STEREOCHEMISTRY

Franco Cozzi
Dipartimento di Chimica Organica e Industriale, Universita' degli Studi di Milano, Italy

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Summary

The aim of this chapter is to provide the reader with the basic concepts necessary to deal with the stereochemical aspects of organic chemistry. As in any other interpretation of stereochemistry that aspires to be rational, also in this one a detailed knowledge of the symmetry properties of a molecule and of the relationship between symmetry properties and molecular behavior at all levels is considered of fundamental importance. Another central point is the strict distinction between chirality and stereogenicity that underlines all the discussion both as an inspiring principle and guidance to the use of a correct stereochemical language. In addition to classic topics such as isomer classification, stereochemical descriptors, and consequences of enantiomeric composition, a short presentation of the principal methods for obtaining enantiomerically pure compounds is included.

1. Introduction

According to the Merriam-Webster Online Dictionary, stereochemistry is: "a branch of chemistry that deals with the spatial arrangement of atoms and groups in molecules". The Oxford Dictionary of English defines stereochemistry: "the branch of chemistry dealing with composition of matter as affected by relations of atoms in space". Thus, in agreement with the etymology of the word (in ancient Greek, the adjective "*stereòs*" indicated the rigid nature of a solid object like a cube), both sources emphasize the fact that stereochemistry, a term coined in 1878 by Viktor Meyer of the University of Heidelberg, studies the properties attained by a molecule from the fact that it is a three-

dimensional object.

The origins of stereochemistry as an independent science date back to the early years of the 19th century when a group of scientists (Fresnel, Malus, Biot, Arago) were the first to realize the existence of a relation between the rotation of circularly polarized light and the structure of matter. Then in 1848 Louis Pasteur, a chemist and microbiologist at the Ecole Normale Superieure in Paris and then at the University of Strasbourg, was able to relate optical rotation to molecular dissymmetry by isolating non-superposable mirror image crystals of sodium ammonium tartrate and showing that their solutions gave opposite rotation of circularly polarized light. Finally in 1874, Jacobus van 't Hoff and Joseph-Achille Le Bel independently proposed the tetrahedral nature of the carbon atom, whose "tertavalence" had just been postulated by August Kekule', thus providing solid theoretical justification to Pasteur's observations.

Since then, stereochemistry has gained a constantly increasing relevance in chemistry. This leading role became even more central when the knowledge of molecular structure was recognized to be fundamental to understand the chemical bases of life in its broadest meaning, the biological world working essentially with chiral molecules. No branches of modern chemistry, from the synthesis of new drugs to the invention of molecular devices, from the development of new materials to molecular biochemistry, can overlook the detailed knowledge of how the three-dimensional structure of a molecule determines its behavior. Still, even this multi-faceted and far-reaching science is based on few basic principles, the application of which allows one to deal with any stereochemical problem in a perfectly rational fashion. The aim of this chapter is to provide the readers with these principles and to teach them how to use these basic concepts as a compass to navigate the wide seas of the stereochemical world.

2. Symmetry

2.1. Molecular Models and Symmetry Evaluation

Any rational discourse in stereochemistry must be rooted in molecular symmetry. The evaluation of the symmetry of a molecule requires the use of a molecular model. This is an iconic representation of the molecule, of which the model is called to share the form but neither the scale nor the function. The model (that must remain rigid and immutable during the symmetry evaluation procedure) must depict the molecule in the most symmetric atom disposition compatible with its structural features. For instance, a molecular model of cyclohexane should feature six carbon-carbon bonds of equal length arranged in the usual cyclic, chair-like disposition that respects the tetrahedral arrangement of sp^3-hybridized carbon atoms. Neither a flat, hexagonal model nor a boat-like disposition of atoms with two juxtaposed opposite vertices, would properly represent the cyclohexane molecule. Nevertheless, it is well possible to evaluate the symmetry of a hypothetically flat, "benzene-like" cyclohexane: just, one must be aware of the fact that that model does not correspond to a structure in which cyclohexane is likely to exist. It must also be mentioned at this stage that the evaluation of the symmetry of an idealized molecular model is quite different from a symmetry determination based on an experiment. Using again the cyclohexane example, the structure of cyclohexane as determined for instance by ^{1}H-NMR analysis at room

temperature could well correspond to that of the flat, hexagonal object that we have just dismissed as a chemical absurdity, as the consequence of the observation of a set of rapidly interconverting atom dispositions. In other words, the response that can be obtained from an experimental evaluation of symmetry crucially depends on the time-scale required for the experiment itself.

2.2. Symmetry Elements and Symmetry Operations

The symmetry of a molecular model and, hence, of a molecule (this distinction will not be emphasized anymore and the two terms will be used interchangeably) can be readily evaluated by ascertaining the presence or the absence of some symmetry elements in the model. The symmetry elements and the corresponding symmetry operations of relevance in organic chemistry are shown in Table 1:

Symmetry elements	Symbol	Order	Symmetry operations
rotation axis	C_n ($n = 1, 2, 3, ...\infty$)	first	Rotation around the axis of $360°/n$
mirror plane	σ	second	reflection from the plane
center of inversion	i	second	inversion of co-ordinates (x,y,z to $-x,-y,-z$)
roto-reflection axis	S_n ($n = 1, 2, 4, 6...$)	second	rotation around the axis of $360°/n$ combined with a reflection through a plane perpendicular to the axis ($S_1 = \sigma$, $S_2 = i$).

Table 1: Symmetry elements and corresponding symmetry operations

Symmetry elements are geometric entities (a straight line, a plane, a point) that intersect (C_n, σ) or lie within (i) the molecule. Not necessarily a symmetry element must coincide with or intersect an atom or a bond. When a symmetry operation is carried out, the geometric points of the symmetry element remain invariant, that is, do not change their position. An object is said to possess a given symmetry element if application of the corresponding symmetry operation yields an object superposable point by point to the original one. To explain how the existence of an element is verified, consider the symmetry evaluation of the molecular model of formaldehyde shown in Figure 1.

A line coextensive with the C=O double bond and bisecting the H-C-H bond angle is an axis of rotation for this model (Figure 1a). Indeed, after a 180° rotation around that axis (the sense of rotation is immaterial) a model perfectly coincident with the original is obtained (Figure 1a'). Accordingly, formaldehyde possesses a C_2 rotation axis. On the other hand, rotation around an axis perpendicular to the molecular plane and passing through the C atom (Figure 1b), does yield a model (Figure 1c) that is not coincident with the original, and therefore that axis is not a symmetry element for formaldehyde. It can also be seen that formaldehyde possesses two mirror planes of symmetry: One is perpendicular to the plane of the paper and bisects the H-C-H bond angle so that one H

atom is mirrored by the other H atom (Figure 1d); the other plane slices the molecule into two halves formally lying one above and one below the plane (Figure 1e). Figures 2 and 3 illustrate examples of molecules possessing rotation axes and mirror planes.
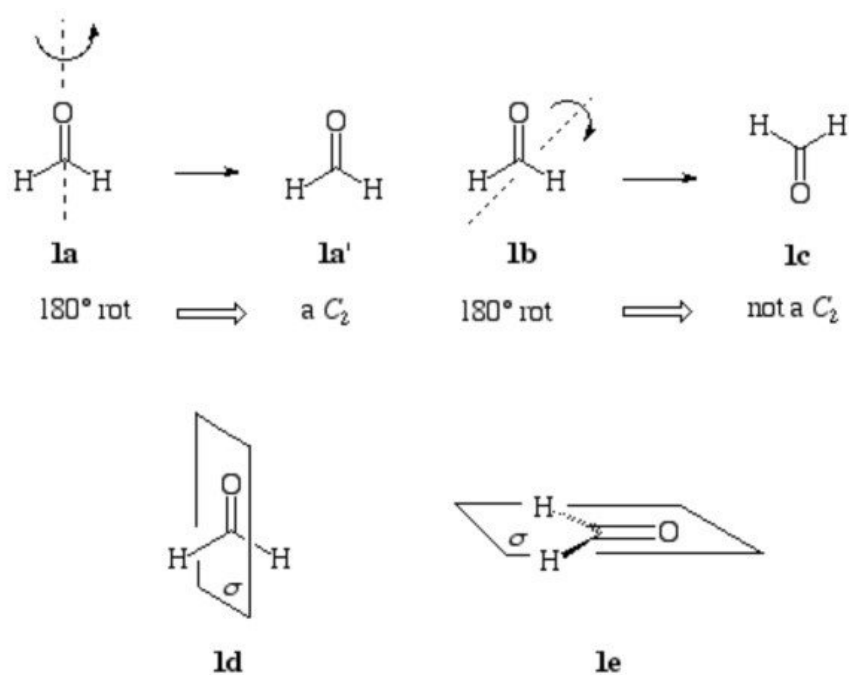
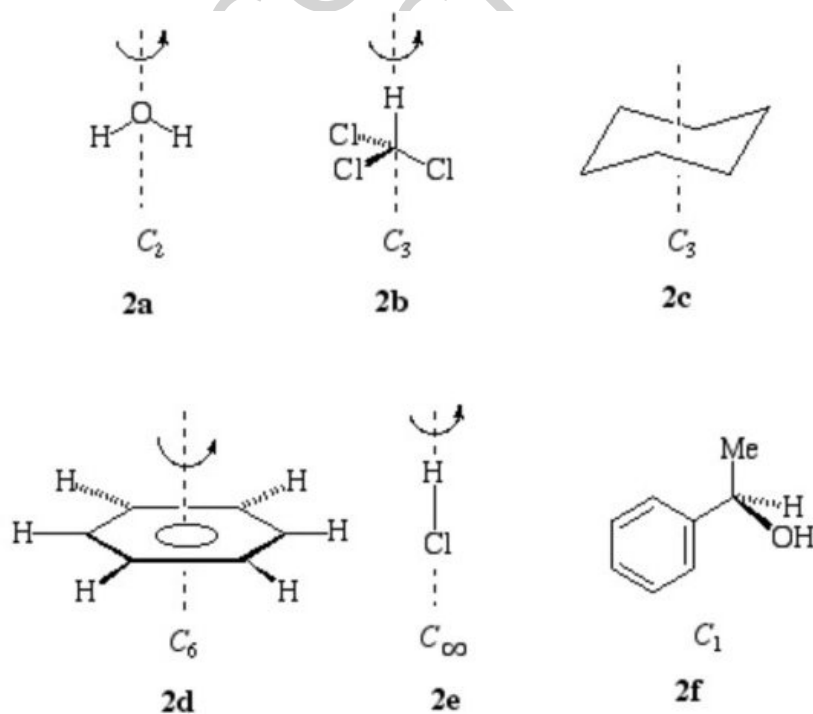Figure 1: Symmetry evaluation of formaldehyde

Figure 2: Examples of molecules possessing rotation axes

In commenting on the examples in Figure 2, it can be noted that an axis might pass through an atom (as the C_2 axis in water, Figure 2a), coincide with a bond (as the C_3 axis in chloroform, Figure 2b), intersect a molecule without touching either an atom or a bond (as the C_3 axis in cyclohexane, Figure 2c), or passes through all the atoms of a molecule (as the C_∞ axis in hydrogen chloride, Figure 2e). A molecule can have several axes: for instance, in addition to the shown C_6 axis, benzene has three C_2 axes connecting opposite vertices and three C_2 axes connecting the midpoints of opposite bonds (Figure 2d). Molecules that possess only C_1 axes do exist. The models of these molecules can be brought to coincidence with themselves only by a 360° rotation around an axis passing anywhere through the model (this rotation is referred to as the "identity operation"). The secondary alcohol (Figure 2f) represents an example of this class of molecules.
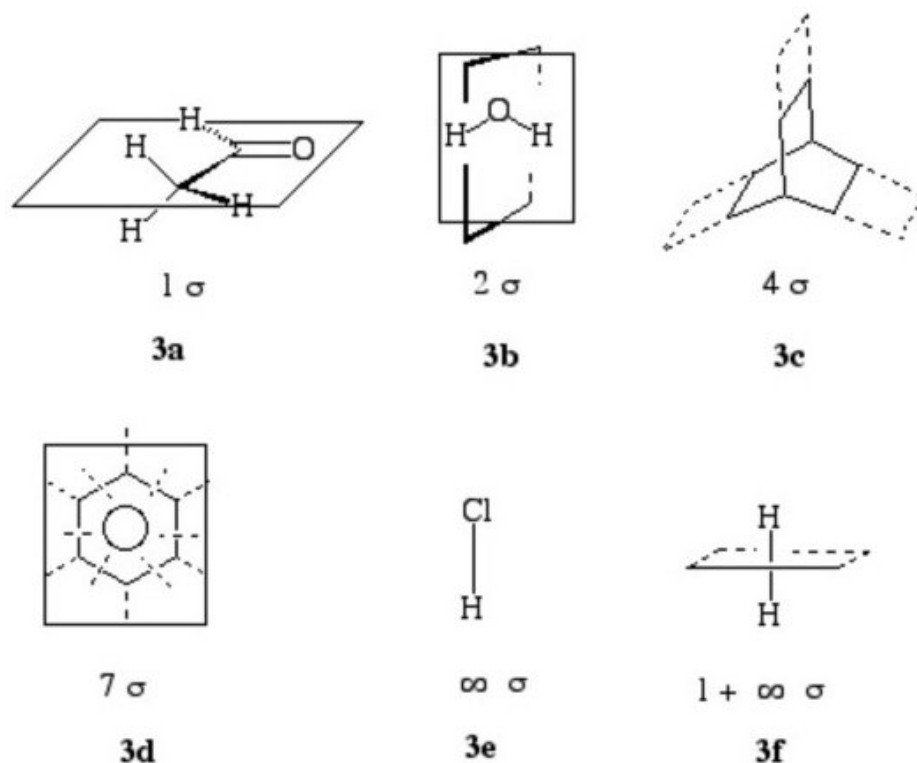

Figure 3: Examples of molecules possessing mirror planes

In commenting on the examples in Figure 3, it can be noted that, in the atom disposition (or conformation, see below) shown, acetaldehyde has a mirror plane containing the formyl H atom, the carbonyl and methyl C atoms, the oxygen atom, and one H atom of the methyl group, and bisecting the H-C-H bond angle (Figure 3a). A 180° rotation around the C-C bond would yield the only other model of acetaldehyde with a mirror plane. Strictly speaking, any atom disposition of acetaldehyde other than the two just mentioned does not contain a plane of symmetry. However, from a practical point of view these distinctions are disregarded. Indeed, the fast rotation around the C-C bond does not allow one to distinguish among the three H atoms of the methyl group, and, on the average, acetaldehyde is experimentally determined to contain a plane of symmetry.

Since rotation around single bonds is generally very fast, similar reasoning can be applied whenever needed (see the Section on conformation).

The water molecule contains two perpendicular mirror planes intersecting on the symmetry axis depicted in Figure 2: one of these contains all the atoms of the molecule (Figure 2b). Four planes of symmetry can be found in 2,2,2-bicyclooctane (Figure 3c): three of them contain adjacent methylene groups and intersect on the C_3 axis connecting the methyne groups; the fourth plane bisects the three CH_2-CH_2 bonds, cutting the molecule into two halves. Benzene (Figure 3d) has seven mirror planes: in addition to the molecular plane (that is, the one containing all the atoms), there are also six planes perpendicular to it and containing the six C_2 axes mentioned before. The HCl molecule has an infinite number of planes all coincident on the bond that is coextensive with the C_∞ axis (Figure 3e). Also the H_2 molecule has an infinite number of planes intersecting on the bond, but in addition, it has another plane that bisects the H-H bond (Figure 3f). Molecules that do not possess any mirror plane do exist. The secondary alcohol in Figure 2 represents an example of this class of molecules.

The center of inversion (i) and the roto-reflection axis (S_n, $n = 4, 6, ...$) are symmetry elements by far less frequently encountered than the rotation axis and the mirror plane. Examples of molecules containing these elements are shown in Figure 4.
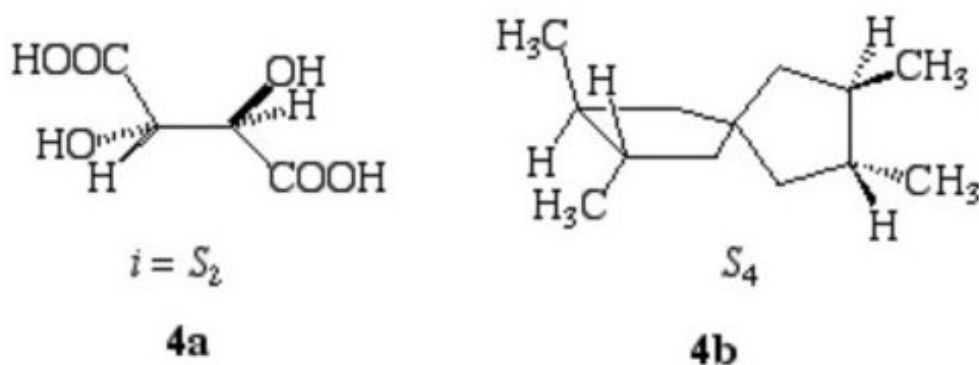

Figure 4: Examples of molecules possessing a center of inversion or a roto-reflection axis

The midpoint of the C2-C3 carbon bond of (Figure 4a) coincides with a center of inversion: indeed, moving along a straight line in opposite directions from that point, the same atoms or groups of atoms can be found at the same distance. The midpoint of the C=C double bond of ethylene and the center of gravity in benzene represent other examples of centers of inversion. The tetramethyl substituted spirane (Figure 4b) provides an example of a molecule containing a roto-reflection axis. The order of this axis is four: a rotation of 90° around an axis passing through midpoints of the $(CH_3)CH$-$CH(CH_3)$ bonds and the spiro carbon atom, followed by a reflection from a plane perpendicular to the axis yields back a model superposable to the original structure. Methane and benzene provide examples of molecules containing a S_4 and a S_6, respectively. It is important to note that, by definition, $\sigma = S_1$ (a 360° rotation

followed by a reflection) and $i = S_2$ (a 180° rotation followed by a reflection). Thus, all the symmetry elements of the second order (see the beginning of this section) can be expressed as S_n ($n = 1, 2, 4, 6, ...$).

2.3. Point Groups

The examples presented in Figures 2-4 show that often a molecule has more than one symmetry element. This set of elements necessarily share at least one point that is the point of the model that has the symmetry of all the coincident elements. There are shorthand notations for briefly indicating all the symmetry elements belonging to a given molecule: these are called point groups. Those sufficient to deal with the vast majority of organic molecules can be classified into two sets depending on whether they include or not symmetry elements of the second order (see Table 2).

Only elements of the first order (dissymmetric point groups)	At least one element of the second order (nondissymmetric point groups)
$C_n = C_n$ only $D_n = C_n + n\, C_2$ only	$C_s = \sigma$ only $S_n = i$ (n = 2) and S_n (n = even >2) (no σ) $C_{nv} = C_n + n\, \sigma_v$ only $C_{nh} = C_n + \sigma_h$ only $D_{nd} = C_n + n\, C_2 + n\, \sigma_v$ (but on σ_h) $D_{nh} = C_n + n\, C_2 + n\, \sigma_v + \sigma_h$ $T_d = 4C_3 + 3\, C_2 + 6\, \sigma$

Table 2: Classification of mirror planes as σ_v or σ_h

Examples of molecules belonging to these point groups are shown in Figure 5 and 6.

Molecules belonging to the C_1 point group are called asymmetric, that is without symmetry. They are represented (among others) by any atom arrangement featuring a tetrahedral central atom with different substituents at the vertices of the tetrahedron (typically an sp^3 C atom with four different substituents as in Figure 5a). A 1,2-propadiene with four different substituents at the 1,3 carbon atoms (Figure 5b) or a biphenyl with four different substituents in the *ortho* and *ortho'* positions (Figure 5c) represent other examples of asymmetric molecules. Note that in the two latter cases, asymmetry is maintained even if two of the substituents are identical: these, however, must not be connected to the same allene carbon or to the same phenyl ring (otherwise the molecule would contain a plane of symmetry).
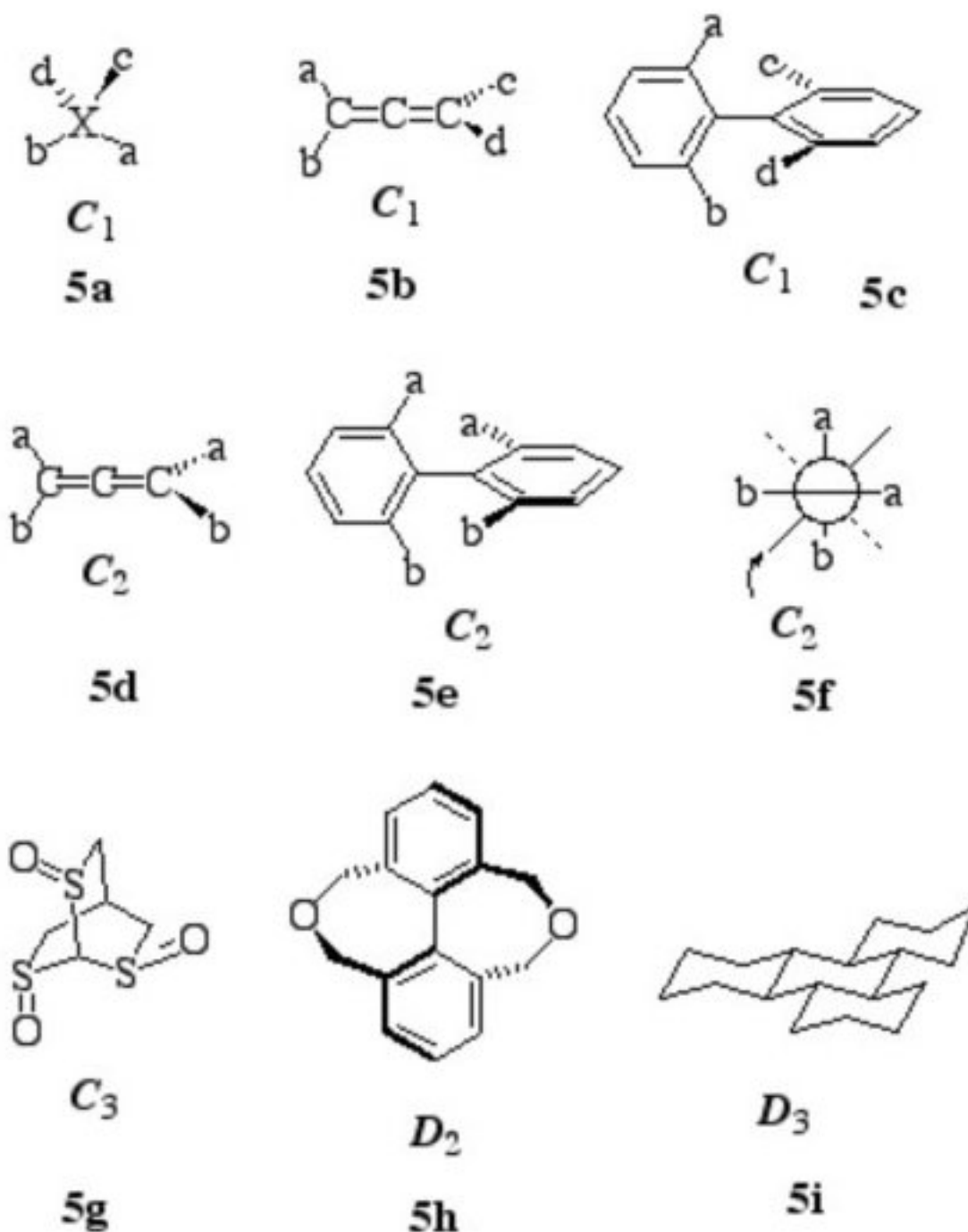
Figure 5: Examples of molecules of the dissymmetric point groups

Molecules belonging to the C_n ($n > 2$) point group are called dissymmetric. C_2 molecules are represented (*inter alia*) by allenes and biphenyls carrying two pairs of different substituents, as in Figures 5d and 5e. Obviously, this substitution pattern in a tetrahedral structure would result in a molecule containing mirror planes. The symmetry axis intersects the allene on the central C atom of the cumulene bond at a 45° angle with respect to the cumulene array (the axis is shown as a solid line in **5f**; the dashed line is

not a symmetry axis for these molecule). In biphenyl (Figure 5e), the axis bisects the midpoint of the biaryl bond at a 45° angle. The tris-sulfoxide (Figure 5g) is an example of a C_3 symmetric molecule, the axis passing through the methyne groups.

Also molecules belonging to the D_n $(n > 2)$ point group are called dissymmetric. In this case, there is one axis of order n plus n C_2 axes perpendicular to the former. Therefore, in molecules belonging to the D_2 point group, represented by the biaryl (Figure 5h) bridged at the *ortho* and *ortho'* positions, there are three C_2 axes that intersect on the midpoint of the biaryl bond. Perhydrotriphenylene (Figure 5i) is an example of D_3 molecule: the C_3 axis passes through the center of gravity of the structure where it is intersected perpendicularly by three C_2 axes that form 120° angles among them.
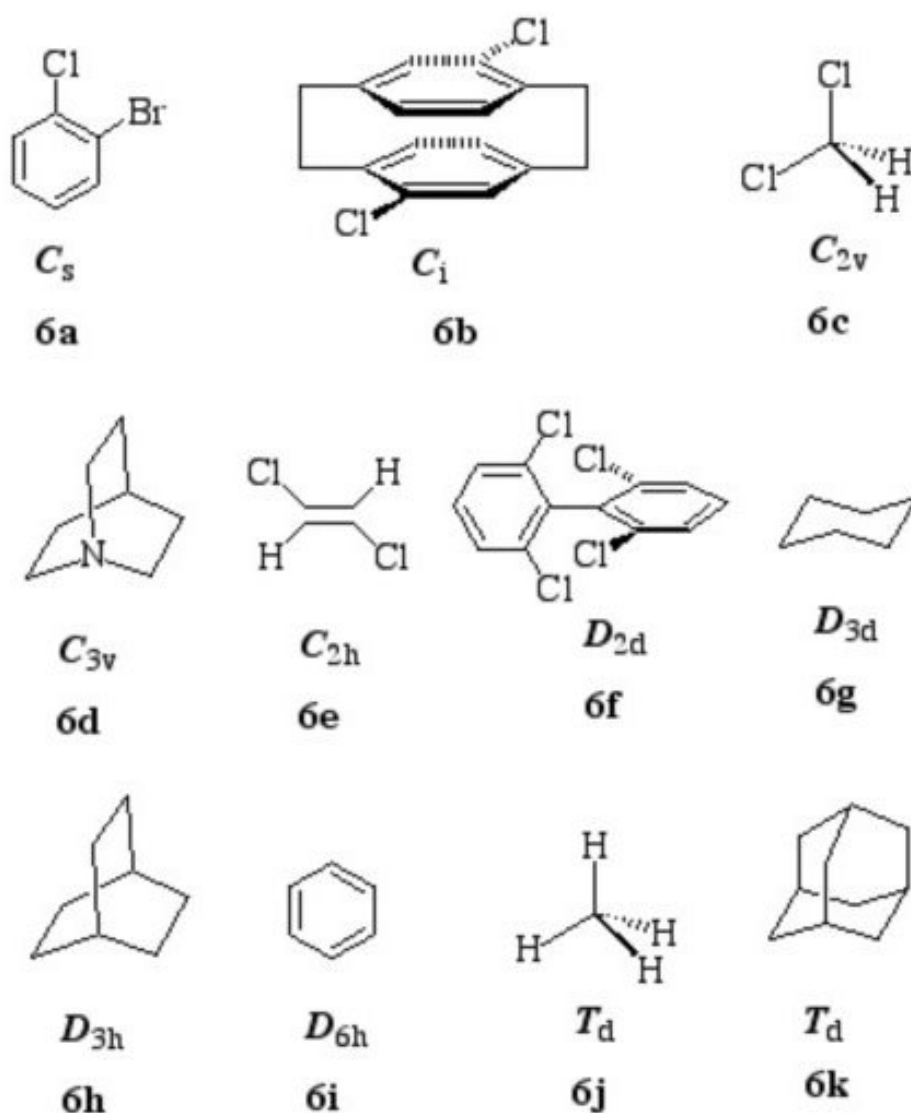

Figure 6: Examples of molecules of the symmetric point groups

Molecules belonging to the C_s point group contain a single mirror plane often, but not necessarily, containing all the atoms of that molecule as in 2-chlorobromobenzene (Figure 6a) (see acetaldehyde in Figure 3a for an example of a non planar C_s molecule). A limited number of molecules contain a center of inversion i ($= S_2$) as their only symmetry element. Dichloroparacyclophane (Figure 6b) represents an example; molecule (Figure 4a) is another example. Molecules containing only a S_n roto-reflection axis with n even and > 2 are extremely rare (see (Figure 4b) as an example of S_4; in this molecule the S_4 axis is coincident with a C_2 axis).

Molecules containing a combination of rotation axes and mirror the planes are ubiquitous. The geometric relation between the axis of higher order and the mirror plane(s) allows to classify the latter as vertical (v, containing the axis) and horizontal (h, perpendicular to the axis). The water molecule contains a C_2 axis (Figure 2a) that lays at the intersection of two vertical planes (Figure 3b): accordingly, water belongs to the C_{2v} point group; dichloromethane (Figure 6c) is another example of a C_{2v} molecule. Chloroform (Figure 2b) belongs to the C_{3v} point group as does quinuclidine (Figure 6d): in the latter the C_3 axis passes through the N atom on one side and the methyne group on the other side of the molecule; the three symmetry planes (each containing adjacent methylenes, the N atom and the methyne group) intersect each other on the axis. *Trans*-1,2-dichloroethylene (Figure 6e) is an example of C_{2h} molecule in which the plane of symmmetry (containing all the atoms) is perpendicular to the C_2 axis that passes through the center of the C=C double bond. 2,2',6,6'-Tetrachlorobiphenyl (Figure 6f) is an example of a D_{2d} molecule. It contains three C_2 axes and two symmetry planes. The latter intersect each other on the C_2 axis coextensive with the biaryl bond (and therefore are vertical planes); the remaining two axes pass through the midpoint of the biaryl bond at a 45° angle to the other axis. Therefore none of the axes is perpendicular to any of the planes. Also 1,2-propadiene (allene) belongs to the D_{2d} point group. Cyclohexane in its chair disposition (Figure 6g) provides an example of a D_{3d} molecule featuring a C_3 axis (see Figure 2c), three mirror planes (passing through diametrically opposite methylenes and intersecting on the C_3 axis), and three C_2 axes passing through the midpoints of diametrically opposite bonds. When a molecule contains more than one axis and a plane perpendicular to one of these axes, then it belongs to the D_{nh} point group. Examples of D_{2h} molecules are provided by ethylene and naphthalene; 2,2,2-bicycloöctane (Figure 6h) belongs to the D_{3h} point group (note the difference with Figure 6d); benzene (Figure 6i) to the D_{6h} point group (see Figure 2d and Figure 3d for the identification of the symmetry elements of benzene). Finally, methane (Figure 6j, point group T_d) is the prototype of a tetrahedral molecule. In this point group, as in other describing the symmetry of molecule whose structure recalls that of the Platonic solids (tetrahedron, cube, octahedron, dodecahedron), several axes of order $n > 2$ can be found. For instance methane has four C_3 axes (each coextensive with a C-H bond), three C_2 axes (each laying in a H-C-H plane and bisecting an opposite H-C-H bond angle), and six planes of symmetry (each coincident with a H-C-H plane and bisecting an opposite H-C-H bond angle), none of which is perpendicular to an axis (hence the symbol "d"). Another representative of the T_d point group is

adamantane (Figure 6k).

The following Flow Chart provides a simple guide to correctly assign point groups by checking if the molecule under investigation does or does not possess the symmetry element(s) indicated in each box.
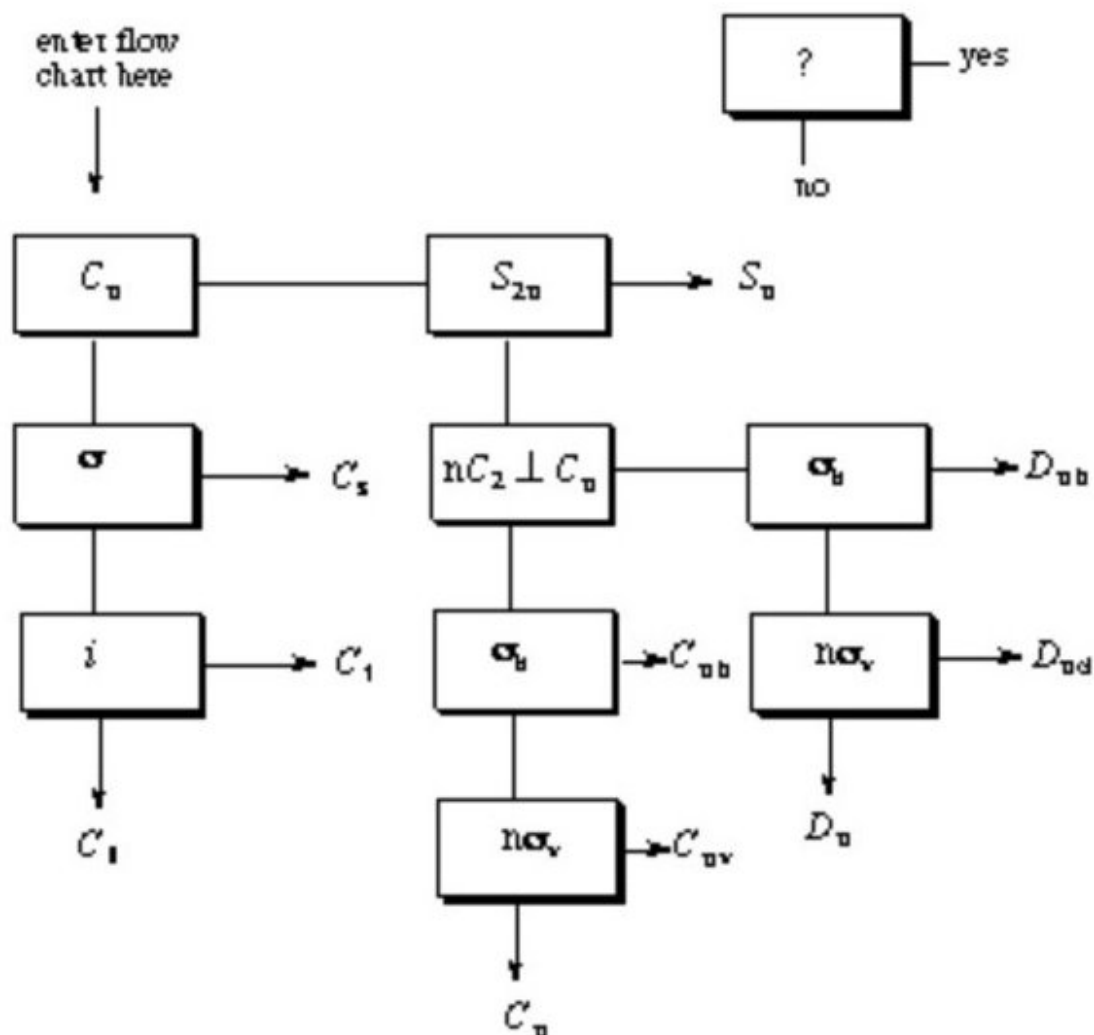
Flow Chart: A simple guide to correctly assign point groups to molecules

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Biographical Sketch

Franco Cozzi was born in Milano in 1950. He graduated in Chemistry at the University of Milano in 1974 (advisor Fernando Montanari). After two years with Kurt Mislow at Princeton University (1978-1980), he moved to the University of Cagliari, and then came back to the University of Milano where he is professor of Organic Chemistry since 1994. His major research interest has been the study of the theoretical and applied

aspects of organic stereochemistry.