Minireview Article

New Chemical Dualities Illustrated by *Meso* and C_2 Symmetrical (*CTS*) Compounds

ABSTRACT

The most important relationship between chemistry and genetics is nonetheless the corpuscular nature of their objects, molecules (or atoms) and genes, respectively. On the other hand, one states, without a substantial proof, that philosophy should be one step ahead all sciences. Here is a proof that the reverse can also be true. Two internal enantiomeric halves of *meso* compounds or the two chiral halves of C_2 symmetrical isomers constitute pairs of entities suitable to work as duality phenomena in science. Four types of isomers have been identified: (A) *meso*, (B) C_2 symmetrical (*CTS*), (C) *irre*gular *chi*ral (*irrechi*) and (D) *constitutional* (*constit.*). *Meso* and *CTS* are characteristic to plants and microorganisms. Almost all natural micromolecular compounds from vertebrate tissues are asymmetric, i.e. they are *constit*. isomers. An exception to this rule is *meso*-inositol, an isomer of hexoses, which are themselves, as their congeners asymmetric. By comparing the real (envisaged) *meso* isomers of these compounds with the asymmetric ones of vertebrate tissues, the reason for nature selected the latter became quite evident: it is the omission of a suite of structural restrictions. Delivering of *meso* isomers of natural compounds discloses a huge chemical philosophical potential of this issue. 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, i.e. good candidates for a duality concept. Moreover, a good deal of material is indicated, i.e. *CTS* isomers, whose sides are chiral and identical, for a new type of duality in philosophy, strongly expressed in nature by a chemical language.

Keywords: isomers, meso, C_2 symmetrical, irregular chiral (irrechi), constitutional, comparative chemistry, integrative, duality, mirror plane of symmetry

1. INTRODUCTION

Biochemical and genetic center running today is formed almost exclusively of genome [1-3]. All products, their molar ratios, phenomena of molecular and isomeric diversity, as well as entropy buffers are produced by the genome. However, genetic apparatus is tested especially by its products. Duality phenomena are known especially in physics, e.g. light duality [4-7]. The two opposed sides of a duality phenomenon should be well defined, equally (comparably) strong concerning their meaning, and relatively known (consecrated). In chemistry duality phenomena are of less amplitude [8-10] than in physics, and this can be correlated with the relative lower oldness of this science, as based on firm and general principles, in comparison with physics. One might suppose that the birth certificate of physics was signed by Pythagoras (abt 532 BC) when he found a mathematical relationship between sound quality, the length, thickness and tension of the producing string (or pipe) [11]. Chemistry began probably at the same time, but a series of occult influences slowed its development.

Structural analysis of numerous natural compounds as well as *in silico* integrative approach of isomers generated by the same molecular formula, applied to a large diversity of natural compounds and some synthetic ones, led to four groups (types) of compounds identified and defined within the same molecular formula: (A) *meso*, (B) C_2 symmetrical (*CTS*), (C) *irre*gular *chi*ral (*irrechi*) and (D) *constitutional* (*constit.*) [12-17].

(A) *Meso*, are either based on a mirror plane of symmetry (A1), or devoid of a mirror plane of symmetry but specified in this way as a result of Cahn-Ingold-Prelog rules [18,19] (A2). One can assert that molecules of the latter group are formed of two imaginary enantiomeric halves separated by an imaginary mirror plane of symmetry. Related to *meso* isomers are compounds characterized by a center of symmetry (A3) or an alternating axis of symmetry

(A4). The molecule of (A1)-(A3) is formed of two enantiomeric halves. *Meso* isomers are optically inactive (optinactive) due to an internal compensation.
At the time when Fischer invented xylitol [20], an optinactive polyol, at least one *meso* isomer was known, i.e. *meso*-tartaric acid, discovered by Pasteur [21,22]. *Meso*-tartaric acid has a homodimeric structure (an even number chain), and xylitol a heterodimeric (an odd number chain). Mirror plane of symmetry cuts a bond of *meso*-tartaric acid, and four atoms of xylitol (C, H, OH). One might theorize that mirror plane of symmetry hides (masks) the atoms cut by it from polarized light, and what remains, as evidenced by this physical instrument, is an entity containing an even number of atoms, i.e. a homodimer. Mirror plane of symmetry has to be regarded as an intrinsic property of *meso* compounds, both a physical instrument and a natural phenomenon.
Meso heterodimers constitute a chemical duality, the two opposed sides of duality are their heterodimeric character, on one hand, and their expression as homodimers, on the other. According to Kelvin and Prelog theory [23-25] "*meso* compounds are internally heterochiral. There is a fundamental difference between the mirror plane of symmetry in macrocosmos and at physical-chemical level in microcosmos. In the first case, the mirror plane of symmetry just indicates the limit of the two enantiomeric halves. At physical-chemical level, it can cut atoms and hide them, not of our seeing, but of polarized light. As will be evident of this paper, this spectacular property of mirror plane of symmetry plays an extremely important role in systematization of isomers emerging of the same molecular formula".
Imprecise breaking of identity of the two halves of *meso* isomers leads to two enantiomers [26] i.e. the internal enantiomerism is externalized. (In our days chemists try to overturn this feature of *meso* compounds and to predominantly (or even exclusively) prepare one product only [27-31]).
(B) "***C_2 symmetrical* (*CTS*)** compounds have been defined in relation with an axis and a rotation of 180°. After this maneuver the same atoms should be regained as initially" [32-34]. All *CTS* compounds are chiral and optically active (optactive). Fischer demonstrated the existence of some chiral compounds with identical ends, that produced exclusively one derivative, by reactions randomly affecting their ends. E. g. D- and L-mannitol [35], D- and L-iditol [36], and their aldaric acids, as well as D- and L-threitol [37] and the enantiomers of tartaric acid [38]. Besides these compounds whose molecule is formed exclusively of two identical chiral halves, there are *CTS* combinations where the two chiral halves are linked on a matrix. E. g. 3-keto- and 3-deoxyxylitol, 3-keto- and 3-deoxyribitol, D- and L-diaminopimelic acid [15], etc. The chiral units of the third *CTS* group molecules can be recognized especially by Cahn-Ingold-Prelog rules [18,19]. According to Kelvin and Prelog theory [23-25], "*CTS* formed exclusively of two identical chiral halves are homochiral with each other" and internally homochiral [34,39]. Of this reason, they could be named also *twin* molecules [40]. "The exceptional properties of *twin* (*CTS*) compounds" were also noticed by Vickery [41]. "Homodimeric *CTS* compounds constitute a chemical duality, the two opposed sides of duality are optical activity, on one hand, and their symmetry, on the other. There is one universal rule concerning *CTS* compounds: every member of this group possesses a real or imaginary, but plausible, *meso* isomer. Some more clearings are requisite. Compounds based on 1,2-diamino-cyclohexane [29,33,42,43] are *CTS* as long as they are trans". "Their cis isomer should be *meso* only by adopting a planar cycle, as for allo-inositol. Of the six *meso* isomers of inositol [44,45], five are characterized by 1,4 mirror plane of symmetry, while allo-inositol is devoid of such a plane. Its *meso* nature ca be explained only by a planar structure, hence the mirror plane of symmetry cuts two opposed bonds". (One can write a *meso* isomer of 1,2-diamino cyclohexane as 1,2-cyclobutane derivative).
"The first *CTS* combinations, the two enantiomers of tartaric acid, have been separated by Pasteur (1848) by crystallization from a racemic mixture that had been prepared by Kestner (1822)" [21,22,46]. "Pasteur noticed two types of crystals, that were enantiomorphic with one another. He separated the two types of crystals and found out that their aqueous solutions were dextrorotary and levorotary, respectively. Dextro-tartaric acid had been discovered by

Scheele (1770) in the sediment deposited in the vats during the grape juice fermentation" [47,48]. "Stereochemical theory of tetrahedral and asymmetric (chiral) carbon atom [49,50] led van't Hoff to molecular models based on tetrahedrons which unequivocally represented every chiral carbon atom". "By constructing and using these models, van't Hoff expanded the idea of enantiomorphism from crystals to molecules, a process initiated by Pasteur. (Dots and wedges representations of today come from van't Hoff's models). However, at that time no scientist could rationally associate structural models with the two enantiomers" [51]. "In fact, the discovery of Pasteur increased the dilemma of representation, i. e., the relationship between a sample of an optactive compound and the unique, characteristic, structural model possibly assigned to it. This dilemma was solved by X-ray diffraction, i. e., of zirconium Kα rays, by sodium rubidium tartrate of the dextrorotary species, and the obtained model was assigned to (+)-tartaric acid" [52]. "Configuration of chiral centers of (–)-tartaric acid became also known, by the virtue of the law of enantiomorphism. By an impressive coincidence, this configuration of (+)-tartaric acid had been hypothetically attributed by E. Fischer" [38]. "Configuration of the two enantiomers has been connected with other chiral compounds, beginning with (–)- and (+)-glyceraldehyde" [53,54]. "A chemical relationship has been found between E. Fischer and his son, H. O. L. Fischer" [55,56]," due to a derivative of D- and L-mannitol prepared by the latter, i.e. 1,2-5,6-di-O-isopropylidene mannitol (*CTS*). By integration of finding of H. O. L. Fischer in the strategy of E. Fischer, a remarkable shortcut to structure elucidation of linear aldohexoses is obtained" [57].

The theory of van't Hoff and Le Bel was confirmed by three independent arguments. (**a**) Synthesis by E. Fischer of the major part of monosaccharides indicated by this theory [58]. (**b**) In a model of diamond based on crystal structure determined by X rays diffraction, C atoms appeared on the apices of an endless lattice of regular tetrahedrons [59]. (**c**) Pauling [60,61] explained "this model in mathematical-physical terms by using a concept, hybridization, taken from biology. Pauling demonstrated that by mixing three p orbitals, each having two lobes and being perpendicular to one another, with a spherical s orbital, four hybrid sp^3 orbitals are obtained, that are identical and oriented along the axes of a regular tetrahedron".

A remarkable and unique feature of *CTS* compounds is that chemical modification of one of the two component chiral halves produces the same result.

(C) *Irrechi*. "The third subgroup of isomers of *meso* compounds are also chiral and they are characterized by a molecular skeleton identical to *meso* and *CTS*, i.e. a phenomenon of isoskeletomeric relationship" [62]. Still, chiral carbons are irregularly distributed in their molecule [14,15] (*irregular chiral*, *irrechi*). *Meso* isomers are characterized by a 1:1 ratio of numbers of R and S carbons while in *CTS* ones this ratio is n:0, 0:n or 1:1. In *irrechi* combinations the ratio R/S has other values.

(D) "***Constitutional*** (positional) (*constit*.) isomers form the fourth group. They are isomer with the preceding ones but their skeleton is different. They are either optactive or optinactive" [14]. With relatively few exceptions, compounds currently met in living things, especially in vertebrate tissues, are *constit*. isomers. They are probably the most abundant in these living things.

The term diastereomer has been destined to include all isomers that are not enantiomers [63-68]. Hence, it included all types of isomers mentioned above. However, since they have developed as independent groups, we considered that the term diastereomer became obsolete and have replaced it with the four redefined terms.

A direct application of our systematization to monosaccharides discovered/invented by Fischer would clearly indicate our strategy. Galactitol, iditol, xylitol, ribitol, erythritol, are *meso*, mannitol and iditol are *CTS*, altritol, glucitol, gulitol, talitol, arabinitol, lyxitol are *irrechi*, hamamelitol and apitol are *constit*. What has been affirmed for polyols is also valid for their aldaric acids.

"Concerning limits and possibilities of reciprocal changing of types mentioned above, both *CTS* and *irrechi* can be transformed into *meso*. Some interesting facts should be mentioned:

the molecule of iditols and idaric acids possesses an equal number of R and S carbons, similarly with galactitol, allitol, galactaric and allaric acids. However they are not *meso* but optactive" [44]. The difference can be explained probably by the fact that the molecule of the former is formed of two identical chiral halves and the latter of two chiral enantiomeric halves.

The two hydrogen atoms of central methylene of a *meso* derivative, i.e. 3-deoxyxylitol, 3-deoxyribitol, *meso*-diaminopimelic acid, etc., are not equivalent. If they are alternatively replaced by a hydroxyl function, the products are different. The two central hydrogen atoms of *CTS* compounds, i.e. 3-deoxyarabinitol, 3-deoxylyxitol, L,L- and D,D-diaminopimelic acid, etc., are equivalent: if they are alternatively replaced by a hydroxyl function, exclusively one product is obtained.

"The isomeric diversity is connected with the following factors: (**i**) Structures as diamond [59], graphite and fullerenes [69,70] illustrate the best the ability of C atoms to bind with each other". However, "the three forms present a very limited structural variety. (**ii**) What really confer molecular diversity to C combinations is the association of this element with hydrogen and this is evidenced by the remarkable molecular variety of aliphatic hydrocarbons" [45,71,72]. "Isomeric diversity is a physical-chemical magnitude concerning the ability of a compound to present a large number of isomers. (**iii**) Chemical functional groups, in relative low proportion, also favor molecular diversity. (**iv**) Aromatic hydrocarbons present the lowest isomeric diversity of all organic combinations. They contain an exceeding number of chemical functions, and they are in a state of advanced oxidation. In fact, they fill an intermediate place between elementary carbon and aliphatic hydrocarbons. Another remarkable feature of aromatic hydrocarbons is the fact that they do not present *meso* form as atropisomers. (**v**) Isomeric diversity increases exponentially with molecular weight" [63,72,73]. (**vi**) "Carbon dioxide is a terminal facet of metabolism and combustion of organic compounds. It is characterized by a high chemical inertia. Carbon dioxide has to be attached to a preexisting structure, as a piece of metal in a lathe, and stepwise reduced, the energy of sun playing an essential role in this process called photosynthesis" [74].

About eight classes of natural compounds contain *meso* isomers. **Monosaccharides**: *meso*-tartaric acid [22,49,75,76], erythritol [77], butanediol [78], galactitol [26,79], allitol [80], xylitol [81], ribitol [82,83], allaric acid [84], xylaric acid [85], ribaric acid [86], galactaric acid [26], D-galactitol-3R,4S-cinnamicacetal [87], galaoctitol [88-90].

Amino acids and their derivatives: *meso*-cystine [91,92], *meso*-diaminopimelic acid [74,92-96], *meso*-lanthionine [96-98], L,D-homolanthionine [99], *meso*-DKP of pipecolic acid [100], dragmacidin B [101], fellutanines A and C [102], dimethyl fellutanine A [103], fellutanine D [104,105], trans-dragmacidin C [101], chimonanthine [106,107], petrobactin [108,109], phenazostatin D [110,111].

Carotenoids and carotenes: zeaxanthin [(3R,3'S)-β,β-carotene-3,3'-diol] [112-115], (2R,2'S)-2,2'-dihydroxy-β-carotene [(2R,2'S)-β,β-carotene-2,2'-diol] [116], tunaxanthin D [(3R,6S,3'S,6'R)-ε,ε-carotene-3,3'-diol] [117-122], tunaxanthin E [(3R,6R,3'S,6'S)-ε,ε-carotene-3,3'-diol] [117,120], *meso*-astaxanthin [(3R,3'S)-3,3'-dihydroxy-β,β-carotene-4,4'-dione] [123,124], (6R,6'S)-3,3'-diketo-ε-carotene [(6R,6'S)-ε,ε-carotene-3,3'-dione] [119,122], ε-carotene [(6R,6'S)-ε,ε-carotene] [125], γ,γ-carotene [(6R,6'S)-γ,γ-carotene] [119], glabrescol [126], squalane [127], lycopane [128], carotane [128-130], isorenieratane [131], renierapurpurane [131], 1,10-bis[2',2',6'-trimethylcyclohexyl]-3,8-dimethyldodecane [132,133].

Lignans: nordihydroguaiaretic acid [134], *meso*-dihydroguaiaretic acid [134], machilin A [135], dimethyl *meso*-dihydroguaiaretic acid [136], saururin A [137], pre-gomisin [138,139], 7,7'-dioxodihydroguaiaretic acid [140], 3,3'-didemethoxynectandrin B [134], nectandrin B [135,141,142], galgravin [143,144], zuonin B [145], 4-O-Me-saurucinol J [146], isonectandrin B (tetrahydrofuroguaiacin B) [142], di-O-Me tetrahydrofuroguaiacin B [146], *meso*-secoisolariciresinol [147,148].

Neolignans: asarolignan A [149].

Cyclobutane derivatives: endiandrin B [150,151], cinbalansan [152], heterotropan [152], α-diplicatin B [153], piplartine dimer A [154], α-truxillic acid, γ-truxillic acid, epi-truxillic acid, ε-truxillic acid, peri-truxillic acid, β-truxillic acid, ω-truxillic acid [155], caracasandiamide [156].
Phenols: (3R,5S)-hannokinol [157], (3S,5R)-octahydrocurcumin [158], (2S,3R)-diolmycin B1 [159], (2S,3R,4S,5R)-hybocarpone [160-162], (2S,3S,4R,5R)-hybocarpone [160-162], eurorubrin [163], isochamaejasmine [164].
Terpenoides: daibudilactone C and daibudilactone D [165]. All this suite of *meso* compounds, the majority of them natural combinations, is meant to indicate that this type of symmetry, i.e. antinomy, is a natural phenomenon, although relatively limited. They are found almost exclusively in microorganisms, plants and/or lower animals [12-14].

2. THE LIMIT OF SYMMETRY OF THE MAJOR METABOLITES

Real and envisaged *meso* isomers. There are few, if any, symmetric compounds produced by vertebrates. Of the common metabolites, only monosaccharides (aldoses and ketoses) possess *meso* isomers as natural compounds. However, the potential of natural metabolites to produce imaginary but plausible *meso* isomers is really huge. The major metabolites containing a significant alkane moiety possess at least one real or envisaged *meso* isomer. A guiding line of this paper is to find out at least one *meso* isomer for every molecular formula. A serious obstructor to this is an advanced degree of unsaturation. It is impossible to find out a *meso* isomer for e.g. $C_4H_4O_4$ (fumaric/maleic acids). However, $C_6H_{10}O_4$ (succinic acid, etc.) or $C_6H_8O_4$ (2,3-dimethyl derivative, etc) have a *meso* form (Fig. 1). Similarly, every tentative to construct a *meso*

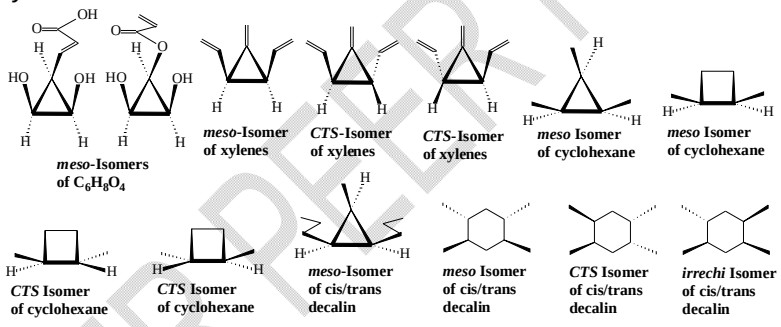

Figure 1. *Meso* isomers of unsaturated (fumaric/maleic acid), aromatic, and the latter's saturated derivatives.

isomer of benzene, fails. However, the thing is possible for xylenes, ethylbenzene, propylbenzene, etc. Also, reduction product of benzene, cyclohexane, presents *meso* and CTS isomers. Naphthalene, similarly to benzene, fails to give *meso* isomers, decalines instead presents all four types of isomers (Fig. 1). Compounds unable to produce symmetric isomers have been called by us *archaic*. Chemical transformations only intermediate between the two groups. For numerous *archaic* compounds a molecule of H suffices to convert them to symmetric entities.
At least two dozens of isomers with molecular formula $C_3H_7NO_2$ can be written, just by using the consecrated valence of every component element. However, of the envisaged isomers only some present elements of symmetry: two are *meso* (cis-1,2-dihydroxy-3-amino cyclopropane and cis-2,4-dihydroxy-azetidine), and two are *CTS* (trans-2,4-dihydroxy-azetidine, two enantiomers), and all the others, including (R)- and (S)-alanine, are *constit*.
Polygonal representations of *meso* isomers. *Meso* representations in this paper, of compounds with at least a minimum degree of unsaturation, are polygonal – triungular, square, pentangular, hexangular. An exception to this are saturated compounds (alkanes,

alcohols, etc). For a triangular representation (Fig. 2), a mathematical equation (1) have been imagined to illustrate *meso* isomers.

$$n-3=2x+2y+z+w \quad (1)$$

In equation (1), n is the number of atoms in molecular skeleton, x, y, z, w, are suitably selected numbers. In triangular representation there is a connection between x, y, z, w, and R1, R2, R3, R4, respectively.

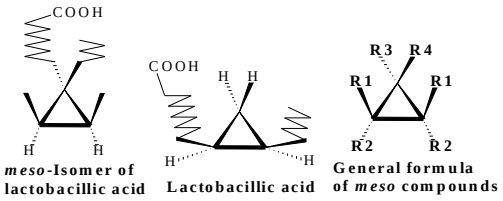

Figure 2. Lactobacillic acid as model for *meso* isomer. The sense of mathematical equation.

The rings of three or four atoms, as cycles or heterocycles, synthetic [30,166-168] or found in natural materials, are well known. “Cis- and trans-1,2-dimethyl cyclopropane are indistinguishable of thermodynamic point of view” [169]. “1,2,3-Trihydroxycyclopropane is known as an unstable combination” [170,171], however “no attempt was made to stabilize it. 1,2-Dihydroxycyclopropane has been prepared by a reduction reaction of a diketone derivative” [172]. “Cis-1,2-dihydroxycyclopropane has been discovered in natural material as a glycoside of α-D-galactopyranose [173] as well as in the constition of mycolic acids” [174] and lactobacillic acid [74] (Fig. 2). Oxirane ring has been identified as (3*S*)-2,3-oxidosqualene in sterols biosynthesis. Two syntheses of cis-1,2,3,4-tetrahydroxy cyclobutane have been reported [175]. Numerous real or envisaged *meso* isomers have been presented in the following (Figs. 3-10).

3. NATURAL COMPOUNDS WITH BIOCHEMICAL IMPLICATIONS

3.1. The fundamental amino acids. “Compounds with a ubiquitous distribution in living matter, the twenty fundamental amino acids are characterized by an unequaled structural variety. These amino acids are met especially integrated in proteins and in this state they manifest themselves by their tails” [74]. An interesting picture presents the real and envisaged symmetric isomers of the twenty fundamental amino acids: without any exception, they present *meso* isomers (Fig. 3), hence no one is *archaic*. Besides *constit*. isomers, Gly, Ala, Val, Pro, Thr, Asp, Arg, present *meso* and *CTS* isomers. Leu, Ile, Glu, Asn, Lys, present all four types. Trp, Phe, Tyr, His, Ser, Gln, Cys, Met, possess, beside *constit*., *meso* and *irrechi* isomers. It is evident that all these compounds present symmetric isomers and implicitly dimeric character. The twenty fundamental amino acids, with different molecular formula, are related with each other by their common

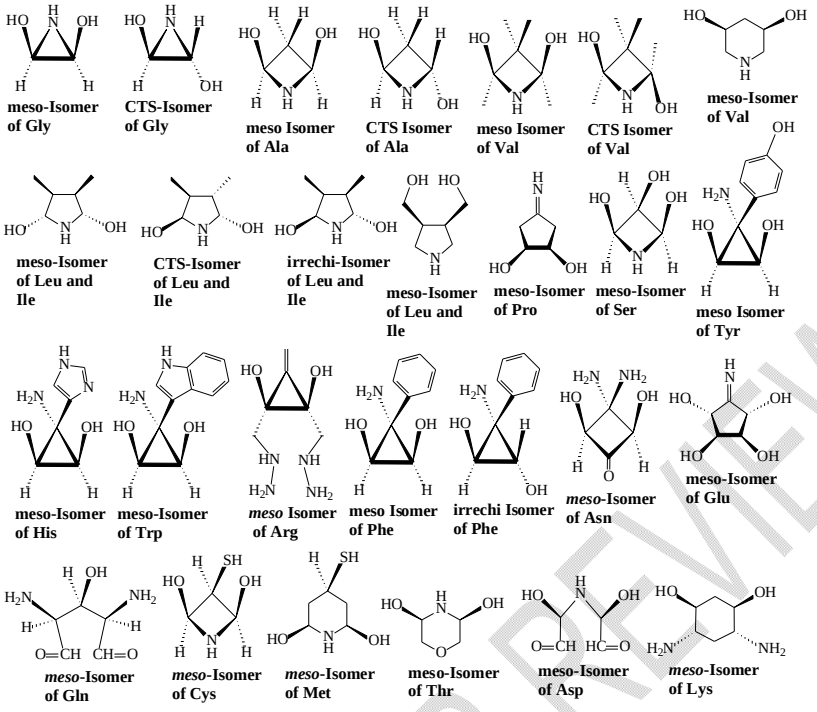

Figure 3. *Meso* isomers of the twenty fundamental amino acids. (see also text).

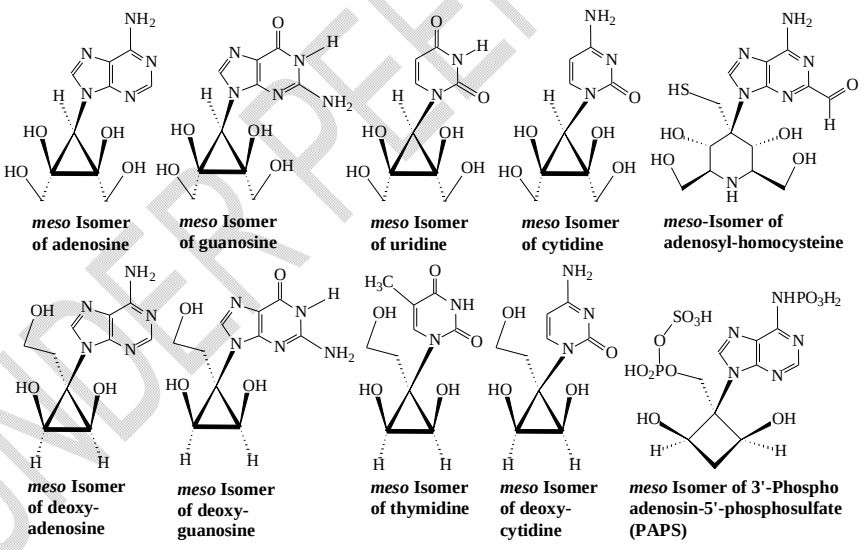

Figure 4. Meso isomers of nucleotides, deoxynucleotides, adenosyl-homocysteine and PAPS.

functional groups and by their biochemical role. The association by this criteria of amino acids is consecrated and supported by numerous arguments. On the other hand, their relationship within the same molecular formula, although quite obvious, is more discrete. L-Ala is associated with e. g. cis-2,4-dihydroxy azetidine due to the same molecular formula,

i.e. a chemical and a philosophical relationship. Although discrete, the relationship *via* molecular formula is undeniable.

3.2. Nucleotides and deoxy-nucleotides. Nucleosides and nucleotides, as the constituents of all types of RNA, and their deoxy counterparts, as constituents of DNA, are represented by their *meso* isomers (Fig. 4); adenosin is cis-3,4-dihydroxy-cis-2,5-dihydroxy-1-adenin cyclopentane. We have also added *meso* isomers of adenosyl homocysteine, a compound involved in methylation reactions, and 3'-phosphoadenosyl-5'phosphosulfate (PAPS), the major sulfate donor.

3.3. Hydrosoluble vitamins and their coenzymes. Hydrosoluble vitamins represented by thiamine (vitamin B1), isoaloxazine, pyridoxol (vitamin B6), biopterin, pantoic acid, vitamin biotin, nicotinamide have a variety of *meso* isomers. The planar structure of benzenoid compounds has been succesfully used in *meso* isomers of hydrosoluble vitamins (Fig. 5): cis-2,4-dihydroxy-3-methyl-3-adenin oxetane (biopterin), cis-2,4-dihydroxy-3-propyl-3-(3,4-diamino-thiophene-2)oxetane (biotin), 2,4-diphosphonate-3-hydroxy-amino-pyrimidine-3-thiazol (thiamine; vitamin B1), 1-hydroxy cis-2,6-diphosphate-cis-3,5-ethyleneglycol-3-dihydroxyisoalloxazine-3-adenin-cyclohexane (vitamin B2) (as $FADH_2$ and $FMNH_2$), and even pyridoxol (vitamin B6), coenzyme A and NADH. In order to write *meso* isomer of $FMNH_2$ we extracted an O atom from a keto bond, however leaving redox system intact. An excellent alternative to this is to link the isoalloxazine system and a phosphonic residue on C-3 of ribitol. A component of coenzyme A, pantoic acid, has tetrahydroxy cyclohexane as a *meso* pair.

3.4. Sterols are represented by a diversity of structures, however all of them present *meso* isomers (Fig. 6). "Sterols have been exemplified by cholesterol, stigmasterol, sitosterol, campesterol, ergosterol and digitoxygenin. Digitoxygenin also presents the four types of isomers. A similar solution has been found for estrone, C_{19} (5α-androstanolone), C_{21} (prednisolone, 11β-hydroxy-progesterone, pregnenolone, progesterone, corticosterone, cortisol, aldosterone), C_{24} (biliary acids: cholic, chenodeoxycholic, deoxycholic, lithocholic). Squalene presents at least one *meso* compound" [17].

3.5. Lipophilic vitamins. All lipophilic vitamins – A, D, E, K – present *meso* isomers (Fig. 7). Vitamin E is represented by α-tocopherol and α-tocotrienol, but all members of this vitamin have *meso* isomers, and the same are vitamins K1 and K2. Both *meso* isomers of vitamin K1 and K2 are indicated.

3.6. Fatty acids, sphingosines, prostaglandins. "Saturated, mono- and polyenoic fatty acids are represented by the isomers of stearic acid, oleic and eicosapentaenoic acid (the famous omega-3) (Fig. 8). As is obvious, an isomer of $C_{18}H_{36}O_2$ (cis-1,3-dihydroxy-cis-4,6-diheptyl-cyclohexane) present all four type of isomers: *meso* (cis-1,3-dihydroxy-cis-4,6-diheptyl-cyclohexane), *CTS* (as pairs of enantiomers) (trans-1,3-dihydroxy-trans-4,6-diheptyl- cyclohexane, etc.), *irrechi* (cis-1,3-dihydroxy-trans-4,6-diheptyl-cyclohexane, etc.) *constit*., (stearic acid, etc.). A general formula has been elaborated for mono- and polyunsaturated fatty acids" [17]. For long chain bases (LCB) (sphingosines), LCB d18:1 and LCB d18:0 have been selected. *Meso* isomers have been also found for LCB t16:0, LCB d16:0, LCB d16:1, LCB t18:0, LCB t18:1, LCB t20:0, LCB t20:1. *Meso* isomers of saturated LCB should use *meso* isomer of nonanol as a model. All prostaglandins have matching *meso* isomers, as indicated by PGE1, PGF2α, PGE2, PGF3α (Fig. 8).

3.7. Aliphatic hydrocarbons: alkanes, alkenes (cycloalkanes), alkynes (alkadienes). A tentative to evaluate molecular diversity of C_8H_{18} indicated 18 [73] or 19 [72] isomers. If one takes into account optical activity [67], the total number of isomers for C_8H_{18} is 24. Of these 24, one is *meso*, two are *CTS* [176] (Fig. 9) and the others are *constit*. An unequivocal conclusion can be drawn: all alkanes beginning with C_8H_{18} present at least one *meso* isomer, and all alkanes below this limit are *archaic*. The first term of C_nH_{2n}, alkenes or cycloalkanes, according to our reasoning, is the *meso* isomer cis-1,2-dimethyl cyclopropane (C_5H_{10}) [177]. For C_nH_{2n-2} (alkynes and alkadienes) the first term is C_7, cis-1,2-dimethyl-3-

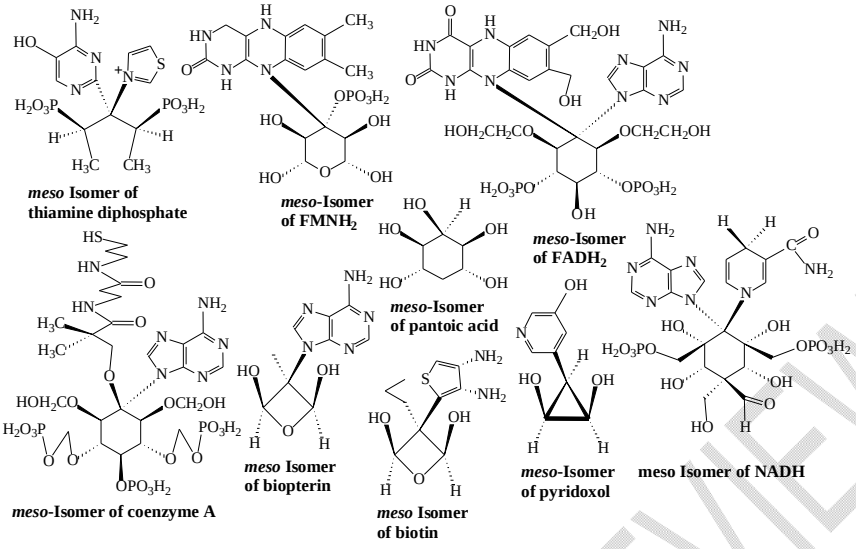

Figure 5. Hydrosoluble vitamins and their natural reagents (FADH2, FMN, NADH, coenzyme A).

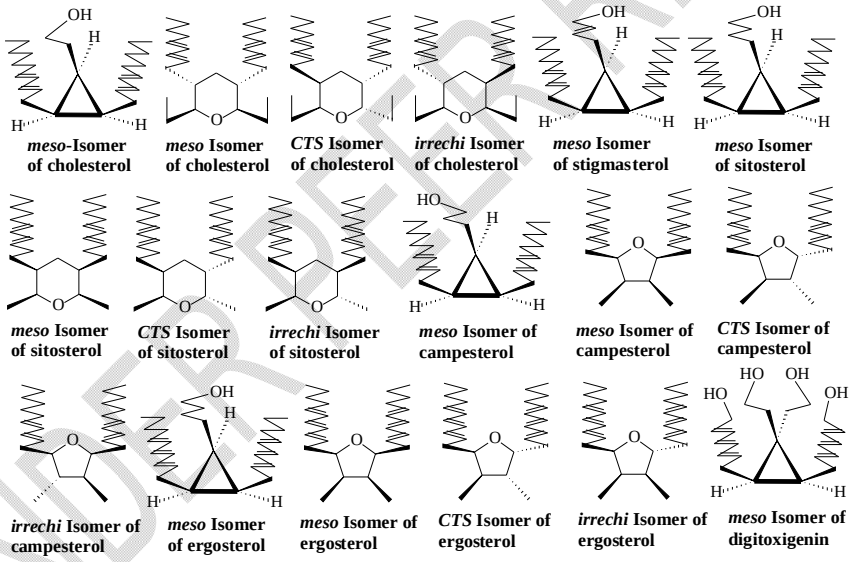

Figure 6. *Meso* isomers of some natural sterols.

vinyl cyclopropane or cis-1,3-dimethyl-2-methylene cyclobutane; compounds below C_7 are *archaic*.

3.8. Serial compounds with functional groups. For monohydroxylic alcohols the first term is C_9 (3,5-dimethyl-4-hydroxy heptane) (Fig. 10). For aldehydes and ketones the first term is C_5 (cis-1,2-dimethyl-3-hydroxy-cyclopropane), and similar combinations below C_5 are *archaic*. The first term of organic acid is C_3 (cis-1,2-dihydroxy-cyclopropane). C_3 yet, as well as C_4 and C_5 have three types of isomers only (*meso*, *CTS*, *constit*.), while C_6 and higher terms possess four; saturated organic acids below C_3 are *archaic*. The first term of monoenoic acids is C_5 (cis-1,2-dihydroxy-3-allyl cyclopropane), and the first term of dienoic acids is C_7 (cis-1,2-dihydroxy-3-(1-butadienyl) cyclopropane).

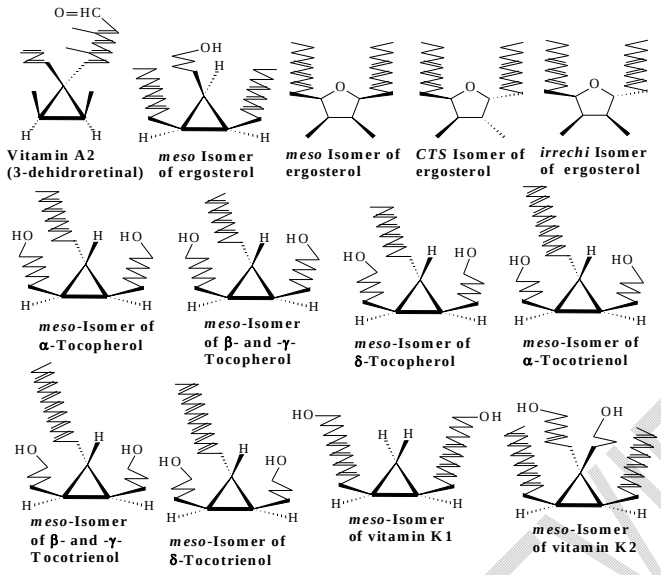

Figure 7. *Meso* isomers of lipophilic vitamins.

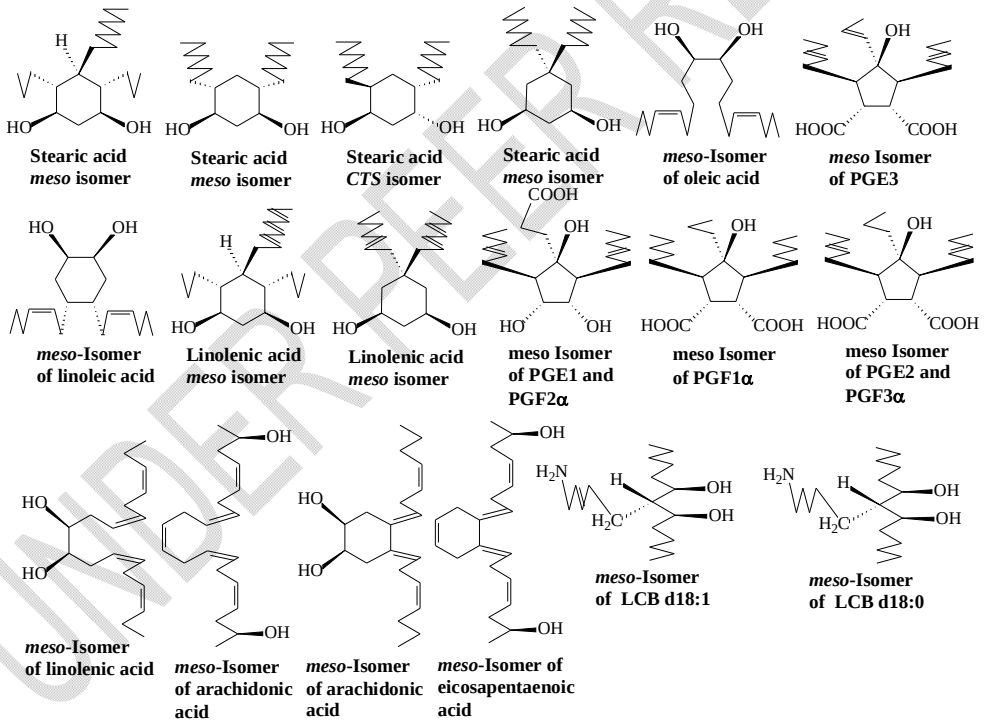

Figure 8. *Meso* isomers of fatty acids, prostaglandinds and sphingosines (long chain bases, LCB).

"The following isomers are considered *constit*. isomers of valproic acid (2-propyl pentanoic acid; $C_8H_{16}O_2$): 2-ethyl-3-methyl pentanoic acid, di-isopropyl acetic acid, (R)-2-isopropyl pentanoic acid, (S)-2-isopropyl pentanoic acid, octanoic acid" [178]. According to our systematics, we have to begin with the finding of a $C_8H_{16}O_2$ *meso* isomer. This can be cis-

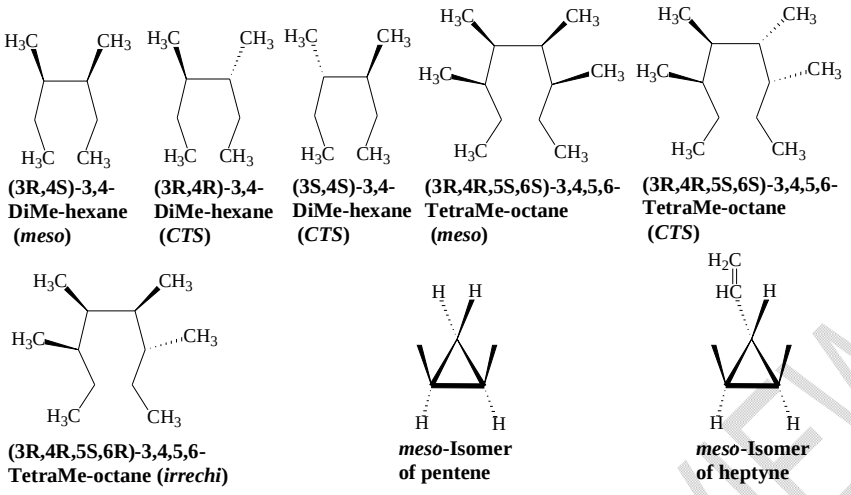

Figure 9. *Meso* isomers of saturated and unsaturated hydrocarbons.

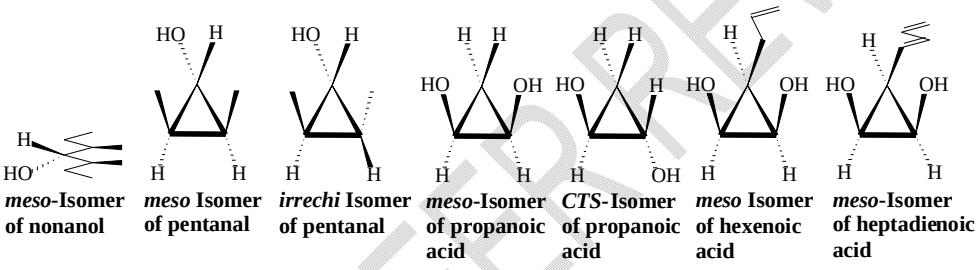

Figure 10. *Meso* isomers of some serial compounds with functional groups.

1,2-dihydroxy-1,2-diethyl-3-methyl cyclopropane, cis-1,3-dihydroxy-2,2-diethyl-cyclobutane, 1β,2β,3α,4α-1,2-diethyl-3,4-dihydroxy cyclobutane, or 1β,3β,4α,6α-1,3-dihydroxy-4,6-dimethyl-cyclohexane, or others. As can be seen from their structure, the latter three isomers present also *CTS* and *irrechi* forms. And the $C_8H_{16}O_2$ isomers mentioned earlier, valproic acid inclusively, are all *constit*.

4. AN EXERCISE OF COMPARATIVE CHEMISTRY GIVES AN ANSWER TO AN UNANSWERED QUESTION – WHY WERE CONSTITUTIONAL ISOMERS FAVORED ?

A question should be raised concerning the hierarchy [62] of the four types of isomers, in other words which of them fills the top place. 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. Of this reason, nine philosophers of ten, probably, would declare *meso* group as being on the top. We ourselves have selected them as structural reference since we thought they have a higher rank than *CTS* and *irrechi*. Nonetheless, that some people could be fascinated by *CTS* molecules, since they are produced by doubling of the same entity. If we compare the four types, it's quite obvious that *meso*, *CTS* and even *irrechi* are characterized by some structural restrictions. *Constit*., molecules are characterized by the least such structural restrictions. Of this reason, probably, natural chemistry opted for them. The structure of all natural compounds is written in a program, i. e. a genome. Hence this hierarchy is registered in fact in genome, and the

evolution process from plants and microorganisms to vertebrates 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 never met, according to our knowledge. 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*, *CTS* 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. Somehow, this phenomenon is a chemical expression of freedom, inscribed in genome.

In different classes of compounds which constitute series, a limit has been noticed, and above this limit at least *meso* isomers are possible, or even all four types. Compounds under this limit have to be considered as *archaic*. They can reach to the group of combinations 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 *meso* form; however, propenoic acid is again *archaic*. Fischer [58,179,180] illustrated this by preparing a variety of C_6 monosaccharides from formaldehyde or C_3 derivatives.

Natural micromolecular organic combinations can be also classified in a different manner, partially superposing with the afore mentioned classification: (**i**) symmetric (*meso* and *CTS*); (**ii**) potential symmetry generators (*irrechi, constit.*); (**iii**) *archaic*. There is yet a vast group of natural compounds, i.e. products of desymmetrization reactions. Nonetheless, they can be integrated in one of the preceding groups (types).

5. C_2 SYMMETRICAL COMPOUNDS OR TWIN DIMERIC CHIRALITY – A NEW TYPE OF CHEMICAL DUALITY

Compounds as trans-3,4-divinyl-1-cyclobutene, trans-1,2-dimethyl-cyclobutane, 1α,2α,4β,5β-1,2,4,5-tetramethyl cyclohexane (Fig. 1), trans-2,3-dihydroxy aziridine, trans-2,4-dihydroxy azetidine, trans-2,4-dihydroxy-3,3-dimethyl azetidine, 2β,3β,4α,5α-2,5-dihydroxy-3,4-dimethyl pyrollidine (Fig. 3), and many other types of compounds – steroids (Fig. 6), lipophilic vitamins (Fig. 7), saturated and polyunsaturated fatty acids, etc., are possibly C_2 symmetrical. Beside, an impressive number of natural C_2 symmetrical compounds is known [39, 181-184]. It seems that the number of C_2 symmetrical compounds is about ten times higher than their *meso* isomers. Hence, there are much unexploited material for chemical philosophy, and some improvement is needed for the present concepts of the so called the science of sciences.

6. CONCLUSIONS

1. At most four types (groups) of isomers have been found, in natural things or as envisaged structures: *meso*, *C_2 symmetrical*, *irrechi*, *constitutional*.
2. Practically all fundamental natural combinations, found as *constitutional* isomers in vertebrates, are able to form symmetric isomers. Hence, they keep symmetry as a potentiality and not as a reality.
3. An exercise of comparative chemistry is presented between the real *constitutional* isomers and the envisaged *meso* ones.
4. At chemical level symmetry phenomenon is much better represented in plants and microorganisms than in vertebrates.

5. The mirror plane of symmetry has been defined as an area capable to hide (mask) atoms or planar structures of polarized light, and to transform a heterodimer in a homodimer.
6. Two duality phenomena have been identified in chemistry of natural compounds. For one of them the two component sides are opposed chemically, spatially and optically, and they lead to two different (enantiomeric) compounds when distinctively affected.
7. The duality formed of chiral dimers (*CTS*), uniformly linked with each other or on a more or less complex matrix, constitutes a novelty for chemical philosophy.

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