended P/M symbols.

We believe that the introduction of the steric elements by Hirschmann and Hanson (7, 13a, 13b) does not solve the problem of stereoisomer description for two reasons. First, as recognized by the authors, a factorization of a molecule into independent steric elements is a difficult task which, similar to the factorization of a molecule into elements of chirality, cannot be fully formalized. Secondly, in spite of the authors' minor criticism concerning the CIP (6) and Prelog and Helmchen (14a) notations of configuration, they do not propose any system of isomer description to denote stereoisomers on the basis of their steric elements. In their approach Hirschmann and Hanson have also intentionally given up the interrelation between the number of steric elements in a molecule, or that of the independent elements of chirality present in it, and the maximum number of stereoisomers due to their existence. We believe that this relation and the possibility of suitable means for computer coding of stereoisomers are of great practical importance in the domain of chirality validating the preservation of the idea of chirality elements. On the other hand, the factorization into steric elements or elements of chirality in complexes with coordination number bigger than 4 seems insignificant since for such molecules possessing highly symmetrical "cores" stereoisomers can be easily enumerated on the basis of the Polya theorem or similar procedures (23). Thus, we believe that the Hirschmann and Hanson approach, which is unrelated to enumeration and description of stereoisomers, does not fulfill the purposes for which such elements should serve in conformity with the conditions formulated above.

Similarly, the Mislow and Siegel (11) total critique of the classification, concluding in the denial of the usage of the elements of chirality, seems unacceptable. The authors advocated the idea that the description of stereoisomers due to existence of elements of chirality in a molecule can be fully carried out on the basis of stereogenicity but their definition of the stereogenic unit cutting off all molecules possessing chiral skeletons does not allow its application to the molecules like helicenes **6**, biphenyls with frozen rotation **9a - d**, molecules **10 - 12**, **13a**, *etc.* Keeping in mind that there exist molecules which are stereogenic and achiral, like **15** and **16**, and those which are chiral and nonstereogenic like **18**, we believe that the essential difference between stereogenic and chiral properties of a molecule first noticed by Mislow and Siegel precludes the defining of the elements of chirality in terms of stereogenic units.



To summarize, in spite of its wide usage the CIP classification possesses some essential deficiencies since the definitions of the elements of chirality are formulated in terms of stereogenic properties. As a consequence, chirality of the molecules with chiral skeletons cannot be analyzed on the basis of the definition and the use of the R/S and P/M symbols is inconsistent (16, 17, 33, 34) and can lead to contradictory designations (16). On the other hand, the Mislow and Siegel and Hirschmann and Hanson denial of the elements of chirality seems premature since the possibility of simple and suitable for computer coding means of stereoisomers designation is of great practical importance validating the preservation of the idea of chirality elements. As stated above, we believe that the elements should be defined in a different way than in terms of stereogenic units in agreement with the Mislow and Siegel (11) observation on the essential difference between stereogenicity and chiropticity.

The deficiencies of the definitions of the elements of chirality forming the basis of the CIP classification and their non-uniform or even contradictory applications for notation of molecular chirality and stereoisomer designation discussed above prompted us to develop its modification with the aim to remove the discrepancies and unclarities involved in it, but leaving unchanged as much as possible in conformity with established chemical practice. In particular, the R/S system of gradation of substituents as being a keystone of configurational assignment should have been fully preserved. On the other hand, it will be shown that, with small extensions, the R/S and P/M systems of descriptors have provided a simple suitable for computer coding mean of description of stereoisomers due to existence of elements of chirality in a molecule under investigation supporting the practical importance of elements of chirality. We also feel that conformational chirality has not been fully appreciated both in the classification and its practical applications. Rapid development of experimental techniques in recent years has enabled experimental observation of the effects due to internal rotation and inversion and their freezing. Thus, in classifying molecular chirality one should state whether a frozen or averaged conformation is analyzed in conformity with the IUPAC recommendations for stereochemical nomenclature (10) demanding a precise specification of conformation of the molecule under investigation. On the other hand, two important topics loosely related to the classification, *i. e.* chirality functions introduced by Ruch (35) and the Klyne and Prelog stereoisomers notation (36), will not be discussed here.

The proposed modification : definitions

A general remark : within this work a molecule is considered as a rigid system of point atoms with a coordination number less than or equal to four. This limitation does not seem to be a real restriction since for molecules containing atoms with bigger coordination numbers there exist excellent mathematical procedures yielding the number and type of stereoisomers (in particular those of chiral stereoisomers) (23) while factorization of molecular complexes with coordination number greater than four into elements of chirality is not unequivocal.

The basis of our definition of the elements of chirality is the observation cited by Prelog and Helmchen (14a) on the existence of only two chiral four-point nonplanar arrangements in a three-dimensional space, *i. e.* the one corresponding to an asymmetric carbon atom and the one corresponding to three nonplanar consecutive vectors (usually bonds) representing a screw (Fig. 2). It should be stressed that there is an essential difference between these arrangements. To determine a sense of chirality of the first arrangement a system of preference of substituents such as the R/S one proposed in the CIP classification for a centre of chirality (6) has to be introduced

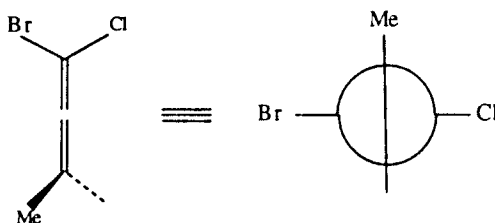
while for the arrangement of the second kind the chirality sense (P or M) is defined by the sense of the screw and no substituents at all should be involved since the sense of the screws defined in Fig. 1 depend solely on the vectors arrangements not on the substituents. On the other hand, the two arrangements bear similarities: an a, b, c, d tetrahedron can be built on both arrangements and the second one corresponds to the first one with connectedness constraints added. These similarities yield as a consequence the possibility of equivocal descriptions of chirality sense for certain molecules, *i. g.* allenes **2**, spiranes **4**, *etc.* discussed below.

The existence of only two chiral four-point arrangements in three-dimensional space (14a) seemed to indicate that instead of three elements (a centre, an axis and a plane of chirality) and two additional types of chirality (conformational chirality of the *gauche* butane type and helicity of secondary structures) introduced in the CIP classification only two different elements of chirality exist, *i. e.* a centre of chirality analogous to that introduced in the CIP classification but differing from the CIP one in some rare implementations, and the second element which in contrast to the chirality axis of the CIP classification has been called a helical axis. Thus, a centre of chirality is present in a molecule if there exist exists a permutation of substituents in enantiotopic positions of this element of chirality causing a change of the sense of chirality of the centre. The concept of enantiotopic positions is derived from the Mislow and Raban concept of enantiotopic groups. Two positions in an element of chirality are enantiotopic if a permutation of different substituents in these positions yields the enantiomer of the original element. It can be shown that for a group of four different substituents not lying in a plane an odd permutation of them produces the enantiomer while an even permutation does not change the sense of chirality of the group. It should be stressed that the above definition of the centre as well as the R/S designation of its sense of chirality do not depend on the localization and sometimes even on the existence of the central carbon atom involved in agreement with the Cahn, Ingold and Prelog (6) and Mislow and Siegel (11) constatement that the centre must not necessarily coincide with any atom.

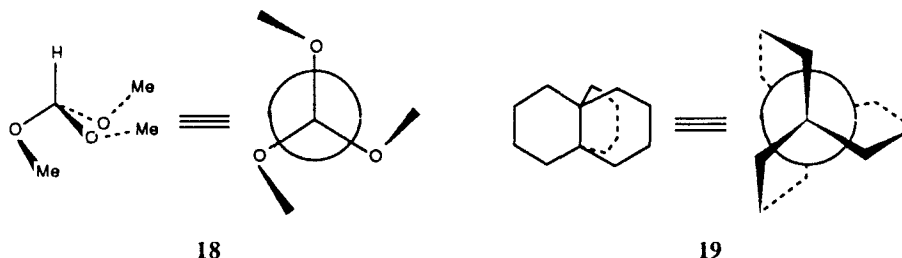
A helical axis is present in a molecule if there is a screw-like fragment corresponding to a nonplanar arrangement of three consecutive vectors usually corresponding to bonds. It should be stressed that presence of different substituents is immaterial for the existence of helical axes in a molecule but it can generate additional centres of chirality. On the other hand, the substituents can be helpful for choosing certain independent helical axes for chirality description (see below).

Similarly to the Prelog and Helmchen recommendation (14a) in the proposed modification the R/S system of designation of the sense of chirality is to be applied only to chiral centres whereas the P/M system should be used exclusively for helical axes. This removes some inconsistencies present in some applications of the CIP classification but, as will be discussed further, some ambiguities still remain since most molecules possess several interdependent elements of chirality and the choice of the independent ones is often very difficult and unequivocal and it cannot be formalized. This is similar to the situation existing with the Hirschmann and Hanson steric elements (13a, 13b) discussed above.

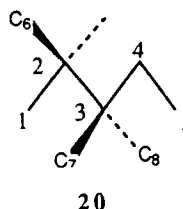
We believe that with the above definitions of the elements of chirality both the R/S and P/M systems of chirality designations given in the original CIP version should be defined in a more precise way. The former system is fully preserved here and, for instance, the R and S designators are retained for all asymmetric atoms. A slightly more complicated description will be needed for a small number of systems for which a position of a centre of chirality is ill-defined since it is not located on an asymmetric atom. Thus, for 1-bromo-1-chloro-3-methylallene in the configuration shown in formula **17** (see discussion of allene chirality below) the designation 1-bromo-1-chloro-3-methyl(S)allene can denote mutual localization of the chloro, bromo, methyl and hydrogen substituents on the allene skeleton. The alternative use of the P/M symbols to denote chirality of this molecule will be discussed below.



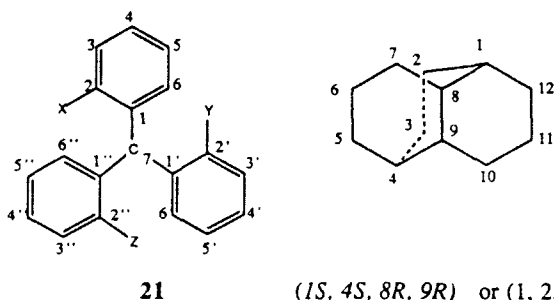
Similarly, we believe that a sense of a helical axis in a molecule should be given together with the numbering of atoms defining this axis or as a single P or M letter descriptor for screw-like or propeller-like molecules to denote overall chirality in agreement with the CIP recommendation (6). In the latter case, *e. g.* for hexahelicene **8**, 1,1,1-trimethoxymethane in a conformation possessing C_3 symmetry **18** or for [4.4.4]propellane **19**, an inspection of molecular models clearly reveals the corresponding screws if one looks at the models along the helix axis for helicenes or in the direction of C_n symmetry axes for the two remaining molecules as shown in



the formulae. In the former case when a definite helical axis is specified in a molecule, four numbers of the atoms defining the axis should be given together with a P or M descriptor. For instance, for *n*-pentane there are two independent helical axes, defined by positions of the atoms 1, 2, 3, 4 and 2, 3, 4, 5 and every chiral conformation of the molecule can be described in terms of (1, 2, 3, 4)P or M and/or (2, 3, 4, 5)P or M descriptors instead of the more usual g^+ and g^- designators. Both types of descriptors conform to the IUPAC recommendations (19) and there is no need to introduce new diastereoisomer descriptors for 2,3,3-trimethylpentane **20** as is done in Ref. 24. The application of this system to stereoisomer notation for substituted triaryl methanes **21** studied by Mislow (25) and to tricyclo[6.4.0.0^{4,9}]dodecane **22** studied by Juergensen (26) will be given below.



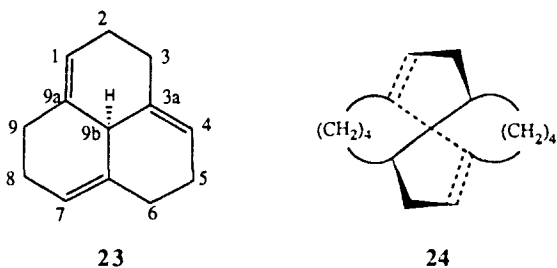
As stated above, there were some suggestions in the literature (21, 9) advocating an extension of the formula relating the maximum number of stereoisomers of a molecule 2^n and the number of asymmetric atoms n causing its stereoisomerism to include all elements of chirality but the idea has not come into practice (19c, 22). We believe that this could be done in the following way: let n_1 be the number of centres of chirality in the molecule under consideration, n_2 be the number of helical axes corresponding to two-minima potential hindering internal rotation around the axis, n_3 - the number of the helical axes corresponding to analogous three-minima potential, *etc.* Then, the maximum number of stereoisomers due to the existence of these elements of chirality is given by $2^{n_1} \cdot 2^{n_2} \cdot 3^{n_3} \cdot \dots$ multiplied by terms corresponding to helical axes of higher orders of little practical importance since there are two possible orientations corresponding to stereoisomers for a biphenyl-type helical axis, but three orientations around a central bond with a three-fold barrier, one of which corresponds to the achiral *trans* conformation. The last formula is of importance only for very small molecules possessing few independent elements of chirality or for the molecules with highly symmetrical skeletons like triarylmethanes **21** (25) discussed below for which the number of independent elements of chirality can easily be determined.



As pointed out by Hirschmann and Hanson (13b) the problem of factorization of a molecule into fragments corresponding to elements of chirality is very difficult and cannot be fully formalized. As stated above there is a great number of elements of chirality in molecules many of which are not independent. The choice of all independent elements is a very difficult and somewhat equivocal task to which one can apply the Hirschmann and Hanson statement referring to steric units (13b): "The selection of appropriate units calls for improvisation and ingenuity, which makes the subject unsuitable for systematic treatment". The molecule 22 clearly reveals ambiguities encountered by the choice of the elements of chirality necessary for stereoisomer description. To denote them the author gives the senses of chirality of four asymmetric carbon atoms, *e. g.* (1*S*, 4*S*, 8*R*, 9*R*) for the configuration depicted by the formula 22 while one of them or one helical axis suffices for the enantiomeric pair description and the (1, 8, 9, 4)M symbol, corresponding to the negative sense of the C1C8C9C4 screw clearly seen on a molecular model, fully describes this configuration. This example as well as the other discussed by Hirschmann and Hanson (13b) shows the complexity of the problem of factorization of molecular chirality into the elements of chirality or the Hirschmann and Hanson steric elements. Nevertheless, we believe that some general practical rules for the choice of the elements of chirality can be given and the following is devoted to applications of the above definitions with the aim to show how the selection could be carried out in the most interesting and most frequently met cases.

Exemplification of the applications of the proposed definitions

Keeping in mind the Hirschmann and Hanson statement let us look at the applications of the above definitions of the elements of chirality to some interesting molecules to see the differences between the CIP approach and the one proposed here. As stated above molecules possessing asymmetric atoms are treated in the same way in the CIP classification and by our approach. The *R/S* system of preference of substituents is retained by us since it precisely describes configuration on an asymmetric atom and is deeply rooted in chemical practice. The designation and description of the elements of chirality in the molecules 23 and 24 and similar ones have to be changed in our approach as compared to the CIP one. The molecules are classified as exhibiting centres of chirality by Cahn, Ingold and Prelog (although the atoms proximal to their central atoms are identical) and are thought to have helical axes by us. For the conformations depicted in the formulae only one axis is independent and chirality descriptors can be found conveniently if one looks at molecular models of the molecules. Then, the screws directions are clearly seen on the model, *e. g.* (H9b, C9b, C3a, C4)M, *etc.*, for the depicted configuration of 23, and we believe that this simplicity, instead of considering rather vague differences among the substituents on the central atoms in the molecules 23, 24, is an argument in favour of our classification. (By the cyclohexene ring inversion freezing the torsional angles (C4, C5, C6, C6a), *etc.* should also be specified). Therefore, for rare molecules of this kind both the element of chirality and its designation had to be changed in our approach.



On the other hand, the elements of chirality in the molecules 2, 5 and similar ones can be classified in a different way in the CIP classification and in our approach, but the same R/S system of chirality descriptors can be used for them in both approaches in conformity with the established chemical practice (18, 27). One can describe the sense of chirality of these molecules in terms of the centre of chirality retaining the R/S symbols or, alternatively, one can describe it in terms of helical axes as shown below for allene 17. This equivocality reflects the dual character of the elements of chirality discussed above. In case of alternative assignment of elements of chirality in the molecules 2 and 5 in terms of helical axes, which is possible in our approach and is in detail described below, the numbering of atoms forming axes precludes any misunderstandings analogous to those encountered by description of cyclophanes chirality (17).

The molecules 3, 4 and 9 undergo rapid rings inversion or internal rotation at room temperature. In the CIP classification their chirality has been analyzed under an unformulated assumption of rapid internal motion, thus, leading to overlooking of chirality of spiro[5.5]undecanes 4 with $m = n = 2$, $a = b = c' = d'$ and biphenyls 9 with nonplanar and nonperpendicular ring arrangement and $a = b = c' = d'$. Therefore, their chirality in the averaged conformations will be discussed here while analysis of chirality of their conformations with frozen internal motions (*i. e.* rings inversion and internal rotation) will be given below. With rapidly rotating or inverting rings the parent molecules (and their homotetrasubstituted analogues) are achiral and chirality of their derivatives is induced by the substituents. Thus, chirality of the molecules 3, 4, 9 is essentially the same as that of the molecules 2, 5 and 13a and duality of the description of the chirality elements present in the latter group is preserved in the former one. Contrary to the CIP classification in our approach chirality of all these molecules can be described in terms of a centre of chirality or of one independent helical axis. The former application is possible because an exchange of a and b (or c' and d') substituents produces the enantiomer of the system. The important point is that a permutation of the primed and non-primed substituents is not allowed here since the primed and non-primed positions are not enantiotopic with respect to each other and an odd permutation of primed and non-primed substituents leads to constitutional isomers in case of the molecules with four different substituents. As discussed above, the possibility of two different ways of description of chirality of certain molecules in terms of a centre of chirality or helical axis is due to similarities in the two arrangements presented in Fig. 2 but this duality cannot create any misunderstanding.

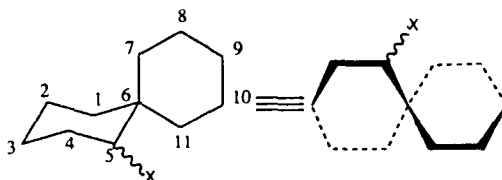
Allenes 2, rapidly inverting alkylidenecyclohexanes 3, 1,1,5,5-tetrasubstituted adamantanes 5 and rapidly rotating biphenyls 9 provide very interesting examples of the chiral centres for which localization is ill-defined. We believe that this is of no importance, since the existence and sense of chirality of the centre is fully determined by the substituents. It should be stressed once more that although the classification of the elements of chirality present in the above molecules has been changed in our approach as compared to the CIP one, the usual R/S designators of their sense can be preserved, thus, there can be no practical change involved by the introduction of our modification. On the other hand, the possible description of the chirality of the same molecules in terms of helical axes is straightforward and cannot create any ambiguity if the atom numbers used to define torsional angles for the P/M descriptors are given. For instance, the sense of chirality for the allene 17 can also be given in terms of the (C₂, C1, C2, Me)M symbol.

An analysis of molecules containing helical axes should begin with *gauche* butane as the simplest chiral molecule possessing such an axis. This kind of chirality was called the conformational chirality in the original CIP paper (6). The P/M system of designation for acyclic hydrocarbons and for saturated cycles in frozen conformations was also proposed there. It has not been accepted in the literature and in the revised version of the classification published by Prelog and Helmchen in 1982 (14a) chirality of this kind has not been mentioned. It is interesting to stress once more the usually unrecognized fact that the conformational descriptors developed for such molecules, *i. e.* g^+ and g^- describe the sense of chirality of their helical axes. The lack of uniformity of the stereoisomer description of this simple and most intensively studied group of compounds is revealed by the recent paper (24) on the stereoisomerism of pentanes discussed above.

Numerous helical axes are present in larger branched chain and cyclic hydrocarbons in addition to chiral centres and a determination of the number of the independent elements of chirality and that of diastereoisomers becomes a very difficult problem. The choice of the independent elements is considerably simplified in cyclic molecules since a condition for cycle closure significantly lowers the number of degrees of freedom in a molecule. For instance, for cyclohexane in a chair or boat conformation the sum of torsional angles is equal to zero assuming equal bond lengths (see formula 26 for chirality description used for the chair conformation of the molecule in Ref. 6). This means that to each helical axis in the molecule corresponds another one with a reciprocal sense of chirality.

Rings are treated inconsistently within the CIP classification and its application to them leads to discrepancies. These molecules possess several helical axes, not all of which are independent. Thus, their treatment within the CIP rules will be given first, then discrepancies and unclarities caused by its application will be discussed and finally our approach to the molecules will be shown.

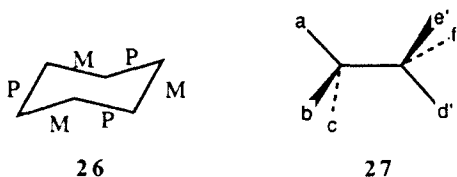
As stated above, within the CIP classification (6) tetrasubstituted biphenyls **9** are analyzed under an unformulated assumption of rapid rotation around the central bond and under this assumption chirality of the parent biphenyl (and that of spiro[5.5]undecane **25**) has been overlooked. On the other hand, chirality of **9** with frozen internal rotation cannot be in general classified using the Prelog and Helmchen definition (14a) since the lack of the achiral skeleton in the molecule precludes the application of their definition. The R/S system of the designation of biphenyl chirality sense commonly used in the literature (33, 34) contradicts once more the Prelog and Helmchen (14a) recommendation of the exclusive use of the P/M system for molecules possessing the axis. To analyze the elements of chirality in the parent unsubstituted biphenyl with the frozen internal rotation let us consider it as a system of D_2 symmetry. There are four different torsional angles defining the mutual orientation of the rings but due to its high symmetry only one independent helical axis is present in this molecule and the sign of the smaller torsional angle formed by the rings should be adopted for the P/M designation of the sense of chirality of the molecule. In our modification tetrasubstituted biphenyl **9** in a frozen conformation possesses two independent elements of chirality, thus, two chirality descriptors have to be used simultaneously for this molecular conformation. One can describe stereoisomers in the molecule either by naming senses of two chiral axes, *e. g.* (a, Cl, Cl', c')P, (b, Cl, Cl', d')P or, in addition to one helical axis (a, Cl, Cl', c')P, one names a centre of chirality defined by four a, b, c', d' substituents for an averaged structure with a perpendicular rings arrangement. In the latter case the restricting condition that the substituents can be permuted exclusively within non-primed or primed groups has also to be preserved. The latter way of factorization which requires the removal of helical axes present in the molecule to be able to define the chiral centre, is analogous to the separate consideration of asymmetric centres in a molecule **27** where chirality of the C1 carbon atom is analyzed as bearing four different a, b, c, C2 substituents (independently on the substituents on the C2 carbon atom), a permutation of which produces the enantiomer. Thus, in our modification tetrasubstituted biphenyl with nonplanar and nonperpendicular rings arrangement possesses two independent elements of chirality and according to the formula for stereoisomers count it can exist as two diastereomeric pairs of enantiomers **9a** - **9d** unless bulkiness of substituents enforces perpendicular rings arrangement. In this case one of the elements suffices to describe molecular chirality and stereoisomerism, since a pair of enantiomers **9e**, **9f** is present for the molecule in such conformation as well as for the averaged structure with the same rings arrangement.



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Similar to the biphenyl case, the analysis of the chirality of spiranes **2** was limited to averaged structures and controversies regarding their chirality are reflected by the O'Loane review (31) in which the chirality of spiranes is totally neglected. Thus, the chirality of the parent unsubstituted spiro[5.5]undecane **25** has been overlooked until recently when one of us (H. D.) described the molecule according to the CIP classification (28, 29) as a very interesting example exhibiting a centre of chirality with four formally identical substituents $C_{aaa'a'}$. Contrary to the CIP approach applied in Ref. 28, we now believe that, similarly to the treatment of chirality of allenes **2** and unsubstituted biphenyl **9** with frozen internal rotation with $a = b = c' = d' = H$, chirality of spiro[5.5]undecane **25** ($X = H$) with frozen ring inversion can be described both in terms of helical axes or a centre of chirality. Only one of the axes is independent for the chair conformation of the rings since one torsional angle suffices to determine their mutual orientation. Also in this case the helical axes are clearly seen by inspection of molecular models. If one looks at a Dreiding model of the molecule along the C_2 symmetry axis one can easily see two spirals which are equivalent due to the symmetry of the molecule and the sense of these spirals can be applied to designate the sense of chirality of the independent helical axis in the molecule. Thus, the P/M system proposed for spiro[5.5]undecane **25** in (30) finds its justification. On the other hand, if the molecule is treated as

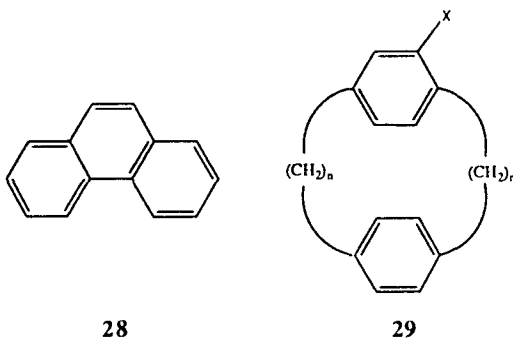
having a centre of chirality as advocated by Prelog (29) and Dodziuk (28) then the R/S symbols have to be used to describe chirality. It is not clear why the interrelation between the existence of two centres of chirality in monosubstituted spiro[5.5]undecane **25** ($X \neq H$) and its existence as a mixture of two diastereomeric pairs of enantiomes could be questioned by Tavernier (30) since this interrelation corresponds to the 2ⁿ rule of stereoisomer count (37).



Chirality of many symmetrical molecules can be described in terms of a single screw analogous to that present in spiro[5.5]undecane. Among other the molecules **13a**, **18** and **19** and the previously discussed ones **22** and **23** can be named.

As stated above, we believe that only two elements of chirality are necessary to describe chirality of three-dimensional four-point objects, thus, there is no need to introduce a third element of chirality such as a plane of chirality in the CIP classification. Then, the molecules such as **6**, **10** - **12**, **28** exhibiting the plane within the CIP classification have helical axes in our approach. Also in these cases the sense of chirality is given by the sense of a screw in the P/M system. For the bridged aryls **6**, **28** the presence of the substituent X, but not its kind, is of importance since its existence serves only one aim, namely, it should differentiate the right and left sides of the ring which are equivalent in the achiral unsubstituted molecule. As discussed above and in Ref. 16, the convention used to describe chirality of cyclophanes is contradictory and can lead to serious misunderstandings. Therefore, we believe that the need of its change is especially pressing and we advocate the use of the P/M symbols in this case.

Similarly, there is no necessity to introduce helicity as a special kind of chirality since helical structures such as helicene **8**, phenanthrene **29** and helices of biological systems possess, according to our definitions, helical axes. Such an axis must not necessarily associated with a group of four consecutively bound atoms. For the DNA spiral and for helicenes the axis of the spiral determines the corresponding helical axis and its sense of chirality is given by the sense of the screw formed by the spiral.



A pictorial example of the application of the R/S and P/M symbols precized by us to the isomer description suitable means for machine coding is provided by triarylmethanes **21** studied by Mislow (25). The author applied elegant mathematical procedures to analyze the static and dynamic stereochemistry of the molecules and found that they can exist as 16 diastereomeric *d, l* pairs. One chiral R or S descriptor was used by him for the central atom of the molecules and matrices specific to the structure or formulae with shaded half-rings have been applied to denote stereoisomers. We believe that description of the static stereoisomers in this case can be carried out in terms of the R/S and P/M chirality symbols for the central atom and helical axes, respectively, instead of writing matrices specific to the stereoisomers or full formulae with shaded rings halves as was done in Ref. 25. In addition to the R (or S) chirality of the central atom and to a P or M symbol of the overall propeller-like structure seen when looking

at the H₇C₇ bond direction, the senses of three helical axes corresponding to signs of three torsional angles should be given, *e. g.* (C₇, C₁, C₂, X)P, (C₇, C₁', C₂', Y)P, (C₇, C₁'', C₂'', Z)P. These five symbols correspond to five independent elements of chirality present in the molecule **21**. They fully describe 32 stereoisomers possible for the molecule ($2^5 = 32$) and we believe this stereoisomer description to be particularly suitable means for computer coding.

To summarize, almost all molecules which possess a centre of chirality within the CIP classification (6, 14a) are treated in the same way in our approach and the R/S system of configurational assignment is fully preserved for them. The only exceptions seem to be molecules of the types **23**, **24** which within the CIP classification possess a centre of chirality while we postulate for them the existence of helical axes clearly seen in their molecular models. Allenes **2**, rapidly inverting alkylidenecyclohexanes **3**, rapidly inverting spiranes (or those possessing planar rings) **4**, 1,1,5,5-tetrasubstituted adamantanes **5**, rapidly rotating biphenyls **9** and [n]vespirenes **13a** with n = 6 - 8 are classified in different ways in both approaches. The molecules are said to have axes of chirality in the CIP classification but their sense of chirality can be expressed in terms of centres of chirality or in terms of helical axes in our approach. The R/S system of preferences of substituents, used for them in the original version of the CIP classification, can be preserved in the former case but the possible use of the P/M designators in conjunction with the numbers of the atoms defining helical axes is straightforward and cannot create any inconsistencies analogous to those existing in the description of cyclophane chirality discussed by Schloegel (17). Helical axes are present in chain and branched hydrocarbons and their heteroanalogues (but g^+ , g^- chirality descriptors are in common use for them), as well as in unsubstituted biphenyl **9** and spiro[5.5]undecane **25** in frozen conformations and in [n]vespirenes **13a**. Helical axes are also present in the molecules **6**, **10** - **12**, **28** which according to the CIP classification possess a plane of chirality. As stated above we believe that the inconsistencies in the description of cyclophane chirality discussed by Schloegel (17) demand revision consisting in the exclusive use of the P/M descriptors for these molecules. Systems exhibiting helicity within the CIP classification (helicenes, phenathrenes and DNA spirals) also possess helical axes in our approach.

Conclusions

The advantages of the modifications of the CIP classification presented here in comparison to the original version of the classification (6, 14a) are as follows :

1. Instead of three (or five if helicity and conformational chirality are taken into account) only two elements of chirality *i. e.* a centre and a helical axis, are introduced here and the elements are inherently related to the properties of a three-dimensional space.
2. The emphasis is laid down on the precise description of the conformation of the molecule under investigation in accordance with the IUPAC rules on stereochemistry (10). This is contrary to the discussion of chirality of alkylidenecyclohexanes **3**, spiranes **4** and biphenyls **9** which until recently have been treated under the unformulated assumption of rapid internal rotation or ring inversion (5, 14a, 18, 19b). Even if this assumption is valid for most experiments described in the literature it is not general and requires at least the explicit formulation. It seems that conformational chirality introduced in the original CIP paper (6) was until recently outside the scope of most standard chemical experiments and it has been underestimated in chemical practice. The development and wide application of low-temperature NMR and similar techniques will, in our opinion, raise the importance of such studies of molecules possessing helical axes proposed in our modification.
3. The presence of helical axes in some cyclic molecules such as **23** and **24** for which the assignment of the elements of chirality had to be changed is easily seen in molecular models and conceptually seems to be much simpler than the idea of the presence of a centre of chirality in these molecules.
4. A dichotomic use of the R/S and P/M systems of chirality descriptors proposed in the Prelog and Helmchen work (14a) has not always been followed in practice. Analogously, we propose to use the R/S symbols to describe senses of the centres of chirality and the P/M ones to describe senses of chirality of helical axes. Such an approach allows one to overcome some discrepancies encountered by the use of the R/S and P/M symbols in the original version of the CIP classification but it cannot remove the duality of the description of chirality sense present in substituted allenes **2** and some other molecules discussed above.

5. The small extension of the R/S and P/M systems of chirality descriptors demanding naming of the atoms defining the element under consideration yields the simple and suitable for computer coding means for description of isomerism due to the existence of the elements of chirality in a molecule under investigation.
6. A formula relating the number of independent chiral centres n_1 and those of helical axes of different multiplicity n_2, n_3 , respectively, and the maximum number of stereoisomers due to the existence of the elements in the molecule is given, but its practical importance is limited to very small and/or highly symmetrical molecules since in most molecules there are many mutually interdependent elements of chirality and the choice of independent ones is difficult and equivocal.

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