**REVIEW**

# Organic Stereochemistry

Part 1[1])

## Symmetry Elements and Operations, Classification of Stereoisomers

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This review initiates a general presentation of the principles of stereochemistry with special reference to medicinal compounds. The general focus of this and the following *Parts* is twofold, namely *a*) broad statements of *stereochemical principles*, and *b*) illustration of these with special reference to the *biochemistry and pharmacology of medicinal compounds*. As for the graphical format of this work, its readers will find it essentially identical with that of a previous series of seven reviews on the *Metabolism of Drugs and Other Xenobiotics* published between October 2006 and October 2009 by *B. T.* and *Stefanie Krämer* in *Chemistry & Biodiversity* [1], and also published in book form in 2008 (Vol. 1) and 2010 (Vol. 2) [2]. The present *Part 1* introduces this new series by presenting and illustrating basic concepts on which the edifice of stereochemistry is built. At the most basic level of such foundations, we find symmetry as presented here in terms of its elements, operations, and point groups. This is followed by a classification of isomeric molecular structures, as well as a classification of steric relationships between molecular fragments.

[1]) For the other *Parts*, see *Helv. Chim. Acta* **2013**, *96*, 1 – 3.

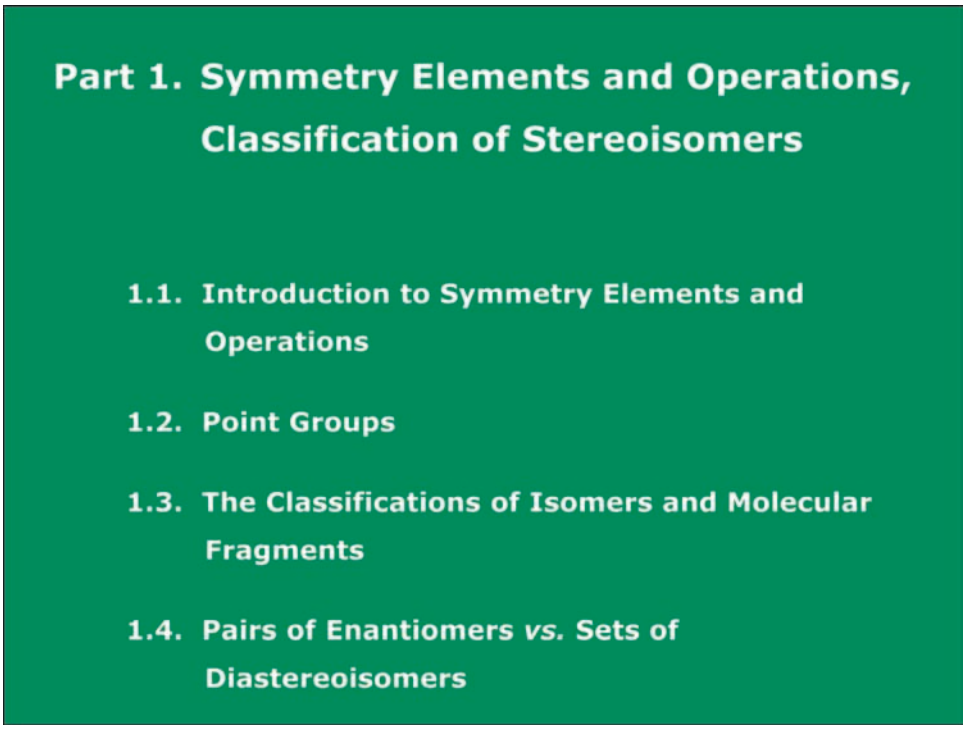



**Fig. 1.1.** At the most basic level of stereochemistry, we find symmetry as presented here in terms of its elements, operations, and points groups. Symmetry (from the Greek '*summetria*' meaning 'with measure') conveys an idea of equilibrium and harmony, and as such has a distinct aesthetic value. In science, the concept provides a way to describe the geometric properties of macroscopic as well as microscopic objects and, significantly in our case, of molecules [3–19]. To specify the symmetry properties of molecules or of any object, a shorthand is used based on *point groups*. Thus, the point group of a molecule 'M' is the ensemble of all *symmetry operations* which transform M into a molecule unto which it is superimposable. These symmetry operations depend on *symmetry elements*, both terms being necessary to define symmetry properties.

This introduction to symmetry is followed by a classification of *isomeric* molecular structures (stereoisomers). In turn, the latter classification will serve to outline steric relationships between molecular fragments.

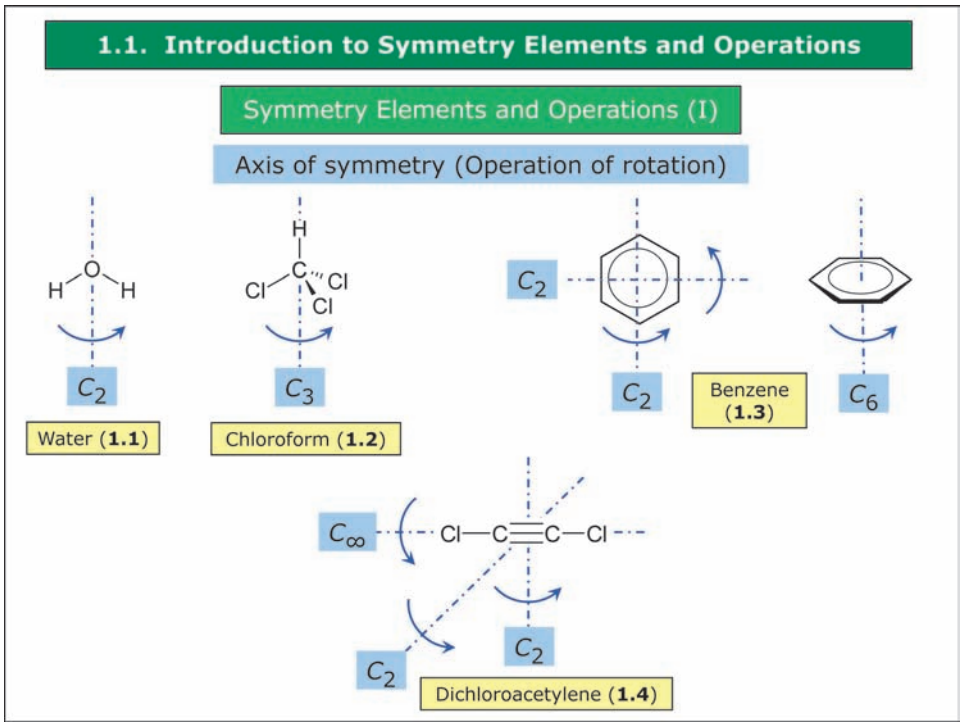



**Fig. 1.2.** In chemistry, a *symmetry operation* is defined as a permutation that transforms a molecule into an arrangement of atoms indistinguishable from the original. The permutations to be considered are the operations of *translation*, *rotation*, *reflection*, and *inversion*, and certain *combinations* of these. *No intramolecular flexibility is allowed* during such operations. An understanding of symmetry operations is necessary to define *symmetry elements*, and *vice versa*. Therefore, the two terms lack independent meanings and must be considered together.

The *Figure* presents the simple case of the axis of symmetry and its associated operation of rotation (*proper rotation*). A molecule has an *axis of symmetry* ($C_n$; $n \geq 2$) of order '$n$' if a rotation by 360°/$n$ about this axis yields an arrangement fully identical with the original. Thus, the molecular structure of $H_2O$ (**1.1**) has a twofold axis of symmetry, and the molecular structure of $CHCl_3$ (**1.2**) a threefold axis. Benzene (**1.3**) offers a more complex example, as it has two $C_2$ axes in its molecular plane, and a sixfold axis ($C_6$) perpendicular to its plane and passing through its center; $C_6$, having the highest order in this molecule, is the *principal axis* and by convention becomes the $z$-axis in a *Cartesian* coordinate system. Symmetric linear molecules such as dichloroacetylene (**1.4**) have a $C_\infty$ axis, since even an infinitesimal rotation ($360°/\infty$) results in an arrangement indiscernible from the original. In addition, such molecules have two orthogonal $C_2$ axes passing through their molecular center. The *identity operation* ($I$, not illustrated) converts any object into itself, *e.g.*, $C_1$ which denotes rotation by 360°, and is possessed by every molecule.

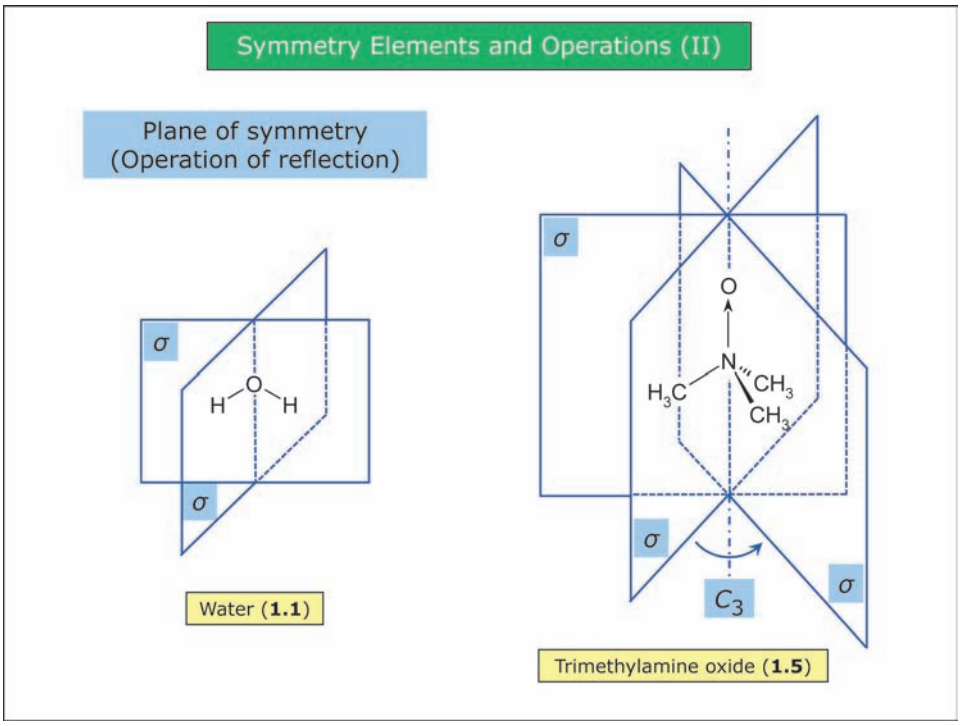



**Fig. 1.3.** As we just saw, the operation of rotation implies that the entire molecule is rotated as an undeformable object. The operation of *reflection* differs from rotation in that each atom in the molecule is '*mirrored*' in a plane; should the new three-dimensional arrangement be indistinguishable from the original, the molecule is said to possess *reflection symmetry*. In a molecule with a *plane of symmetry*, all atoms out of the planes exist in pairs. This is illustrated here with $H_2O$ (**1.1**) and its two planes of symmetry ($\sigma$). Similarly, $CHCl_3$ (**1.2**) has three such planes intersecting along its $C_3$ and each including H–C–Cl. To use a larger molecule, the same operations of symmetry are exemplified here with trimethylamine oxide (**1.5**), showing its $C_3$ axis and its three $\sigma$ planes.

All planar molecules have at least one plane of symmetry, which is identical with the molecular plane. Linear molecules possess an infinite number of $\sigma$ planes, intersecting along $C_\infty$. Planes of symmetry perpendicular to the principal axis are designated $\sigma_h$ (h = horizontal), while those containing the principal axis are marked as $\sigma_v$ (v = vertical). In other words, the planes of symmetry in $H_2O$, $CHCl_3$, and trimethylamine oxide are all $\sigma_v$ planes. In contrast, the molecular plane in benzene is a $\sigma_h$ plane.

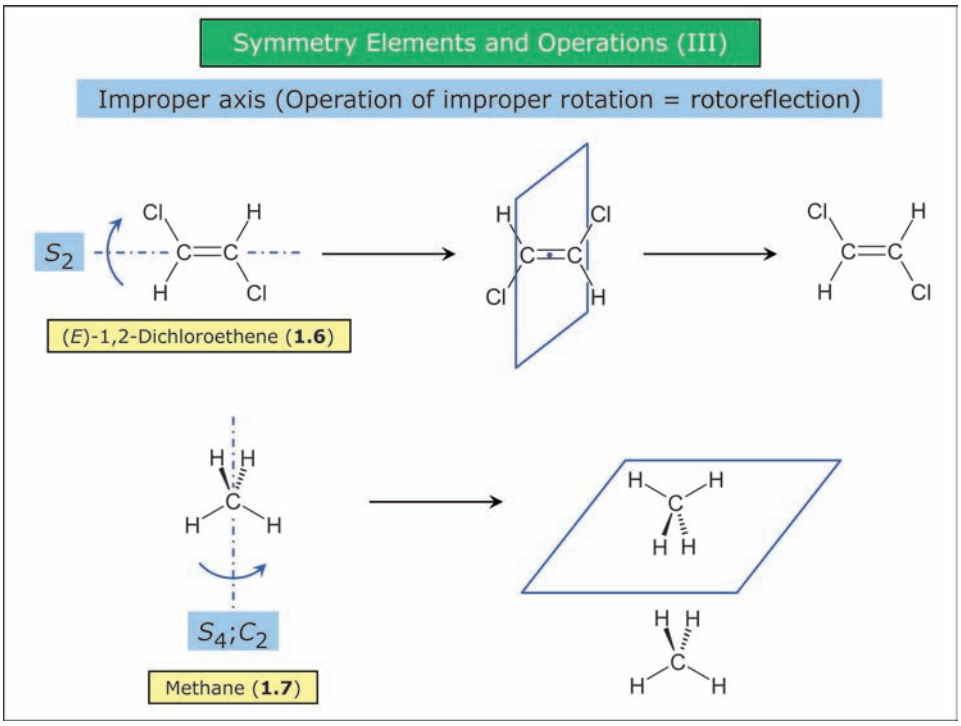



**Fig. 1.4.** The symmetry operation called as *rotation-reflection* ($S_n$) and also known as *improper rotation*, *rotary reflection*, or *rotoreflection*, involves two manipulations considered separately as $C_n$ and $\sigma$ in *Figs. 1.2* and *1.3*, respectively, but these operations must be performed consecutively to ascertain *rotoreflection symmetry*. These two operations are a *rotation* of $360°/n$ about an *improper axis* designated as $S_n$ ('S' for 'Spiegel', German for mirror), preceded or followed by a *reflection* through a plane *perpendicular* to $S_n$, and either passing through the center of the molecule or located outside the molecule. The first case is illustrated here with (*E*)-1,2-dichloroethene (**1.6**) where the improper axis is $S_2$, and the reflection plane passes through the molecule. As for $CH_4$ (**1.7**), it possesses three orthogonal improper $S_4$ axes in addition to its three orthogonal proper $C_2$ axes, while the three corresponding reflection planes are located outside the molecule. Note that the *Figure* shows only one of each symmetry element of $CH_4$.

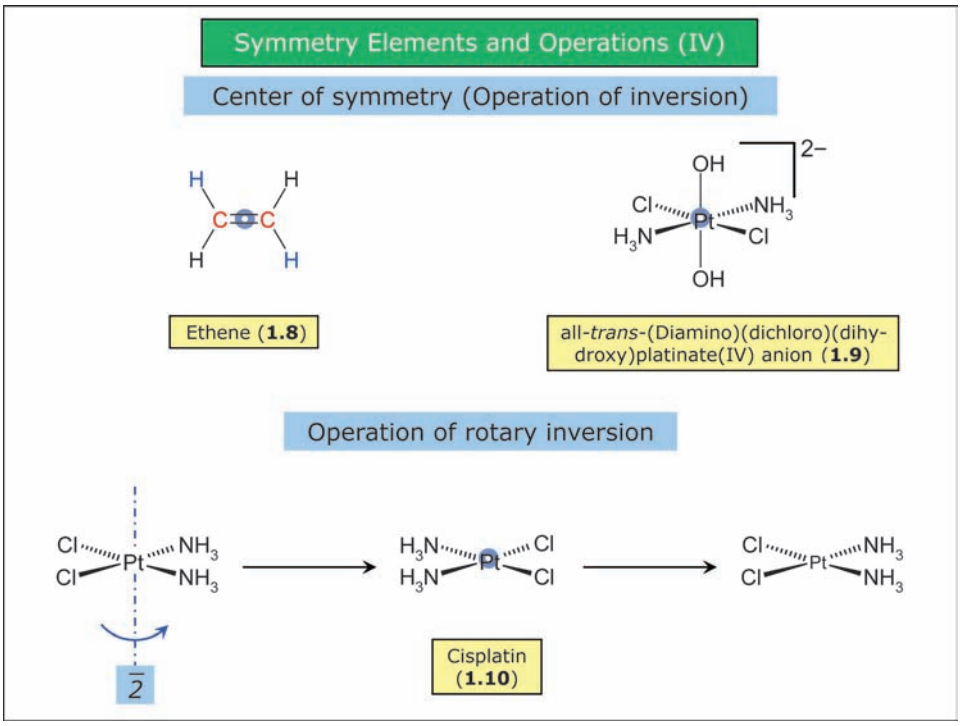



**Fig. 1.5.** The *operation of inversion* (also knwon as *point reflection*) also involves a kind of reflection, but this time through a single point called the *center of symmetry* represented here as enclosed in a blue ring. In molecules with a center of symmetry (*i.e.*, having *central symmetry*), each atom has a symmetrical and identical opposite relative to this center. That is to say, inversion of all atoms results in a three-dimensional arrangement indistinguishable from the original. This is illustrated here with ethene (**1.8**), its three pairs of symmetrical atoms each having a distinct color (red for the two symmetrical C-atoms, *etc.*). A second and more complex example is provided by the all-*trans*-(diamino)(dichloro)(dihydroxy)platinate(IV) anion (**1.9**), where one easily sees that the center of symmetry overlaps with the Pt-atom, the three pairs of identical ligands being opposite relative to this center. No more than one center of symmetry can exist per molecule.

An operation closely related to that of rotoreflection is that of *rotoinversion*, also known as *rotary inversion*. It is the combination of a rotation and an inversion in a point on the axis. This composite operation is illustrated here with cisplatin (**1.10**), where a rotation along the improper axis, plus central inversion, returns the original orientation of the object.

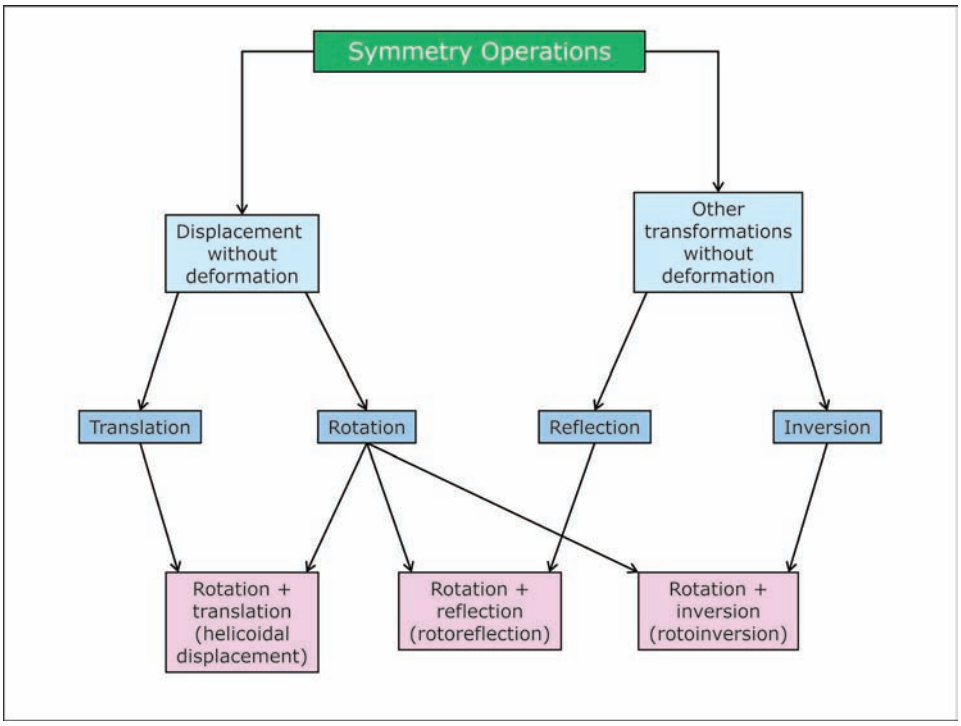



**Fig. 1.6.** This *Figure* offers an overview and a classification of symmetry operations, all of which occur without deformation of the molecule under scrutiny. That is to say, these operations preserve *isomorphism*. *Translation* (not discussed here) and *rotation* result from a displacement, meaning that the molecule is 'displaced' either without change in its orientation (in case of translation) or with change (in case of rotation). The combination of a translation and a rotation yields a *helicoidal displacement*, a path along a helix. *Helical chirality* will be discussed in *Part 3*.

The other transformations (*reflection* and *inversion*) have been presented in *Figs. 1.3* and *1.5*, respectively, and imply that each atom lying outside the element of symmetry (plane or center) has an opposite, namely a symmetrically located identical 'twin'. The combinations of either reflection or inversion with rotation (rotoreflection and rotoinversion, resp.) have been presented in *Figs. 1.4* and *1.5*.

From a chemical perspective, it is important to note that physical properties and wave functions must be invariant with respect to symmetry operations. This is an important law to which we shall return.

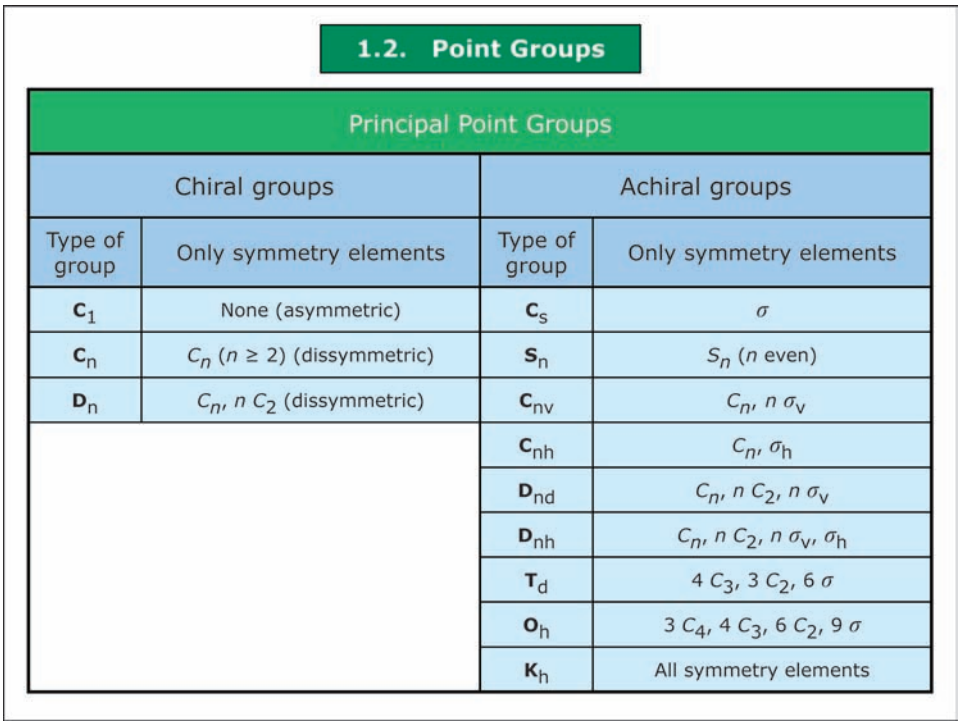



**Fig. 1.7 – 1.9.** A symmetry group is the ensemble of all symmetry operations that can convert a given object into orientations indistinguishable from the original. In other words and as far as we are concerned here, it is the ensemble of all symmetry elements of a given molecule. These ensembles are called *point groups* (they describe the symmetry of objects of finite dimensions) in contrast to *space groups* which are associated with periodic structures and do not concern us. Point groups are classified into those *lacking reflection symmetry* (no $\sigma$ plane), and those which do possess reflection symmetry. The structures having no $\sigma$ plane are called *chiral*. *Chirality* (from the Greek '*cheir*' meaning hand) is the property of any object that '*cannot be brought to coincide*' with its mirror image, meaning that it is not superimposable on its mirror image, a property also called '*handedness*' [20]. In other words, a chiral structure can not have a $\sigma$ plane. If no other symmetry element is present (except the trivial identity operation), the structure is called *asymmetric* (the prefix 'a' means 'without') and belongs to *point group* $\mathbf{C}_1$. An asymmetrically substituted tetrahedral C-atom illustrates this point group, as exemplified here with bromochloroiodomethane (**1.12** in *Fig. 1.9*). It can easily be seen that the two are not superimposable, and none of the symmetry operations is able to interconvert them.

If one or more $C_n$ ($n \geq 2$) are present, we have *dissymmetric* structures which are *not asymmetric* ([20], see also below) and belong to *point groups* $\mathbf{C}_n$. These point groups are exemplified here with 1,3-dibromopropadiene (**1.11** in *Fig. 1.8*), a chiral molecule occuring as two enantiomers whose $C_2$ symmetry is best seen using the *Newman* projections shown in the lower part of the *Figure*. (*Newman* projections will

be discussed in *Part 4* of this work; suffice it to say here that they are a conventional way of looking at a molecule from the end of a bond axis, as suggested by the two observers on the left and right borders of the *Figure.*)

Symmetrically richer yet still dissymmetric point groups are $\mathbf{D}_n$; these groups contain the molecules possessing a principal $C_n$ axis plus $n$ $C_2$ axes perpendicular to $C_n$.

Molecules with reflection symmetry are called *non-dissymmetric* or *achiral* rather than the ambiguous term 'symmetric'. When only a $\sigma$ plane is present (no $C_n$), the structures belong to the point group $\mathbf{C}_s$ (see *Fig. 1.7*). There also exist molecules having a $S_n$ axis but no $\sigma$ plane (point groups $\mathbf{S}_n$, $n$ even), but the presence of an improper axis implies rotoreflection. The spiropentane derivative **1.13** shown in *Fig 1.9* has an $S_4$ axis coincident with a $C_2$ axis, but no $\sigma$ plane. After a 90° rotation along $S_4$, the molecule is superimposable on its mirror image.

In many cases, however, achiral molecules have both $\sigma$ planes and $C_n$ axes. With one $C_n$ and $n$ $\sigma$ planes intercepting at $C_n$, the point groups are $\mathbf{C}_{nv}$ and the planes $\sigma_v$. For example, the molecule of $H_2O$ (**1.1**) belongs to $\mathbf{C}_{2v}$ and $CHCl_3$ (**1.2**) to $\mathbf{C}_{3v}$ (*Fig. 1.3*).

Molecules with one $C_n$ axis and one $\sigma_h$ plane, but no $\sigma_v$ plane, belong to point groups $\mathbf{C}_{nh}$. (*E*)-1,2-Dichloroethene (**1.6** in *Fig. 1.4*) is such a case ($\mathbf{C}_{2h}$). Molecules having one $C_n$ axis and $n$ $C_2$ axes (dihedral symmetry), and $n$ $\sigma_v$ planes, but no $\sigma_h$ plane, belong to the $\mathbf{D}_{nd}$ groups (d, diagonal). If the $\sigma_h$ plane is also present, the point groups are $\mathbf{D}_{nh}$. $\mathbf{D}_{nd}$ and $\mathbf{D}_{nh}$ are groups of higher symmetry than the previous ones. For example, benzene (**1.3** in *Fig. 1.2*) has $\mathbf{D}_{6h}$ symmetry (one $C_6$, six $C_2$, six $\sigma_v$, and one $\sigma_h$), while dichloroacetylene (**1.4** in *Fig. 1.2*) has $\mathbf{D}_{\infty h}$ symmetry (cylindrical symmetry).

Point groups of a higher symmetry have several $C_n$ axes ($n > 2$). They include group $\mathbf{T}_d$ (tetrahedral symmetry), group $\mathbf{O}_h$ (octahedral symmetry), and the centrosymmetric group $\mathbf{K}_h$ (spherical symmetry; see *Fig. 1.7*).

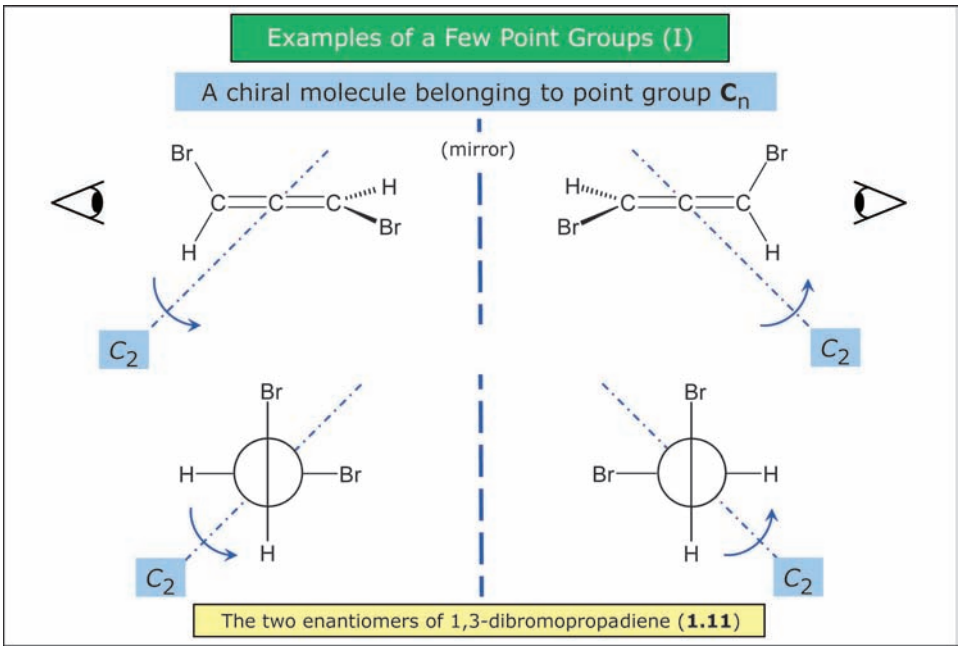

Examples of a Few Point Groups (I)
A chiral molecule belonging to point group $C_n$
(mirror)
Br
H
C
Br
H
$C_2$
The two enantiomers of 1,3-dibromopropadiene (1.11)

**Fig. 1.8.**

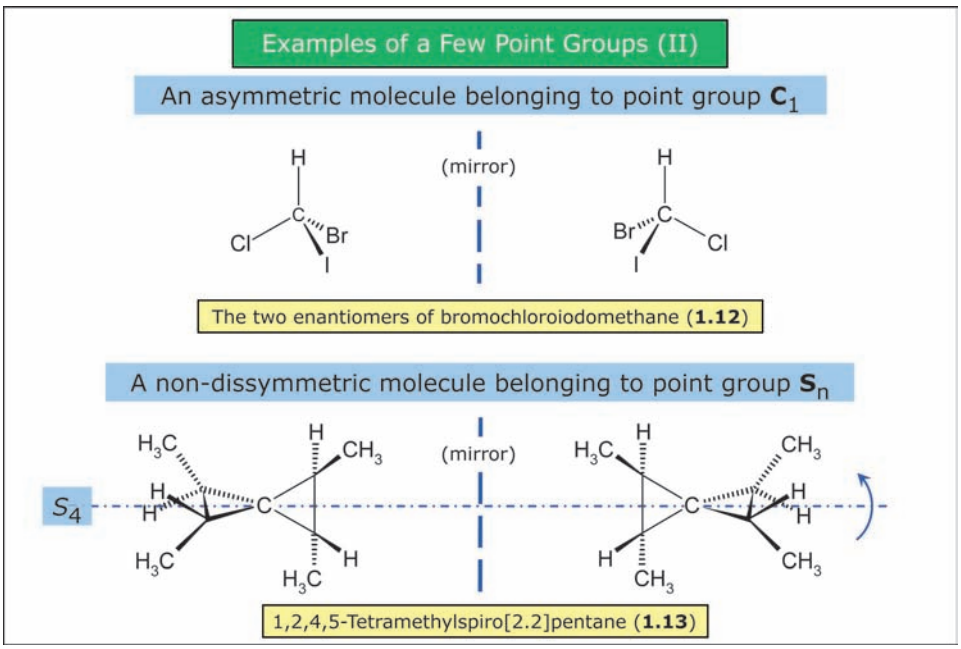

Examples of a Few Point Groups (II)
An asymmetric molecule belonging to point group $C_1$
(mirror)
H
C
Cl
Br
I
The two enantiomers of bromochloroiodomethane (1.12)
A non-dissymmetric molecule belonging to point group $S_n$
$S_4$
$H_3C$
$CH_3$
The two enantiomers of 1,2,4,5-Tetramethylspiro[2.2]pentane (1.13)

**Fig. 1.9.**

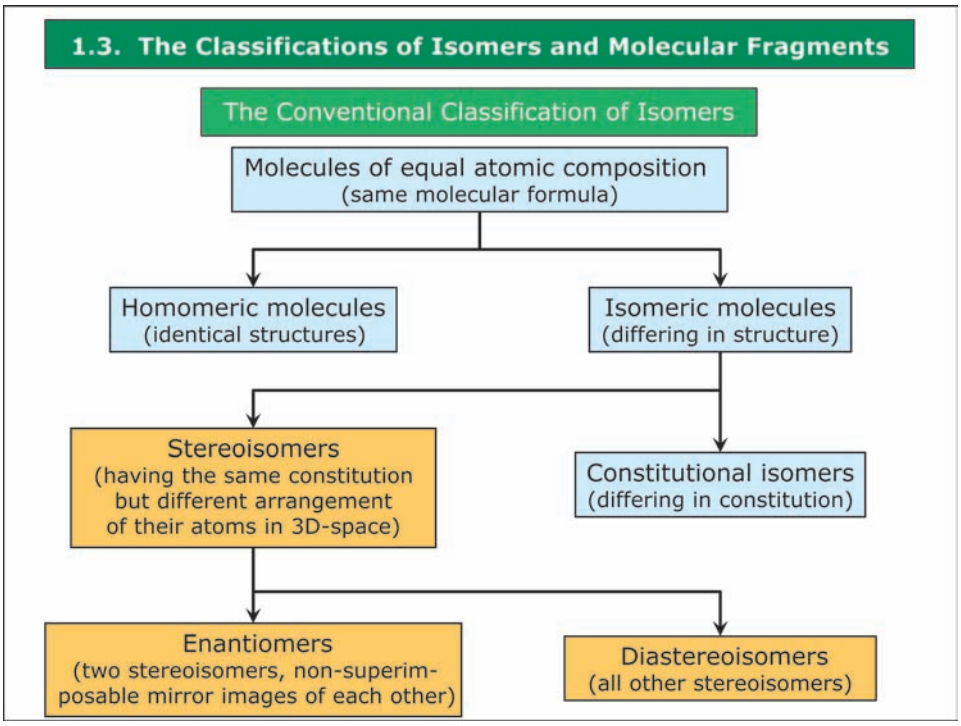



**Fig. 1.10.** The classification of molecular structures shown here present fundamental structural relations among molecules sharing the same *composition* (*i.e.*, having the same *molecular formula*) [21][22]. Such molecules may be identical in every other aspects, in which case they are *homomeric*, a term meaning 'identical'. However, what interests us here are molecules sharing the same molecular formula which prove different when their molecular structure is examined in greater detail. Such molecules are called *structural isomers*. These are defined as molecular entities sharing a common atomic composition but differing in some other structural feature. Thus, they may differ in their *atom connectivity* (*constitution*), making them *constitutional isomers*.

Should structural isomers share the same constitution yet still be different, they are called *stereoisomers*, which means that they differ in the arrangement of their atoms in three-dimensional space. Stereoisomeric structures can share two types of relations. Either *two stereoisomers* are related to each other as non-superposable mirror images or they are not. In the former case, the two stereoisomers share an *enantiomeric relationship* and they are *enantiomers* of each other. This implies that the molecules are chiral: *chirality* is the necessary and sufficient condition for the presence of enantiomers.

Stereoisomers which are not enantiomers are called *diastereoisomers* and have a *diastereoisomeric relationship*. For example, (*E*)-1,2-dichloroethene (**1.6** in *Fig. 1.4*) has a diastereoisomer ((*Z*)-1,2-dichloroethene) having the two Cl-atoms on the same side of the C=C bond.

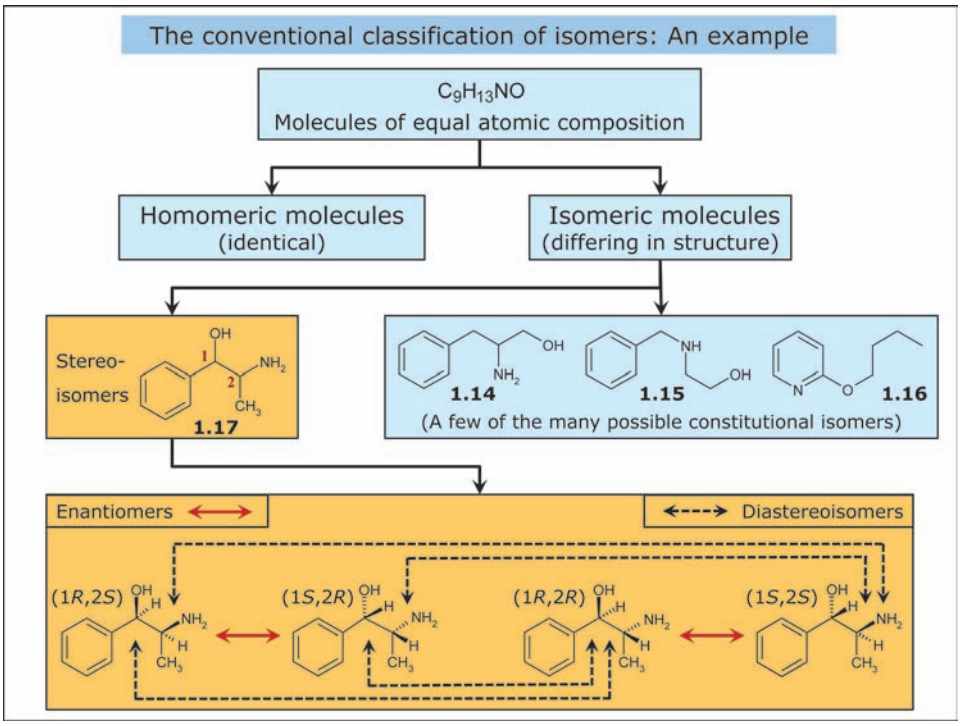



**Fig. 1.11.** This *Figure* illustrates the previous one on the basis of an example. Given its implicit structural diversity and didactic interest, the *molecular formula* $C_9H_{13}NO$ was chosen as an example. A large number of *isomeric* molecules are possible with this atomic composition; most of these are *constitutional isomers*, as illustrated here with a few examples. Among these numerous constitutional isomers, some are *regioisomers*, meaning that they differ in the location of a functional group. For example, the regioisomers of the pyridine derivative shown here, 2-butoxypyridine (**1.16**), are 3-butoxy- and 4-butoxypyridine. Also, some of the constitutional isomers are chiral, *e.g.*, 2-amino-3-phenylpropan-1-ol (**1.14**). A most relevant isomer is norephedrine (**1.17**) whose two centers of chirality (*stereogenic* centers) allow the occurrence of four *stereoisomers*.

These four stereoisomers consist in *two pairs of enantiomers*, as identified in the lower box by a double-headed red arrow. In other words, each of the four stereoisomer shares an *enantiomeric relationship* with one, and one only, of the other three stereoisomers. In addition, it shares a *diastereoisomeric relationship* with the two remaining stereoisomers, as identified by the dotted double-headed black arrows. Norephedrine thus offers an example of an essential fact to be kept in mind, namely that a given stereoisomer can share an *enantiomeric relationship* with one and only one other stereoisomer, while also sharing a *diastereoisomeric relationship* with one or more other stereoisomers. (The absolute configuration of the individual stereoisomers is identified by the *Cahn–Ingold–Prelog* convention (*stereodescriptors*) to be discussed at length in *Part 2*).

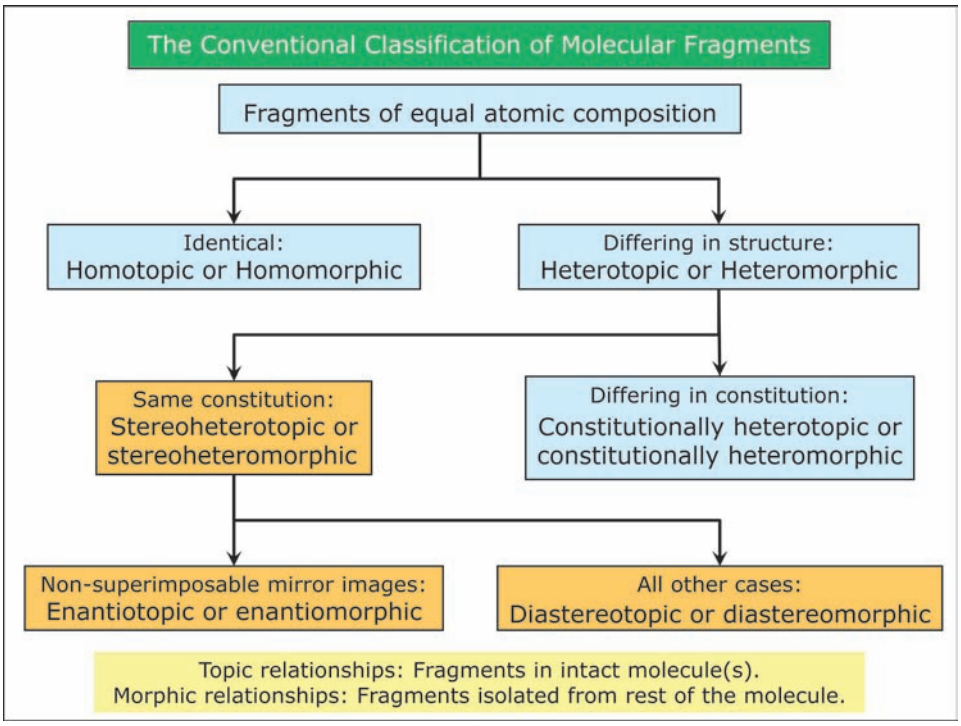



**Fig. 1.12.** *Steric relationships* are not restricted to whole molecules but occur also in *fragments* thereof, *i.e.*, functional groups, moieties, or substituents, provided, of course, such fragments are of equal atomic composition [21–24]. When such fragments are considered in isolation, that is to say separated from the remainder of the molecule, their relationships are called *morphic* (from *morhê* in Greek, meaning shape, form). In contrast, when the fragments are examined *in situ* (in the intact molecule), one speaks of *topic relationships*. The latter are of greater significance in our context, and we will encounter them in *Part 8* when discussing *prostereoisomerism* and *product stereoselectivity*. As evidenced in this *Figure*, both topic and morphic relationships are based on criteria analogous to those used in the traditional classification of isomers (*Figs. 1.10* and *1.11*).

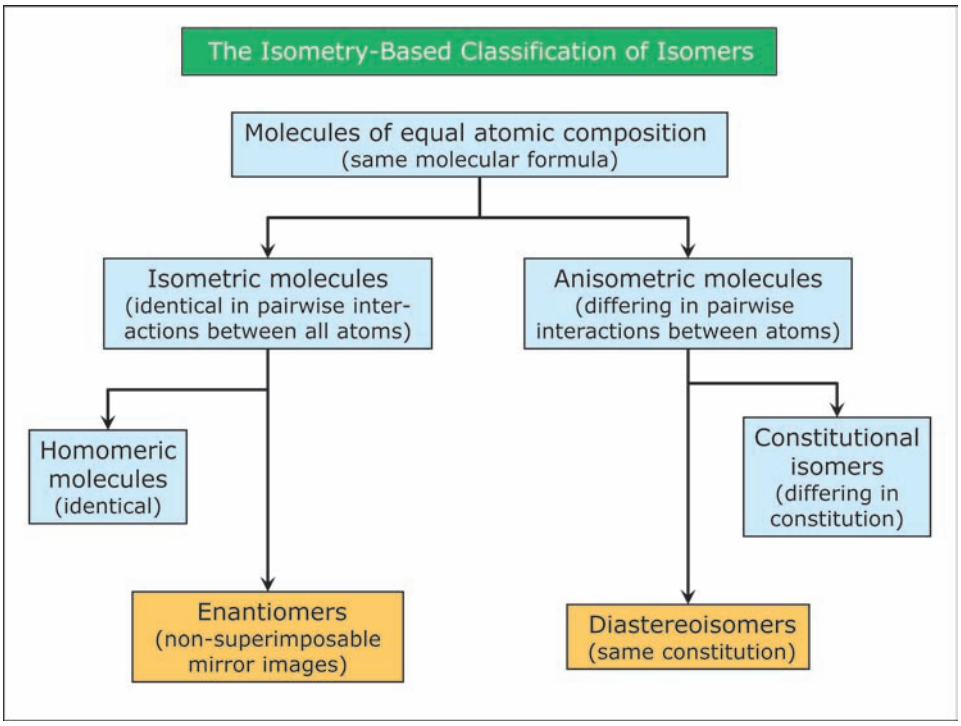
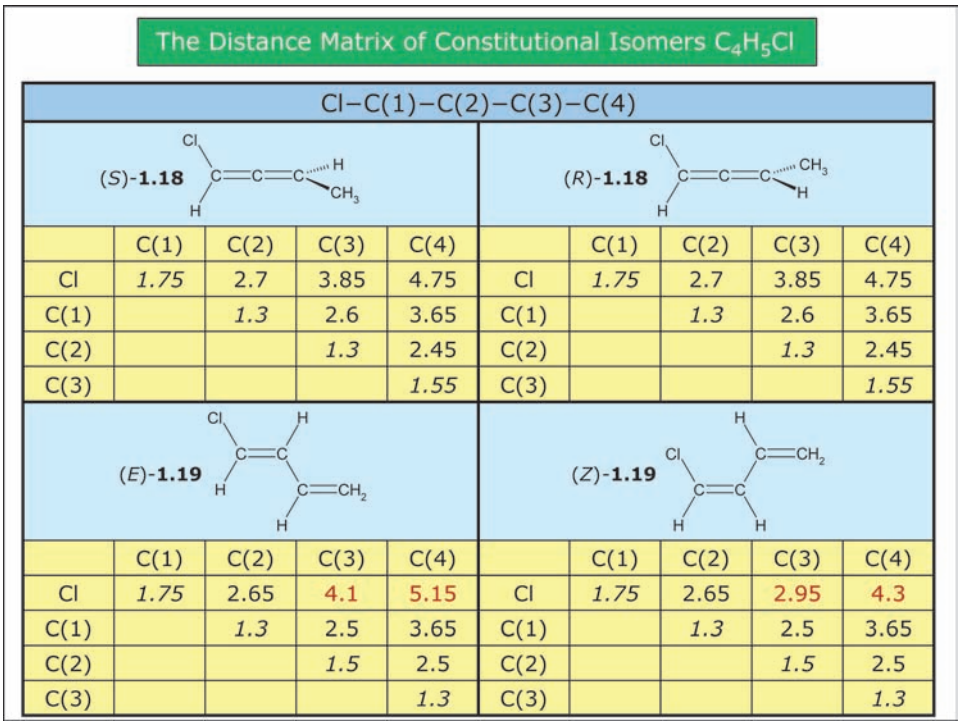



**Fig. 1.13.** The *conventional classification* presented in *Fig. 1.10* is based on the bonding connectivity of atoms. This results in a discrimination between identically connected isomers (*stereoisomers*) and those that are not (*constitutional isomers*). This classification is widely accepted but is not fully satisfactory, as cogently argued by *Mislow* [21][23]. As we shall discuss below, *enantiomers* have identical chemical and physical properties, while diastereoisomers differ in every property, however small the difference. As such, *diastereoisomers* have more in common with *constitutional isomers* than they have with *enantiomers*. Also, the conventional classification separates *enantiomers* and *homomers*, an awkward result, given that, in achiral environments, enantiomers behave as if they were homomers.

The new classification put forward by *Mislow* is not based on the sole bonding connectivity of atoms, but on the pairwise interactions between *all* atoms in a molecule. This is easily seen, for example, in a *distance matrix of all non-H-atoms* (see *Fig. 1.14*). Applying the isometry operation to molecules having the same molecular formula, two categories emerge, *isometric and anisometric molecules*. The former are *homomeric* or *enantiomeric* depending on whether they are superimposable mirror images or not. As for anisometric molecules, they will be *diastereoisomeric* or *constitutionally isomeric*, depending on whether or not they have the same constitution. Although not shown here, it is also applicable to molecular fragments in an analogous manner.

The 'isometry'-based classification of isomers is unambiguous, but it has no use for the well-known terms '*structural isomerism*' and '*stereoisomerism*'.




| | C(1) | C(2) | C(3) | C(4) |
|---|---|---|---|---|
| Cl | *1.75* | 2.7 | 3.85 | 4.75 |
| C(1) | | *1.3* | 2.6 | 3.65 |
| C(2) | | | *1.3* | 2.45 |
| C(3) | | | | *1.55* |

| | C(1) | C(2) | C(3) | C(4) |
|---|---|---|---|---|
| Cl | *1.75* | 2.7 | 3.85 | 4.75 |
| C(1) | | *1.3* | 2.6 | 3.65 |
| C(2) | | | *1.3* | 2.45 |
| C(3) | | | | *1.55* |

| | C(1) | C(2) | C(3) | C(4) |
|---|---|---|---|---|
| Cl | *1.75* | 2.65 | 4.1 | 5.15 |
| C(1) | | *1.3* | 2.5 | 3.65 |
| C(2) | | | *1.5* | 2.5 |
| C(3) | | | | *1.3* |

| | C(1) | C(2) | C(3) | C(4) |
|---|---|---|---|---|
| Cl | *1.75* | 2.65 | 2.95 | 4.3 |
| C(1) | | *1.3* | 2.5 | 3.65 |
| C(2) | | | *1.5* | 2.5 |
| C(3) | | | | *1.3* |

**Fig. 1.14.** Here, we illustrate distance matrices of all pairwise interactions, namely all distances between bonded atoms, as well as distances between nonbonded atoms, as measured with *Dreiding* molecular models. To this end, four isomeric molecules of molecular formula $C_4H_5Cl$ are used. To simplify the tables, only heavy atoms are considered; the H-atom-suppressed matrices obtained in this manner are simpler and easier to understand than all-atom matrices, without loss of exactness. We begin with 1-chlorobuta-1,2-diene (**1.18**), a compound that shows chirality by virtue of an axis of chirality, as discussed in *Part 3*. As seen in the upper part of the *Figure*, the distance matrices of the two enantiomers of 1-chlorobuta-1,2-diene are identical.

In contrast, 1-chlorobuta-1,3-diene (**1.19**; taken here in its planar, extended conformation) is an achiral compound occuring as a pair of (*E*)/(*Z*) diastereoisomers. As shown in the lower part of the *Figure*, the distances between the Cl-atom and the distal –CH=$CH_2$ moiety are different in the two diastereoisomers. This leads to different chemical and physicochemical properties of the diastereoisomers, as discussed below.

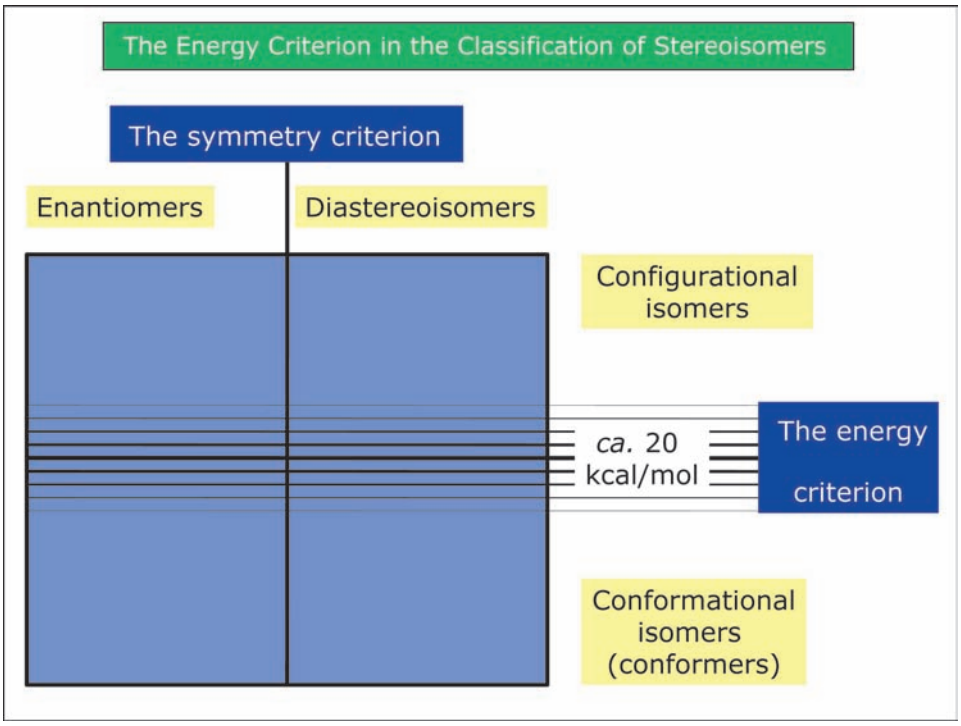



**Fig. 1.15.** *Figs. 1.10*, *1.11*, and *1.14* have introduced us to a fundamental difference between enantiomers and diastereoisomers. This difference is based on *symmetry arguments* and is, therefore, a sharp and unambiguously defined one, as long as molecules are taken as rigid [25]. This is illustrated here with a vertical line neatly dividing the square symbolizing the ensemble of all stereoisomers. But as stated earlier, symmetry arguments are based on the *assumption of rigid molecules.*

Indeed, a second criterion of classification exists to discriminate between stereoisomers – the *energy criterion*. Far from being a rigid entity (a '*statue*'), a molecule shows flexibility and can be compared to a *ballerina* [26][27]. The *energy classification* is concerned with the energy necessary to convert a given stereoisomer into an isomeric form. Here, the *energy barrier* separating the two stereoisomers becomes an important criterion of classification. In semi-quantitative terms, stereoisomers which are separated by a (comparatively) high-energy barrier differ in *configuration*, *i.e.*, they are *configurational isomers.* A (comparatively) low-energy barrier separates isomers differing in their *conformation*, *i.e.*, *conformers* [28].

Within the energy criterion, a precise differentiation between configuration and conformation is rendered difficult by the variety of existing definitions. The IUPAC [29] has reached the following consensual definition of conformers: '*The spatial arrangement of the atoms affording distinction between stereoisomers which can be interconverted by rotations about formal single bonds. Some authorities extend the term to include inversion at trigonal pyramidal centres and other polytopal rearrangements*'. In our opinion, it is helpful to apply the energy criterion to all stereoisomers, whatever

the mechanism of interconversion. As we will discuss in *Part 2*, *pyramidal inversion*, for example, in tertiary amines is a typical low-energy inversion process requiring a limited number of kJ/mol. Furthermore, even some asymmetrically substituted tetrahedral C-atoms ($sp^3$ C-atoms) are configurationally unstable and can undergo inversion (see *Part 2*). Calling such fast interconverting enantiomers 'configurational isomers' does not seem appropriate, but we recognize that to term them 'conformers' may also sound strange to some.

Unlike the fuzziness surrounding the definition of conformers, that of configurational isomers has the merit of being clear and independent of the high-energy mechanism underlying a potential interconversion. Indeed, such a mechanism may be *rotation about C=C bonds* (*Part 3*) in (*Z*)- and (*E*)-isomers, *e.g.*, (*E*)-1,2-dichloroethene (**1.6** in *Fig. 1.4*) and its (*Z*)-diastereoisomer discussed in the caption of Fig. *1.10*. Alternatively, the conceptual mechanism of configurational interconversion may be *rotation about a C–C bond* in comparatively stable *atropisomers* (*Part 3*), or *inversion* of stable asymmetrically substituted $sp^3$ C-atoms (*Part 2*). It thus seems to us that, like the definition of configurational isomers, that of conformers should be disconnected from any underlying mechanism of interconversion.

This being said, the main difficulty when applying the *conformation/configuration dichotomy* to stereoisomers lies in the lack of a well-defined energy level giving a clear separation of the two classes. If conformation refers to a 'low'-energy barrier, and configuration ot a 'high'-energy one, how are intermediate cases to be classified? Should an arbitrary cutoff level be set in a continuous range of values, calling for accurate knowledge of energy barriers as a condition for classification? We believe that the boundary between conformation and configuration should be viewed as a broad range of activation free energies around the value of 20 kcal/mol (*ca.* 84 kJ/mol) which corresponds to a half-life of *ca.* 1 min at 20°. Such a fuzzy criterion should not be viewed as a drawback considering that experimental conditions (solid *vs.* dissolved state, nature of solvent, *etc.*) can have a huge influence on the rate of interconversion. A graphical translation of this fuzziness is offered in the *Figure*, a series of parallel lines of varying thickness symbolizing the *fuzzy separation between configurational and conformational isomers*. This classification of stereoisomers based on the two independent criteria of symmetry and energy will be used throughout this work.

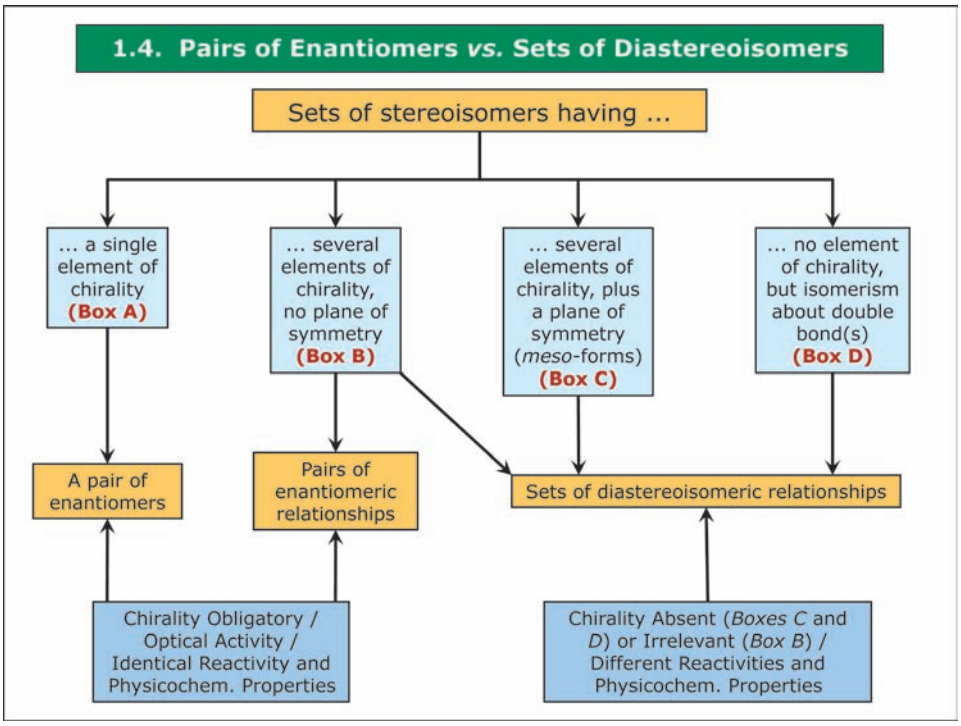



**Fig. 1.16.** As illustrated in *Fig. 1.11* with norephedrine (**1.17**), there exist sets of stereoisomers whose members share enantiomeric relationships with one other member in their set, while simultaneously sharing diastereoisomeric relationships with the other members (*Box B*). This tells us that *enantiomerism* and *diastereoisomerism* are concepts based on *intermolecular relationships*, and that such relationships sometimes need to be stated explicitly. Common language often uses the words '*enantiomers*' or '*diastereoisomers*' without explicitely mentioning relationships, an unambiguous situation when referring to the cases described by *Boxes A* and *D*. The same is true for the *meso-forms* (*Box C*) to be discussed in *Part 2*; there, two or more elements of chirality (mainly centers) are present, but the presence of a plane of symmetry renders the molecules achiral and allows only for diastereoisomeric relationships.

The principle to emerge from this discussion is that *enantiomers are chiral by necessity and definition*. In contrast, some diastereoisomers are chiral (*Box B*) and others are not (*Boxes C* and *D*). Pure enantiomers and mixtures containing an excess of one enantiomer (*non-racemic mixtures*) do show *optical activity* [30–38]. Furthermore, as illustrated in subsequent figures, two isomers which share an enantiomeric relationship have *identical chemical reactivity and physicochemical properties*; only in the presence of a '*chiral handle*' (a chiral solvent, stationary phase, derivatizing reagent, a plane-polarized light, *etc.*) can they be separated or simply distinguished. In contrast, isomers sharing diastereoisomeric relationships have different reactivities and physicochemical properties, however small the differences. Furthermore, it is important to note that optical activity is irrelevant as far as diastereoisomeric relationships are concerned.

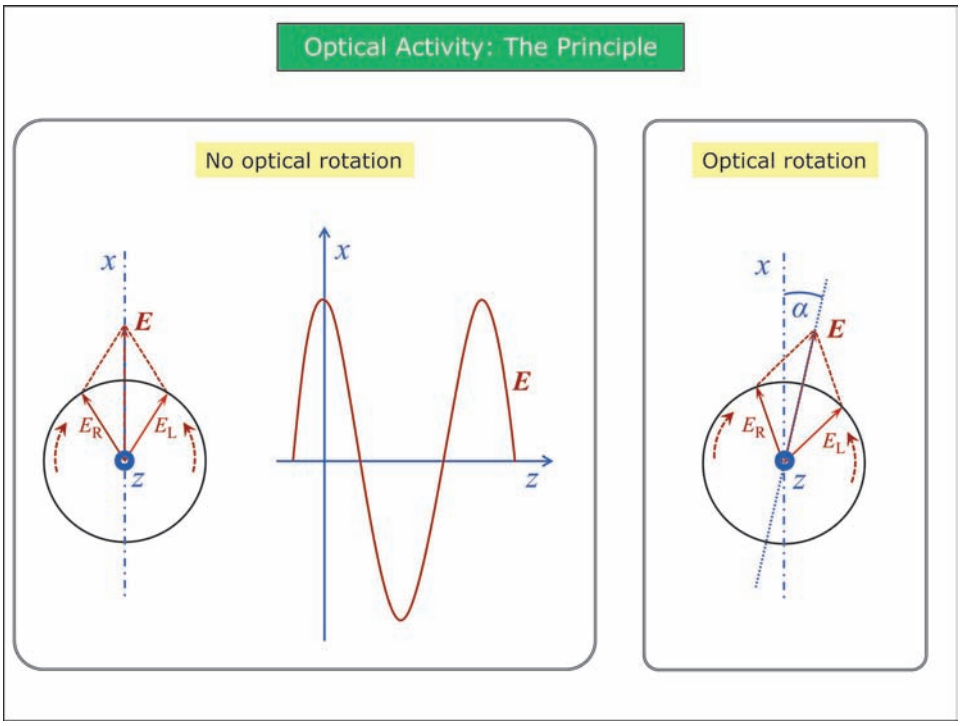



**Fig. 1.17.** A beam of *plane-polarized light* as produced in a polarimeter can be considered as being the result of a *left-handed* and a *right-handed circularly polarized in-phase beam*. The *vector* **E** of the associated electrical field is the result at any moment of the two *vectors* $\mathbf{E}_R$ *and* $\mathbf{E}_L$ (left box in the *Fig.*). The beam of plane-polarized light travels along axis $z$, while its associated vector **E** traces a two-dimensional sinusoidal path in the $xz$ plane, as shown. As for the two vectors $\mathbf{E}_R$ and $\mathbf{E}_L$, they trace out *helical paths* of opposite chirality (designated *P* and *M*; see *Part 3*). This is the situation in the absence of an optically active compound in the path of the beam.

In the *presence of a chiral solute*, the two helical paths enter their role of '*chiral handles*' [39], meaning that they now elicit a diastereoisomeric interaction with the solute. This discrimination is detected experimentally as differences in the *refractive indices* of the two components ($n_L \neq n_R$) and as differences in their *molar extinction coefficients* ($\varepsilon_R \neq \varepsilon_L$). The difference in refractive indices is called *circular birefringence* and corresponds to the slowing of one circular component relative to the other. As a result, the plane of polarization is rotated by an *angle α called the angle of rotation* (right box in the *Fig.*). A medium showing optical rotation is called *optically active.*

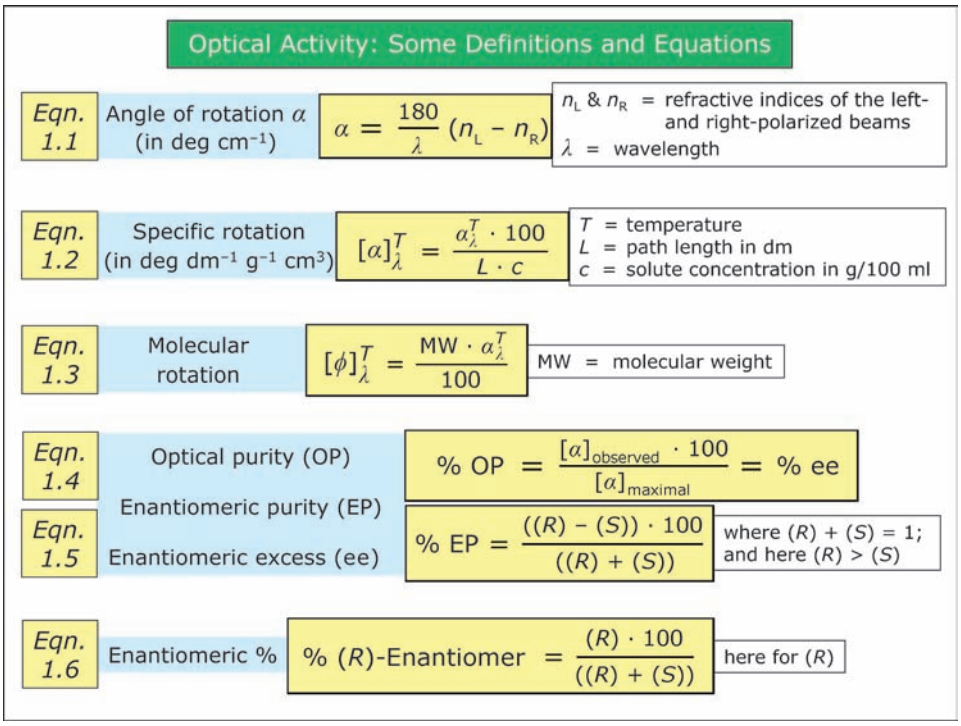



**Fig. 1.18.** A number of equations describe and explain optical activity, as compiled here [40–42]. The *angle of rotation* $\alpha$ is given by *Eqn. 1.1*, showing it to be a function of the wavelength ($\lambda$), and to depend on the difference between the refractive indices of the left- and right-polarized beams, $n_L$ and $n_R$, respectively. The magnitude of $\alpha$ for a given solute is also dependent on solvent, temperature, and the number of molecules in the path of the beam (assuming ideal behavior, *i.e.*, no interaction between molecules). Experimentally, what is determined is usually a *specific rotation* $[\alpha]$ (*Eqn. 1.2*) or a *molecular rotation* $[\phi]$ (*Eqn. 1.3*) at a given $\lambda$ and $T$.

A frequent problem when working with chiral compounds is to have a good measure of the *degree of optical purity* or the relative proportions of the two enantiomers in the sample under consideration. The *percentage of optical purity* is thus defined experimentally (*Eqn. 1.4*) as the ratio ($\times 100$) of the observed to the maximal angle $\alpha$ (known independently to correspond to practically 100% purity). Note that a similar experimental definition is given to a descriptor frequently used by synthetic chemists, that of *enantiomeric excess* (ee). In molecular terms, % optical purity and % ee are equivalent also to *enantiomeric purity* (*Eqn. 1.5*). The latter equation shows that, in these definitions, what is substracted from the total is the amount of racemate (*RS*). In contrast, *enantiomeric percentage* (*Eqn. 1.6*) is not directly related to optical activity but to the proportion of the two enantiomers in the mixture, as determined, *e.g.*, by chiral chromatography.

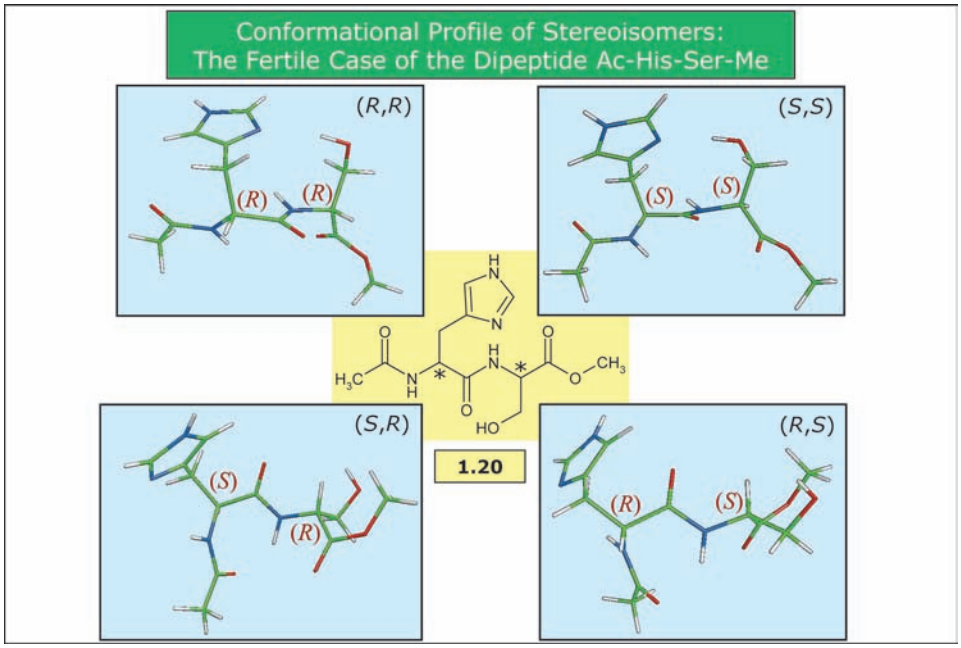



**Fig. 1.19.** As stated when commenting *Fig. 1.13*, enantiomers have identical physicochemical properties, while diastereoisomers differ in every property, however small the difference. The relevance of such a fundamental difference can be understood by examining the conformational behavior and property profiles of the four possible stereoisomers for the protected dipeptide Ac-His-Ser-OMe (**1.20**). This dipeptide was chosen for its marked structural flexibility favored in part by the intermittent formation of a H-bond between the side chains. The ionizable groups were protected to avoid a conformational bias caused by a strong intramolecular ionic bond.

The *Figure* shows the lowest-energy geometry (preferred conformers) of the four stereoisomers as derived by combining clustered *Monte Carlo* (MC) analyses[2]) with PM6 semi-empirical calculations[3]). Conventionally, C-atoms are indicated in green, H-atoms in white, N-atoms in blue, and O-atoms in red. A bird's eye examination of these conformers shows that the (*R*,*R*)- and (*S*,*S*)-enantiomers have *mirror-image conformations* stabilized by an intramolecular H-bond between the two side chains involving the serine OH group and the N($\pi$)-atom of the histidine imidazolyl ring. Similarly, the (*R*,*S*)- and (*S*,*R*)-enantiomers have *mirror-image conformations* stabilized by H-bonds between the backbone atoms, while the side chains are too distant to elicit significant contacts. In other words, the *diastereoisomers differ in their preferred conformations* due to different intramolecular forces caused in turn by different steric constraints. A few implications in terms of physicochemical properties are illustrated and discussed in *Figs. 1.20–1.22*.

[2]) The conformational profile of the four stereoisomers was evaluated *in vacuo* by a clustered Monte Carlo analysis which generated 1,000 conformers by randomly rotating the rotors. All geometries so obtained were optimized to avoid high-energy rotamers. The 1,000 conformers were clustered according to their similarity to discard redundant ones; in this analysis two geometries were considered as non-redundant when they differed by more than 60° in at least one torsion angle.

[3]) The lowest-energy geometries as derived by MC calculations underwent a semi-empirical optimization by MOPAC7 (Keywords: 'PM6', 'PRECISE', 'GEO-OK').

Behavior of the Ac-His-Ser-Me dipeptide *in vacuo*

| Isomer | Distance OH–N($\pi$) [Å] | Radius of gyration [Å] | Log $P_{MLP}$ | Difference in log *P* between diastereoisomers | Log *P* range |
|---|---|---|---|---|---|
| (*R*,*R*) Optimized geometry | 2.27 | 3.34 | –0.35 | Optimized geometry: 0.09<br>Mean values: 0.01 – 0.02 | – |
| (*R*,*R*) Mean from MD | 5.97 | 3.33 | –0.43 | | 0.44 |
| (*S*,*S*) Optimized geometry | 2.27 | 3.34 | –0.35 | | – |
| (*S*,*S*) Mean from MD | 6.12 | 3.34 | –0.43 | | 0.45 |
| (*R*,*S*) Optimized geometry | 6.59 | 3.44 | –0.44 | | – |
| (*R*,*S*) Mean from MD | 7.85 | 3.50 | –0.45 | | 0.55 |
| (*S*,*R*) Optimized geometry | 6.64 | 3.45 | –0.44 | | – |
| (*S*,*R*) Mean from MD | 7.68 | 3.53 | –0.44 | | 0.56 |

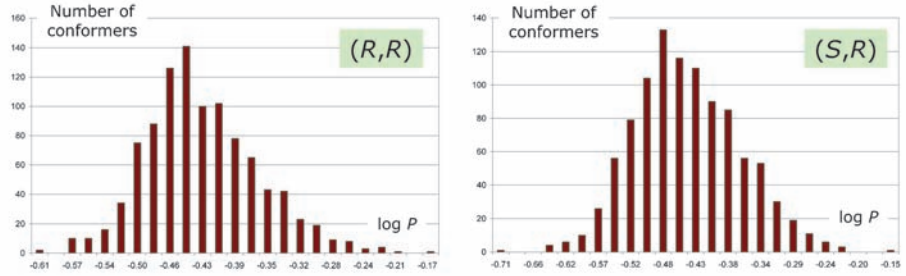



**Fig. 1.20 – 1.22.** *Fig. 1.20* and the two following ones outline the results of computations aimed at illustrating similarities between enantiomers and differences between diastereoisomers. *Molecular dynamics* (MD) *simulations* were carried out with the four stereoisomers presented in the previous *Figure*. This yielded the *conformational space* of the compounds, namely a sampling of all energetically possible and realistically different conformers. A number of structural and physicochemical properties were then computed for the single optimized geometries and for the populations of conformers. The MD simulations were carried out in three media, namely *in vacuo* (*Fig. 1.20*), in $H_2O$ as representing an achiral environment (*Fig. 1.21*), and in (*S*)-*sec*-butanol as a chiral solvent (*Fig. 1.22*). Specifically, the analyses were focused on lipophilicity as represented by log *P* (log of partition coefficient) computed by a Molecular Lipophilicity Potential (MLP) [43] using the VEGA suite of programs [44]. *Lipophilicity* is a well-known, conformer-dependent physicochemical property of high relevance in drug design [43]. The structural properties we report are the *radius of gyration*, which encodes molecular size and shape [45], and a pure geometric descriptor, namely the *distance between the serine OH group and the histidine N($\pi$)-atom*. The dynamic profile of the monitored properties was analyzed by exploiting the *property space concept*, in which the profile of a given conformer-dependent property can be described by its distribution as encoded, for example, by the *range of values* it covers [26][27].

The *identical profile of the enantiomers* finds the expected confirmation when examining the structural and physicochemical properties compiled here. Indeed, the two enantiomers in each pair show identical values for all monitored properties, the only non-significant exception being the mean OH–N($\pi$) distance due to a computational artefact. As far as *differences between diastereoisomers* are concerned, the H-bond between the side chains in the (*R*,*R*)- and (*S*,*S*)-enantiomers result in a much more folded geometry (shorter OH–N($\pi$) distance) and a slightly smaller lipophilicity than in the (*R*,*S*)- and (*S*,*R*)-enantiomers. Intriguingly, the differences between diastereoisomers become markedly less pronounced when going from a single minimized geometry to a population of conformers computed by MD[4]). Yet, despite the comparable mean log*P* values of diastereoisomers, their lipophilicity space shows significant differences as seen in the corresponding *histograms*. Indeed, such histograms reveal both the *range and distribution of lipophilicity* among conformers, reflecting the conformational differences observed during MD simulations.

*Fig. 1.21* shows the results obtained by MD simulations of the four stereoisomers in a *water cluster*[5]). All computed structural and physicochemical properties remain practically identical between enantiomers, while the differences between diastereoisomers are decreased compared to results in a vacuum. What is more, the lipophilicity spaces as encoded by range and distribution and shown in the *histograms of two diastereoisomers* are practically identical. This suggests that an achiral medium will tend to *decrease differences* in properties between diastereoisomers. This can be explained considering that the dynamic profile of all stereoisomers is equally affected by strong H-bonds with water molecules. *Hydration* is indeed a well-known factor favoring extended geometries, as confirmed here by the high values of the structural descriptors (OH–N($\pi$) distance and radius of gyration).

While an achiral medium tends to minimize the differences between isomers, a *chiral medium* is expected to amplify them, as illustrated in *Fig. 1.22*. (*S*)-*sec*-Butanol was used as a representative *chiral medium*[6]), revealing that each stereoisomer now behaves toward all three of the others as if it were a diastereoisomer. This was due to the fact that each of the four stereoisomers formed *transient aggregates* with a few solvent molecules, and that these aggregates differed from one stereoisomer to the

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[4]) The 10-ns MD simulations had the following major characteristics: *a*) *Newton*'s equation was integrated every fs using the *Verlet*'s method; *b*) the temperature was maintained at $300 \pm 10$ K by means of *Langevin*'s algorithm; *c*) a frame was stored every 10 ps, yielding 1000 frames; and *d*) no constraints were applied to the systems. The simulations were carried out in two phases: an initial period of heating from 0 K to 300 K over 6000 iterations (6 ps, *i.e.*, 1 K/20 iterations), and a monitored phase of simulation of 10 ns.

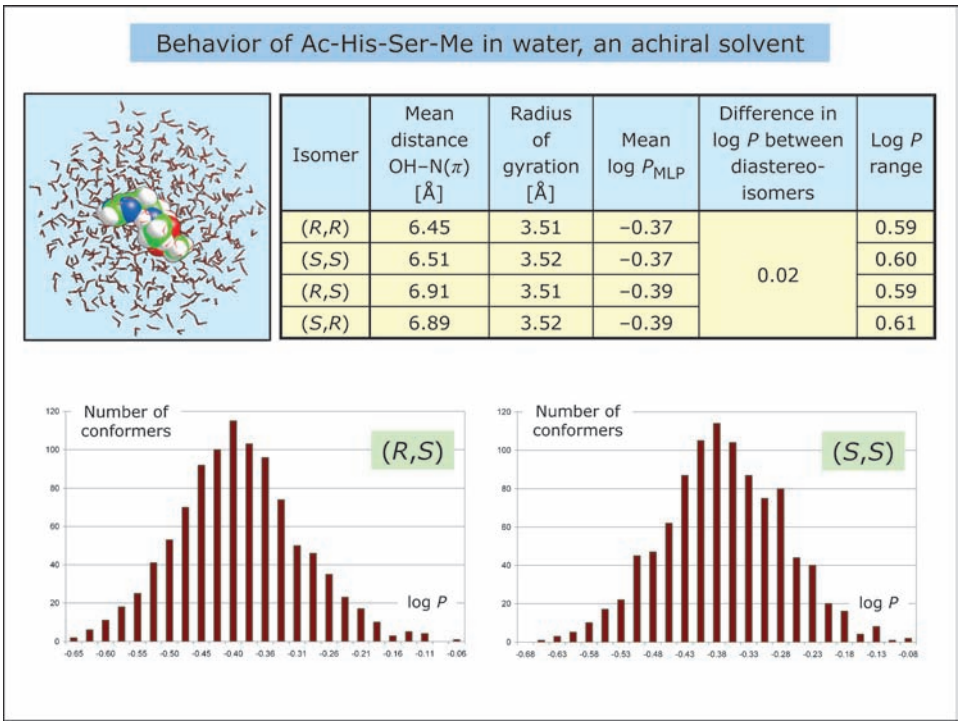
[5]) The isomers were inserted into a 15-Å radius sphere of $H_2O$ molecules, and, after a minimization to optimize the relative position of solvent molecules, the obtained systems underwent 10-ns MD simulations with the same characteristics as already described in *Footnote 4* apart from the introduced spherical boundary conditions to stabilize the simulation space.

[6]) A 60-Å side box of (*S*)-*sec*-butanol molecules was generated using the solvent builder as implemented in VEGA and minimized to optimize the relative position of solvent molecules. The isomers were inserted into a 25-Å radius sphere of (*S*)-*sec*-butanol molecules, and, after a preliminary minimization, the obtained systems underwent 10-ns MD simulations with the same characteristics as already described in *Footnotes 4* and *5*.

other. As a result, each stereoisomeric peptide saw its conformational space, and hence its property spaces, differently and independently constrained.

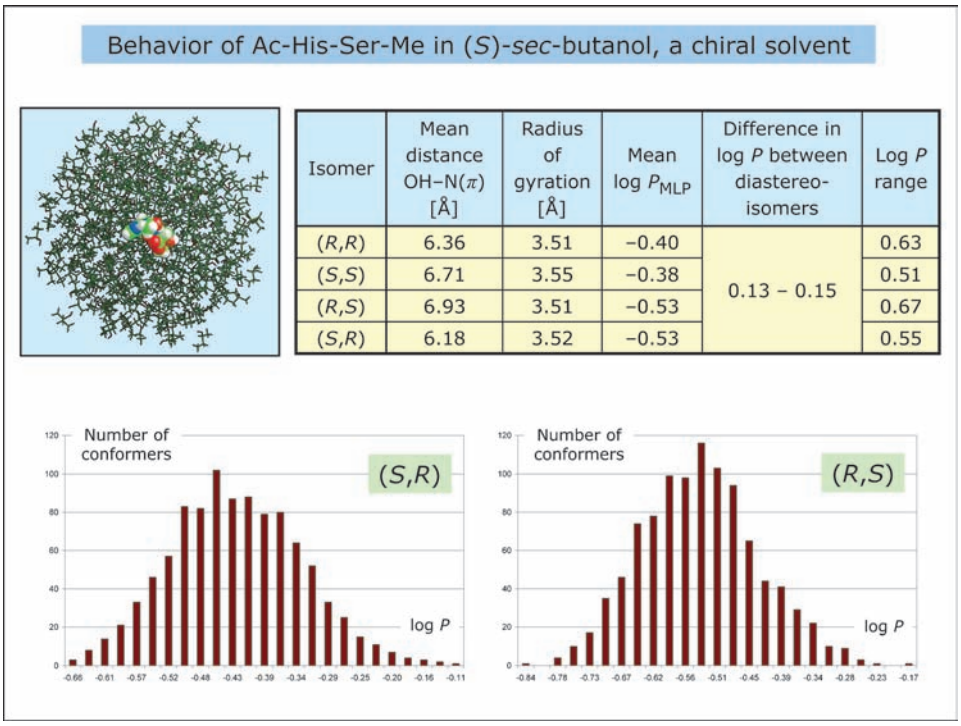
To repeat, interactions with the chiral solvent influenced the differences between diastereoisomers (as seen with the mean log *P* values) and, more importantly, those between enantiomers. The latter differences involved both the averages of OH–N($\pi$) distance and, to a greater extent, the lipophilicity spaces which indeed show marked differences both in range and distribution as illustrated by the *histograms comparing two enantiomers*. These results highlight the stereoselective effects that a chiral medium can exert on property spaces, thus emphasizing the relevance of such a concept to characterize better the dynamic profile of chiral molecules.

Taken globally, *Figs. 1.20 – 1.22* confirm the identical profile of enantiomers and the differences between diastereoisomers, when simulated *in vacuo* or in achiral environments. Such differences appear more pronounced with geometrical descriptors than with physicochemical properties, although property space parameters can also evidence significant diastereoisomeric differences. Finally, chiral media can induce differences in properties between enantiomers, even in their property space parameters.




| Isomer | Mean distance OH–N($\pi$) [Å] | Radius of gyration [Å] | Mean log $P_{MLP}$ | Difference in log *P* between diastereo-isomers | Log *P* range |
|---|---|---|---|---|---|
| (*R*,*R*) | 6.45 | 3.51 | –0.37 | 0.02 | 0.59 |
| (*S*,*S*) | 6.51 | 3.52 | –0.37 | | 0.60 |
| (*R*,*S*) | 6.91 | 3.51 | –0.39 | | 0.59 |
| (*S*,*R*) | 6.89 | 3.52 | –0.39 | | 0.61 |

**Fig. 1.21.**




| Isomer | Mean distance OH–N($\pi$) [Å] | Radius of gyration [Å] | Mean log $P_{MLP}$ | Difference in log $P$ between diastereo-isomers | Log $P$ range |
|---|---|---|---|---|---|
| (*R*,*R*) | 6.36 | 3.51 | –0.40 | 0.13 – 0.15 | 0.63 |
| (*S*,*S*) | 6.71 | 3.55 | –0.38 | | 0.51 |
| (*R*,*S*) | 6.93 | 3.51 | –0.53 | | 0.67 |
| (*S*,*R*) | 6.18 | 3.52 | –0.53 | | 0.55 |

**Fig. 1.22.**

REFERENCES

[1] B. Testa, S. D. Krämer, '*The Biochemistry of Drug Metabolism – An Introduction – Part 1. Principles and Overview*', *Chem. Biodiversity* **2006**, *3*, 1053 – 1101; '*Part 2. Redox Reactions and Their Enzymes*', *Chem. Biodiversity* **2007**, *4*, 257 – 405; '*Part 3. Reactions of Hydrolysis and Their Enzymes*', *Chem. Biodiversity* **2007**, *4*, 2031 – 2122; '*Part 4. Reactions of Conjugation and Their Enzymes*', *Chem. Biodiversity* **2008**, *5*, 2171 – 2336; '*Part 5. Metabolism and Bioactivity*', *Chem. Biodiversity* **2009**, *6*, 591 – 684; S. D. Krämer, B. Testa, '*Part 6. Inter-individual Factors Affecting Drug Metabolism*', *Chem. Biodiversity* **2008**, *5*, 2465 – 2578; '*Part 7. Intra-individual Factors Affecting Drug Metabolism*', *Chem. Biodiversity* **2009**, *6*, 1477 – 1660.

[2] B. Testa, S. D. Krämer, 'The Biochemistry of Drug Metabolism: Principles, Redox Reactions, Hydrolyses', Verlag Helvetica Chimica Acta, Zürich, and Wiley-VCH, Weinhein, 2008, Vol. 1, 319 p.; 'The Biochemistry of Drug Metabolism: Conjugations, Consequences of Metabolism, Influencing Factors', Vol. 2, 2010, 588 p.

[3] R. C. Powell, 'Symmetry, Group Theory, and the Physical Properties of Crystals', Springer-Verlag, Berlin, 2010, 225 p.

[4] D. J. Willock, 'Molecular Symmetry', John Wiley & Sons, Hoboken, 2009, 438 p.

[5] M. Hargittai, I. Hargittai, 'Symmetry through the Eyes of a Chemist', 3rd edn., Springer-Verlag, Berlin, 2009, 520 p.

[6] S. F. A. Kettle, 'Symmetry and Structure – Readable Group Theory for Chemists', 3rd edn., John Wiley & Sons, Hoboken, 2007, 436 p.

[7] A. M. Lesk, 'Introduction to Symmetry and Group Theory for Chemists', Springer-Verlag, Berlin, 2004, 122 p.

[8] J. S. Ogden, 'Introduction ot Molecular Symmetry', Oxford University Press, Oxford, 2001, 90 p.
[9] A. Vincent, 'Molecular Symmetry and Group Theory: A Programmed Introduction to Chemical Applications', 2nd edn., Wiley , Hoboken, 2001, 192 p.
[10] Y. Öhrn, 'Elements of Molecular Symmetry', Wiley-VCH, Weinheim, 2000, 292 p.
[11] R. L. Carter, 'Molecular Symmetry and Group Theory', John Wiley & Sons, Hoboken, 1998, 320 p.
[12] T.-L. Ho, 'Symmetry – A Basis for Synthesis Design', John Wiley & Sons, Hoboken, 1995, 584 p.
[13] D. M. Bishop, 'Group Theory and Chemistry', Clarendon Press, Oxford, 1973, reprinted by Dover Publications, Mineola, 1993, 300 p.
[14] E. Heilbronner, J. D. Dunitz, 'Reflections on Symmetry in Chemistry … and Elsewhere', Verlag Helvetica Chimica Acta, Zürich, and Wiley-VCH, Weinheim, 1993, 154 p.
[15] F. A. Cotton, 'Chemical Applications of Group Theory', 3rd edn., John Wiley & Sons, Hoboken, 1990, 480 p.
[16] B. Bunch, 'Reality's Mirror: Exploring the Mathematics of Symmetry', John Wiley & Sons, Hoboken, 1989, 286 p.
[17] L. D. Barron, '*Symmetry and Molecular Chirality*', *Chem. Soc. Rev.* **1986**, *15*, 189 – 223.
[18] K. Mislow, '*Molecular Chirality*', *Top. Stereochem.* **1999**, *22*, 1 – 82.
[19] M. Nakazaki, '*The Synthesis and Stereochemistry of Chiral Organic Molecules with High Symmetry*', *Top. Stereochem.* **1984**, *15*, 199 – 251.
[20] R. Bentley, '*Chiral: a Confusing Ethymology*', *Chirality* **2010**, *22*, 1 – 2; K. Mislow, '*Stereochemical Terminology and Its Discontents*', *Chirality* **2002**, *14*, 126 – 134; J. Gal, '*Louis Pasteur, Language, and Molecular Chirality. I. Background and Dissymmetry*', *Chirality* **2011**, *23*, 1 – 16; J. Gal, '*Stereochemical Vocabulary for Structures That Are Chiral but not Asymmetric: History, Analysis, and Proposal for a Rational Terminology*', *Chirality* **2011**, *23*, 647 – 659.
[21] K. Mislow, '*On the Classification of Pairwise Relations between Isomeric Structures*', *Bull. Soc. Chim. Belg.* **1977**, *86*, 595 – 601.
[22] K. R. Hanson, '*Concepts and Perspectives in Enzyme Stereochemistry*', *Annu. Rev. Biochem.* **1976**, *45*, 307 – 330.
[23] K. Mislow, M. Raban, '*Stereoisomeric Relationships of Groups in Molecules*', *Top. Stereochem.* **1967**, *1*, 1 – 38.
[24] K. Mislow, J. Siegel, '*Stereoisomerism and Local Chirality*', *J. Am. Chem. Soc.* **1984**, *106*, 3319 – 3328.
[25] K. Mislow, P. Bickart, '*An Epistemological Note on Chirality*', *Isr. J. Chem.* **1977**, *15*, 1 – 6.
[26] B. Testa, G. Vistoli, A. Pedretti, A. J. Bojarski, '*Atomic Diversity, Molecular Diversity, Chemical Diversity: The Concept of Chemodiversity*', *Chem. Biodiversity* **2009**, *6*, 1145 – 1151.
[27] G. Vistoli, A. Pedretti, B. Testa, '*Partition Coefficient and Molecular Flexibility: The Concept of Lipophilicity Space*', *Chem. Biodiversity* **2009**, *6*, 1152 – 1169.
[28] H. Dodziuk, 'Modern Conformational Analysis: Elucidating Novel Exciting Molecular Structures', John Wiley & Sons, New York, 1995, 276 p.
[29] International Union of Pure and Applied Chemistry (IUPAC), Organic Chemistry Division, 'Basic Terminology of Stereochemistry', http://www.chem.qmul.ac.uk/iupac/stereo/, last accessed November 2012.
[30] J. P. Riehl, 'Mirror-Image Asymmetry', John Wiley & Sons, Hoboken, 2010, 250 p.
[31] G. H. Wagnière, 'On Chirality and the Universal Asymmetry', Verlag Helvetica Chimica Acta, Zürich, and Wiley-VCH, Weinheim, 2007, 247 p.
[32] D. G. Morris, 'Stereochemistry', The Royal Society of Chemistry, London, 2001, 170 p.
[33] E. L. Eliel, S. H. Wilen, M. P. Doyle, 'Basic Organic Stereochemistry', John Wiley & Sons, New York, 2001, 704 p.
[34] E. L. Eliel, S. H. Wilen, 'Stereochemistry of Organic Compounds', John Wiley & Sons, New York, 1994, 1267 p.
[35] B. Testa, 'The Geometry of Molecules: Basic Principles and Nomenclatures', in 'Stereochemistry', Ed. C. Tamm, Elsevier, Amsterdam, 1982, pp. 1 – 47.
[36] B. Testa, 'Principles of Organic Stereochemistry', Dekker, New York, 1979, 248 p.
[37] F. D. Gunstone, 'Guidebook to Stereochemistry', Longman, London, 1975, 110 p.
[38] K. Mislow, 'Introduction to Stereochemistry', Benjamin, New York, 1966, 193 p.

[39] N. Harada, '*Chiral Auxiliaries Powerful for Both Enantiomer Resolution and Determination of Absolute Configuration by X-Ray Crystallography*', *Top. Stereochem.* **2006**, *25*, 177 – 203.
[40] A. D. McNaught, A. Wilkinson, 'Compendium of Chemical Terminology', 2nd edn. (the IUPAC 'Gold Book'), Blackwell Scientific Publications, Oxford, 1997; XML on-line corrected version, http://goldbook.iupac.org; (2006 – ) created by M. Nic, J. Jirat, B. Kosata; updates compiled by A. Jenkins, doi: 10.1351/goldbook.
[41] M. Raban, K. Mislow, '*Modern Methods for the Determination of Optical Purity*', *Top. Stereochem.* **1967**, *2*, 199 – 230; R. D. Shah, L. A. Nafie, '*Spectoscopic Methods for Determining Enantiomeric Purity and Absolute Configuration in Chiral Pharmaceutical Molecules*', *Curr. Opin. Drug Discovery Dev.* **2001**, *4*, 764 – 775.
[42] V. Schurig, '*Terms for the Quantitation of a Mixture of Stereoisomers*', *Enantiomer* **1996**, *1*, 139 – 143; K. Faber, '*The Enantiomeric Ratio – Beware of Confusion*', *Enantiomer* **1997**, *2*, 411 – 414.
[43] P. Gaillard, P.-A. Carrupt, B. Testa, A. Boudon, '*Molecular Lipophilicity Potential, a Tool in 3D-QSAR. Method and Applications*', *J. Comput.-Aided Mol. Des.* **1994**, *8*, 83 – 96.
[44] A. Pedretti, L. Villa, G. Vistoli, '*VEGA: a Versatile Program to Convert, Handle and Visualize Molecular Structure on Windows-Based PCs*', *J. Mol. Graphics* **2002**, *21*, 47 – 49.
[45] C. Vree, S. G. Mayr, '*Dynamics and Diffusive–Conformational Coupling in Polymer Bulk Samples and Surfaces: a Molecular Dynamics Study*', *New J. Phys.* **2010**, *12*, 023001, doi: 10.1088/1367 – 2630/12/2/023001.

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