CHEMICAL MORPHOLOGY, A PURE CHEMICAL SYSTEMATIZATION OF MICRO MOLECULAR ORGANIC COMPOUNDS

.

ABSTRACT

There are two circumstances to consider every micro molecular organic compound: (a) near its similar non-isomeric combinations, i.e. an amino acid with other amino acids, an organic acid with other organic acids, a steroid with other steroids, etc., (b) exclusively with its isomers, as a constituent of a multitude generated by its molecular formula (MF). The latter approach is the aim of this paper, and if undertaken systematically it could constitute a new chapter of physical chemical sciences, chemical morphology.

MFs are inherently uncertain phenomena. They cannot be known and described but *via* the compounds they produce. Generation of isomers by a MF illustrates the big bang of micro molecular organic compounds, e.g. MF C_{59} of alkanes produces about 2.66 Avogadro's number of entities.

No matter how large a multitude is, five types of compounds only can be distinguished inside it: (A) *meso*, (B) *C_2 symmetrical* (*C_2 symm.*), (C) *irrechi* (*configurational*), (D) *constitutional* (*constit*.), (E) *archaic* (*primitive*). The molecule of *meso* isomers is characterized by two enantiomeric halves, and that of *C_2 symm*. by two identical chiral halves. The skeleton of *irrechi* molecule is similar to *meso* and *C_2 symm*., however the pattern of its chiral carbons is different. A combination whose MF is unable to produce a *meso* isomer, real or imaginary, is *archaic* (*primitive*). Two necessary and sufficient conditions have to be fulfilled by a compound to be *constitutional* (*constit*.): (i) to be devoid of chemical elements of symmetry at the level of its molecule and (ii) its MF be able to produce at least one *meso* isomer, real or imaginary.

***constit* Compounds are much more numerous in living things than *meso*, *C_2 symm.* and *irrechi* taken together. MFs including at least a *meso* isomer, real or imaginary, are the best proof that chemistry is a dualistic science.**

Keywords: systematization; dualistic; meso, C2 symmetrical; irrechi; constitutional; molecular formula; chemical multitude

1. INTRODUCTION

On the chemical multitudes. Almost every molecular formula (MF) generates a chemical multitude. Multitudes containing two isomers appeared in the beginning: silver fulminate and silver cyanate (Liebig, 1823) and ammonium cyanate and urea (Wöhler, 1828). Pasteur discovered three isomers: (+)- and (–)-tartaric acid (1848) and *meso*-tartaric acid (1853). (+)-Tartaric acid had been discovered by Scheele (1770) (Swedberg, 2012) in the wine sediment. Butlerov (1868) expanded this picture to C_4 hydrocarbons and alcohols. Van't Hoff (1874) has accomplished a mathematical approach. Based on his tetrahedral model of C atom valences, he calculated the number of linear aldohexoses as being 16 (two sets of eight), and 10 of their hexitols. In less than two decades, the major part of them have been discovered/invented (Fischer, 1891). Chemical multitudes produced by MFs C_6H_{12}-C_8H_{16} as derivatives of cyclopropane and cyclobutane have been shown (Balaban, 1978). When calculation of the number of chemical entities has been applied to different classes of substances, it became clear that some of them include a bigger number of isomers than all combinations known at that time (Schmidt, 1986; Laine, 1994). A good illustration of magnitude and dimensions of a chemical multitude is given by MF $C_{27}H_{46}O$. This chemical multitude include also cholesterol, an unsaturated hydroxy steroid containing eight chiral carbons. (A steroid is a compound producing Diels' hydrocarbon when heated with Se (Finar, 1964)). Hence the number of chiral isomers with the same skeleton, is $2^8 = 256$. Many other isomers coming of MF $C_{27}H_{46}O$, possibly devoid of steroid skeleton, can be written. For C_{27} alkane, Fujita (2007) counted over three billion isomers.

To alkanes, Fujita (2007) presented 100 chemical multitudes, from C_1 to C_{100}. The numeric discrepancy between Fujita and Pólya (1937), in the sense that the latter omits some entities, has to be indicated. To MF $C_{12}H_{26}$, Pólya found 355 isomers, and Fujita 509. Really huge numbers, some bigger than Avogadro's number, can be found among the Fujita's 100 MFs. This is in agreement with the remark that the increase of the number of isomers of MFs, as a function of the latter is faster than exponential equation (Balaban, 1976).

The elements of symmetry in chemistry acquired their full sense only when the hypothesis of van't Hoff (1874) and Le Bel (1874), concerning the tetrahedral distribution of carbon valences, transcended in a veritable theory, due especially to the works of E. Fischer (1891, 1894), J. Wislicenus (1888) and other chemists.

Two types of symmetry function in chemistry: geometrical (*G. symm.*) and chemical. Both types are based on planes of symmetry. A plane of symmetry is a physical chemical phenomenon and an instrument. When applied, it cuts (intersects) either a bond or one or more atoms. In chemistry, the plane of symmetry has the property to hide (or to mask) of polarized light, some chemical groups cut by it (or situated in it). C_2 symmetry (see below) is also chemical, as well as symmetries based on axis and center (point) of symmetry (Hoffmann, 2003; Smith and March, 2007). In case of *G. symm*., the two halves evidenced by the planes of symmetry are identical and devoid of handedness. In chemical symmetry, the plane of symmetry separates exclusively enantiomeric halves, and is called mirror plane of symmetry.

Every micro molecular organic natural, or synthetic, compound can be considered in two types of circumstances: (i) with its similar compounds, i.e. an amino acid (alanine, Ala) with other amino acids (Vickery and Schmidt, 1931), (preferentially with the other amino acids coded in DNA) an organic acid (caproic acid) with other organic acids (from C_1 to C_{20}, or even C_{100} (Fujita, 2007)), a steroid (estrone) with other steroids, etc., and (ii) exclusively with compounds having the same MF, i.e. with its isomers: Ala with isomers generated by MF $C_3H_7NO_2$, caproic acid inside the molecular diversity given by MF $C_6H_{12}O_2$, and estrone with molecules produced by MF $C_{18}H_{22}O_2$, etc. Our aim is to exploit the latter alternative, almost completely ignored till now, according to our knowledge. Development of this idea could probably constitute a new chapter of physical-chemical sciences, chemical morphology.

One can imagine, or even find, five types (or moldings) of isomers for the most MFs: (A) *meso*, (B) *C_2 symmetrical* (*C_2 symm.*), (C) *irrechi* (*configurational*), (D) *constitutional* (*constit*.), (E) *archaic* (*primitive*). There is still a small group, characteristic to (saturated) cyclic compounds, that are simultaneously *meso* and *C_2 symm*., and called of this reason *doublesymmetric* (*DoSymm*.) (Iga, 2004). The types (molds) (A) (B) and (D) are well known. The type (C), (E) and *DoSymm*. ones have been identified, characterized and introduced in this paper.

(A) *meso* Compounds

The molecule of a *meso* compound is formed either of two chiral enantiomeric halves uniformly linked with each other (homodimers) or linked on a mono- or polyatomic support (heterodimers) (Magnuson, 1995; Hoffmann, 2003). The uniform character of the bond means that it is made between atoms with the same rank in the monomeric units. The linking support can be variable, hence a homodimeric *meso* can produce numerous equivalent heterodimeric *meso* compounds. Linking support is recognized since some of its atoms are cut by (contained in) the mirror plane of symmetry. On the other hand, every heterodimeric *meso* combination possesses an equivalent *meso* homodimer, the latter being obtained by removing the linking support (Iga, 2024). The binding support can be of the type >CRR', or of the type >CR_2. *meso* Compounds are characterized by their mirror plane of symmetry and they are distinguished by the fact that in homodimers it intersects only bonds, while in heterodimers it intersects one or more atoms.

If the two enantiomeric halves of erythritol, a homodimeric *meso*, are linked on a >HC(OH) residue, xylitol or ribitol, both heterodimeric *meso*, are produced. Similar heterodimeric *meso* compounds are obtained if the two enantiomeric halves of erythritol are connected to –CH_2– (in deoxyxylitol or deoxyribitol) (Anderson, 1965; Oka et al., 1984), or simultaneously on two residues: –HC(OH)– and –O– (in 1,5-anhydro-xylitol) (Fletcher and Hudson, 1947), –HC(OH)– and –CH_2– (in 2,4-methylene-xylitol), –HC(O-CH_2-O-CO-CH_3)– and –CH_2– (in 3-acetoxy-methyl-2,4-methylene-xylitol) (Hann et al., 1944); hence, the linking support can be even fragmented.

The first *meso* isomer was discovered by L. Pasteur (1853), as *meso* tartaric acid, a compound devoid of optical activity and noncleavable by physical-chemical or biological methods. When the theory of tetrahedral carbon appeared (van't Hoff, 1874; Le Bel, 1874), the spacial representations elaborated by van't Hoff indicated that the model of *meso*-tartaric molecule has a mirror plane of symmetry.

Fischer and Stahel (1891) invented xylitol by reduction of D-xylose, and Fischer (1893) discovered ribitol (adonitol) in the plant *Adonis vernalis*, two monosaccharides representing a new type of *meso* compounds, heterodimers (Hoffmann, 2003; Iga, 2024).

Fischer and Hertz (1892) worked on galactitol and galactaric acid in order to illustrate the phenomenon of *meso* symmetry. They reduced galactaric acid (a *meso* homodimer) with Na-amalgam and obtained a racemic mixture of D- and L-galactonic acid. This was the first reaction of desymmetrization in chemistry. They separated the two enantiomers of the mixture as salts of strychnine. Of every enantiomer they prepared the matching aldohexose, i.e. D- and L-galactose. As expected, both aldohexoses gave the same galactitol or galactaric acid, by reduction with Na-amalgam or oxidation with nitric acid, respectively. By this experiment, Fischer proved that the molecule of *meso* homodimers is formed of two enantiomeric halves. On the other hand, by Fischer's procedure, the internal *meso* phenomenon became externalized. Allitol presented the same behavior (Wolfrom and Schumacher, 1955). Since NMR does not distinguish between the two enantiomeric halves, they appear as identical in this technique, and only half of them are detected by NMR (Yamamura et al., 1982; Ishii et al., 1991; Fang et al., 1992; Ali et al., 1998; Sugahara et al., 2007). This is quite obvious by comparing the number of C atoms evidenced by NMR with the number found by molecular weight determination.

(B) C_2 Symmetrical isomers

The first discovered *C_2 symm*. compounds have been tartaric acids (Scheele, 1770; Pasteur, 1848; Fischer, 1896), D- and L-mannitol (Fischer and Hirschberger, 1889; Fischer, 1891), D- and L-iditol (Fischer and Fay, 1895), and their aldaric acids. Elaboration of molecular models (van't Hoff, 1874) for the two enantiomers, (+)- and (–)-tartaric acid, that had been isolated by Pasteur (1848), disclosed a scientific and philosophical dilemma: which model to which enantiomer (Hoffmann and Laszlo, 1991) should be assigned? A preliminary and useful answer has been given by Fischer (1896) by probabilistic reasoning. This dilemma has been truly solved by X-ray diffraction, i. e., zirconium Kα rays, by sodium rubidium tartrate of the dextrorotary species (Bijvoet et al., 1951). Bijvoet et al., showed that (+)-tartaric acid is (2R,3R)-(+)- or L-(+)-tartaric acid. Removing of a carboxyl group of (2R,3R)-(+)-tartaric acid gives (S)-(–)- or L-(–)-glyceraldehyde [Klyne and Buckingham, 1978]. By an impressive coincidence, the same configuration of (+)-tartaric acid had been hypothetically attributed by Fischer (1896).

Configuration of chiral centers of (–)-tartaric became also known, by the virtue of the law of enantiomorphism. The nomenclature of the two enantiomers became L-(+)-tartaric and D-(–)-tartaric acid, according to the recommendations of Fischer (1891), Rosanoff (1906) and Wohl and Momber (1917).

D-(–)-Tartaric acid is interconvertible with D-(+)-glyceraldehyde, and L-(+)-tartaric acid is related with L-(–)-glyceraldehyde, either by chain elongation (Kiliani, 1885, 1886, 1887) or chain shortening (Malaprade, 1928a, b; Klyne and Buckingham, 1978; Jäger and Wehner, 1989). As a result, the configuration of the two aldotrioses was elucidated (Iga, 2018).

The molecule of *C_2 symm*. compounds is formed of two identical chiral halves uniformly linked with each other (homodimers) or on a linking support of the $>CR_2$ form (heterodimers). Alternative imaginary dimerization of the two enantiomeric halves of a *meso* compound produces one of the following: (a) two chiral *C_2 symm*. enantiomers; (b) a combination being concomitantly *meso* and *C_2 symm*., and called of this reason *doublesymmetric* (*DoSymm*.). The groups (a) and (b) constitute a rational definition of *meso* compounds (Iga, 2024). However, it was Fischer who demonstrated how *C_2 symm*. isomers work. Fischer and Hirschberger (1888, 1889) noticed that kinetic oxidation of D-mannitol produced one aldohexose only, D-mannose. The same physical-chemical behavior was noticed to L-mannitol and D- and L-iditol. This was also among the first reactions of desymmetrization in organic chemistry. Other hexitols instead, produced two different monosaccharides (diastereomers called epimers). They concluded that the molecules of D- and L-mannitol and D- and L-iditol as well as their aldaric acids, are formed of two identical chiral halves (homodimers). Inspired of this concept, a series of homo- and heterodimeric *C_2 symm*. catalysts with spectacular qualities have been synthesized (Dang and Kagan, 1971; Kagan and Dang, 1972; Burk et al., 1996; Ghosh et al., 1998; Pfaltz and Drury III, 2004). A defining property of *C_2 symm*. isomers is the following: their rotation by 180° around an axis produces the same structural context. This rule knows also exceptions: compounds 7, 9, 10, etc., (Magnuson, 1995), terreusinone (Lee et al., 2003; Saleem et al., 2007), all 2,5-diketopiperazines of the same amino acid with the same configuration (Borthwick, 2012), etc.

Imaginary alternative dimerization of the two halves of allitol produces D- and L-mannitol, while galactitol gives D- and L-iditol. The same imaginary process applied to a *meso* compound usually gives rise to two enantiomeric *C_2 symm*. isomers. Vickery (1957) noticed *C_2 symm*. isomers as a distinct group, and Reusch (2011), similar to Fischer (1891), used this quality of D-mannitol in demonstration of configuration of C-2.

At first sight, at least, chiral compounds possessing an equal number of R and S chiral carbons, disclosed by Cahn-Ingold-Prelog criteria (1966), are considered *meso* isomers. This rule has some exceptions. D- And L-iditol have the same number of R and S centers in their molecule, however they are *C_2 symm*. Also *C_2 symm*. are numerous natural and synthetic compounds having an equal number of R and S chiral carbons: (3R,4S,6S,7R)-3,7-dimethyl-4,6-dihydroxy-1,8-nonadien, (3S,4R,6R,7S)-3,7-dimethyl-4,6-dihydroxy-1,8-nonadien (Gao et al., 2011), tunaxanthin C [(3R,6S,3'R,6'S)-ε,ε-carotene-3,3'-diol], tunaxanthin J [(3S,6R,3'S,6'R)-ε,ε-carotene-3,3'-diol] (Ikuno et al., 1985), hybocarpone-(2R,3S,4S,5R), hybocarpone-(2S,3R,4R,5S) (Nicolaou and Gray, 2004), (7R,8S,8'S,7'R)-7.O.7',8,8'-lignan, (7S,8R,8'R,7'S)-7.O.7',8,8'-lignan (Fonseca et al., 1979; Cui et al., 2014; Lenta et al., 2015), (S,R,R,S)-quadrigemine and (R,S,S,R)-quadrigemine (Canham et al., 2015), etc.

Less studied compounds presents a similar picture: (3R,4S,6S,7R)-3,4,6,7-tetraMe-5-methylene-nonane, (3S,4R,6R,7S)-3,4,6,7-tetraMe-5-methylene-nonane, (1S,3S,4R,5R)-1,3,4,5-tetraMe-2-methylene-cyclopentane, (1R,3R,4S,5S)-1,3,4,5-tetraMe-2-methylene-cyclopentane, (3R,4S,5S,6R)-1,7-dien-3,4,5,6-tetraMe-octane, (3S,4R,5R,6S)-1,7-dien-3,4,5,6-tetraMe-octane, (3R,4S,5S,6R)-3,4,5,6-tetraMe-octane, (3S,4R,5R,6S)-3,4,5,6-tetraMe-octane, (2R,3S,4S,5R)-2,5-dihydroxy-3,4-diMe-hexane, (2S,3R,4R,5S)-2,5-dihydroxy-3,4-diMe-hexane, (2R,3S,4S,5R)-2,3,4,5-tetraMe-THF, (2S,3R,4R,5S)-2,3,4,5-tetraMe-THF, (3R,4S,6S,7R)-3,4,6,7-tetraMe-5-keto-nonane, (3S,4R,6R,7S)-3,4,6,7-tetraMe-5-keto-nonane, (1R,2R,3S,4S)-1,2-dihydroxy-3,4-diMe-cyclobutane, (1S,2S,3R,4R)-1,2-dihydroxy-3,4-diMe-cyclobutane.

In this paper, compounds that possess chemical elements of symmetry in their molecule – *meso*, C_2 *symm*., as well as compounds characterized by a center or an axis of symmetry, are preferentially taken into consideration.

(C) Irrechi isomers

Sustaining of a new group of isomers needs two conditions: (a) to possess a significant number of components; (b) to possess characteristics that are unique and different of other groups, in other words to submit to a new principle of construction (molding).

Diastereomers have been defined as isomers that are not enantiomers to a given chiral compound. By this statement diastereomers are not defined by themselves but relative to another compound, outside them. Of the large family of diastereomers, two groups are distinct: *meso* (Fang et al., 1992; McAuliffe et al., 2001; Hoffmann, 2003; Sugahara et al., 2007) and C_2 *symm*. (Ghosh et al., 1998; Pfaltz, 1993, 1996; Mamidi et al., 2012). The investigation of a large number of compounds has led us to a third distinct group of diastereomers, i.e. configuration isomers. We have temporarily called them *irrechi* [ai'rekai] (from irregular distribution of chiral carbons), and they are of two types: (i) on one hand isomers having the same skeleton with some real or imaginary *meso* or C_2 *summ*. ones, but a different pattern of chiral carbons; (ii) dimers produced by a non-uniform dimerization, i.e. based on a linkage formed between atoms with different ranks in the monomeric units. Since the latter superposes to *constit*. isomers, we adopted the latter classification. MFs producing *meso* isomers containing two chiral carbons would produce only C_2 *symm*. ones, while MFs with three asymmetric carbons satisfying the same condition would produce *irrechi*, besides *meso* and not necessarily C_2 *symm*. E.g. $C_4H_{10}O_4$ gives erythritol, two enantiomeric threitols and hydroxymethyl glycerol. $C_5H_{12}O_5$ gives ribitol and xylitol, both *meso*, D- and L-arabinitol, both *irrechi* (Fischer and Stahel, 1891; Fischer, 1893) and hydroxytetritol (*constit*.). A similar picture is known for the isomers of trihydroxyglutaric acid (Wheeler and Tollens 1889; Fischer and Bromberg, 1896; Fujita, 2016). MFs able to give *meso* isomers with four asymmetric carbons are archetypes similar to $C_6H_{14}O_6$: galactitol and allitol are *meso*, D- and L-mannitol and D- and L-iditol are C_2 *symm*., D-glucitol (L-gulitol), L-glucitol (D-gulitol), D-talitol (D-altritol), L-talitol (L-altritol) are *irrechi*, and hamamelitol is *constit*. The role of *irrechi* compounds is not less justified than *meso* and C_2 *symm*. A remark should be made: the most MFs of organic compounds can alternatively adopt all the five molds: *meso*, C_2 *symm*., *irrechi*, *constit*., *archaic*. (see below).

(D) Constitutional

Constitutional (*constit*.) isomers form the fourth group. Compounds devoid of chemical elements of symmetry, and whose MF is able to produce at least one *meso* isomer are constitutional. E.g. MF $C_{18}H_{22}O_2$ gives *meso*-hexestrol (Suzuki and Shapiro, 2009); all the other isomers given by this MF – estrone (Suzuki and Shapiro, 2009), trenbolone, (4-butylphenyl)(4-methoxy)-methanol, 1,4-dibutoxy-2,5-diethynylbenzene (He et al., 2011), (8S,9S,13S,14R,17S)-estra-1(10)-2,4,6-tetraene-14,17-diol (Wefelscheid et al., 2007), hexyl-naphthalene-2-acetate, 3-hydroxy-estra-1,3,5 (10)-trien-16-one (Suzuki and Shapiro, 2009), etc., are *constit*. Bis(1-methyl-1-phenylethyl) peroxide (Su et al., 2008) is symmetric but it is neither *meso* nor C_2 *symm*., but *G. symm*. Consequently, it cannot be invoked as an argument for the major task of this paper, that chemistry is a dualistic science. MF $C_{27}H_{46}O$ has no known *meso* compound, according to our knowledge. However, one can imagine numerous *meso* isomers as coming from the above MF. Hence, cholesterol, cholestanone, etc., are *constit*., as related to *meso* isomers. Nonetheless, we consider MFs containing *meso* isomers as privileged, since they are suitable to the above exercise: to convert all non-*meso* isomers in *meso* one(s), and finally to MF. This exercise can be conceived as a phenomenon of reversible volatility.

Every *constit*. compound belong to a population of isomers including at least one *meso* combination, real or imaginary, a proof that chemistry can be considered a dualistic science. They are devoid of elements of symmetry, they are either optically active or inactive, and are much more numerous in living things than *meso*, C_2 *symm.* and *irrechi* taken together.

Concerning the hierarchy of the four types of isomers, the following arguments have to be taken into account. An intrinsic property of *meso* combinations is their character of dimerism, hence their molecule is formed of two entities that are contrary in a spatial, chemical and optical sense. In structural terms, they have the lowest freedom degrees of all four molds, hence they have the lowest rank. On the other hand, they undoubtedly indicate that chemistry is a dualistic science. Of this reason they are used as reference compounds in this work. *Constit*. molecules are characterized by the least such structural restrictions. Of this reason, probably, natural chemistry opted for them, and they possess the highest rank. The structure of all natural compounds is written in a program, i. e. a genome. Hence the hierarchy itself is registered in genome, and the evolution process has been accomplished at this level.

When physical chemistry appeared and developed, biologists and other scholars connected with biomolecules, hoped that physical chemists would discover a marker for natural compounds, as density is for gold. Till now such hope has been only partially fulfilled (Metzler and Metzler, 2003). Nonetheless, natural combinations possess some unique characteristics, and one of them, in our opinion, is the fact that they are less restricted, in structural sense, than *meso*, C_2 *symm.* and *irrechi*. A proof for this assertion is the fact that as soon as a living thing dies, nature sends a thousand messengers to recover its component materials. We reckon that at least one of these characteristics is that *constit*. compounds have a higher number of structural freedom degrees, in comparison with the other types.

It should be stressed that a compound is *constit*. only and only if its MF can produce at least one *meso* isomer.

Archaic (primitive) compounds

Compounds coming from MFs unable to produce *meso* isomers are *archaic* (*primitive*). C_6H_6, C_7H_8, $C_{10}H_8$, $C_{14}H_{10}$, C_6H_6O, $C_{10}H_8O$, etc., produce archaic compounds.

In different classes of compounds which constitute series, small groups can be found whose components are unable to possess *meso* isomers, and of this reason they have been called *archaic* (*primitive*). *Archaic* compounds can reach the level where they are able of producing *meso* isomers only by chemical transformations. E. g. propane belongs to *archaic* group, however, by oxidation it becomes propanoic acid, an advanced form able to present a *meso* isomer; however, propenoic acid is *archaic*. Fischer [Fischer and Passmore, 1889; Fischer, 1894] illustrated this phenomenon by preparing a variety of C_6 monosaccharides from formaldehyde. Compounds as C_1-C_7 alkanes, C_2-C_4 alkenes, C_2-C_6 alkynes (alkadienes), C_1-C_8 monohydroxylic alcohols, C_1-C_4 aldehydes/ketones, C_1-C_2 saturated carboxylic acids, arenes (benzene, toluene, naphthalene, anthracene, phenanthrene, diphenyl), fumaric/maleic acids, benzoic acid, phthalic acid, heterocyclic compounds (sepiapterine, niacin (nicotinic acid, nicotinamide), xanthopterin, leucopterin, pyrrole, imidazole, indole), choline, glycerol, salicylic acid, belong to *archaic* group. Compounds of the series, with MF above the limit of archaic have at least *meso* isomers, besides *constit*., or even all five types.

Natural micromolecular organic combinations can be also classified in a different manner, partially superposing with the afore mentioned classification: (**i**) symmetric (*meso* and C_2 *symm.*); (**ii**) potential symmetry generators (*irrechi, constit.*); (**iii**) *archaic*.

Total or even partial reduction, or adding more atoms to the latter compounds, increase their status. Cyclohexane, methylcyclohexane, tetrahydronaphthalene, etc., are no more archaic. Systematically, archaic compounds will be met among the first terms of the functional (progressive) series (see below).

In the following, systematization and principles proposed in this paper would be applied to different classes of compounds, hence their value and their limit would become obvious.

1. The big bang of micro molecular organic compounds

MFs give rise to a large variety of numbers of isomers, from one or two or three entities to a dozen of Avogadro's number, and even more. Development of the content of a MF constitutes a spectacular phenomenon, a real big bang (Levinton, 1992) of micro molecular organic compounds. Fujita (2007) enumerated over three billion (3.344.714.436) isomers to MF $C_{27}H_{56}$, the alkane matching to cholesterol. MF C_{59} produces about 2.66 Avogadro's number of entities. One wonders if any other science could equalize chemistry by possesing such a concentrated symbolization. Fig. 1 illustrate this phenomenon by a much lower MF, $C_8H_{10}O_4$.

On the other hand, although isomers of the same MF are not interchangeable by the known chemical rules, we can imagine that they are all equivalent, interconvertible and reducible to one of them, and finally to their MF, but never to zero, in the virtue of laws of matter conservation. This constitutes an example of reversible volatility or a reversibility of the big bang of micro molecular organic compounds, and it applies to all multitudes (Fig. .2).

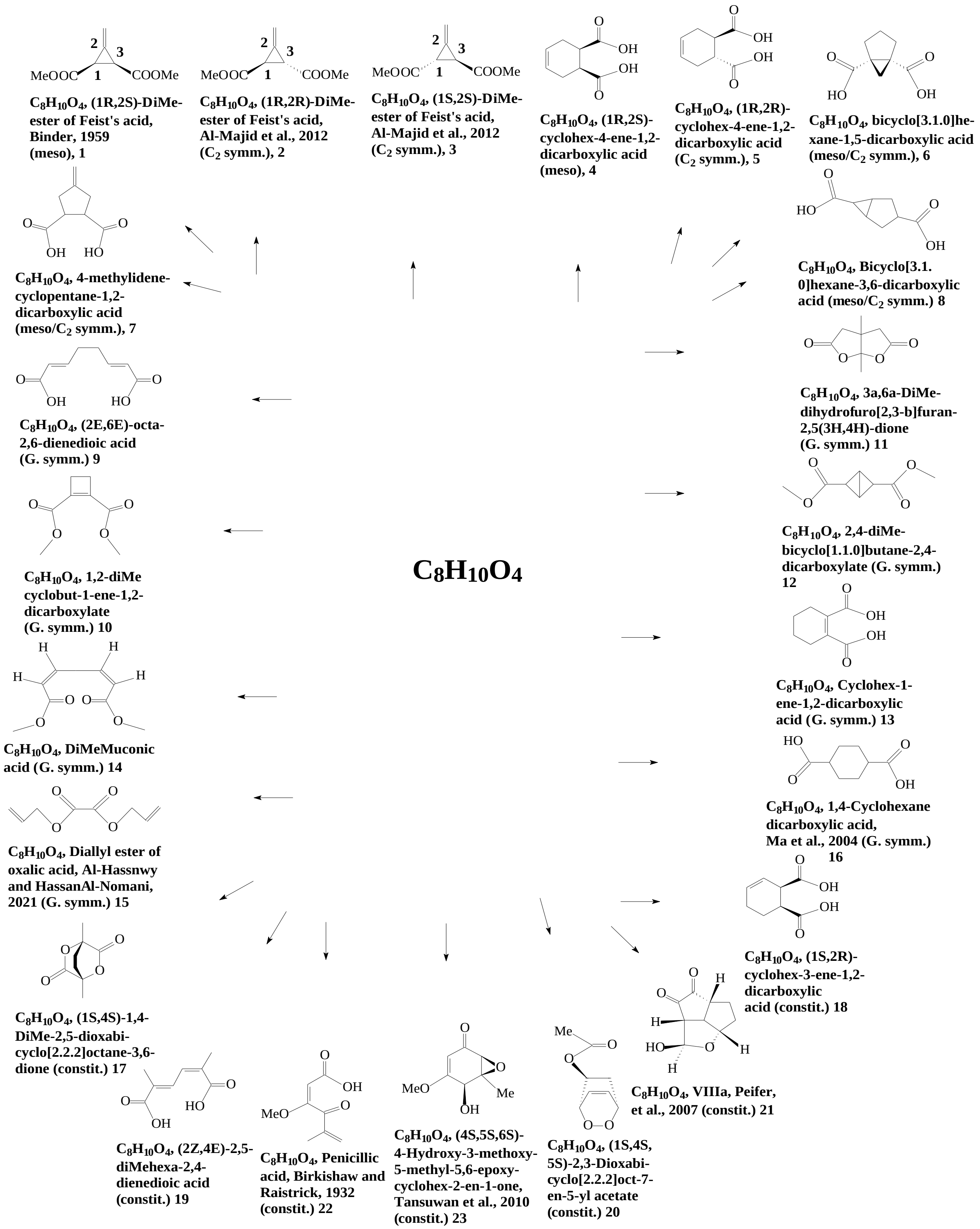
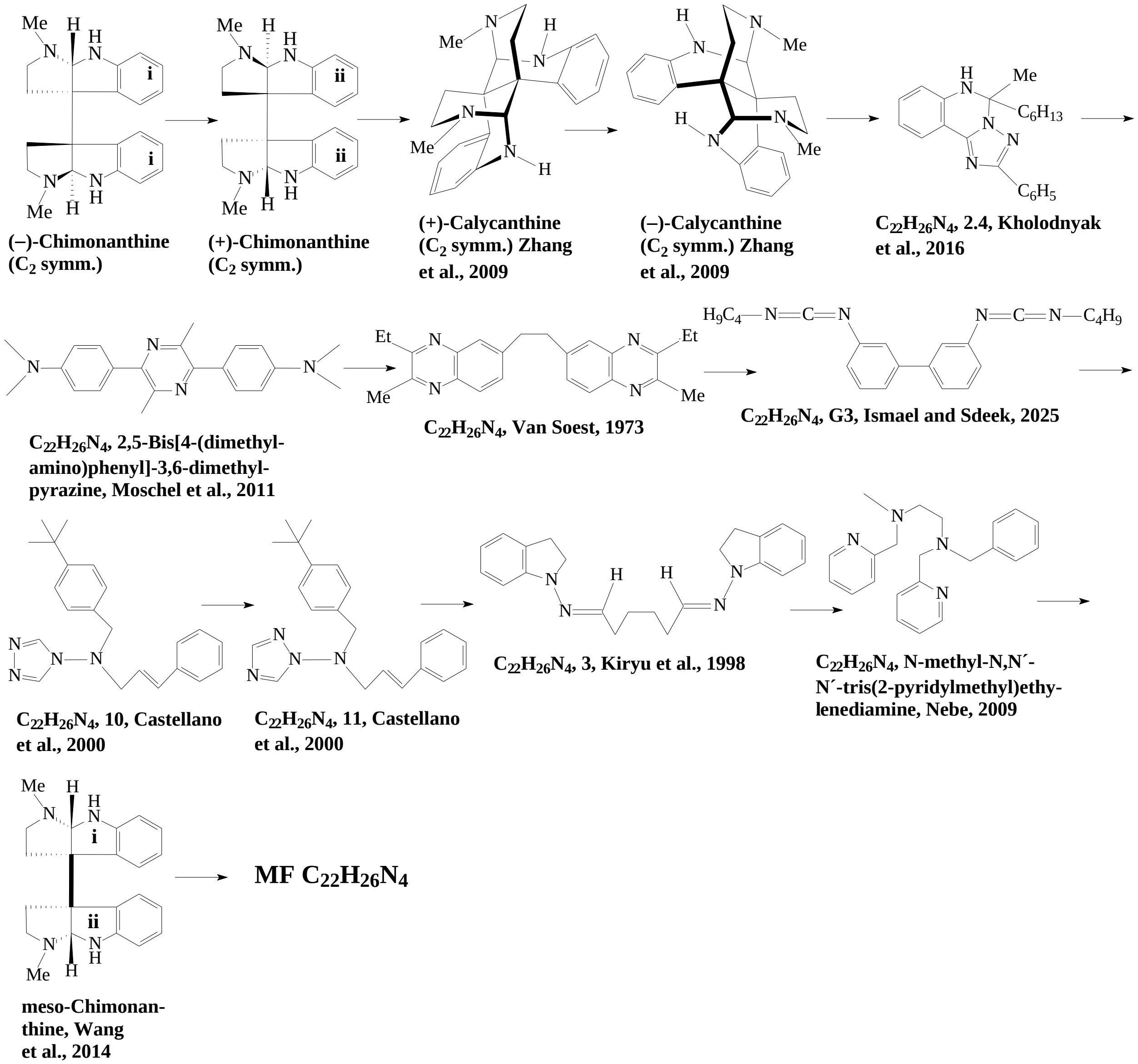


Figure 1. Big bang exemplification of micro molecular organic compounds with $C_8H_{10}O_4$.



(–)-Chimonanthine (C_2 symm.)

(+)-Chimonanthine (C_2 symm.)

(+)-Calycanthine (C_2 symm.) Zhang et al., 2009

(–)-Calycanthine (C_2 symm.) Zhang et al., 2009

$C_{22}H_{26}N_4$, 2.4, Kholodnyak et al., 2016

$C_{22}H_{26}N_4$, 2,5-Bis[4-(dimethyl-amino)phenyl]-3,6-dimethyl-pyrazine, Moschel et al., 2011

$C_{22}H_{26}N_4$, Van Soest, 1973

$C_{22}H_{26}N_4$, G3, Ismael and Sdeek, 2025

$C_{22}H_{26}N_4$, 10, Castellano et al., 2000

$C_{22}H_{26}N_4$, 11, Castellano et al., 2000

$C_{22}H_{26}N_4$, 3, Kiryu et al., 1998

$C_{22}H_{26}N_4$, N-methyl-N,N´-N´-tris(2-pyridylmethyl)ethylenediamine, Nebe, 2009

meso-Chimonanthine, Wang et al., 2014

Figure .2. Reversible volatility by MF $C_{22}H_{26}N_4$, in support of big bang exemplification of micro molecular organic compounds.

2. Compounds of homologous (progressive) series

Compounds of homologous series, or compounds with functional groups (Reusch, 2011), constitute an important chapter of organic chemistry, and their systematization is due especialy to analytical reactions and to methods for molecular weight determination (Avogadro, 1811; Cannizzaro, 1858). An interesting characteristic of these series is the fact that their first term is relatively different of the next terms. It is as if they show some inertia to start to develop their series.

2.1. C_nH_{2n+2}, ALKANES

Scholars with double qualification, chemistry and mathematics, approached the enumeration of alkanes as a function of MFs (Polya, 1937; Robinson et al., 1976; Fujita, 2007; Fujita, 2016). There is a significant difference between the results of Polya and Fujita since the former omits optical isomers, and other tridimensional aspects.

In the increasing series of alkanes, C_1-C_7 are archaic, however, C_7H_{16} is the first term able to show itself as two pairs of enantiomers (Robinson et al., 1976) (Fig. 3).

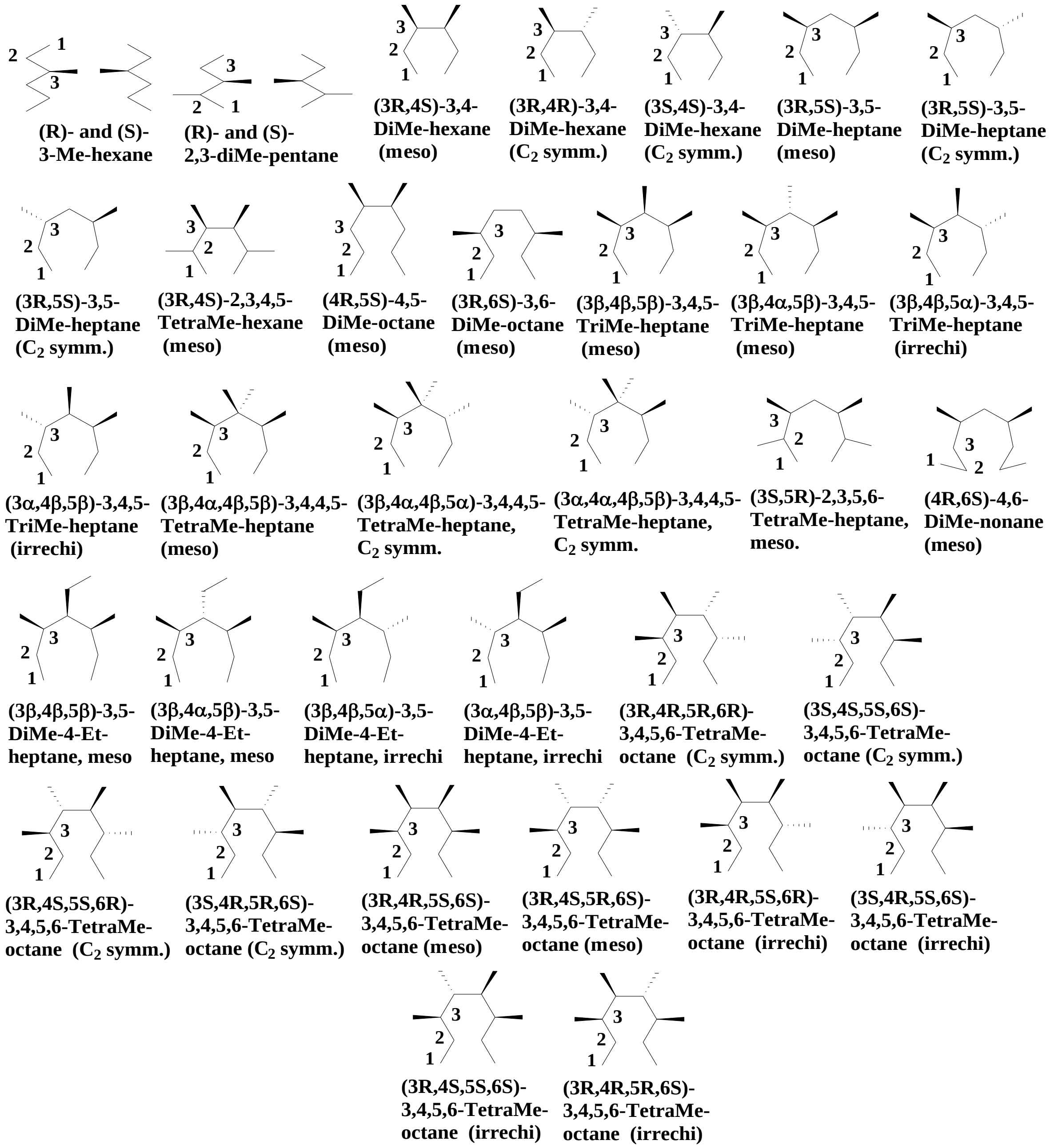
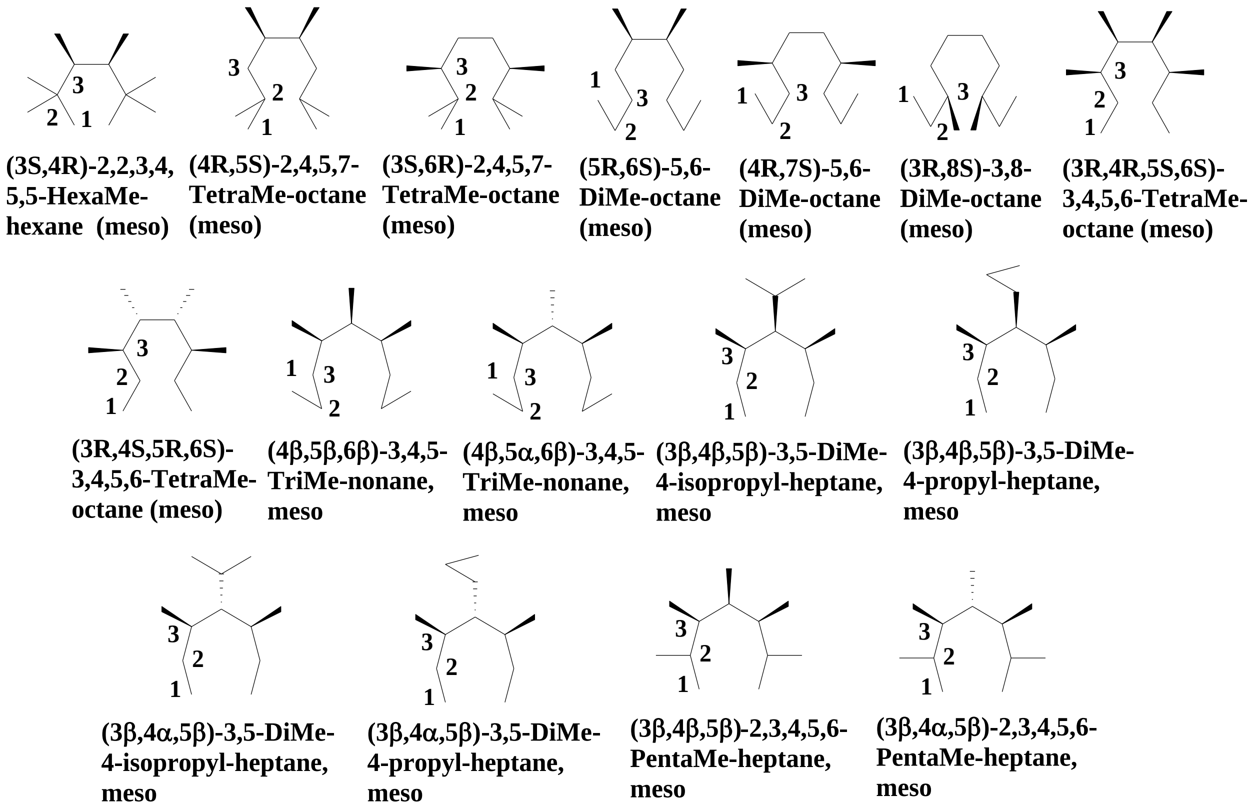


Figure 3. Chiral, *meso*, *C₂ symm*. and *irrechi* alkanes.

Hence, C_7H_{16} presents only one type (mold) of nine isomers, all *constit*., that can be achiral (5) or chiral (4) (Fujita, 2007, 2016). MF C_8H_{18} presents one *meso*, two enantiomeric *C_2 symm*. and 16 *constit.* isomers. MF C_9H_{20} has the same, but 35 *constit.* isomers. MF $C_{10}H_{22}$ (88 isomers) has three *meso* isomers, two as diMe-octane and one as tetraMe-hexane, and every *meso* of these has two *C_2 symm*. Moreover, $C_{10}H_{22}$ has two *meso* isomers as triMe-heptane, two *irrechi* with the same skeleton, but no *C_2 symm*. The latter isomerism is similar to pentitols (Fischer and Stahel, 1891; Fischer, 1893) and trihydroxyglutaric acid (Fischer and Bromberg, 1896; Wheeler and Tollens 1889; Fujita, 2016).

An interesting chapter of chemistry appeared in connection with detection and measuring of infinitesimal values of optical activity. Fischer's techniques consisting in ends equalization reactions has stressed his unmovable belief in the unity of structure and physical-chemical properties. When Kiliani studied L-arabinitol, he concluded this compound is devoid of optical activity, since he measured zero value (in fact a very low value) for this parameter (Kiliani, 1887). But Fischer, having in mind the structure of L-arabinitol, insisted to find out a defined value of optical activity, and he succeeded by adding an optical activity enhancer, borax (Fischer and Stahel, 1891). However, in case of xylitol they found zero value both in the absence and presence of borax. A similar problem regarded the measuring of small optical activity of alkanes. By mixing an alkane, with a relatively small value of optical activity, with a nematic liquid crystal, a cholesteric mesophase with measurable optical rotation is formed (Robinson et al., 1976).

MF $C_{11}H_{24}$ (203 isomers) has two *meso* and two *irrechi* isomers (no *C_2 symm*.) as di-Me-Et-heptane, and *meso* and *C_2 symm*. as tetraMe-heptane (no *irrechi*). MF $C_{12}H_{26}$ (a total of 509 isomers), as well as all higher alkanes, demonstrate the existence, real or envisaged, of all four fundamental moldings. The latter MF has 16 *meso* isomers (Fig. 4), eight homo-



(3S,4R)-2,2,3,4,5,5-HexaMe-hexane (meso); **(4R,5S)-2,4,5,7-TetraMe-octane (meso)**; **(3S,6R)-2,4,5,7-TetraMe-octane (meso)**; **(5R,6S)-5,6-DiMe-octane (meso)**; **(4R,7S)-5,6-DiMe-octane (meso)**; **(3R,8S)-3,8-DiMe-octane (meso)**; **(3R,4R,5S,6S)-3,4,5,6-TetraMe-octane (meso)**

(3R,4S,5R,6S)-3,4,5,6-TetraMe-octane (meso); **(4β,5β,6β)-3,4,5-TriMe-nonane, meso**; **(4β,5α,6β)-3,4,5-TriMe-nonane, meso**; **(3β,4β,5β)-3,5-DiMe-4-isopropyl-heptane, meso**; **(3β,4β,5β)-3,5-DiMe-4-propyl-heptane, meso**

(3β,4α,5β)-3,5-DiMe-4-isopropyl-heptane, meso; **(3β,4α,5β)-3,5-DiMe-4-propyl-heptane, meso**; **(3β,4β,5β)-2,3,4,5,6-PentaMe-heptane, meso**; **(3β,4α,5β)-2,3,4,5,6-PentaMe-heptane, meso**

Figure 4. *meso* Isomers of $C_{12}H_{26}$, indicating C_2 *symm*. and *irrechi*.

and eight heterodimers, hence 16 C_2 *symm*. and four *irrechi*; the rest to 509 are *constit*. *meso* And C_2 *symm*. isomers need at least two asymmetric carbons, while *irrechi*s need at least three. A comparison of the number of isomers as a function of MW, between the values of Polya (1937) and Fujita (2016) indicates a difference increasing with MW, since Fujita is very careful with optical isomers, still commencing with alkanes. In fact, the latter author prefers the term *3D structural* (or stereoisomers (Fujita, 2006; Fujita, 2007)) instead of the favourite bidimensional representation of Polya, *constitutional*. To MF $C_{12}H_{26}$ Polya (1937) presents 355 isomers and Fujita (2016), 509.

Diastereomers have been defined as isomers that are not enantiomers to a given chiral compound. However, since diastereomers are not of a unique type, every type should possess a specific, independent definition. Of the large family of diastereomers, two groups are considered distinct till now: *meso* (Hoffmann, 2003) and C_2 *symm*. (Pfaltz, 1993, 1996). The investigation of a large number of compounds has led us to another distinct group of isomers, *irrechi*. According to our reasoning, the ten linear hexitols can be sorted out in the way described above.

2.2. Establishing of levels of evolution in chemistry

A good illustration of a philosophical law – quantitative accumulations determine qualitative transformations (Spirkin, 1990) – can be seen among the first terms (C_1-C_{12}) of alkanes. Four steps can be noticed: (i) *archaic* (*primitive*) stage; (ii) *chirality*; (iii) *meso* and C_2 *symm*. isomerisms; (iv) *irrechi* (*configurational*) isomerism. Terms that cannot present *meso* isomerism have been called *archaic* (or *primitive*).

If one takes into account optical activity [Toth et al., 1989; McMurry, 2008], the total number of isomers for C_8H_{18} is 20. Of these 20, one is *meso*, two are C_2 *symm*. [Robinson et al., 1976; Fujita, 2016], and the others are *constit*. (chiral or achiral). Similar to other molds of isomers, those called by us *irrechi* are distinctly recognized, by NMR and MS.

The best connection between chemistry and philosophy are compounds based on homologous series: alkanes, alkenes (cycloalkanes), alkynes (alkadienes), alcohols (monohydroxyl alkanes), diols (dihydroxyl alkanes), triols (tridroxyl alkanes), carbonyl compounds (aldehydes and ketones), organic acids (monocarboxylic acids), etc.

Systematization of micro molecular organic compounds facilitates identification of degrees of evolution in chemistry. The appearance of two chiral heptanes [2,3-dimethylpentane (**1**) and 3-methylhexane (**2**)] (Robinson et al., 1976) in the series of alkanes means a qualitative spring since chiral heptanes, contrary to C_1-C_6 alkanes, are able to interact with polarized light and with other chiral compounds in a characteristic manner. The second qualitative spring in alkane series is given by some isomers produced by MF C_8H_{18}. Although presented in an equivocal manner by Robinson et al., (compd **7**), in reality they are (3R,4S)-3,4-DiMe-hexane (*meso*), (3R,4R)-3,4-DiMe-hexane (C_2 *symm*.) and (3S,4S)-

3,4-DiMe-hexane (*C_2 symm.*), since *meso* isomer molecule is formed of two enantiomeric halves, and every *C_2 symm.*, of two identical chiral halves. If compounds (**8-16**) (Robinson et al., 1976) are regarded as a progressive series of alkanes, (**15**) is identical to (**7**), and both are equivalent to tartaric acids as isomerism; (**16**) is the same, but if a hydroxy group is linked on C-4 of the latter, *C_2 symm.* isomers become forbidden for the new construction.

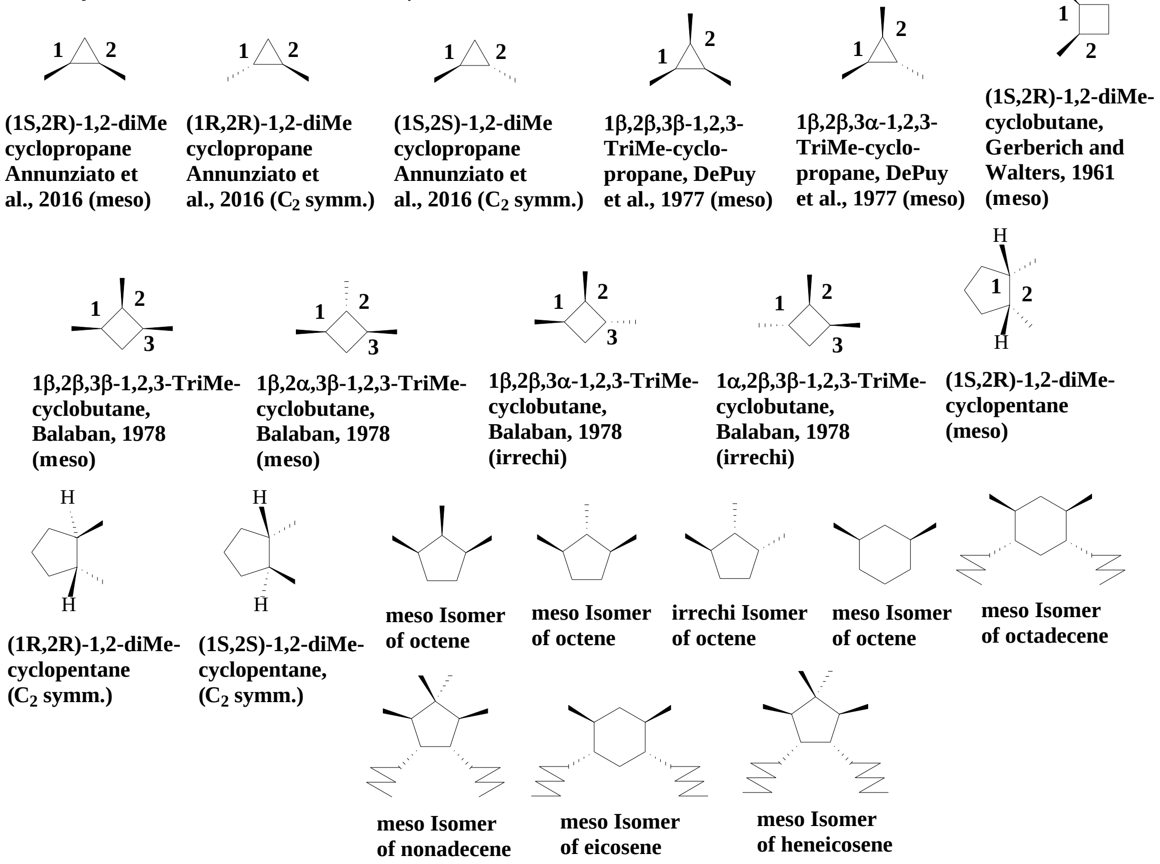
The third qualitative spring in alkane series is shown by some isomers of MF $C_{10}H_{22}$, that offers two isomers *meso*, (3β,4β,5β)-3,4,5-triMe-heptane and (3β,4α,5β)-3,4,5-triMe-heptane, two *irrechi*, (3β,4β,5α)-3,4,5-triMe-heptane and (3α,4β,5β)-3,4,5-triMe-heptane, but no *C_2 symm.*, with this skeleton. The latter isomerism is similar to linear pentitols. A better expression of the four types, that resembles to linear hexitols, is found to tetraMeoctane (Fig.1).

2.3. C_nH_{2n}, ALKENES AND CYCLOALKANES

Isomers coming from MFs of this series express their morphological variety in two ways: in cyclic and in open form (Fig. 3 and 4).

i. Cyclic isomers. C_2-C_4 items are *archaic*. C_5, as cyclopropanes derivatives, and C_6, as cyclobutane derivatives (as 1,2-dimethyl), present a *meso* and two enantiomeric *C_2 symm.* isomers (Fig. 3) (Annunziato et al., 2016; Setser and Rabinovitch, 1962; Gerberich and Walters, 1961). Trimethylcyclopropane can exist only as *meso* isomers (DePuy et al., 1977). C_7 shows, beside *meso* and *C_2 symm.* isomers (all three as cyclopentane derivatives), two *meso* isomers – (1β,2β,3β)-1,2,3-triMecyclobutane and (1β,2α,3β)-1,2,3-triMecyclobutane – and two *irrechi* (all with cyclobutane ring) – (1β,2β,3α)-1,2,3-triMecyclobutane and (1α,2β,3β)-1,2,3-triMecyclobutane – (Balaban, 1978). C_9 presents *meso*, *C_2 symm.* and *irrechi* isomers (as 1,2,3,4-tetraMecyclopentane), and two *meso* and two *irrechi* as 1,2,3-triMecyclohexane; 1,3,5-triMecyclohexane can show only *meso* isomers. C_{10} shows all types of isomers only as 1,2,3,4-tetraMecyclohexane, while 1,2,3,4,5-pentaMecyclopentane has exclusively *meso* isomers, similar to pentahydroxycyclopentane (Collins, 2006). C_{11} behaves similarly to 1,2,3,4-tetraMecyclopentane (as 1,1,2,3,4,5-hexaMecyclopentane and to pentaMecyclohexane, *C_2 symm.* is forbidden). 1,2,3,4,5,6-HexaMecyclohexane mimics inositols, and 1,4-diEt-2,3-diMecyclohexane mimics 1,2,3,4-tetraMecyclohexane. Higher terms submit to the same rules, as indicated by C_{18} - C_{21}.

ii. Isomers with open chain. C_nH_{2n} Isomers with open chain present the whole variability except DoSymm (Fig. .4). In this case C_2-C_9 are *archaic*. C_{10} allows *meso* and *C_2 symm*, and beginning with C_{14} only, *irrechi*. The latter has four asymmetric carbons, hence it presents ten isomers with the same skeleton: two *meso*, four *C_2 symm*, and four *irrechi*.



(1S,2R)-1,2-diMe cyclopropane Annunziato et al., 2016 (meso)

(1R,2R)-1,2-diMe cyclopropane Annunziato et al., 2016 (C_2 symm.)

(1S,2S)-1,2-diMe cyclopropane Annunziato et al., 2016 (C_2 symm.)

1β,2β,3β-1,2,3-TriMe-cyclo-propane, DePuy et al., 1977 (meso)

1β,2β,3α-1,2,3-TriMe-cyclo-propane, DePuy et al., 1977 (meso)

(1S,2R)-1,2-diMe-cyclobutane, Gerberich and Walters, 1961 (meso)

1β,2β,3β-1,2,3-TriMe-cyclobutane, Balaban, 1978 (meso)

1β,2α,3β-1,2,3-TriMe-cyclobutane, Balaban, 1978 (meso)

1β,2β,3α-1,2,3-TriMe-cyclobutane, Balaban, 1978 (irrechi)

1α,2β,3β-1,2,3-TriMe-cyclobutane, Balaban, 1978 (irrechi)

(1S,2R)-1,2-diMe-cyclopentane (meso)

(1R,2R)-1,2-diMe-cyclopentane (C_2 symm.)

(1S,2S)-1,2-diMe-cyclopentane, (C_2 symm.)

meso Isomer of octene

meso Isomer of octene

irrechi Isomer of octene

meso Isomer of octene

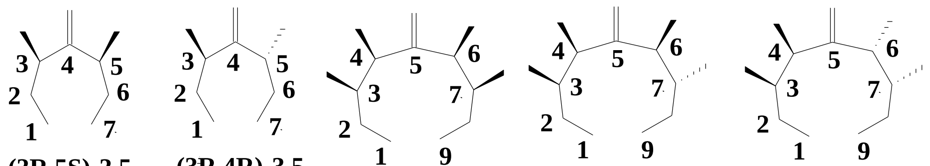
meso Isomer of octadecene

meso Isomer of nonadecene

meso Isomer of eicosene

meso Isomer of heneicosene

Figure 5. Structural variety of cycloalkanes in ring form: *meso*, *C_2 symm.*, *irrechi*.



(3R,5S)-3,5-DiMe-4-methylene-heptane (meso)

(3R,4R)-3,5-DiMe-4-methylene-heptane (C_2 symm.)

(3R,4R,6S,7S)-3,4,6,7-Tetra-methyl-5-methylene-nonane (meso)

(3R,4R,6S,7R)-3,4,6,7-Tetra-methyl-5-methylene-nonane (irrechi)

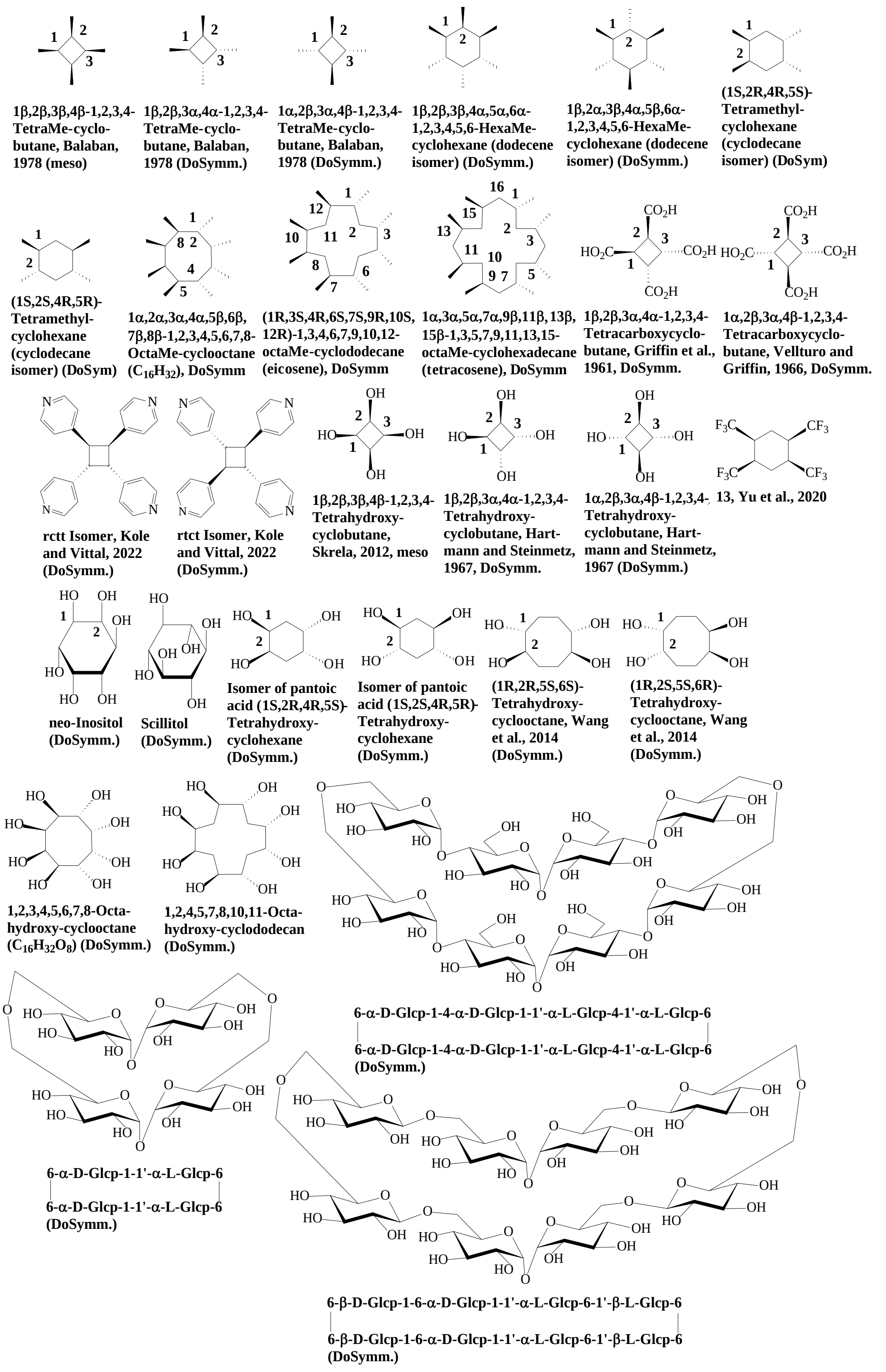
(3R,4R,6R,7R)-3,4,6,7-Tetra-methyl-5-methylene-nonane (C_2 symm.)

Figure 6. Symmetric alkenes as open chain: *meso*, *C_2 symm.*, *irrechi*.

2.4. Double symmetry (DoSymm.)

A rule has been inferred from a paper of Fischer and Hertz (1892) concerning *meso* compounds, i.e. alternative dimerization of the two enantiomeric halves of a *meso* compound leads to two enantiomeric *C_2 symm*. isomers. We have shown that this rule applies to numerous compounds (Iga, 2024). On the other hand, it was found out that some *meso* compounds do not submit to this rule (Fig. 5), since by alternative dimerization of their two enantiomeric halves they lead to an isomer being concomitantly *meso* and *C_2 symm*. We have tentatively called this phenomenon supersymmetry, but we had to admit that this term is a monopoly of supersymmetry described in physical/mathematical language. In this work, we advance a new proposal for this phenomenon, that is *doublesymmetry* (*DoSymm*.).

A *meso* compound, 1β,2β,3β,4β-1,2,3,4-tetraMecyclobutane (Balaban, 1978; Wieland et al., 1996) gives 1β,2β,3α,4α-1,2,3,4-tetraMecyclobutane, a combination that is concomitantly *meso* (it has a mirror plane of symmetry) and *C_2 symm*. (when rotated by 180° around an axis, one arrives at the same structural context). Due to its unique qualities, the latter combination has been called *doublesymmetric* (*DoSymm*.). If the same treatment of dimerization is applied to 1β,2β,3α,4α-1,2,3,4-tetraMecyclobutane, another *DoSymm*. product is obtained, 1α,2β,3α,4β-1,2,3,4-tetraMecyclobutane (Balaban, 1978; Wieland et al., 1996) (Fig. .5), although as a *meso* isomer it is heterodimer. (1β,2β,3β,4α,5α,6α)-1,2,3,4,5,6-HexaMecyclohexane, (1β,2α,3β,4α,5β,6α)-1,2,3,4,5,6-hexaMecyclohexane, (1S,2R,4R,5S)-tetraMecyclohexane (cyclodecane isomer), (1S,2S,4R,5R)-tetraMecyclohexane, as well as isomers of hexadecene, eicosene, tetracosene, etc., could be also *DoSymm*. isomers. (1S,2R,4R,5S)-Tetrahydroxycyclohexane and (1S,2S,4R,5R)-tetrahydroxycyclohexane, as well as their isomer (1S,2R,4S,5R)-tetrahydroxycyclohexane are symmetric derivatives of pantoic acid (Metzler and Metzler, 2003). (1R,2R,5S,6S)-1,2,5,6-Tetrahydroxy-cyclooctane has been synthesized from a dihydroxyepoxide (Wang et al., 2014). C_{16}, C_{20} and C_{24} *DoSymm* involve the hypothesis that they present *meso* isomers with the indicated rings. Instead, 1β,2β,3α,4α-1,2,3,4-tetracarboxy-cyclobutane (Griffin et al., 1961), 1α,2β,3α,4β-1,2,3,4-tetracarboxy-cyclobutane (Vellturo and Griffin, 1966), (1β,2β,3α,4α)-1,2,3,4-tetra(4-pyridyl)-cyclobutane (rctt isomer, a homodimer) and (1β,2α,3β,4α)-1,2,3,4-tetra(4-pyridyl)-cyclobutane (rtct isomer, as heterodimer) (Kole and Vittal, 2022), are proven *DoSymm*. Hydroxy groups of cis-inositol have been alternatively replaced by –OH, –OAc, –OBz, –CO_2H, –CO_2Me, –CO_2Bn, –Me, –F, trifluoromethyl (Yu et al., 2020). Nine inositols (hexahydroxycyclohexanes) are known [Pigman, 1957, Finar, 1964], two are *C_2 symm*., chiral and enantiomeric, and seven devoid of optical activity. Of all the latter, only cis-inositol and muco-inositol can be treated as homodimeric *meso*. Alternative dimerization of the two enantiomeric halves of cis-inositol gives neo-inositol (Iga, 2024). The latter is a special molecule: it has a mirror plane of symmetry containing some atoms, hence it is a heterodimer. On the other hand, it has an axis of symmetry, and when rotated by 180° around this axis, the same structural context is found, that is a feature of *C_2 symm*. compounds. Of this reason neo-inositol (Fig. .5) has to be considered *DoSymm*. When treated as *meso* heterodimer, and its linking support removed, neo-inositol gives another *Dosymm*. combination, i.e. (1β,2β,3α,4α)-1,2,3,4-tetrahydroxy-cyclobutane. allo-Inositol is a homodimer with a mirror plane of symmetry. When its enantiomeric halves are alternatively dimerized, the symmetry is perturbed and two chiral, *C_2 symm*. enantiomers are produced, D-(+)-chiro- and L-(−)-chiro-inositol. allo Inositol is the only inositol isomer with a typical behavior of *meso* compound, giving two enantiomeric *C_2 symm*. products, by the alternative dimerization of its halves. Alternative dimerization of the two enantiomeric halves of muco-inositol, gives another *Dosymm* combination, scillitol. Hartmann and Steinmetz (1967) have synthesized two isomers of tetrahydroxy-cyclobutane, and Skrela (2012) prepared 1β,2β,3β,4β-tetrahydroxy-cyclobutane. Based on these works we have used three such derivatives – 1β,2β,3β,4β-1,2,3,4-tetrahydroxycyclobutane, 1β,2β,3α,4α-1,2,3,4-tetrahydroxy-cyclobutane, 1α,2β,3α,4β-1,2,3,4-tetrahydroxycyclobutane, in our theoretical considerations. Three DoSymm. oligosaccharides have been mentioned (Fig. .5), that are isomer to three *irrechi* cyclodextrines. Cyclodextrines are cyclic oligosaccharides formed of six, seven and eight glucose moieties (Koizumi et al., 1991; Shirashi et al., 1993). Oligosaccharides indicated in this work contain some non-glycosidic (ether) bonds. However they are natural bonds (Zhao and Ma, 2016). For *Dosymm*. structure, see also MF C_8H_8.



1β,2β,3β,4β-1,2,3,4-TetraMe-cyclobutane, Balaban, 1978 (meso)

1β,2β,3α,4α-1,2,3,4-TetraMe-cyclobutane, Balaban, 1978 (DoSymm.)

1α,2β,3α,4β-1,2,3,4-TetraMe-cyclobutane, Balaban, 1978 (DoSymm.)

1β,2β,3β,4α,5α,6α-1,2,3,4,5,6-HexaMe-cyclohexane (dodecene isomer) (DoSymm.)

1β,2α,3β,4α,5β,6α-1,2,3,4,5,6-HexaMe-cyclohexane (dodecene isomer) (DoSymm.)

(1S,2R,4R,5S)-Tetramethyl-cyclohexane (cyclodecane isomer) (DoSym)

(1S,2S,4R,5R)-Tetramethyl-cyclohexane (cyclodecane isomer) (DoSym)

1α,2α,3α,4α,5β,6β,7β,8β-1,2,3,4,5,6,7,8-OctaMe-cyclooctane ($C_{16}H_{32}$), DoSymm

(1R,3S,4R,6S,7S,9R,10S,12R)-1,3,4,6,7,9,10,12-octaMe-cyclododecane (eicosene), DoSymm

1α,3α,5α,7α,9β,11β,13β,15β-1,3,5,7,9,11,13,15-octaMe-cyclohexadecane (tetracosene), DoSymm

1β,2β,3α,4α-1,2,3,4-Tetracarboxycyclobutane, Griffin et al., 1961, DoSymm.

1α,2β,3α,4β-1,2,3,4-Tetracarboxycyclobutane, Vellturo and Griffin, 1966, DoSymm.

rctt Isomer, Kole and Vittal, 2022 (DoSymm.)

rtct Isomer, Kole and Vittal, 2022 (DoSymm.)

1β,2β,3β,4β-1,2,3,4-Tetrahydroxy-cyclobutane, Skrela, 2012, meso

1β,2β,3α,4α-1,2,3,4-Tetrahydroxy-cyclobutane, Hartmann and Steinmetz, 1967, DoSymm.

1α,2β,3α,4β-1,2,3,4-Tetrahydroxy-cyclobutane, Hartmann and Steinmetz, 1967 (DoSymm.)

13, Yu et al., 2020

neo-Inositol (DoSymm.)

Scillitol (DoSymm.)

Isomer of pantoic acid (1S,2R,4R,5S)-Tetrahydroxy-cyclohexane (DoSymm.)

Isomer of pantoic acid (1S,2S,4R,5R)-Tetrahydroxy-cyclohexane (DoSymm.)

(1R,2R,5S,6S)-Tetrahydroxy-cyclooctane, Wang et al., 2014 (DoSymm.)

(1R,2S,5S,6R)-Tetrahydroxy-cyclooctane, Wang et al., 2014 (DoSymm.)

1,2,3,4,5,6,7,8-Octahydroxy-cyclooctane ($C_{16}H_{32}O_8$) (DoSymm.)

1,2,4,5,7,8,10,11-Octahydroxy-cyclododecan (DoSymm.)

6-α-D-Glcp-1-4-α-D-Glcp-1-1'-α-L-Glcp-4-1'-α-L-Glcp-6
6-α-D-Glcp-1-4-α-D-Glcp-1-1'-α-L-Glcp-4-1'-α-L-Glcp-6
(DoSymm.)

6-α-D-Glcp-1-1'-α-L-Glcp-6
6-α-D-Glcp-1-1'-α-L-Glcp-6
(DoSymm.)

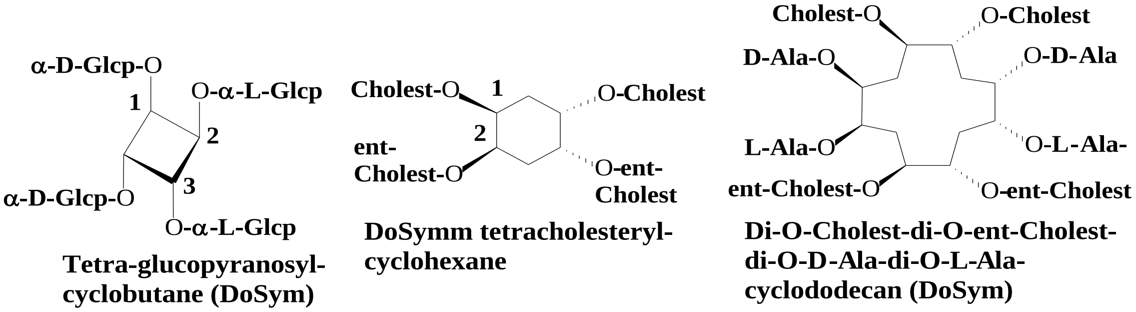
6-β-D-Glcp-1-6-α-D-Glcp-1-1'-α-L-Glcp-6-1'-β-L-Glcp-6
6-β-D-Glcp-1-6-α-D-Glcp-1-1'-α-L-Glcp-6-1'-β-L-Glcp-6
(DoSymm.)

Figure 7. Real and imaginary DoSymm. compounds.

2.5. *ent*-Phenomenon and Doublesymmetrical Templates Generating Chemical Entities

Some *DoSymm*. templates have been elaborated (Fig. 8) based on *DoSymm*. structures. By these templates, the number of *DoSymm*. compounds is limited only by the number of known pairs of enantiomers.

ent- Is another term for enantiomerism, and it has been discovered by Pasteur (1848) at the level of crystals. When van't Hoff (1874) invented chemical models for micro molecular organic molecules, he became aware that the *ent*-counterpart of (+)-tartaric acid, that had been discovered by Scheele (1770), was (–)-tartaric acid, without knowing which acid to which model should be associated. An important contribution to *ent*-phenomenon was brought by Kiliani (1886) and Fischer (1891) when they discovered that the arabinose prepared by chain shortening of glucose was the *ent*-isomer of arabinose prepared from sugar beet and other vegetable materials.



Tetra-glucopyranosyl-cyclobutane (DoSym)

DoSymm tetracholesteryl-cyclohexane

Di-O-Cholest-di-O-ent-Cholest-di-O-D-Ala-di-O-L-Ala-cyclododecan (DoSym)

Figure 8. Supersymmetric templates for generation of supersymmetric compounds.

ent-Compounds are usually synthetic products which are enantiomers of natural ones. *ent*-Glucose (L-glucose) has been synthesized by Fischer (1890) by an isomerization reaction, or from suitable precursors, by two independent paths (Gal et al., 1979; Johnson et al., 1992). It has been included e.g. in a cerebroside, 1-O-β-L-Glucopyranosyl-N-palmitoyl-DL-sphingosine, by chemical means. The two enantiomeric 3-deoxyarabinitols have been prepared also chemically (Boydell et al., 2003). Due to the development of *ent*-amino acids (D-amino acids) a series of *ent*-derivatives have been synthesized: *ent*-carboline (Deveau et al., 2008), *ent*-Win 64821 (Overman and Paone, 2001), *ent*-chaetocin (Iwasa et al., 2010). These combinations facilitate the synthesis of *meso* isomers: *meso*-carboline, *meso*-Win 64821, *meso*-chaetocin, etc.

The general principle, that symmetrical joining of two chiral molecules might lead to a C_2 *symm*. chemical system, applies also to lipids. It was shown that when cholesterol, a chiral molecule with eight asymmetric C atoms, is put in the presence of concentrated sulfuric acid, a dimer, bicholestadiene, is formed, in which cholesterol kept seven asymmetric C atoms (Rapoport and Raderecht, 1972; Niiya et al., 1980). Bicholestadiene is a veritable C_2 *symm*, compound. A dimeric C_2 *symm*. steroid based on a flexible diyne spacer have been synthesized (Valdez-Garcia et al., 2018). On the other hand, *ent*-cholesterol has been prepared (Crowder et al., 2001). It might be supposed that if racemic cholesterol is mixed with sulfuric acid, three types of bicholestadiene are formed, one *meso* and two C_2 *symm*.; and the same applies to cholesterol diyne dimer. Other *ent*-steroids – *ent*-lithocholic, *ent*-chenodeoxycholic, *ent*-deoxycholic acid (Katona et al., 2009; Kristiana et al., 2012) – can serve to different purposes.

Cardiolipin is [bis(1,2-diacyl-*sn*-3-glycero-phosphoryl)-1,3-glycerol or bis(*sn*-3-phosphatidyl)-1,3-glycerol] (Schlame et al., 2005; Schlame, 2008; Kim et al., 2011). (In fact, the display of cardiolipin in *sn*-nomenclature is paradoxical: no matter how is written glycerol in the middle, it is both *sn*-1-and *sn*-3-glycerol-phosphate). By analogy with other compounds, cardiolipin could be named pseudoasymmetric (Smith and March, 2007) or "*pseudo*"-C_2-symmetric (Boydell et al., 2003; Linclau et al., 2003; Gao et al., 2011). Our discussion will concern only cardiolipin formed of one or two types of fatty acids uniformly distributed, or better the product obtained by removing of fatty acids, i. e., [bis(*sn*-3-glycerol-phosphoryl)-1,3-glycerol]. It seems a definitive established rule that phospholipids of higher organisms are based on *sn*-3-glycerol phosphate. However, a group of archaebacteria contains *sn*-1-glycerol phosphate (*ent*-*sn*-3-glycerol phosphate) as a core structure for their phospholipids and glycoglycerolipids (Koga et al., 1993; Koga and Morii, 2005). Hence, one can imagine and synthesize a mixed cardiolipin and polyglycero-phosphate ester containing *sn*-3- and *sn*-1-glycerol phosphate, i. e., [(sn-3-glycerol-phosphoryl)-1-glycerol-3-(sn-1-glycerol-phosphate)]. The latter compounds would have a *meso* structure similar to xylitol (Fischer and Stahel, 1891). Synthesis of *ent*-sphingosine and *ent*-psychosine (Parameswar et al., 2010) opened interesting perspectives in sphingolipids. Synthesis of *ent*-adenosine made possible the production of *meso* derivatives of coenzyme A, ostrerine A (Ouyang, 2006) and nucleoside disulfide [9-(5′-deoxy-5′-thio-β-d-xylofuranosyl)adenine disulfide] (Peng et al., 2010). All these pairs of *ent*-compounds can serve to produce complex *DoSymm*. entities.

2.6. Chemistry follows the law of unity and strugle of contrary sides

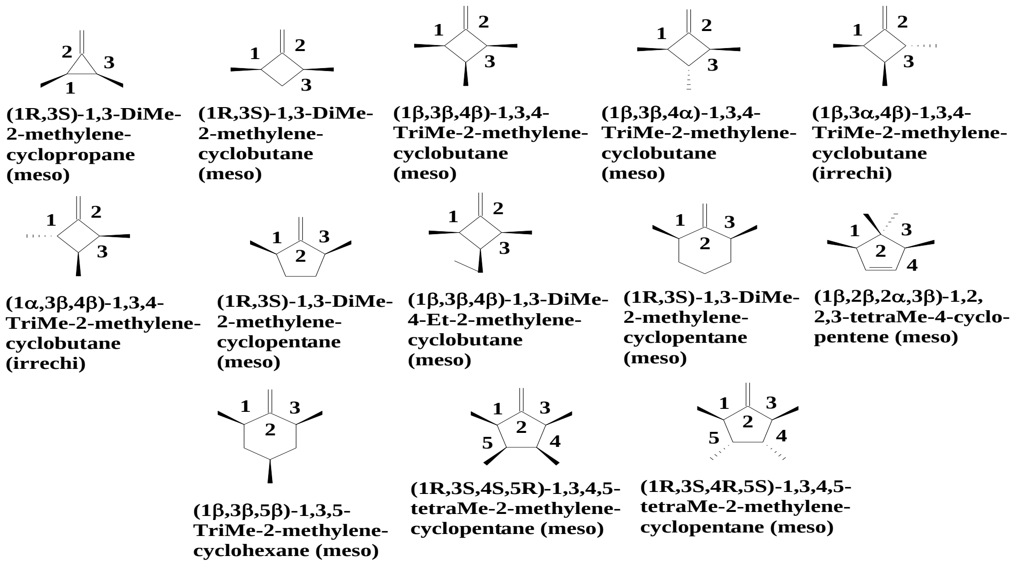
1β,2β,3β,4β-1,2,3,4-tetraMecyclobutane (Balaban, 1978; Wieland et al., 1996) has eight mirror planes of symmetry, identical four by four. Four of them cut only bonds, and they make consider cyclobutane derivative as homodimer. They should probably have a higher priority than the other four planes cutting atoms and of this reason considering the cyclobutane derivative as heterodimer. However, we have comparable proofs for both homodimer and heterodimer. The same is with 1β,2β,3β,4β-1,2,3,4-tetra-carboxy-cyclobutane (Luo et al., 2004), (1α,2α,3α,4α)-tetrahydroxy-1β,2β,3β,4β-tetraMe-cyclobutane (Kahle, 1987), etc. Other *meso* compounds are indicated exclusively as heterodimers by their mirror plane(s) of symmetry – (1S,2R)-1,2-dimethyl cyclopropane (Setser and Rabinovitch, 1962), (2R,3S)-2,3-diMe-oxirane (Durig et al., 1983), (1α,2α,3β)-triEt-carboxylate-cyclopropane, 3aa (Kozhushkov et al., 2003), (1β,2α,3β)-1,2,3-triEt-carboxylate-(1α,2β,3α)-1,2,3-triCN-cyclopropane (Papa, 1968), norpinic acid (Kerr, 1929), rtct isomer (Kole and Vittal, 2022), etc.

There are compounds characterized by both, a geometrical and a mirror plane of symmetry: (1β,3β)-1,3-dicarboxy-cyclobutane (Allinger and Tushaus, 1965), (1β,3β)-1,3-diMe-cyclobutane-dicarboxylate (Allinger and Tushaus, 1965), (1β,3β)-1,3-diMe-cyclobutane (Allinger and Tushaus, 1965), (1β,4β)-1,4-dicarboxy-cyclohexane (Kricheldorf and Schwartz, 1987), (1β,5β)-1,5-dimethyl-cyclooctane, etc. Mirror plane of symmetry indicate a *meso* combination, while the geometrical plane of symmetry indicates its non-*meso* nature.

As situated in the core of cardiolipin, glycerol-1,3-bisphosphate respects both definitions of *sn*-nomenclature, as sn-1 and sn-3 (Schlame et al., 2005; Schlame, 2008; Kim et al., 2011).

2.7. C_nH_{2n-2} ALKYNES (ALKADIENES)

Alkynes (alkadienes) isomers can be presented in cyclic (ring) form (Fig. 9), or in open form (Fig. 10).



(1R,3S)-1,3-DiMe-2-methylene-cyclopropane (meso)

(1R,3S)-1,3-DiMe-2-methylene-cyclobutane (meso)

(1β,3β,4β)-1,3,4-TriMe-2-methylene-cyclobutane (meso)

(1β,3β,4α)-1,3,4-TriMe-2-methylene-cyclobutane (meso)

(1β,3α,4β)-1,3,4-TriMe-2-methylene-cyclobutane (irrechi)

(1α,3β,4β)-1,3,4-TriMe-2-methylene-cyclobutane (irrechi)

(1R,3S)-1,3-DiMe-2-methylene-cyclopentane (meso)

(1β,3β,4β)-1,3-DiMe-4-Et-2-methylene-cyclobutane (meso)

(1R,3S)-1,3-DiMe-2-methylene-cyclopentane (meso)

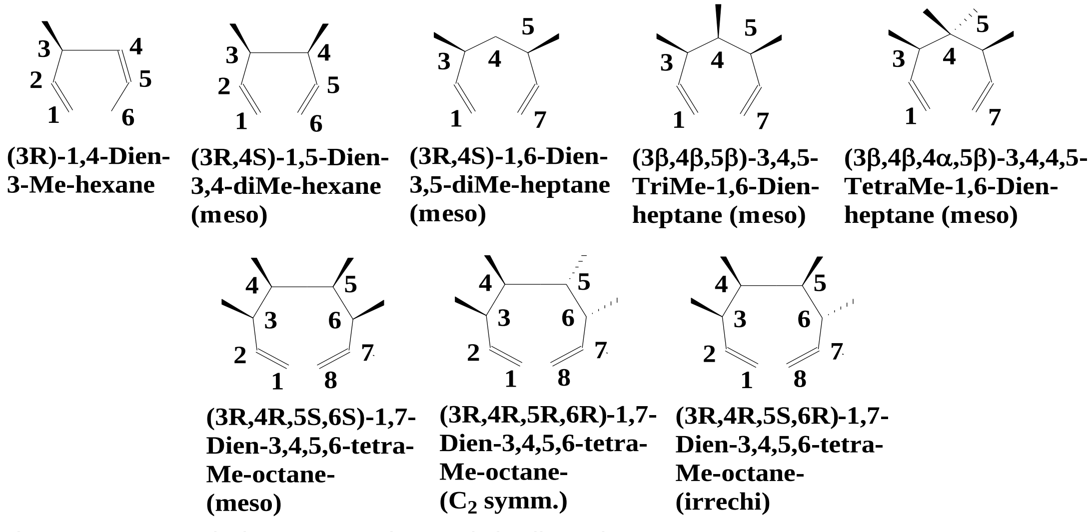
(1β,2β,2α,3β)-1,2,2,3-tetraMe-4-cyclopentene (meso)

(1β,3β,5β)-1,3,5-TriMe-2-methylene-cyclohexane (meso)

(1R,3S,4S,5R)-1,3,4,5-tetraMe-2-methylene-cyclopentane (meso)

(1R,3S,4R,5S)-1,3,4,5-tetraMe-2-methylene-cyclopentane (meso)

Figure 9. Cyclic (ring) C_nH_{2n-2} isomers of alkynes (alkadienes).



(3R)-1,4-Dien-3-Me-hexane

(3R,4S)-1,5-Dien-3,4-diMe-hexane (meso)

(3R,4S)-1,6-Dien-3,5-diMe-heptane (meso)

(3β,4β,5β)-3,4,5-TriMe-1,6-Dien-heptane (meso)

(3β,4β,4α,5β)-3,4,4,5-TetraMe-1,6-Dien-heptane (meso)

(3R,4R,5S,6S)-1,7-Dien-3,4,5,6-tetra-Me-octane-(meso)

(3R,4R,5R,6R)-1,7-Dien-3,4,5,6-tetra-Me-octane-(C_2 symm.)

(3R,4R,5S,6R)-1,7-Dien-3,4,5,6-tetra-Me-octane-(irrechi)

Figure 10. Open chain C_nH_{2n-2}, alkynes (alkadienes).

Ring form of alkynes (alkadienes). C_2-C_5 terms are archaic. C_6H_{10}, as diMe-methylene-cyclopropane and C_7H_{12}, as 1,3-diMe-2-methylene-cyclobutane or 1,4-diMe-2-cyclopentene shows one isomer *meso* and two enantiomeric *C_2 symm*. (Fig. 7). C_8H_{14}, as triMe-methylene-cyclobutane or 1,2,3-triMe-4-cyclopentene show *meso* and *irrechi* isomers (*C_2 symm*. is impossible), while 1,3-diMe-2-methylene-cyclopentane presents one isomer *meso* and two enantiomeric *C_2*

symm. For C_9H_{16}, *irrechi* alternative is possible only as 1,3-diMe-4-Et-2-methylene-cyclobutane, while 1,2,2,3-tetraMe-4-cyclopentene and 1,5-diMe-3-mehylene-cyclohexane allow one isomer *meso* and two enantiomeric *C_2 symm*. $C_{10}H_{18}$ Permits two *irrechi* isomers as 1,3,5-triMe-2-mehylene-cyclohexane and two *meso* tetraMe-2-methylene-cyclopentane. Every latter compound might generate four *C_2 symm*. and four *irrechi* isomers.

Open form of alkynes (alkadienes). In this case, C_2-C_7 terms are archaic. However, one isomer of C_7H_{12} is optically active (Fig. .8). C_8 and C_9 have one isomer *meso* and two enantiomeric *C_2 symm*. The *irrechi* isomers appear at C_{10}, and *meso* and *C_2 symm*. at this MF appear as 3,4-diEt-1,5-dien-hexane. The symmetric isomers of MF $C_{11}H_{20}$ mimic C_9 isomers. Some isomers of MF $C_{12}H_{22}$ might possess four chiral carbons per molecule, hence they follow the archetype of linear hexitols.

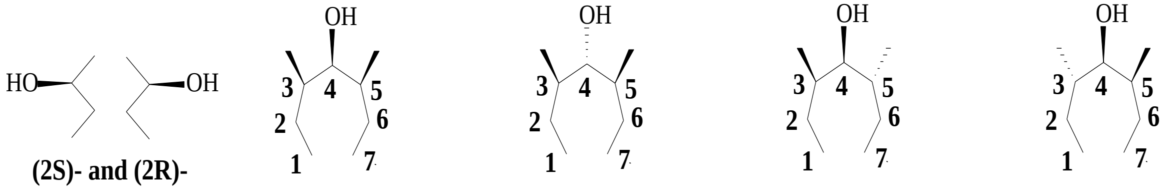
2.8. $C_nH_{2n+1}OH$, Monohydroxylic alcohols

C_1-C_8 Monohydroxylic alcohols are archaic. However, MF C_4H_9OH has chiral isomers (Fig. .9). C_9 Has *meso* as (3β,4β,5β)-3,5-DiMe-4-hydroxy-heptane and (3β,4α,5β)-3,5-DiMe-4-hydroxy-heptane) and *irrechi* as (3β,4β,5α)-3,5-DiMe-4-hydroxy-heptane and (3α,4β,5β)-3,5-DiMe-4-hydroxy-heptane isomers. Monohydroxylic alcohols have no *C_2 symm.* isomers, hence there is a structural limitation for this type of compounds at monohydroxylic alcohols.

2.9. $C_nH_{2n}(OH)_2$, Dihydroxylic alcohols

In the molecule of dihydroxylic alcohols (Fig. 10), the two functional groups can exist on chains of varying length. On the other hand, they can be vicinal or isolated. In vicinal state, they are easily recognized due especially to Malaprade reaction, i.e. susceptibility to periodic acid or lead tetraacetate (Malaprade, 1928a, b).

C_2-C_3 Dihydroxylic alcohols are *archaic*. C_4 Has *meso* ((2R,3S)-butane diol) and *C_2 symm.* ((2R,3R)-butane diol; (2S,3S)-butane diol) isomers. The same is with C_5-C_7, every chain length presents a variety of symmetric isomers. C_8, Dihydroxy-octane has *meso* ((2R,3R,4S,5S)-2,5-dihydroxy-3,4-dimethyl-hexane), *C_2 symm.* ((2R,3R,4R,5R)-2,5-dihydroxy-3,4-dimethyl-hexane) and *irrechi* isomers ((2R,3R,4S,5R)-2,5-dihydroxy-3,4-dimethyl-hexane). Still, C_4 allows the existence of optically active isomers. C_8, as 2,5-dihydroxy-3,4-dimethyl hexane has four chiral carbons hence it might have an archetype similar to linear hexitols.



(2S)- and (2R)-2-hydroxybutane

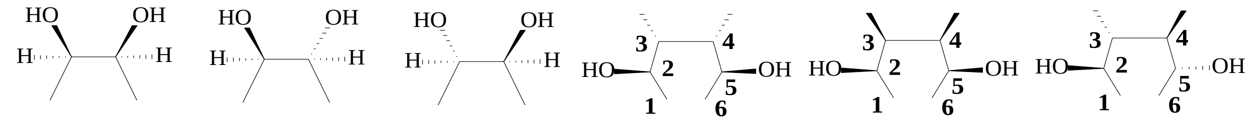
(3β,4β,5β)-3,5-DiMe-4-hydroxyheptane (meso)

(3β,4α,5β)-3,5-DiMe-4-hydroxyheptane (meso)

(3β,4β,5α)-3,5-DiMe-4-hydroxyheptane (irrechi)

(3α,4β,5β)-3,5-DiMe-4-hydroxyheptane (irrechi)

Figure 11. Monohydroxy alcohols.



(2R,3S)-Butane diol (meso)

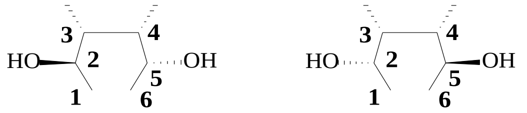
(2R,3R)-Butane diol (C_2 symm.)

(2S,3S)-Butane diol (C_2 symm.)

(2R,3R,4S,5S)-2,5-Dihydroxy-3,4-dimethyl-hexane (meso)

(2R,3S,4R,5S)-2,5-Dihydroxy-3,4-dimethyl-hexane (meso)

(2R,3R,4R,5R)-2,5-Dihydroxy-3,4-dimethyl-hexane (C_2 symm.)



(2R,3R,4S,5R)-2,5-Dihydroxy-3,4-dimethyl-hexane (irrechi)

(2S,3R,4S,5S)-2,5-Dihydroxy-3,4-dimethyl-hexane (irrechi)

Figure 12. Isomers of dihydroxylic alcohols.

2.10. $C_nH_{2n–1}(OH)_3$, Trihydroxy alcohols

C_3-C_4 Trihydroxylic alcohols are archaic. However, C_3 (1,2,3-trihydroxypropane, glycerol) has different ends, consequently its random oxidation gives two chiral enantiomers, D-glyceraldehyde and L-glyceraldehyde, a property found by Fischer and Hertz (1892) at galactitol. Still, glycerol is not *meso*, it can be considered a pro-*meso*, an ancestor of *meso* isomers. In fact, the symmetry of glycerol is considered ambiguous (Hirschmann, 1960); we consider it *archaic.* $C_5H_9(OH)_3$ Gives *meso* as (2β,3β,4β)-2,3,4-trihydroxy-pentane and (2β,3α,4β)-2,3,4-trihydroxy-pentane and *irrechi* as (2β,3β,4α)-2,3,4-trihydroxy-pentane and (2α,3β,4β)-2,3,4-trihydroxy-pentane) (Fig. 11) isomers. Isomers *C₂ symm.* are forbidden for this class of compounds.

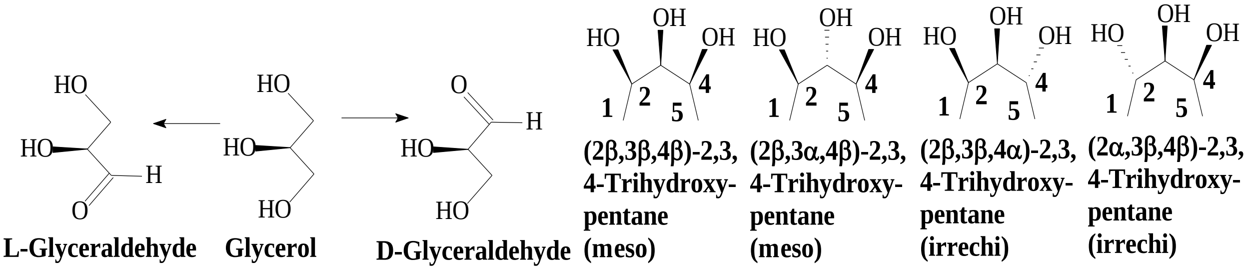


Figure 13. Trihydroxy alcohols isomers.

2.11. $C_nH_{2n}O$, Carbonylic compounds (Aldehydes and ketones)

C_1-C_3 Derivatives of aldehydes and ketones are *archaic* (C_1 and C_2 for aldehydes, C_3 for ketones). C_4 produces *meso*, (2R,3S)-2,3-DiMe-oxirane (Fig. 12) (Durig et al., 1983), and *C_2 symm.*, (2R,3R)-2,3-DiMe-oxirane (Durig et al., 1983) isomers. Isomers *meso*, (2R,3R,4S,5S)-2,3,4,5-tetraMe-THF), *C_2 symm.*, (2R,3R,4R,5R)-2,3,4,5-tetraMe-THF) and *irrechi*, (2R,3R,4R,5S)-2,3,4,5-tetraMe-THF), are given by $C_8H_{16}O$. In fact, the latter MF can generate ten isomers with the same skeleton: two *meso*, four *C_2 symm.* and four *constit.* This pattern is frequently met at compounds possessing at least four chiral carbons and symmetric isomers. The discovery of this pattern is due to lineary hexitols (Fischer, 1891).

In the open form, the first *meso* (3R,5S)-3,5-DiMe-4-keto-heptane and *C_2 symm.* (3R,5R)-3,5- DiMe-4-keto-heptane terms are generated by $C_9H_{18}O$, while for the first *irrechi* $C_{13}H_{26}O$ is needed (Fig. .12).

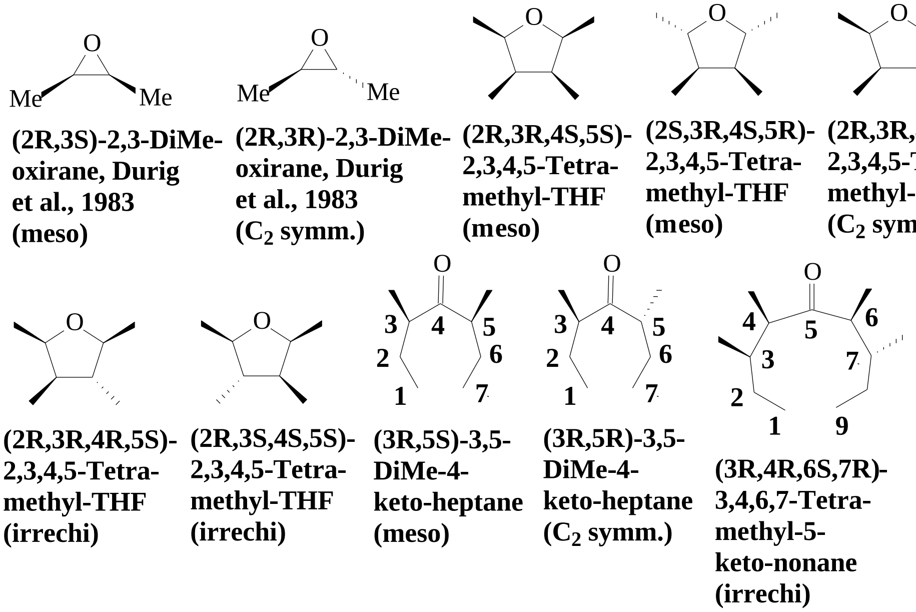
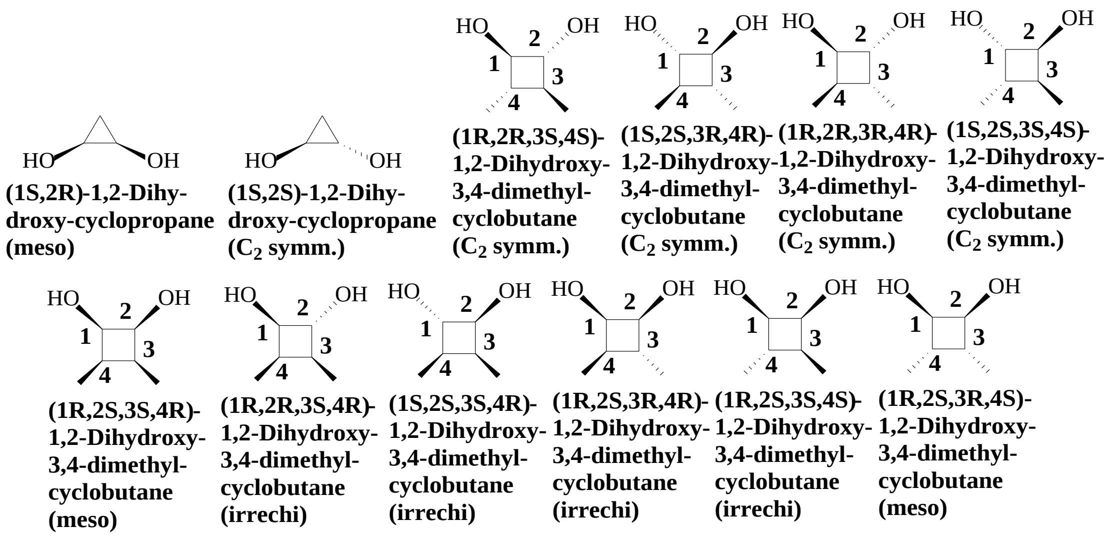


Figure 14. Isomers of $C_nH_{2n}O$ carbonylic compounds (aldehydes and ketones).

2.12. $C_nH_{2n}O_2$, Organic acids

C_1 And C_2 are archaic. C_3: Propanoic acid as a *constit.* mold has a *meso* (1S,2R)-1,2-dihydroxy-cyclopropane and *C_2 symm.* (1S,2S)-1,2-dihydroxy-cyclopropane isomers (Fig. 13). The three types of molds are exhibited by MF $C_6H_{12}O_2$.



(1S,2R)-1,2-Dihydroxy-cyclopropane (meso)

(1S,2S)-1,2-Dihydroxy-cyclopropane (C_2 symm.)

(1R,2R,3S,4S)-1,2-Dihydroxy-3,4-dimethyl-cyclobutane (C_2 symm.)

(1S,2S,3R,4R)-1,2-Dihydroxy-3,4-dimethyl-cyclobutane (C_2 symm.)

(1R,2R,3R,4R)-1,2-Dihydroxy-3,4-dimethyl-cyclobutane (C_2 symm.)

(1S,2S,3S,4S)-1,2-Dihydroxy-3,4-dimethyl-cyclobutane (C_2 symm.)

(1R,2S,3S,4R)-1,2-Dihydroxy-3,4-dimethyl-cyclobutane (meso)

(1R,2R,3S,4R)-1,2-Dihydroxy-3,4-dimethyl-cyclobutane (irrechi)

(1S,2S,3S,4R)-1,2-Dihydroxy-3,4-dimethyl-cyclobutane (irrechi)

(1R,2S,3R,4R)-1,2-Dihydroxy-3,4-dimethyl-cyclobutane (irrechi)

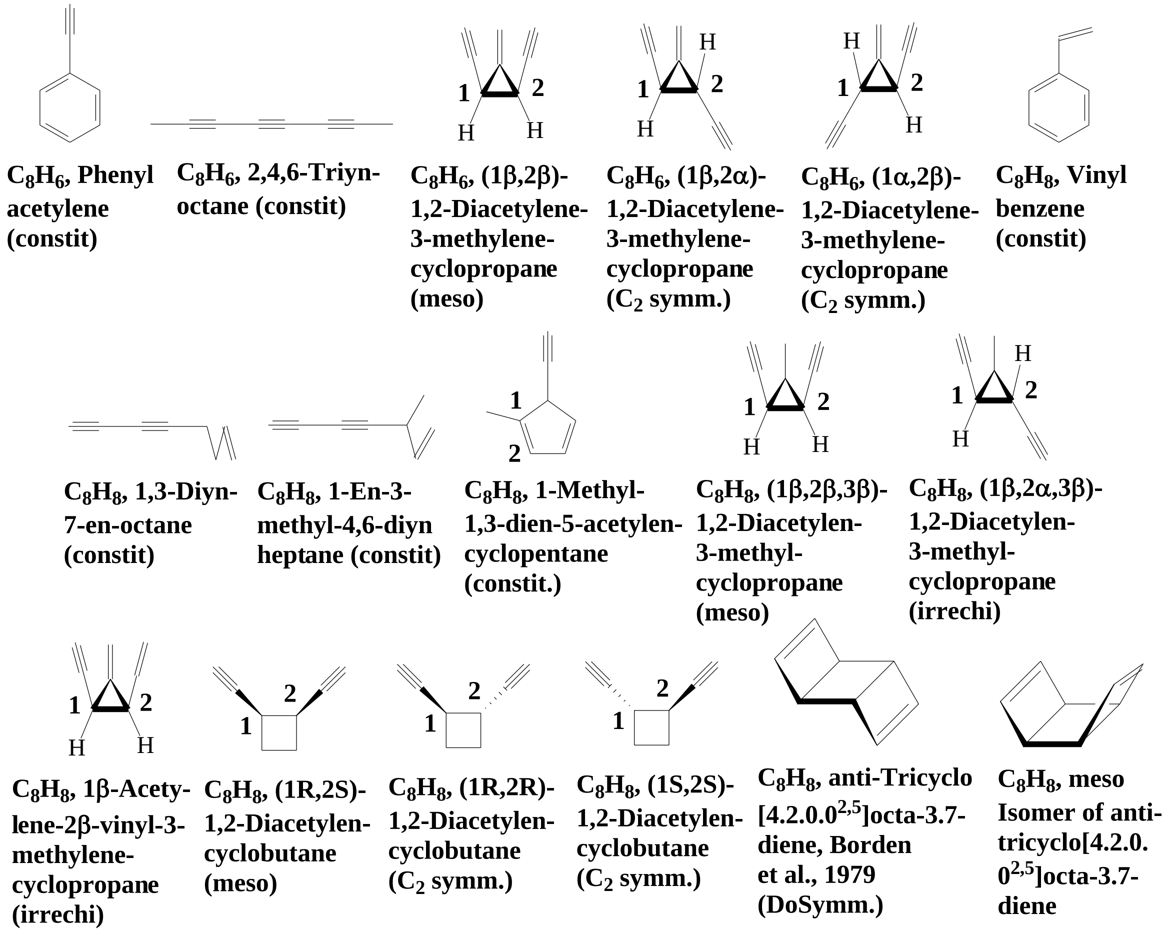
(1R,2S,3S,4S)-1,2-Dihydroxy-3,4-dimethyl-cyclobutane (irrechi)

(1R,2S,3R,4S)-1,2-Dihydroxy-3,4-dimethyl-cyclobutane (meso)

Figure 15. The three types of molds exhibited by organic acids.

2.13. MF C_8H_6, Phenylacetylene; MF C_8H_8, Vinylbenzene

Phenylacetylene, C_8H_6, is a good example of a compound that in spite of its highly oxidated state is able to present *meso* and *C_2 symm*. isomers (Fig. .14). No wonder that a compound relatively richer in hydrogen, C_8H_8, vinylbenzene, would produce a larger pattern of *meso*, *C_2 symm*., and even *irrechi* isomers. It presents also linear and cyclic *constit*. isomers. Borden et al., (1979) synthesized an interesting tricyclo compound. The latter could present a *meso* isomer.



C_8H_6, Phenyl acetylene (constit)

C_8H_6, 2,4,6-Triyn-octane (constit)

C_8H_6, (1β,2β)-1,2-Diacetylene-3-methylene-cyclopropane (meso)

C_8H_6, (1β,2α)-1,2-Diacetylene-3-methylene-cyclopropane (C_2 symm.)

C_8H_6, (1α,2β)-1,2-Diacetylene-3-methylene-cyclopropane (C_2 symm.)

C_8H_8, Vinyl benzene (constit)

C_8H_8, 1,3-Diyn-7-en-octane (constit)

C_8H_8, 1-En-3-methyl-4,6-diyn heptane (constit)

C_8H_8, 1-Methyl-1,3-dien-5-acetylen-cyclopentane (constit.)

C_8H_8, (1β,2β,3β)-1,2-Diacetylen-3-methyl-cyclopropane (meso)

C_8H_8, (1β,2α,3β)-1,2-Diacetylen-3-methyl-cyclopropane (irrechi)

C_8H_8, 1β-Acetylene-2β-vinyl-3-methylene-cyclopropane (irrechi)

C_8H_8, (1R,2S)-1,2-Diacetylen-cyclobutane (meso)

C_8H_8, (1R,2R)-1,2-Diacetylen-cyclobutane (C_2 symm.)

C_8H_8, (1S,2S)-1,2-Diacetylen-cyclobutane (C_2 symm.)

C_8H_8, anti-Tricyclo [4.2.0.0^{2,5}]octa-3.7-diene, Borden et al., 1979 (DoSymm.)

C_8H_8, meso Isomer of anti-tricyclo[4.2.0.0^{2,5}]octa-3.7-diene

Figure 16. Isomers of phenylacetylene and vinyl benzene, C_8H_8.

4. CONCLUSION

The time has probably arrived for a tentative systematization of the micro molecular organic compounds, natural or synthetic. In this paper the key criterion for this task are the symmetry and form of molecules, within a new proposal of a chapter of physical chemical sciences, chemical morphology. Seeing a great part of chemistry as a sum of independent multitudes generated by molecular formulas (MFs), is a relatively novel vision in chemistry. The groups of isomers of natural and synthetic micro molecular organic compounds are unique, spectacular, magnificent multitudes,

A general search in chemistry and physics, for a dual system, led us to the enantiomorphism, in spite of its unnaturalness in chemistry. Of this reason, we have adopted *meso* compounds, defined in physical chemical terms, as the reference ones. Our tentative in fact has been to demonstrate that chemistry is a dualistic science.

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