VI. Geometric Isomerism

Geometric isomerism was first defined by Wislicenus in 1887 as isomerism occurring in compounds where rotation is restricted by double bonds or ring systems. Geometric isomers do not rotate the plane of polarized light (unless they also contain a chiral center), and hence are not optically active.

A. Geometric Isomerism Resulting from Restricted Rotation about Double Bonds

The \( sp^2 \) hybridized carbon atoms of alkenes (olefins) and the atoms or groups attached to these carbons all lie in the same plane, and rotation around the double bond is restricted. As a result, stereoisomerism is possible when each carbon atom of the double bond is asymmetrically substituted. This is illustrated for butene compounds in Fig. 20. In each case, the C==C restricts rotation, but only 2-butene is asymmetrically substituted at each carbon of the double bond. The restricted rotation and planar geometry of the double bond, along with the asymmetry, allow for two distinct stereoisomers or geometric isomers of 2-butene to exist. These isomers may be named as \textit{cis} or \textit{trans} or E or Z, using the rules described below.

![Figure 20. Geometric butene isomers](image)

Table I: Physicochemical Properties of Diastereoisomers

<table>
<thead>
<tr>
<th>Property</th>
<th>Maleic Acid</th>
<th>Fumaric Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point, (^\circ\text{C})</td>
<td>130</td>
<td>286</td>
</tr>
<tr>
<td>( \text{H}_2\text{O} ) solubility at (25^\circ\text{C}), g/L</td>
<td>788</td>
<td>7</td>
</tr>
<tr>
<td>( K_1 ) at (25^\circ\text{C})</td>
<td>(1.5 \times 10^{-2})</td>
<td>(1 \times 10^{-3})</td>
</tr>
<tr>
<td>( K_2 ) at (25^\circ\text{C})</td>
<td>(2.6 \times 10^{-7})</td>
<td>(3 \times 10^{-5})</td>
</tr>
</tbody>
</table>
Geometric isomers are nonsuperimposable, nonmirror images and therefore may be classified as diastereomers. Thus stereoisomers of this type have different physical and chemical properties. This is illustrated by the examples of the geometric isomers maleic and fumaric acid (Table 1). These compounds are distinct chemical entities with different melting points, solubilities, and ionization constants. A number of drugs contain dissymmetrically substituted carbon-carbon double bonds and therefore can exist as two distinct geometric isomers (Fig. 21).

Several systems of nomenclature have been developed to designate the configuration of geometric isomers. Historically, the *cis-trans* system of nomenclature has been applied most frequently. It was developed to assign the configuration of geometric isomers when each isomer contains a like group or atom on each carbon atom of the double bond. For example, in 2-buten e each *sp*² hybridized carbon atom contains a hydrogen atom (Fig. 22). When these hydrogen atoms are located on the same face of the double bond, the isomer is called *cis*; the isomer with the hydrogens on opposite sides is named *trans*.

The *cis-trans* system has proven useful in designating the configuration of alkenes, but it cannot be used unambiguously to assign configurations for all geometric isomers. For example, the *sp*² atoms of the antipsychotic agent thiothixene do not contain a like atom or group (Fig. 23). Thus the *E/Z* notation system was developed to unambiguously assign configurations in all cases of geometric isomerism. This system of nomenclature is applied according to the following rules and is illustrated for thiothixene (Fig. 23).
Priorities are assigned on the basis of atomic number for the two atoms or groups attached to each carbon of the carbon-carbon double bond. The same priorities apply as in the Cahn-Ingold-Prelog sequence rules.

Configuration is assigned based on the relative positions of the highest priority atoms or groups on each carbon of the carbon-carbon double bond. If these groups are on the same side, the Z (zusammen) designation is used. If they are on the opposite side, the E (entgegen) designation is assigned.

The E/Z notation and, when appropriate, the cis-trans nomenclature are also applied to systems with multiple carbon-carbon double bonds. In these cases, as shown in Fig. 24 for vitamin K, isomerism at each double is designated by the appropriate nomenclature and the position of the bond.

![FIG. 24. Geometric isomerism, Vitamin K.](image)

It should also be noted that some compounds may contain both a double bond and one or more asymmetric centers. In these cases, two enantiomeric forms exist for each geometric isomer, resulting in four possible stereoisomers. For example, the metabolite 10-hydroxynortriptyline (Fig. 25) possesses a chiral carbon and asymmetric double bond and therefore four stereoisomers are possible.

![FIG. 25. Geometric and optical isomerism, 10-hydroxynortriptyline](image)

Geometric isomerism is also possible in double-bonded carbon-heteroatom systems such as imines and oximes (C--N), and in azo (N--N) systems. For example, several cephalosporin derivatives contain an alkoxyimino side chain that may exist in E or Z isomeric forms; the azo compound prontosil may display similar isomerism (Fig. 26). A syn-anti system can also be applied to C-N geometric isomers. In these cases, the priority assignments are made as described previously, and the isomer with highest priorities on the same face of the double bond are called syn, whereas those with these groups on opposite sides are named anti.
In a number of amides, thioamides, and related systems, rotation about the single bond is hindered, and distinct geometric isomers can be observed and even isolated. This type of geometric isomerism is referred to as atropisomerism and results from resonance contributions by the nitrogen atom which imparts significant double bond character to the system, thus slowing rotation. Such is the case for the thioamide aldose reductase inhibitor tolrestat shown in Fig. 27. Isomers of this type are also called rotamers and are considered to be conformational isomers since they result from rotation about a single bond.

The substituted carbon atoms of cyclic systems are frequently asymmetric. Therefore, in addition to geometric isomerism, optical isomerism is also possible. For example, 1,2-dimethylcyclohexane has two geometric isomers, cis and trans, and enantiomers of the trans form; the cis form is a meso compound (Fig. 29). Hence, three stereoisomers are possible.
Geometric isomerism is possible in heterocyclic systems where carbon atoms are bearing different groups or atoms. Such is the case in the 3-substituted derivatives of fentanyl (Fig. 30).
When rings are fused through adjacent atoms, the fusion may be *cis* or *trans*, as illustrated by the decalin system (Fig. 31). Such isomerism is obviously present in multicyclic compounds such as those possessing a steroid nucleus. In the naturally occurring steroids the ring junctions are all *trans*, except in the case of the cardiac glycosides where both A/B and C/D junctions are *cis* (Fig. 32). Rings fused through nonadjacent atoms, or bridged systems, may also display stereoisomerism.

**FIG. 31: Geometric Isomers of Decalin**

Geometric isomerism is also possible in inorganic coordination complexes of square planar geometry. For example, platinum complexes such as those used in cancer chemotherapy can exist as *cis* or *trans* forms (Fig. 33). In this case, only the *cis* form or cisplatin is an effective antineoplastic agent.

**FIG. 32: Geometric isomers of steroids**

**FIG. 33: Geometric isomers of platinum complexes.**

**VII. Conformational Isomerism**

In the preceding sections the nature and properties of configurational (optical and geometric isomers) were discussed. It is important to remember that configurational isomers are distinct, separable compounds. Conformational isomers are different three-dimensional arrangements in space of the atoms of a single compound or configurational isomer. Such isomers are called conformers and are interconvertible by free rotation about single bonds.
In alkanes or alkyl systems, an infinite number of conformations is possible as a result of rotation about C—C single bonds, and each conformation has a certain potential energy. A simple compound, such as ethane, has two conformational extremes, one of low and one of high potential energy. These are depicted as Newman projections in Fig. 34. The low-energy or staggered conformation, exhibits minimal steric interaction between the hydrogen atoms of the adjacent carbon atoms. In the high-energy or eclipsed conformation there is maximal steric interaction between these hydrogen atoms. More complex alkyl systems, such as butane, have more conformational extremes (Fig. 35). In this case, the extremes are identified based on the disposition of the two terminal methyl groups relative to each other. The most stable conformer is the anti (antiperiplanar) one, where the distance between the two methyl groups is maximized, thus minimizing steric interactions. The least stable conformer is the fully eclipsed or synperiplanar conformer where the two methyls are closest together. The other conformers, the anticlinal and gauche or synclinal are of intermediate stability.

**FIG. 34. Conformational isomers, ethane.**

**FIG. 35. Conformational isomers, butane.**

Conformational isomerism is believed to be of great significance for drug-receptor and drug-enzyme interactions. For example, catecholamines such as nor-epinephrine and dopamine presumably interact with their receptors in the anti-periplanar conformation. Furthermore, the preferred conformation of interaction of acetylcholine with muscarinic receptors is the synclinal conformer (Fig. 36).
FIG. 36. Pharmacophoric conformations of acetylcholine and norepinephrine.

In ring systems complete rotation about the ring atoms is not possible, but partial rotation is possible, resulting in several different conformational extremes. For example, cyclohexane systems can exist in three distinct conformations: boat, twist boat, and chair. Of these, the chair form is the most stable conformation because steric interactions are minimized (Fig. 37). The substituents present on a ring conformer are designated as axial or equatorial, depending on the direction of projection from the average plane of the carbon skeleton. Substituents that project directly up or down from the ring are axial, and those in the plane of the ring are equatorial (Fig. 37).

FIG. 37. Chair conformation, cyclohexane.

Because of the conformational flexibility of cycloalkanes such as cyclohexane, the ring conformation can invert. During inversion, all axial substituents become equatorial and all equatorial substituents become axial as shown in Fig. 38. The presence of substituents can dictate the conformational preference in cyclic systems. For example, in the more stable conformer of methylcyclohexane the methyl group is equatorial, minimizing unfavorable steric interactions (Fig. 38).

Fig. 38. Conformational inversion and stability
Ring conformations are believed to be important in drug activity. For example, experimental evidence suggests that the analgesic fentanyl binds to opiate receptors preferentially in the conformation shown in Fig. 39, where the bulky substituents are positioned equatorially to minimize conformational instability.

FIG. 39. Conformational isomerism, 3-methylfentanyl.