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The Classification Scheme of Isomers of Organic Molecules

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Abstract A scheme allowing for classification of organic molecules is presented. The need for such a classification and its inherent limitations are discussed briefly. Copyright © 1996 Elsevier Science Ltd

Classification is not the most exciting research topic. However, it enables a better understanding of the inner logic of the branch of science involved establishing relations among the studied objects. In addition, the classification is indispensable in teaching, textbooks, etc. Moreover, as shown in our work on the classification of chirality [1a] and that of organic molecules [2], an incorrect classification [3] reflects misconceptions pointing to the necessity to reconsider the foundations of the particular field, in this case chirality. For instance, as discussed in Ref. 2, there is a lack of understanding of conformational chirality (and conformational enantiomers and diastereomers as well) leading to the overlooking of their role, among others, in drug action. On the other hand, classifying of natural phenomena is a treacherous task in view of their complexity and multiple interrelations. The latter factors do not allow one to introduce an unequivocal hierarchy. For instance, in the scheme presented below the questions concerning topological isomers ("nontrivial topological properties ?" [4]) and that concerning chirality ("Related as object and nonsuperimposable mirror image ?") could be put in the reverse order. Then the distinction between enantiomers and diastereomers would come first followed by the classification into topological, conformational and configurational enantiomers and diastereoismers. Another difficulty arises when the classification of objects depending on a continuously changing parameter is carried out. A classical example here presents the division of stereoisomers into conformers, atropisomers, and configurational isomers. The latter, extremely useful, concepts cannot be precisely defined since they depend on the energy difference between the isomers.

It should be stressed that the classification of organic molecules cannot be founded on a solid physical basis and some questions have to be repeated in different parts of the scheme. We believe that the only requirements that can and have to be fulfilled by such a classification is that it should yield an unequivocal categorization of molecular isomers and be of use to organic chemists. Let us illustrate problems one encounters with the scheme proposed by Mislow [6a] and Dunitz [6b]. At the very beginning (compare Fig. 1 and The Scheme) instead of asking whether the molecules are superimposable, it was proposed to ask whether they are isometric, *i. e.* whether the interatomic distances (taken from X-ray analysis without the introduction of bonds at this point) are the same. As a consequence, an important category of stereoisomers has been lost in this case.

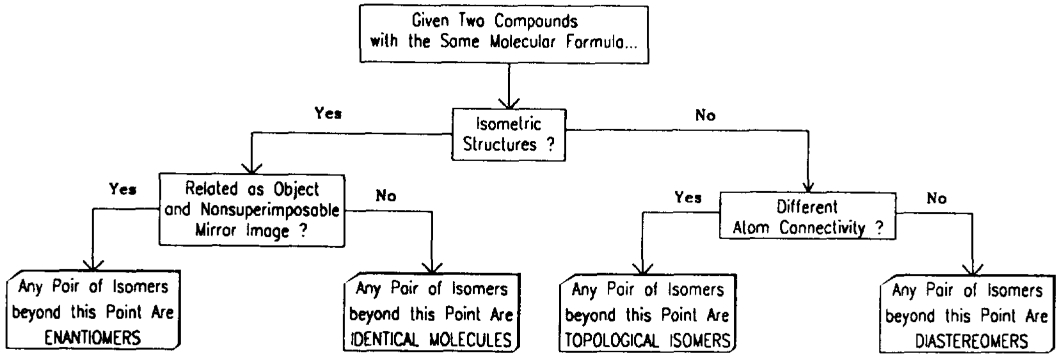
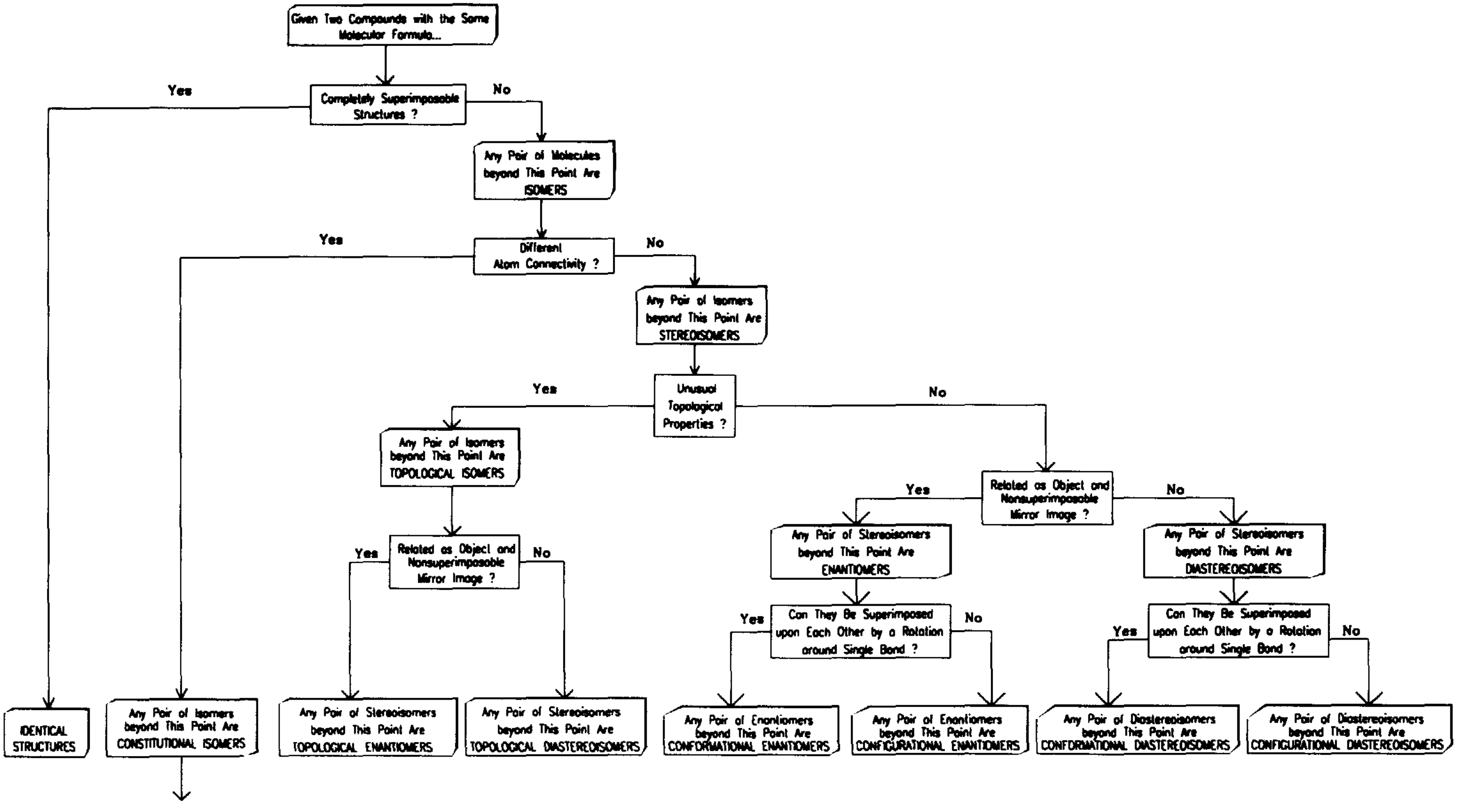


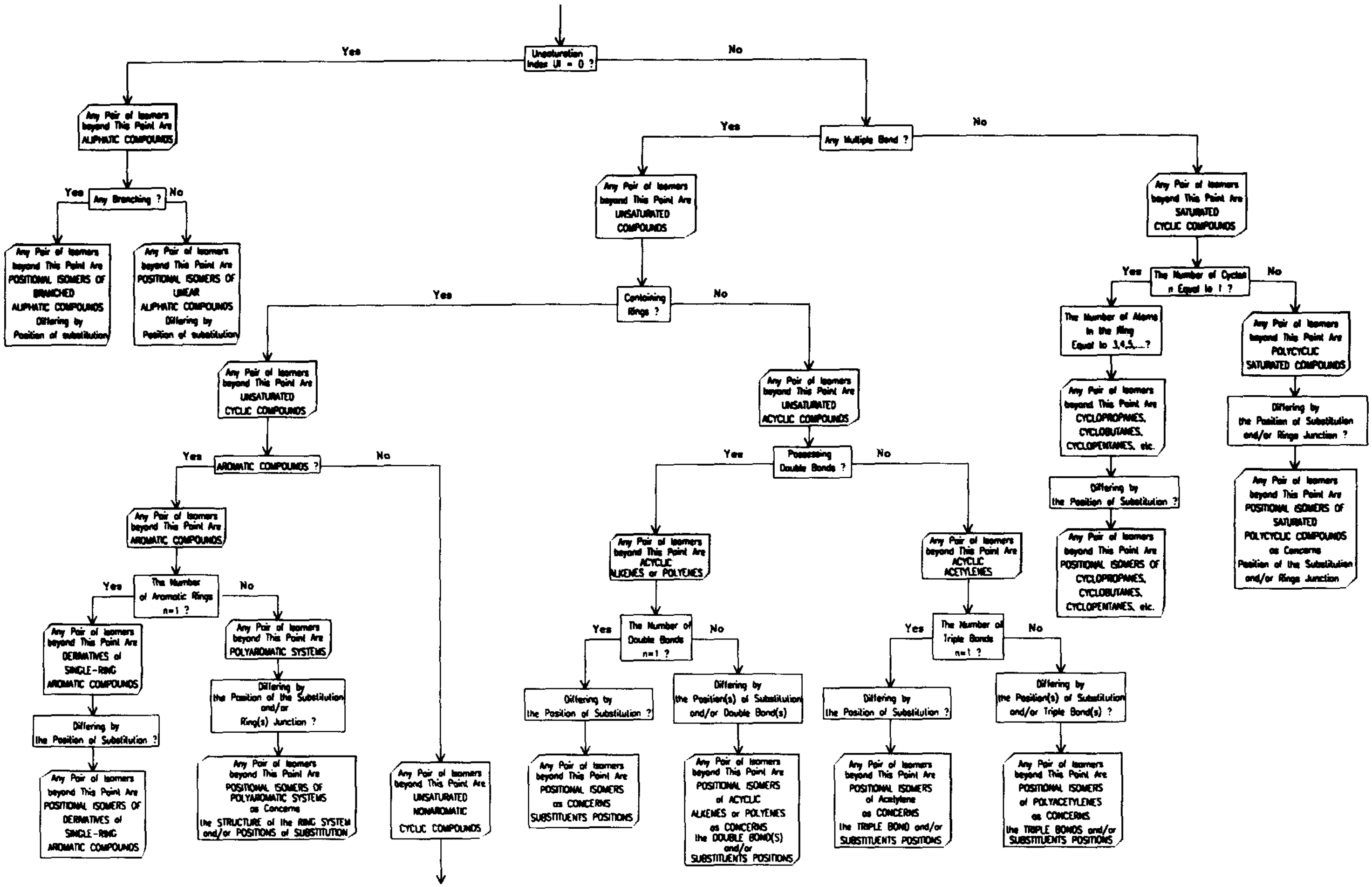
Fig. 1. The beginning of the scheme according to the Mislow and Dunitz proposal.

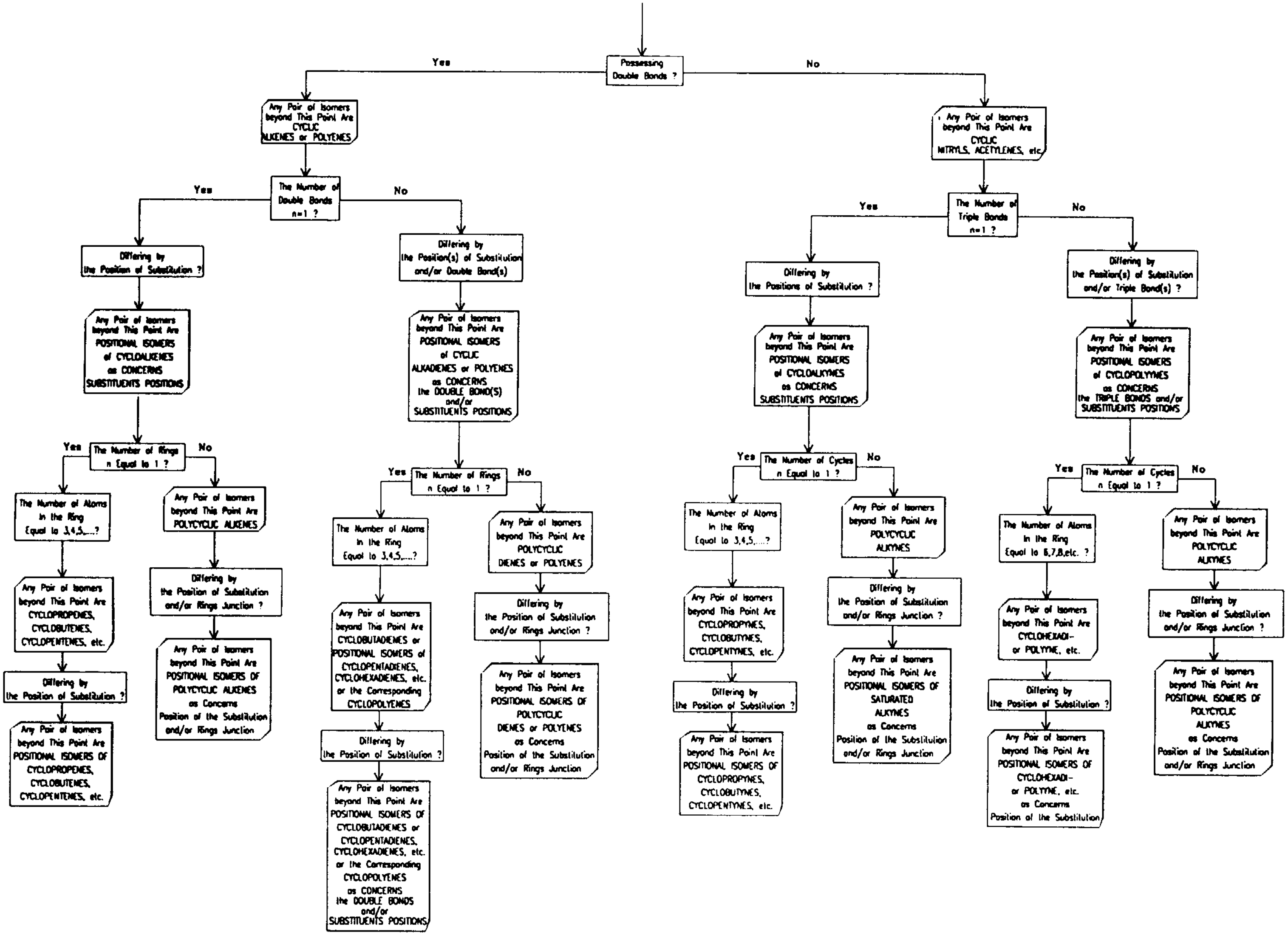
Every classification of molecules depends on the molecular model assumed. In most models a molecule is treated as a set of point masses connected by linear strings representing bonds. A set of partly overlapping spheres can better represent a molecular surface allowing to study how a drug fits into an active site. A choice of the values of ill-defined van der Waals radii is a serious problem in this case. However, the main problem is posed by molecular dynamics, in particular nonrigidity of the molecule under consideration. Let us consider one of the most trivial cases - cyclohexane. Depending on the temperature, its NMR chemical shifts yield information either compatible with the average planar structure (that is never realized) or that of chair structure. There is a multitude of possible conformations for chain hydrocarbons and the all-*anti* conformation is known to be not the most stable one. These problems are not always important in everyday practice of synthetic chemists but they have to be taken into account, for instance, when the intermolecular interactions are taken into account. They are also significant when molecular chirality is considered. Let us look at the butane molecule. In gas state or in solution it is present as a mixture of *anti*-periplanar (*trans*-), and (+)- and (-)-*synclinal (i.e.* (+)- and (-)-*gauche)* isomers. The latter two are chiral but their influences cancel in the absence of a chiral factor. However, in the presence of a chiral solvent or another chiral molecule, the chirality of the *synclinal*-butane isomers cannot be forgotten.

In continuation of our work on the modification [1] of the Cahn, Ingold and Prelog classification of chirality [7], we have recently corrected [2] the Black scheme of classification of organic molecules [3]. However, even the improved version requires several extensions and comments. For instance, no classification of constitutional isomers was given either in Ref. 1b or in other monographs on stereochemistry and/or conformational analysis [8]. Moreover, even the corrected version of the classification [2] does not contain topological molecules [9-11]. Molecules mimicking the Möbius strip, links (i. e. catenanes) and knots [10] characterized by nontrivial topology are known to belong to the latter group. Topological nontriviality of an object is checked by deforming it without cutting or glueing its parts. However, most deformations allowed in topology are physically inadmissible. As discussed in Ref. 10e, in-out isomers of hydrogenated fullerenes have to be considered as topological isomers since their interconversion requires such big elongation of bonds that in reality bonds should break. Similarly, rotaxanes, which formally have not been included into topological molecules, have been often inconsequently discussed together with catenanes [10c, 11]. The work is in progress on precise definitions allowing one to treat rotaxanes and in-out isomers of hydrogenated fullerenes as topological molecules [5]. The formulation of such

Isomeric Relationships Between Organic Compounds




Unsaturation Index UI = 0 ?
Yes
No
Any Pair of Isomers beyond This Point Are ALIPHATIC COMPOUNDS
Any Branching ?
Yes
No
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF BRANCHED ALIPHATIC COMPOUNDS Differing by Position of substitution
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF LINEAR ALIPHATIC COMPOUNDS Differing by Position of substitution
Any Multiple Bond ?
Yes
No
Any Pair of Isomers beyond This Point Are UNSATURATED COMPOUNDS
Containing Rings ?
Yes
No
Any Pair of Isomers beyond This Point Are UNSATURATED CYCLIC COMPOUNDS
AROMATIC COMPOUNDS ?
Yes
No
Any Pair of Isomers beyond This Point Are AROMATIC COMPOUNDS
The Number of Aromatic Rings n=1 ?
Yes
No
Any Pair of Isomers beyond This Point Are DERIVATIVES of SINGLE-RING AROMATIC COMPOUNDS
Differing by the Position of Substitution ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF DERIVATIVES of SINGLE-RING AROMATIC COMPOUNDS
Any Pair of Isomers beyond This Point Are POLYAROMATIC SYSTEMS
Differing by the Position of the Substitution and/or Ring(s) Junction ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF POLYAROMATIC SYSTEMS as Concerns the STRUCTURE of the RING SYSTEM and/or POSITIONS of SUBSTITUTION
Any Pair of Isomers beyond This Point Are UNSATURATED NONAROMATIC CYCLIC COMPOUNDS
Any Pair of Isomers beyond This Point Are UNSATURATED ACYCLIC COMPOUNDS
Possessing Double Bonds ?
Yes
No
Any Pair of Isomers beyond This Point Are ACYCLIC ALKENES or POLYENES
The Number of Double Bonds n=1 ?
Yes
No
Differing by the Position of Substitution ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS as CONCERNS SUBSTITUENTS POSITIONS
Differing by the Position(s) of Substitution and/or Double Bond(s)
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS of ACYCLIC ALKENES or POLYENES as CONCERNS the DOUBLE BOND(S) and/or SUBSTITUENTS POSITIONS
Any Pair of Isomers beyond This Point Are ACYCLIC ACETYLENES
The Number of Triple Bonds n=1 ?
Yes
No
Differing by the Position of Substitution ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS of Acetylene as CONCERNS the TRIPLE BOND and/or SUBSTITUENTS POSITIONS
Differing by the Position(s) of Substitution and/or Triple Bond(s) ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS of POLYACETYLENES as CONCERNS the TRIPLE BONDS and/or SUBSTITUENTS POSITIONS
Any Pair of Isomers beyond This Point Are SATURATED CYCLIC COMPOUNDS
The Number of Cycles n Equal to 1 ?
Yes
No
The Number of Atoms in the Ring Equal to 3,4,5,...?
Any Pair of Isomers beyond This Point Are CYCLOPROPANES, CYCLOBUTANES, CYCLOPENTANES, etc.
Differing by the Position of Substitution ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF CYCLOPROPANES, CYCLOBUTANES, CYCLOPENTANES, etc.
Any Pair of Isomers beyond This Point Are POLYCYCLIC SATURATED COMPOUNDS
Differing by the Position of Substitution and/or Rings Junction ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF SATURATED POLYCYCLIC COMPOUNDS as Concerns Position of the Substitution and/or Rings Junction


Possessing Double Bonds ?
Yes
No
Any Pair of Isomers beyond This Point Are CYCLIC ALKENES or POLYENES
The Number of Double Bonds n=1 ?
Yes
No
Differing by the Position of Substitution ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS of CYCLOALKENES as CONCERNS SUBSTITUENTS POSITIONS
The Number of Rings n Equal to 1 ?
Yes
No
The Number of Atoms in the Ring Equal to 3,4,5,...?
Any Pair of Isomers beyond This Point Are CYCLOPROPENES, CYCLOBUTENES, CYCLOPENTENES, etc.
Differing by the Position of Substitution ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF CYCLOPROPENES, CYCLOBUTENES, CYCLOPENTENES, etc.
Any Pair of Isomers beyond This Point Are POLYCYCLIC ALKENES
Differing by the Position of Substitution and/or Rings Junction ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF POLYCYCLIC ALKENES as Concerns Position of the Substitution and/or Rings Junction
Differing by the Position(s) of Substitution and/or Double Bond(s)
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS of CYCLIC ALKADIENES or POLYENES as CONCERNS the DOUBLE BOND(S) and/or SUBSTITUENTS POSITIONS
The Number of Rings n Equal to 1 ?
Yes
No
The Number of Atoms in the Ring Equal to 3,4,5,...?
Any Pair of Isomers beyond This Point Are CYCLOBUTADIENES or POSITIONAL ISOMERS of CYCLOPENTADIENES, CYCLOHEXADIENES, etc. or the Corresponding CYCLOPOLYENES
Differing by the Position of Substitution ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF CYCLOBUTADIENES or CYCLOPENTADIENES, CYCLOHEXADIENES, etc. or the Corresponding CYCLOPOLYENES as CONCERNS the DOUBLE BONDS and/or SUBSTITUENTS POSITIONS
Any Pair of Isomers beyond This Point Are POLYCYCLIC DIENES or POLYENES
Differing by the Position of Substitution and/or Rings Junction ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF POLYCYCLIC DIENES or POLYENES as Concerns Position of the Substitution and/or Rings Junction
Any Pair of Isomers beyond This Point Are CYCLIC NITRYLS, ACETYLENES, etc.
The Number of Triple Bonds n=1 ?
Yes
No
Differing by the Positions of Substitution ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS of CYCLOALKYNES as CONCERNS SUBSTITUENTS POSITIONS
The Number of Cycles n Equal to 1 ?
Yes
No
The Number of Atoms in the Ring Equal to 3,4,5,...?
Any Pair of Isomers beyond This Point Are CYCLOPROPYNES, CYCLOBUTYNES, CYCLOPENTYNES, etc.
Differing by the Position of Substitution ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF CYCLOPROPYNES, CYCLOBUTYNES, CYCLOPENTYNES, etc.
Any Pair of Isomers beyond This Point Are POLYCYCLIC ALKYNES
Differing by the Position of Substitution and/or Rings Junction ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF SATURATED ALKYNES as Concerns Position of the Substitution and/or Rings Junction
Differing by the Position(s) of Substitution and/or Triple Bond(s) ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS of CYCLOPOLYYNES as CONCERNS the TRIPLE BONDS and/or SUBSTITUENTS POSITIONS
The Number of Cycles n Equal to 1 ?
Yes
No
The Number of Atoms in the Ring Equal to 6,7,8,etc. ?
Any Pair of Isomers beyond This Point Are CYCLOHEXADI- or POLYYNE, etc.
Differing by the Position of Substitution ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF CYCLOHEXADI- or POLYYNE, etc. as Concerns Position of the Substitution
Any Pair of Isomers beyond This Point Are POLYCYCLIC ALKYNES
Differing by the Position of Substitution and/or Rings Junction ?
Any Pair of Isomers beyond This Point Are POSITIONAL ISOMERS OF POLYCYCLIC ALKYNES as Concerns Position of the Substitution and/or Rings Junction

definitions has been founded on the fundamental difference between a real molecule and its model discussed by Mislow and Bickart [12].

Further obvious classification is needed when heteroatoms and/or functional groups are present in the molecule under discussion including their position(s). More complicated procedures are required for aromatic polycyclic systems (cata-, peri-, and corona-fused) as well as for various types of saturated polycyclic molecules [13].

The unsaturation index, UI, used in the classification is defined in the following way :

$$UI = N_4 + 1 - N_1/2 + N_3/2,$$

where N_4 is the number of tetravalent atoms, N_1 that of atoms with single valence, and N_3 is the corresponding number for trivalent atoms in the molecule under study. The index is equal to the sum of the number of rings and multiple bonds in this molecule. For instance, for cyclooctyne C_8H_{12}, UI equals to (8 + 1 - 12/2) = 3 corresponding to one ring and a triple bond.

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