

**Chirality and Stereogenicity :  
the Importance of Conformational Chirality  
in the Classification of Stereoisomers**

Helena Dodziuk

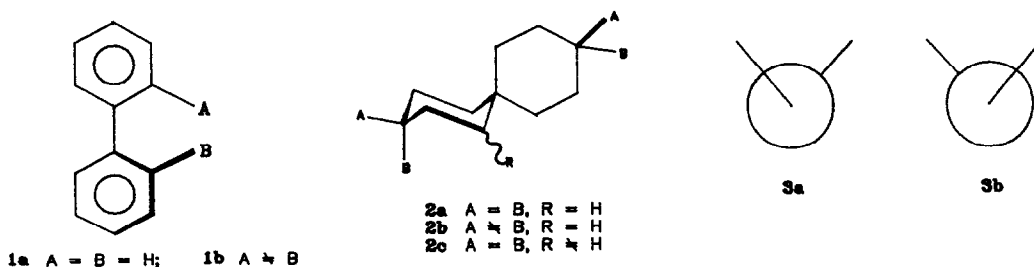
Institute of Organic Chemistry, Polish Academy of Sciences  
01-224 Warsaw, Kasprzaka 44, Poland

*(Received 16 October 1991)*

**Abstract** As we have recently shown, the elements of chirality are not defined in the Cahn, Ingold and Prelog classification leading to imprecisions in the assignment and designation of chiral stereoisomers not involving a centre of chirality. Similarly, conformational chirality was not satisfactorily treated in the classification resulting in its underestimation. A recently published scheme of stereoisomer classification as well as many textbooks on organic chemistry, neglect or improperly treat conformational enantiomers and diastereoisomers. The scheme is corrected to include the latter group of stereoisomers.

As we have recently shown (1) there are many sources of misunderstanding in the basic concepts of chirality. In particular, the elements of chirality are not defined in the first version of the Cahn, Ingold and Prelog (CIP) classification (2) and their definitions given in the Prelog and Helmchen modification of the classification (3) cannot be considered satisfactory. The imprecise introduction of the elements of chirality has many practical consequences. First, it is not clear how the elements should be found in new topologically different chiral molecules such as those modeling a Möbius strip (4). Secondly, within the classification there is no way for computer coding of enantiomers and diastereoisomers not involving a centre of chirality. Third, conformational chirality was unsatisfactorily introduced in

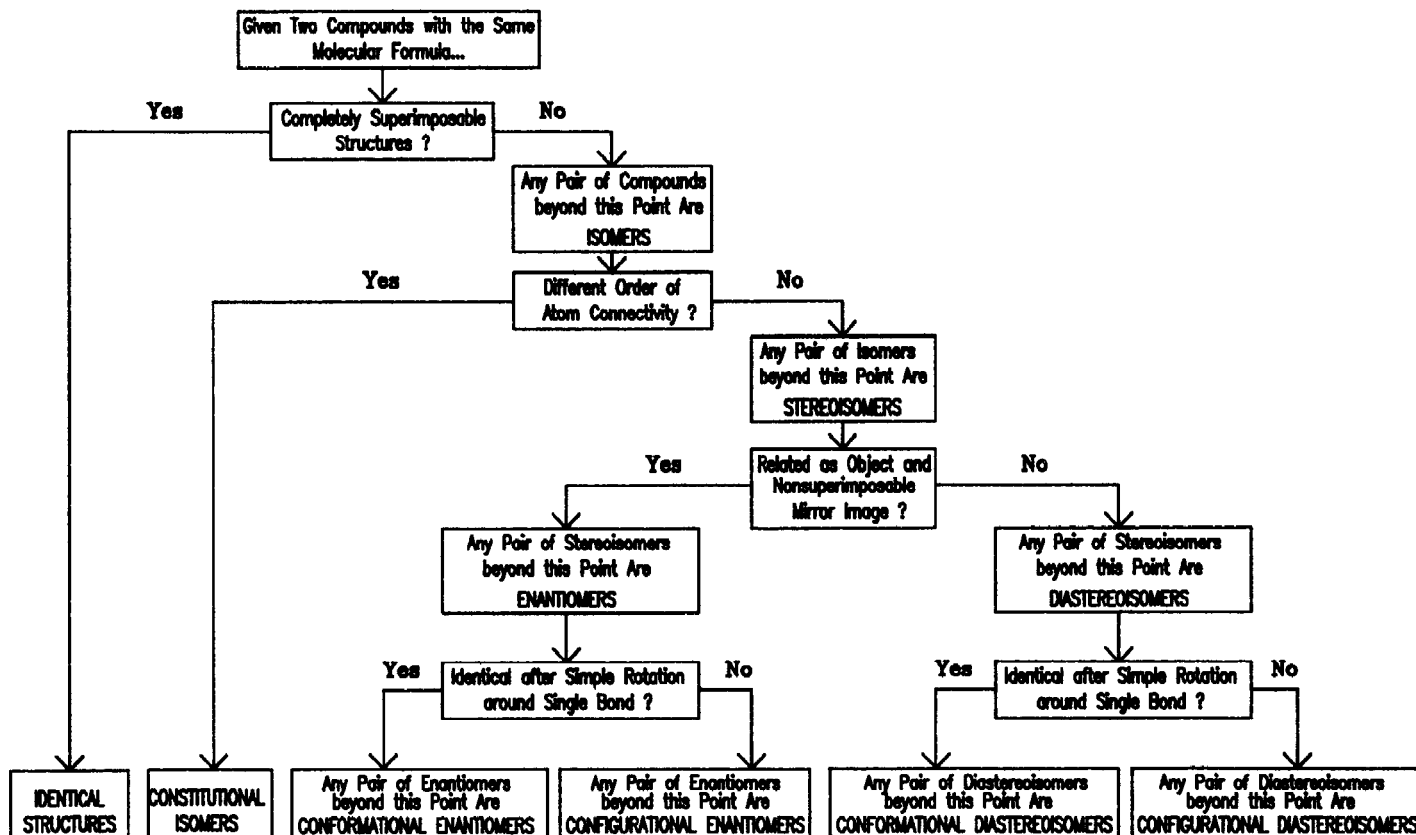
the first CIP paper on the classification (2) and it has not been discussed in the Prelog and Helmchen paper in 1982 (3). In particular, the chirality of the unsubstituted biphenyl 1a and that of the unsubstituted spiro[5.5]undecane 2a has been overlooked. Due to a lack of clarity in the basic ideas in the domain of chirality the P/M system of designation of conformational chirality presented for (+) and (-) *gauche*-butane 3a and 3b, respectively, seems almost totally neglected (5, 6).



The unsatisfactory introduction of conformational chirality in the CIP classification (2, 3) was only briefly mentioned in Ref. 1 although, due to its practical consequences, it deserves a more detailed discussion. Therefore, the way of its presentation in Ref. 2 and 3, leading to the underestimation of the conformational chirality will be discussed in some detail in this note, and improper presentation of stereoisomerism in many textbooks on organic chemistry and stereochemistry will be demonstrated. A recently published, elegant but erroneous, scheme of classification of stereoisomers (7) exemplifies the importance of precise definitions and that of consistency in the domain under discussion. A revision of the scheme enabling its application will be proposed.

As mentioned before, conformational chirality was inconsistently treated in the CIP classification, where chirality of some molecules exhibiting rotational isomerism (e. g. that of aliphatic chain hydrocarbons, cyclohexane, cyclodecane, *cis*- and *trans*-decalins and [4.4.4]propellane) was analyzed in terms of conformational chirality while that of the molecules 1 and 2 was discussed by means of an unformulated assumption rapid internal rotation or ring inversion. This inconsistency has not been cleared up since

# Isomeric Relationships Between Organic Compounds



the formulation of the classification in 1966. In particular, conformational chirality has not been discussed in the Prelog and Helmchen modification of the classification (3). As a result of the assumption on rapid internal motion, conformational chirality of some molecules such as unsubstituted biphenyl 1a, spiro[5.5]undecane 2a and some others was neglected within the classification and chirality of their derivatives 1b and 2b was discussed in Ref. 2 and 3 only for conformations averaged over internal rotation or ring inversion. This leads to achirality of unsubstituted molecular structures at room temperature but the molecules are chiral at low temperatures when the rotation (or inversion) is frozen and the molecules lack improper symmetry axes,  $S_n$ . As discussed in detail in Ref. 1 the fact that their derivatives 1b, 2b and 2c can exist as diastereomeric pairs of enantiomers has also been overlooked in the CIP classification.

The undervaluation or even neglect of conformational chirality (6) is partly due to the fact that conformational enantiomers and diastereoisomers cannot usually be separated at room temperature and spectroscopic techniques do not always differentiate between them. Nevertheless, conformational chirality is of considerable importance since (a) it is indispensable when discussing reaction mechanism in asymmetric synthesis or drug-receptor interactions (7). (b) In the presence of other elements of chirality it gives rise to conformational diastereoisomerism. (c) In rare cases the inversion freezing at low temperatures can lead to very interesting consequences in the low-temperature  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. As discussed in detail in Ref. 8, in a frozen conformation the 1- and 5-positions in 2a and 2c are different leading to small differences in chemical shifts of protons and carbons in the positions next to the spiro atom.

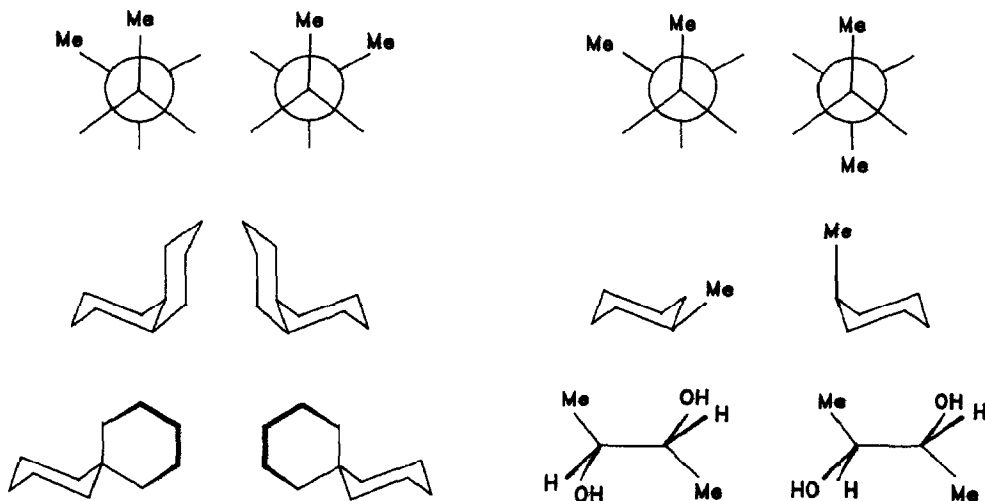
The misunderstanding in the basic ideas in the domain of chirality, influences the way in which stereoisomerism is introduced in textbooks on organic chemistry. Sometimes its discussion starts with enantiomers and diastereoisomers of molecules possessing asymmetric carbon atoms and usually neglects molecular chirality not involving the asymmetric atoms (5). Then, conformational isomerism, geometrical isomerism, etc. are briefly discussed. Other textbooks (6) make use of the Mislow scheme of isomers classification (9a) in which stereoisomers are intentionally divided into enantiomers and diastereoisomers only (9b). Although the latter scheme is precise it does not take into account the rich realm of stereoisomers types. However, the former approach is obviously at fault. Moreover, in everyday practice no clear

distinction is often made between average structures observed at room temperature and the individual isomers which are important in understanding reaction mechanism. Such an approach contradicts the IUPAC Rules on Stereochemistry's (10) demand for precise declaration of the conformation of the molecule under investigation.

Another example of deep misunderstanding in the field of stereochemistry is provided by a recently published classification scheme of molecular stereoisomerism (11). It was developed with the intention of assisting beginning students with this difficult topic. The logical scheme is based on a series of simple questions, the "yes" or "no" answers to which determine unequivocally the type of stereoisomerism of a molecule under investigation. The scheme is simple, very elegant and seems to be of great practical use for the introduction of stereoisomerism but it is erroneous since it does not take into account two important groups of chiral conformational isomers, i. e. conformational enantiomers and diastereoisomers. As can be easily shown, conformational isomers of molecules such as unsubstituted biphenyl 1a and spiro[5.5]undecane 2a as well as those of *gauche*-butane 3, higher chain hydrocarbons and *cis*-decalin can often exhibit stereoisomerism due to chirality, i. e. enantiomerism or diastereoisomerism, and this possibility does not exist in the proposed scheme. In addition, when analyzing relations between stereoisomers the Black scheme (11) mixes together two types of logical categories. Within the scheme it is not taken into account that *cis* and *trans* isomers represent a different type of stereoisomerism than that represented by constitutional, configurational and conformational isomers, enantiomers, etc. since one can speak about a single *cis*-isomer while in the latter group the isomers are always defined with respect to each other. *cis* and *trans* isomers around double bond or in a ring as well as *cis*, *trans* and *gauche* isomers with respect to a single CC bond specify internal relationships within a molecule not the ones between isomeric molecules. They have been omitted in the scheme but can be easily added.

In spite of the basic errors which it contains the Black scheme (11) seems worth improvement as a very useful and efficient tool for stereoisomer classification in introductory courses on organic chemistry. One can modify it by (a) putting the question "Related as object and nonsuperimposable mirror image?" before introducing conformational and configurational isomerism and by (b) repeating the question "Identical after simple rotation around single bond?" twice, i. e. for both enantiomers and diastereomers. Then, all types of isomeric relationships between organic compounds are included in the

scheme. It should be stressed that with the obvious exception of conformational and configurational enantiomers, other types of isomers can consist of both chiral and achiral molecules. This is obvious for identical structures, constitutional isomers and configurational diastereoisomers, but seems not to be well recognized for conformational diastereoisomers. Several very useful small charts providing examples for each group of isomers were given in Ref. 11. Therefore, some examples of conformational enantiomers and diastereoisomers are given here.



Conformational enantiomers

Conformational diastereomers

To summarize, in spite of its indispensability in asymmetric synthesis, drug-receptor interactions and classification of stereoisomers, conformational chirality is strongly undervalued in many textbooks on organic chemistry and stereochemistry. Another example of the underestimation, the Black scheme of classification, has been corrected in this note to take into account conformational enantiomers and diastereoisomers.

#### Acknowledgements

My thanks are due to Prof. J. H. Brewster who expressed the idea on the underestimation of the conformational chirality (12). I am also grateful to Prof. K. Lipkowitz for enabling me to write this note during my stay at Purdue University, Indianapolis. Many fruitful discussions with Prof. J. Jurczak are gratefully acknowledged.

## References

1. H. Dodziuk, M. Mirowicz, *Tetrahedron Asymmetry*, 1 (1990) 171 - 186.
2. R. S. Cahn, G. K. Ingold, V. Prelog, *Angew. Chem., Intern. Ed. Engl.*, 5 (1966) 385 - 415.
3. V. Prelog, G. Helmchen, *Angew. Chem., Intern. Ed. Engl.*, 21 (1982) 567 - 583.
4. D. M. Walba, J. D. Armstrong, III, A. E. Perry, R. D. Richards, T. G. Homan, R. C. Haltiwanger, *Tetrahedron*, 42 (1986) 1883 - 1984.
5. J. C. Kotz, K. F. Parcel, "Chemistry and Chemical Reactivity", The Dryden Press, Philadelphia, 1987, p. 914; A. Streitwieser, Jr., C. H. Heathcock, "Introduction to Organic Stereochemistry", Macmillan Publishing Company, NY, 1985, p. 113; J. E. Brady, "General Chemistry. Principles and Structure"; Solomons, "Organic Chemistry", J. Wiley and Sons, NY, 1990, p. 149.
6. B. Tesla, "Principles of Organic Chemistry", Studies in Organic Chemistry, v. 6, P. G. Gassman, Ed., p. 33; A. S. Wingrove, R. L. Caret, "Organic Chemistry", Harper and Row Publishers, NY, 1981, p. 185.
7. a. I. W. Wainer, A. L. Marcotte, "Stereochemical Terms and Concepts in Drug Stereochemistry", in "Drug Stereochemistry", I. W. Wainer, E. D. Drayer, Ed. Macel Deer, Inc., NY, 1988, p. 31.  
b. The authors divide stereoisomers into chiral, *i. e.* enantiomers and diastereoisomers, and achiral geometrical ones. They totally neglect the chiral conformational isomers which are of primary importance when discussing the mechanism of drug binding in subsequent chapters of the same book.
8. a. H. Dodziuk, *J. Chem. Soc., Perkin Trans. 2*, 249 - 251 (1986).  
b. H. Dodziuk, J. Sitkowski, L. Stefaniak, I. G. Mursakulov, I. G. Gasanov, V. A. Kurbanova, *Struct. Chem.*, in press.
9. a. K. Mislow, *Bull. Soc. Chim. Belg.*, 86 (1977) 595 - 601.  
b. Thus, the scheme does not cover conformational and configurational isomerism, *cis-*, *trans-* and *gauche-*isomerism,

etc., since they either cannot be introduced in a rigorous way or the descriptors refer to a single molecule not to a pair (or to a larger number) of molecules.

10. Commission on Nomenclature of Organic Chemistry, Rules for the Nomenclature of Organic Chemistry, Section E : Stereochemistry (Recommendation 1974).
11. K. A. Black, *J. Chem. Ed.*, 67 (1990) 141 - 142.
12. J. H. Brewster, private communication.