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ISOMERISM IN ORGANIC COMPOUNDS

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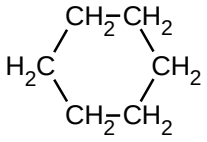
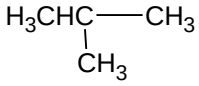
Dr. Gábor Krajsovszky

ISOMERISM IN ORGANIC COMPOUNDS

Isomers are the compounds with the same qualitative and quantitative composition of elements, therefore their relative molecular weights and general formulas are identical, but their structures – including in the 3D arrangement – are different. The compounds propyl chloride and propane are not isomers, since their qualitative composition of elements are different. The compounds propane and propene are not isomers, although they are built from the same elements, but with different quantitative composition of elements. The compounds propene and cyclohexane are not isomers, although they are built from the same elements, with the same ratio of elements, their relative molecular weights are different. However, the compounds butane and isobutane are isomers, since they have the same general formula, but their 3D arrangement is different. Only one compound or many compounds may have the same general formulas. For example, methane (a linear saturated hydrocarbon) is a single compound without isomer, while pentane has 3 isomers, a linear saturated hydrocarbon with 40 carbons has more than 62 trillion isomers.

Identical qualitative composition
Identical quantitative composition
Identical relative molar weight
} identical general formula

Different structures

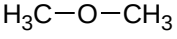
$H_3C-CH_2-CH_2-Cl$	$H_3C-CH_2-CH_3$	not isomers
propyl chloride	propane	
$H_3C-CH_2-CH_3$	$H_3C-CH=CH_2$	not isomers
propane	propene	
$H_3C-CH=CH_2$		not isomers C : H = 1 :2
propene	cyclohexane	
$H_3C-CH_2-CH_2-CH_3$		isomerism of the carbon skeletone
butane	isobutane	

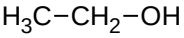
There are versatile types of isomerisms, consequently compounds with identical general formulas may belong to families of compounds quite far from each other. If these families of compounds are closer to each other, then their physical, chemical and biological properties are also similar, but distant relatives may have quite different properties.

I. Structural isomerism

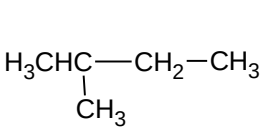
with different connectivity

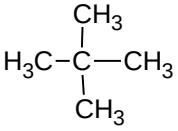
Structural isomerism



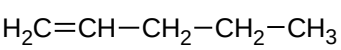


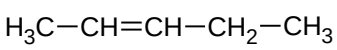
Isomerism of the carbon skeletone

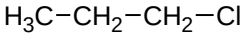


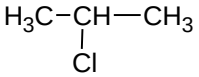


Positional izomerism

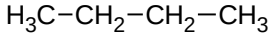


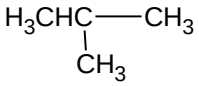






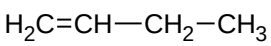
Structural isomers are the compounds with different connectivity. For example, butane has linear chain, while isobutane is the branched isomer. This subtype of structural isomerism is called as *isomerism of the carbon skeletone*. Another example is the comparison of the pentene isomers: the double bond is located between centres 1 and 2 in pent-1-ene (at the beginning of the chain), while it is located between centres 2 and 3 in pent-2-ene (in the middle of the chain). Similarly to it, positions of the chlorine atoms are different in propyl chloride and isopropyl chloride. This subtype of structural isomerism is called as *positional isomerism*. Properties of positional isomers are very close to each other.

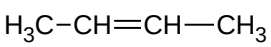




Isomerism of the carbon skeletone

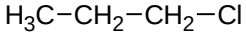
butane isobutane

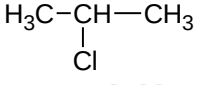




Positional izomerism

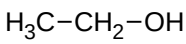
1-butene 2-butene

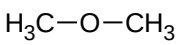




Positional izomerism

propyl chloride isopropyl chloride





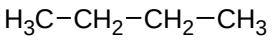
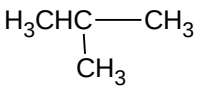
Structural isomerism

ethyl alcohol dimethyl ether

bp: 78.4 °C bp: -23.7 °C

There is much greater difference between ethanol and dimethyl ether. Ethanol has an O-H bond, but O-H bond is missing in dimethyl ether. Properties of these two isomers are rather different. For example, ethanol has bp of 78.4°C, while a dimethyl ether has -23.7°C. Differences in properties are remarkable for most of the structural isomers.

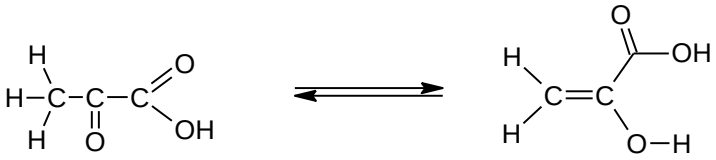
Number of structural isomers

		
	C_4H_{10}	C_4H_{10}
Number of carbons	C_nH_{2n+2}	$C_nH_{2n+1}Cl$
1	1	1
5	3	8
10	75	507
20	366319	5622109
40	~62 trillions	~2000 trillions

A special case of structural isomerism is *tautomerism*. Tautomers are the isomer compounds differing from each other in the position of a double bond and of a mobile hydrogen atom. For example, a hydrogen atom is attached to the oxygen atom in vinyl alcohol, while a double bond is located between carbon atoms. However, the double bond is located between the central carbon atom and the oxygen atom, attaching another hydrogen atom to the side carbon atom.

There is a similar situation with pyruvic acid, which is important for biochemical reasons. Tautomers regularly cannot be separated from each other, due to the easy interconversion of them. Equilibrium of tautomers is usually shifted to one of the tautomers in great ratio. For example, the enol (vinyl alcohol) is present in 0.001%, while the oxo compound (acetaldehyde) is present in 99.999% for the vinyl alcohol − acetaldehyde tautomeric equilibrium. There are many other subtypes of tautomers.

Tautomerism

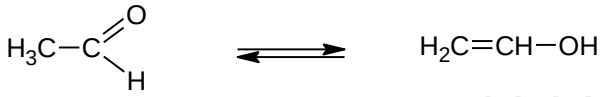


oxo (keto) enol

pyruvic acid

differing in the position
of a mobile H atom and
of a double bond

There are many different subtypes of tautomers



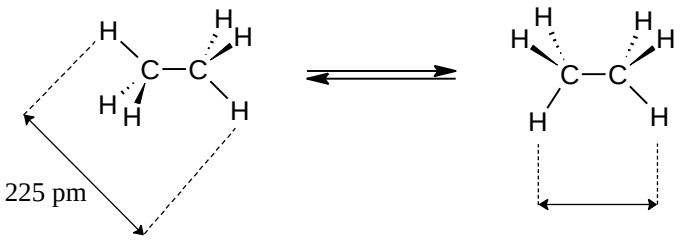
acetaldehyde (oxo) 99.999%

vinyl alcohol (enol) 0.001%

II. Rotational (conformational) isomerism

Some parts of the molecule may rotate compared to other parts of the molecule, around the bonds of the molecule – especially around single bonds -. For example, a methyl groups in ethane molecule may rotate around carbon-carbon bonds. The spatial structures received by rotation are called as conformations, the molecules are called as *conformational* or r*otational isomers* (*conformers* or *rotamers*). The internal energy of the molecule is changing during rotation around carbon-carbon bonds by any degrees. Some conformers represent more significant ones compared to the others.

different conformations

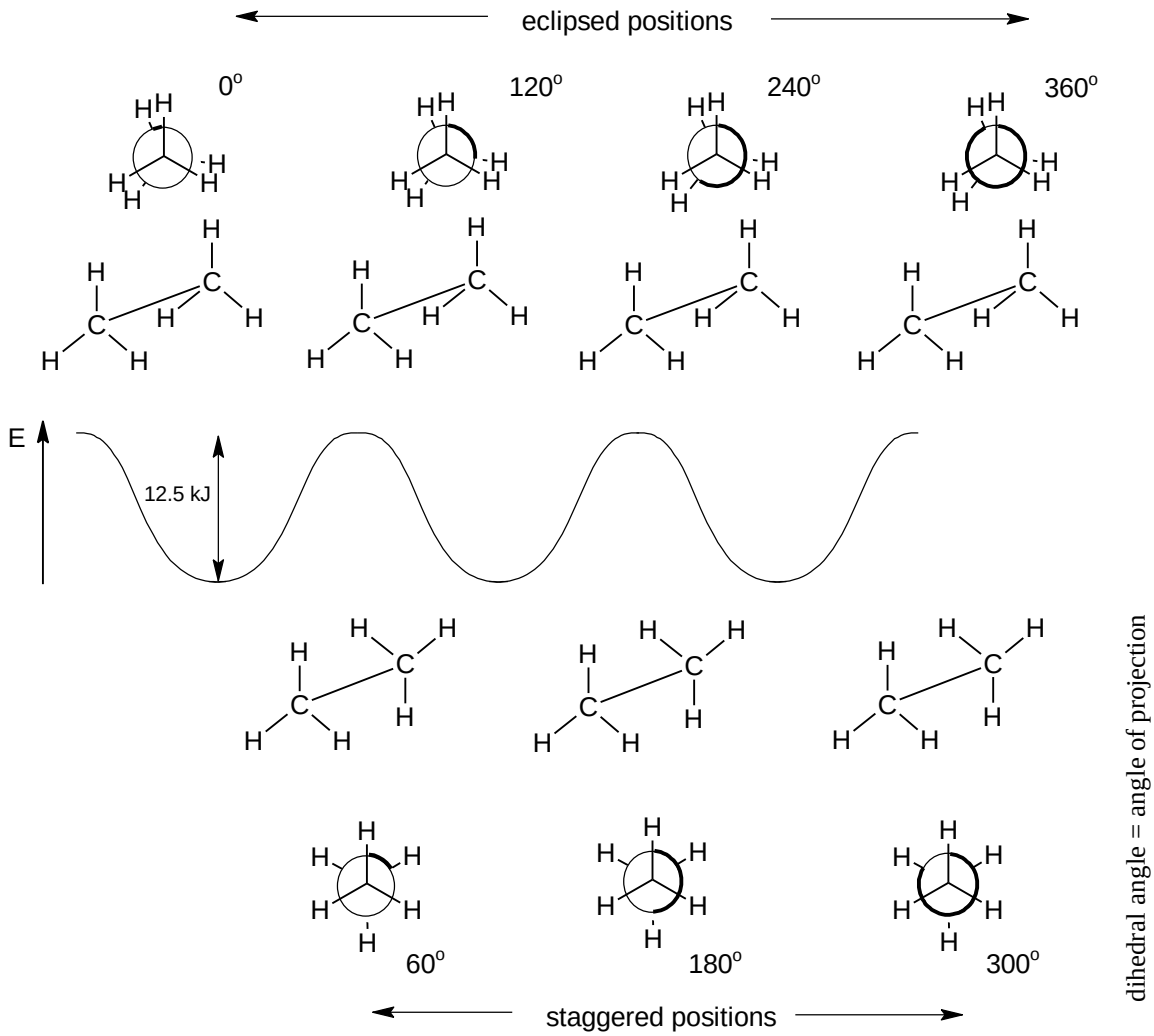


conformers

Rotational isomerism in open-chained compounds

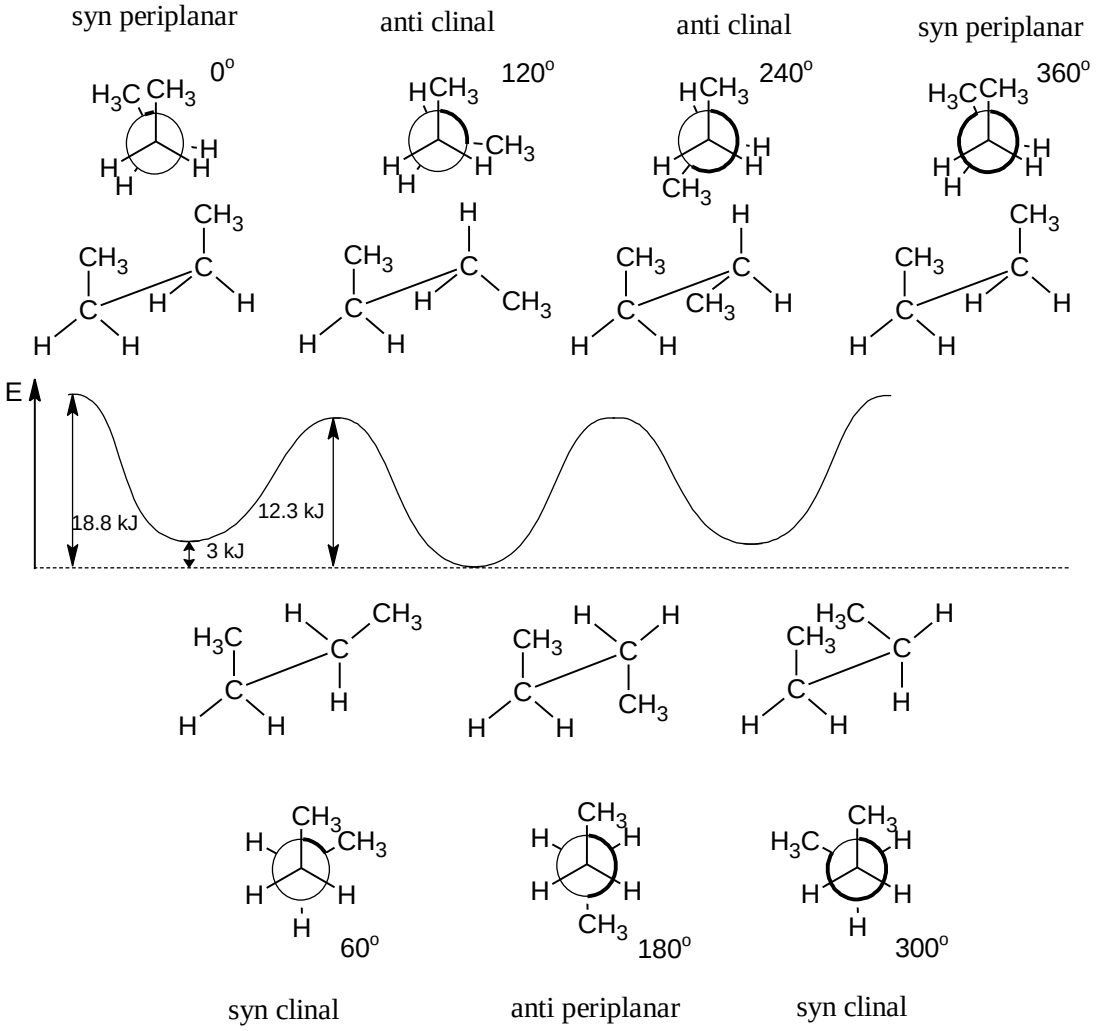
Conformational isomers of ethane can be well studied if the molecule is seen along the carbon-carbon bonds, providing full overlapping of the carbon atoms. The methyl group attached to the front carbon is considered as an immobile one, while the methyl group attached to the back carbon is rotated in clockwise direction.

Let us start from the position, where the hydrogens of the back carbon atom are exactly behind the hydrogens of the front carbon atom. Then the torsional (dihedral) angle of the two C-H bonds is 0°. This position is called as eclipsed position. Rotating methyl group of the back carbon atom by 60° (the torsional (dihedral) angle of the two C-H bonds is 60°) position of the hydrogens of the back carbon atom are just between position of the hydrogens of the front carbon atom. This position is called as staggered position, having lower internal energy for this conformer, than of the eclipsed conformer. Rotating methyl group of the back carbon atom by 60° more (totally by 120°) results in another eclipsed conformer with higher internal energy. Rotating further by 60° more, the staggered and eclipsed conformers are formed alternatively. If a conformer has lower internal energy, then there is greater probability of this conformer within the conformer population of the molecule.



Similar model testing can be carried out with other molecules, as well. Look at the butane molecule through the central carbon-carbon bond and rotate the back carbon

atom around this bond. We start from the eclipsed position where the two carbon atoms (methyl groups) by the two ends of the molecule are located behind each other. This position is called as *syn periplanar* position, and it is especially disadvantageous. There is a staggered conformation at rotation of 60° with dihedral angle of 60° between the two carbon atoms (methyl groups) by the two ends of the molecule. This position is called as *syn clinal* position, and it is advantageous energetically, although the two methyl group are in the vicinity of each other. There is another eclipsed position at rotation of 120°, which is called as *anti clinal* position, with lower energy level than of the *syn periplanar* position, but it is of higher energy level, than of the *syn clinal* staggered conformation. There is a staggered conformation at rotation of 180° with dihedral angle of 180° between the two carbon atoms, and it is an especially advantageous conformation, that it is called as *anti periplanar* staggered conformer, with the methyl groups located in the farthest positions from each other. Rotation by further 60° would result in changes in the opposite order.



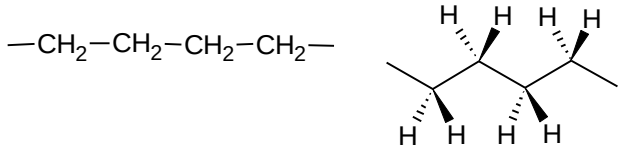
There are many inferences to be drawn:

1. Some parts may rotate around the carbon-carbon bonds (around other bonds, as well), resulting in conformers with different energy and stability.

2. The conformers can be classified as low-energy staggered és high-energy eclipsed conformers.

3. The staggered conformers are especially advantageous, if the largest substituents are located to the fartest position of each other (anti periplanar position). This conformer has the lowest energy in compounds with longer chains, resulting in zigzag arrangement of the chains.

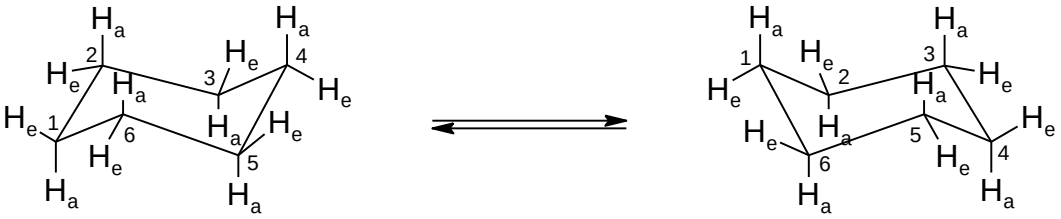
4. If the anti periplanar conformer cannot be realised for any reasons, molecule is arranged into the syn clinal position. Any eclipsed conformation contributes to the conformer population only, if the other parts of the molecule (e.g., cyclic structure) do force it.



There are diverse theories for the explanation of the reasons of the energy difference between the staggered and eclipsed conformations. Some researchers suggest repulsing forces (that would increase the internal energy) between the atoms or groups close to each other in eclipsed conformations. Other researchers argue that bonds in anti periplanar position may attract each other, thus decreasing the internal energy by overlapping. Probably both interactions influence formation of the conformers, but their ratio can be different.

Conformational isomerism in cyclic compounds

There are conformations of limited number in cyclic compounds, as well. The most instructive and the most important ring is the six-membered cycle. Cyclohexane is a saturated hydrocarbon built from 6 carbons. There are many conformations of the cycle. The so-called chair conformation is the most stable among them. The carbon atoms Nos. 1, 3 and 5, as well as the carbon atoms 2, 4 and 6 do determine 2 different parallel planes in this conformation. Hydrogen atoms are positioned to one or the another side of the planes, alternatively. Extra stability of the chair conformation ensues from the staggered conformations of any other carbons and hydrogens atoms attached to the ring. The hydrogen atoms, that are parallel related to the axis (so-called symmetry axis) perpendicular to the above-mentioned plane, are called as of *axial* position. The hydrogen atom, that have narrow angle (19.5°) to these planes is called as of *equatorial* position. Cyclohexane exists as equilibrium mixture of the two identical chair conformers. One of the chair conformers may turn to the other by rotation: then position of each hydrogen atom is changed: the equatorial position turns to be axial, while the axial position turns to be equatorial. The two chair conformations in cyclohexane are indistinguishable.

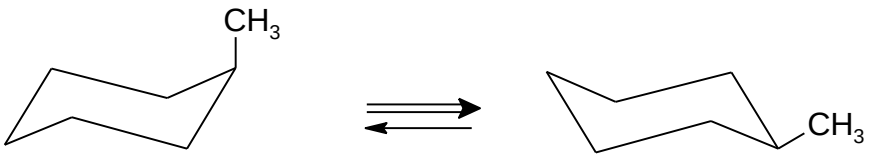


Chair conformations of cyclohexane

H_a: hydrogen atom in axial position

H_e: hydrogen atom equatorial position

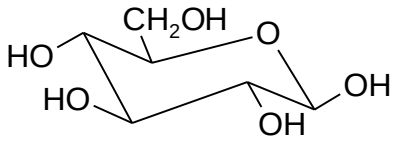
Substituted derivatives of cyclohexane have different conformers. Methyl group can be either in axial, or in equatorial position in methylcyclohexane. The methyl group in axial position may easily turn (without ring opening) to the conformer, where the methyl group is in equatorial position. Conformers with equatorial substituents (e.g., methyl group) are more stable.



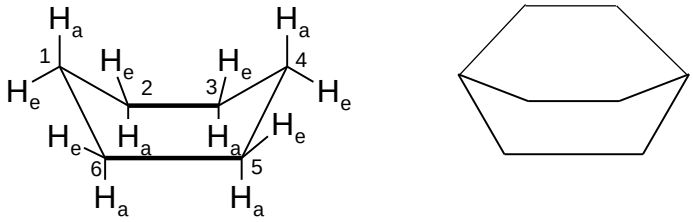
axial methyl 5%

equatorial methyl 95%

Stable conformations have importance not only for carbocycles, but for heterocycles, as well. For example, β-D-glucose, that is with significance in living organisms, has six-membered ring with chair conformation, consisting of five carbon atoms and an oxygen atom (in the so-called pyranose form). The conformer of β-D-glucose is the most stable, where each hydroxy group is of equatorial position.



The structure is also remarkable, where atoms 1, 2, 4 and 5 of the cyclohexane ring are located in the same plane, while atoms 3 and 6 are on one side of this plane. This structure is called as boat conformation, it is on higher energy level due to the eclipsed position for the hydrogens attached to carbons 1 and 2, or 4 and 5. Such conformation can be formed only, if a further ring forces it.



boat conformation

— hydrogens are in eclipsed position along the bold bonds

Boat conformers of cyclohexane

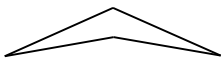
H_a: hydrogen atom in axial position

H_e: hydrogen atom in equatorial position

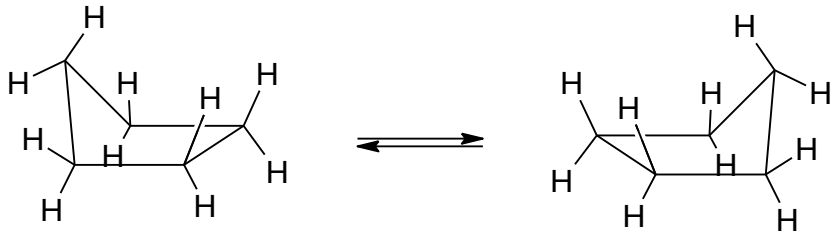
The cyclohexane ring is stable, since its carbon atoms still retain the tetrahedral structure.

Smaller rings have some importance, as well. However, considerable difference of the bond angles between cyclic C-C bonds from the tetrahedral value (109.5°) results in lower stability. This difference of the bond angles is the greatest for three-membered cycles, then it is decreased by increasing ring size, providing greater stability.

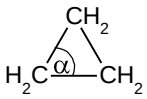
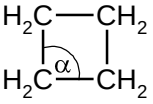
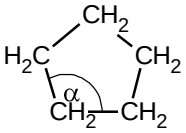
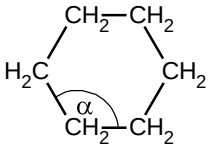
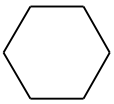
Instability (the internal energy) is increased by the fact, that some of the hydrogens (or other substituents) attached to the ring carbon atoms are in eclipsed position (torsion strain), if the carbon atoms are coplanar. No any deviation is possible in the three-membered ring (cyclopropane) from the planar structure. However, cyclobutane and cyclopentane molecules are partially stabilised (decreasing its energy) by shifting one of the carbon atom out of this common plane. For such reasons, these rings are not coplanar. Instability of the rings is obvious, if the increased values of the combustion heats per one methylene group (-CH_2-) are compared to the similar, but lower value for cyclohexane.



cyclobutane



conformations of cyclopentane

				
				
	cyclopropane	cyclobutane	cyclopentane	cyclohexane
$\frac{109{,}5^o - \alpha}{2}$	~25°	~10°	~1°	~ -5°
heat of combustion in kJ/CH_2	698	686	666	662

Diastereomers

identical connectivity
different internuclear distances

Enantiomers

identical internuclear distances
different spatial order (configuration)

Summary and biological importance

Conformational isomerism is one of the subtypes of stereoisomerism. Stereoisomers are the compounds with the same general formula and connectivity, but have different spatial order. Conformers usually have the same bond angles and bond distances (although there are exemptions), while the internuclear distances among atoms, or atom groups not connected directly to each other usually have different distances in space. Such isomers are called as diastereomers. Consequently, conformational isomerism is a special case of diastereomerism. For example, the distance in space between any two hydrogens in eclipsed position attached to neighbouring carbons of ethane is 229 pm, while the similar distance between two staggered hydrogens is 225 pm.

There is great biological importance of conformations. There are many bioactive molecule with specific conformation in order to have the maximum function. The peptides and proteins, as well as the nucleic acids have certain conformations only. Similarly, carbohydrates and steroids with cyclic structure have certain conformations. Many drugs are known with preferred conformation for the maximum effect.

Biological importance of conformations:

a) in chains: peptides
nucleotides

b) in cycles: carbohydrates
steroids

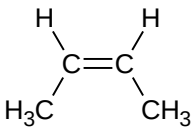
Biological importance of geometrical isomerism:

unsaturated fatty acids
carotenoids (sighting)

III. Geometrical isomerism

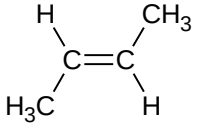
If the rotation is more or less restricted around any bonds, then there is a different subtype of stereoisomerism. For example, there are two stereoisomers of 2-butene: the two methyl groups can be found in the same side of the double bond in one of the stereosomers, while these groups are located in the opposite sides in the other stereoisomer. The first is called as *cis* 2-butene, while the second is called as *trans* 2-butene.

can be isolated



cis

4.6 kJ/mol



trans

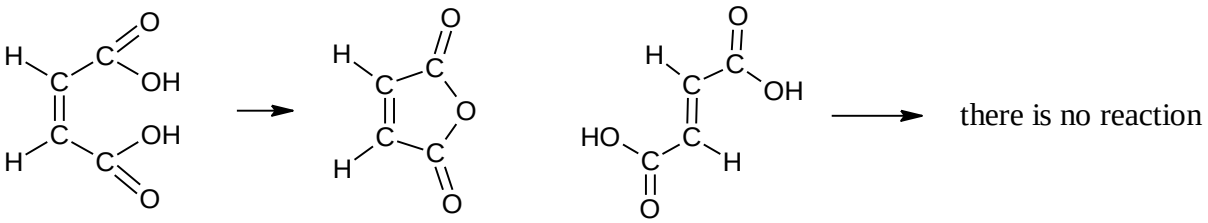
identical substituents

on the same side

on the opposite side

the double bond prevents rotation around carbon-carbon bond

Spatial arrangement of these two structures is similar to the syn periplanar, or to the anti periplanar conformer of butane, their transformation to each other happens at around 500°C only. For comparison, any two butane rotamers are transformed easily to each other at -250°C. Transformation of butene isomers to each other happens at high temperature only, since cleavage of the π-bond is necessary before isomerisation (butane rotamers are transformed to each other without bond cleavage). Stereoisomerism along a double bond is called as *geometrical*, or *cis trans* isomerism, and it is a special case of rotational isomerism. *Geometrical* isomerism is applied, if there are two different substituents attached to both carbon atoms of the double bond. Geometrical isomers may have different properties. For example, maleic acid is transformed to maleic anhydride by heating, while fumaric acid does not react.



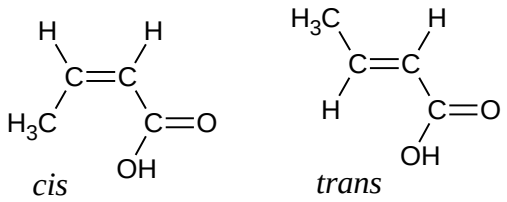
maleic acid

It is clearly seen from the structural formulas, that the two carboxylic groups in fumaric acid are in the farthest position in space, while these groups in maleic acid are close to each other. On the other side, geometrical isomerism is special case of diastereomerism (the two geometrical isomers are not the mirror image of each other).

Notation of geometrical isomerism

There are two notation systems of geometrical isomers.

1. If two of the same atoms or groups are attached to different carbons of the double bond, then we establish *cis* or *trans* configuration for the double bond according to the relative positions of the identical atoms or groups. For example, two hydrogens are attached to different carbons of the double bond in *cis* crotonic acid on the same side of the double bond, while these two hydrogens are in opposite sides of *trans* crotonic acid.

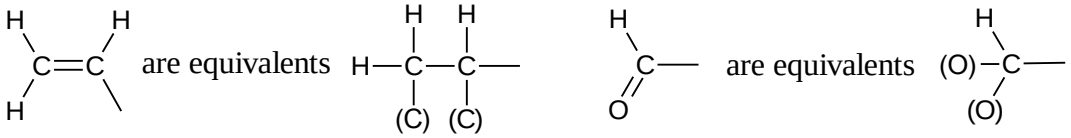


cis *trans*

2. Cahn-Ingold-Prelog notation can be applied, when each substituent of the double bond is different from each other. Establish decreasing order atoms attached to each carbon of the double bond (separately), then the alkene is considered as *Z* isomer if the two atoms attached to different carbons of the double bond with greater priority are found on the same side of the double bond, while the other stereoisomer is considered as *E* isomer.

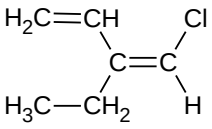
The following three rules must be strictly kept during setting priority orders:

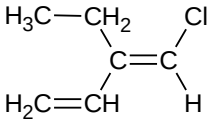
1. Any atom with higher atomic number has greater priority.
2. The double bond counts as two single bonds.



3. If the two atoms attached to the same carbons of the double bond are identical (I. sphere), then go the II. sphere and set decreasing order of atomic numbers for

these atoms. For example, we cannot make a difference between the two carbon atoms attached to the same carbons of the double bond in the following compounds, but consider decreasing order of the elements attached to the II. sphere, thus we would be able to determine which substituent is of greater priority (C, C, H) has greater priority over (C, H, H).

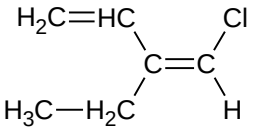


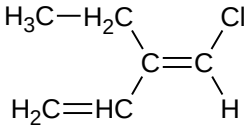


$H_2C{=}CH{-}$ is of greater priority, than $H_3C{-}CH_2{-}$

Cl— is of greater priority, than H—

C, C, H

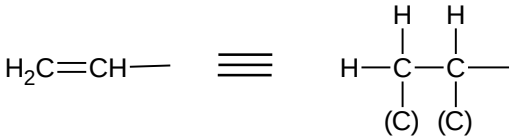




C, H, H *Z* *E*

Priority order (at each carbons of the double bond, separately):

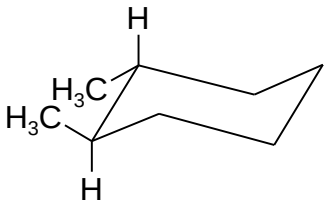
1. greater atomic number
2. double bond goes for two single bonds



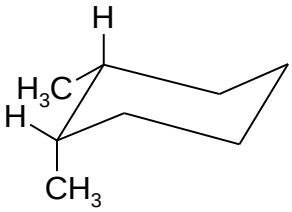
$H_2C{=}CH{-}$ > $H_3C{-}CH_2{-}$ Cl > H

If the atoms with greater priority can be found on the same side of the double bond, then it is of *Z* geometry.
If the atoms with greater priority can be found on the opposite side of the double bond, then it is of *E* geometry.

There is geometrical isomerism whenever the rotation is restricted around any bonds, therefore presence of a double bond is not required. This is the situation for many cyclic compounds. For example, if there are two methyl groups attached to the neighbouring carbons of cyclohexane, the two substituents can be in *cis* position if these are on the same side of the plane of the non-neighbouring carbon atoms, while it is in *trans* position if these are located on the opposite sides.

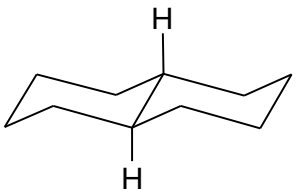


trans

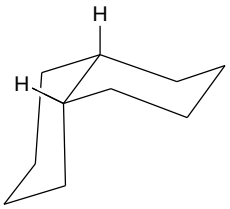


cis

Isomerism of this type has importance for condensed ring systems with two common atoms. Hydrogens attached to the common carbon atoms are located on the opposite sides of the ring system in *trans* decaline, while these hydrogens are positioned on the same side of the ring system in *cis* decaline.



trans

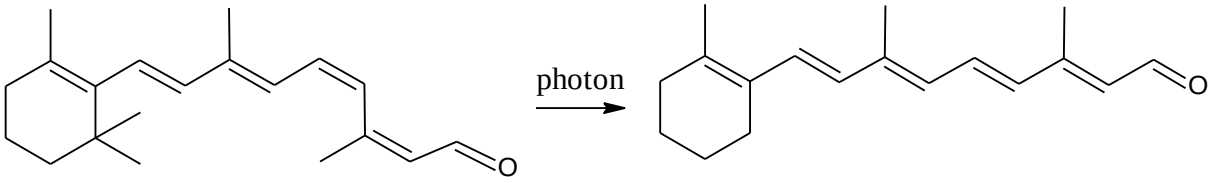


cis

Biological importance

Geometrical isomerism plays important role in biochemical processes. For example, there is formation of fumaric acid with *trans* geometry within the citrate cycle (part of the aerobic decomposition of carbohydrates), while the stereoisomer *cis* compound maleic acid is not formed.

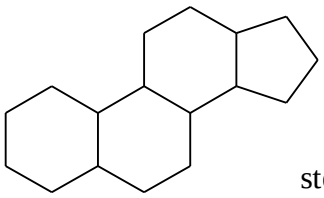
Cis retinal plays important role in biochemistry of sighting. Geometry of *cis* double bond in retinal changes to *trans* isomer due to the energy intake of the incoming light, while it is rearranged to the *cis* stereoisomer during night time.



cis-retinal

trans-retinal

Cis decaline unit can be found in natural compounds with steroid skeletone, while *trans* decaline unit is much less frequent. Enzymes participating in biochemical processes can make differences between the two geometrical isomers.



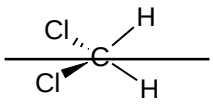
steroid skeletone

IV. Optical isomerism

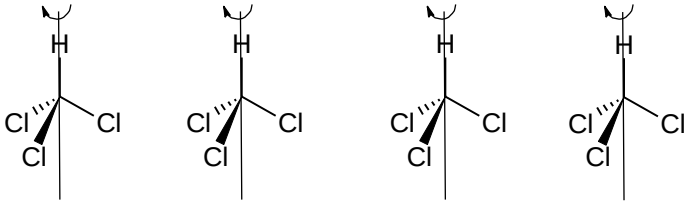
There are two (and not more) stereoisomers of 2-butanol, which are different from each other like a scheme and its mirror image, like right hand is different from left hand. These two compounds are called as *chiral* (”with hands”), these are *enantiomers* of each other, while this special case of stereoisomerism is called as *enantiomerism*. Enantiomerism may happen between such compounds, that do not have internal mirror plane, dividing the molecule into two parts differing from each other like a scheme and its mirror image, meanwhile without any inversion point.

symmetry elements in organic molecules

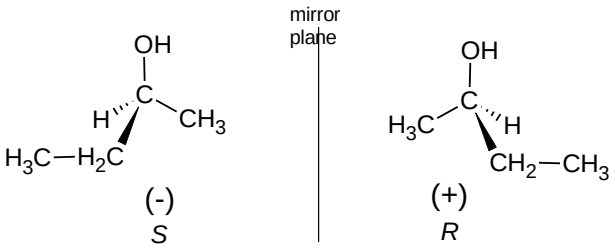
molecule	symmetry		
	axis	plane	
symmetric	+	+	achiral
dissymmetric	+	-	chiral
asymmetric	-	-	chiral



m symmetry plane C_3 symmetry axis



Enantiomers usually have centres of chirality with 4 different substituents attached to it (stereogenic centre or centre of asymmetry). However, this is not a necessary condition of enantiomerism, neither it is a sufficient condition.



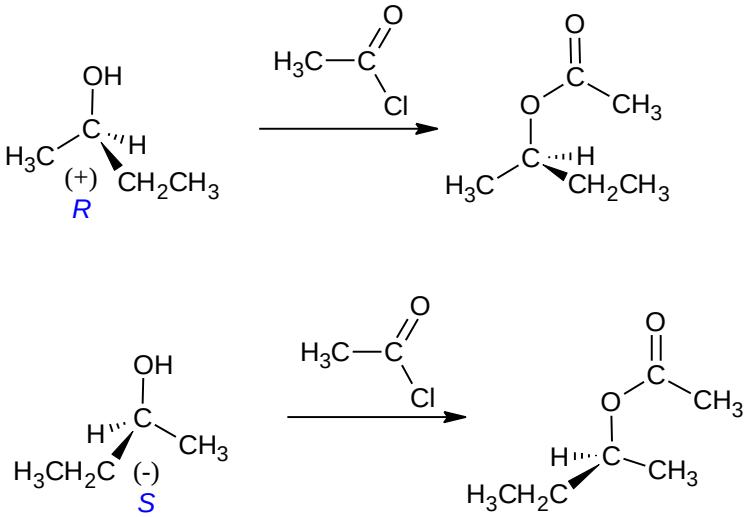
enantiomers

C = stereogenic centre (centre of chirality, centre of asymmetry, asymmetric carbon atom)

chiral molecules

condition: absence of mirroring symmetry axis

The spatial arrangement of atoms and groups attached to the centre of chirality is called as *configuration*. Configurations of the stereogenic centres are opposite in the two enantiomers of 2-butanol. Generally speaking, compounds are enantiomers if all of the stereogenic centres have opposite configurations. Configurational isomers are the compounds differing in the configurations of the centres of chirality. two enantiomers of 2-butanol are configurational isomers of each other. Bond distances and bond angles, as well as the internal energy and stability are identical in enantiomers, and moreover - differing from the diastereomers – the spatial distances among atoms, or groups are also identical. Therefore any physical, chemical and biological properties are identical, if achiral effect is influenced. Direction does not have any role in the achiral effects. For example, melting points of enantiomers are identical, since heating is one of the achiral effects. Similarly, enantiomers react with achiral molecules by the same way and by the same rates. For example, both enantiomers of 2-butanol react with acetyl chloride by the same way and by the same rate, since this compound (acetyl chloride) is achiral.



However, enantiomers behave differently by chiral effects. For example, enantiomers react by different ratios with another chiral compound, providing a chance for their separation. The simplest chiral effect is the light polarised in plane. The chiral molecules rotate the light polarised in plane. this property is called as *optical activity*.

Degree of rotation depends on concentration of the enantiomer in the solution, on the depth of the cuvette as well as on structure of the enantiomer.

$$\alpha=[\alpha] / l_x c$$

Properties of enantiomers:

identical bond distances and bond angles

identical internal energy

identical physical and chemical properties when achiral interaction is applied (e.g., heating, achiral reagent)

different physical and chemical properties if chiral interaction is applied (e.g., polarised light: optical activity)

there is stereoselective reaction with chiral reagent

specific optical rotation: $[\alpha] = \frac{\alpha \text{ x } 100}{l \text{ x } c}$

depends on: wavelength

temperature

solvent

molar optical rotation= $\frac{[\alpha] \text{ x } M}{100}$

The so-called *specific optical rotation* is a characteristic constant of each enantiomer, just like melting point is for other isomers. If the optical rotation is referred to solution with 1 Mol in concentration instead of solution of 1% concentration, then we get the *molar optical rotation*. Either specific optical rotation, or molar optical rotation depends on temperature of the measurement, of wavelength of the light applied and sometimes of concentration of the solution. The two enantiomers of a given compound rotate the light polarised in plane by identical values, but with opposite signs.

Notation of enantiomers

Molecules are arranged in space, therefore it is problematic how can be the 3D structure represented in planar sheets. There are two kind of methods for their projection.

1. The perspectivic formula and the Cahn-Ingold-Prelog (CIP) system

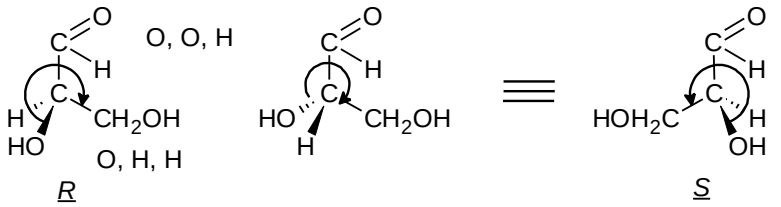
We must consider the fact for the application of the perspectivic formula, that three points, or two straight interlacing lines define any plane. Since the arrangement around the carbon atom is tetrahedral at a centre of chirality, the asymmetric carbon atom and two other atoms (out of four atoms) attached to it are regularly drawn within the sheet of paper, representing these bonds with single thickness. Then one of the remaining two atoms must be in front of this plane, showing it with bold line. The last atom is behind the plane of sheet, represented by dotted line. Apply this method for 2D representation of a compound with two or more centres of chirality, too.

The Cahn-Ingold-Prelog (CIP) notation system is used for differentiation of the enantiomers in the name the most frequently. At first, set decreasing order of priority of

the atoms directly attached to the centre of chirality. The same principles are applied than for differentiation of geometrical isomers. Then apply 3D rotation of the molecule until the atom with the lowest priority (this is a hydrogen atom frequently) is behind the sheet of plane. Then examine, whether the decreasing order of priority of the remaining 3 atoms runs clockwise, or counterclockwise direction. A centre of chirality with clockwise direction gets *R* configuration, while a centre of chirality with counterclockwise direction gets *S* configuration.

Notation of enantiomers

1. perspectívic formula and the Cahn-Ingold-Prelog (CIP) notation system



R-(+)-glycerolaldehyde *S*-(-)-glycerolaldehyde

priority order: OH > —C(=O)H > CH_2OH > H

rotate the group with the lowest priority to the farthest position from us, then the centre of chirality gets
R configuration, if the decreasing order of the other 3 groups follows clockwise direction
S configuration, if the decreasing order of the other 3 groups follows counterclockwise direction

R-(+)-glycerolaldehyde *S*-(-)-glycerolaldehyde

advantage: absolutely clear
disadvantage: it does not represent the configurational relationship

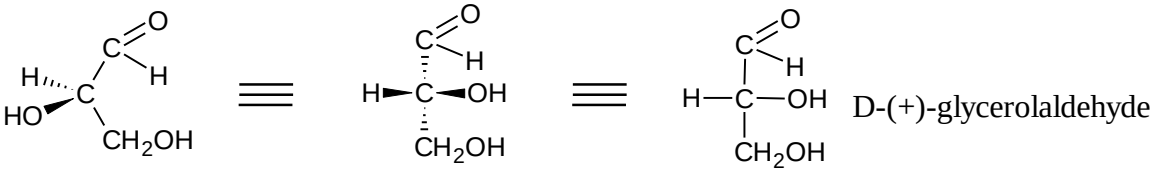
2. Projected formula and Fischer's notations

Fischer's notation is applied for some families of compounds only. There are strict rules for its application.

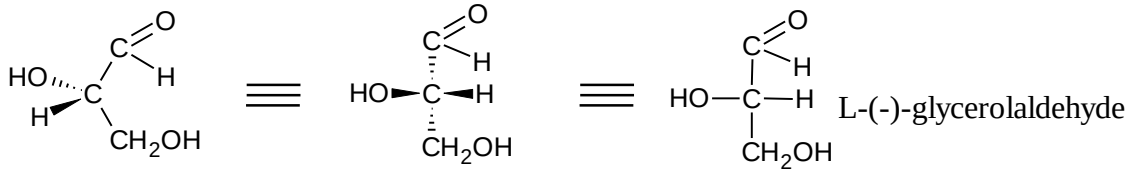
The process is called as projection of the spatial structure to a plane. Imagine the given centre of chirality (asymmetric carbon atom) within the sheet of paper in such a way, that two of the bonds starting from it are behind the sheet of paper up and down, while the rest are in front of the sheet of paper to left and to right. Carbon atom of the centre of chirality is seldom drawn, but imagine into the point of intersection of the bonds. The vertical bonds would have to be drawn by dotted lines according to this arrangement, while the horizontal bonds would have to be drawn by bold lines, but each bond is drawn by identical width, according to the agreement. Fischer's notation of the spatial structure is closely related to the projected formula. Notation of a configuration depends on position of an atom or a group attached to the centre of chirality in the projected formula. If this group is attached to the right, the centre of chirality gets D notation, while if it is attached to the left, the centre of chirality gets L notation.

Projected formulas and Fischer's notation is applied in two families of compounds: 1. to the carbohydrates and closely related compounds; 2. to the amino acids, peptides, proteines and its derivatives. However, for safe and reliable applications of the Fischer's notation, further restrictions must be applied in these families of compounds. The group in the up position must contain the carbon atom with the highest oxidation level in the projected formula. This is the carboxyl group in amino acids and in its derivatives, while it is the oxo group in saccharides. Group in the down position must have the longest chain in the projected formula (with one or more carbon atoms). The amino group in horizontal position ($-NH_2$) would provide Fischer's notation in amino acids, while the hydroxyl group ($-OH$) attached to the centre of chirality in the farthest position from the oxo group would provide Fischer's notation in carbohydrates.

2. the projected formula and the Fischer's notation
rules of projecting:
a) the group on the highest oxidation level is found on the top
b) the longest chain is down
c) both previous groups are behind the plane of the vertical plane
d) the other two groups are located horizontally, in front of the plane of the vertical plane



R-(+)-glycerolaldehyde



S-(-)-glycerolaldehyde

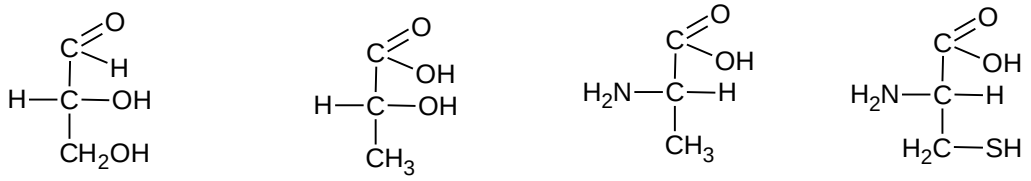
The following limitations come as results of the abovementioned rules of projection. For example, if any two atoms, or groups are replaced by each other in the projected formula (generally saying: replacement of groups by odd number), the centre of chirality with the opposite configuration is generated. Applying replacement of groups by even number, we get the original configuration, but with different arrangement. The projected formula can be rotated by 180° in the sheet of paper, but not by 90° or 270°, since the latter rotations would result in centre of chirality of the opposite configuration, according to the rules of projection. These limitations can be easily checked by molecule models.

Comparing the two notation systems, their advantages and disadvantages would be obvious.

1. Perspectivic formulas show the real spatial positions, but their application can be difficult for a complex molecule. CIP notation system is absolutely unambiguous, can be widely applied, but it does not represent any structural relationship.

2. Projected formulas make the representation to be simpler, but if we are going to apply them for another families of compounds, then further rules (conventions) have to be introduced, making the situation to be much more complex. Fischer's notations are closely related to the rules of projection, therefore cannot be applied generally. However, they represent structural relationship as a great advantage. For example, most of amino acids of proteins are belonging to the L-series, and it is clear by looking at the projected formulas. However, the same amino acids do not get identical notation in the CIP sytem. L-alanine (and many other natural L-amino acid) gets *R* notation in the CIP sytem, while L-cysteine has *S* configuration. This is due to the fact that atomic number of sulfur (16) is higher, than of oxygen atom (8), resulting in change in the priority order around the centre of chirality.

advantage: it represents configurational relationship
disadvantage: can be applied for some families of compounds only
(primarily for carbohydrates, amino acids)



regularly projected formulas

D-(+)-glycerolaldehyde	D-(-)-lactic acid	L-(+)-alanine	L-(+)-cysteine
R-(+)-glycerolaldehyde	*R*-(-)-lactic acid	*S*-(+)-alanine	*R*-(+)-cysteine

It is important!!!
there is no correlation among the following notations:

D, L
R, S
+, -

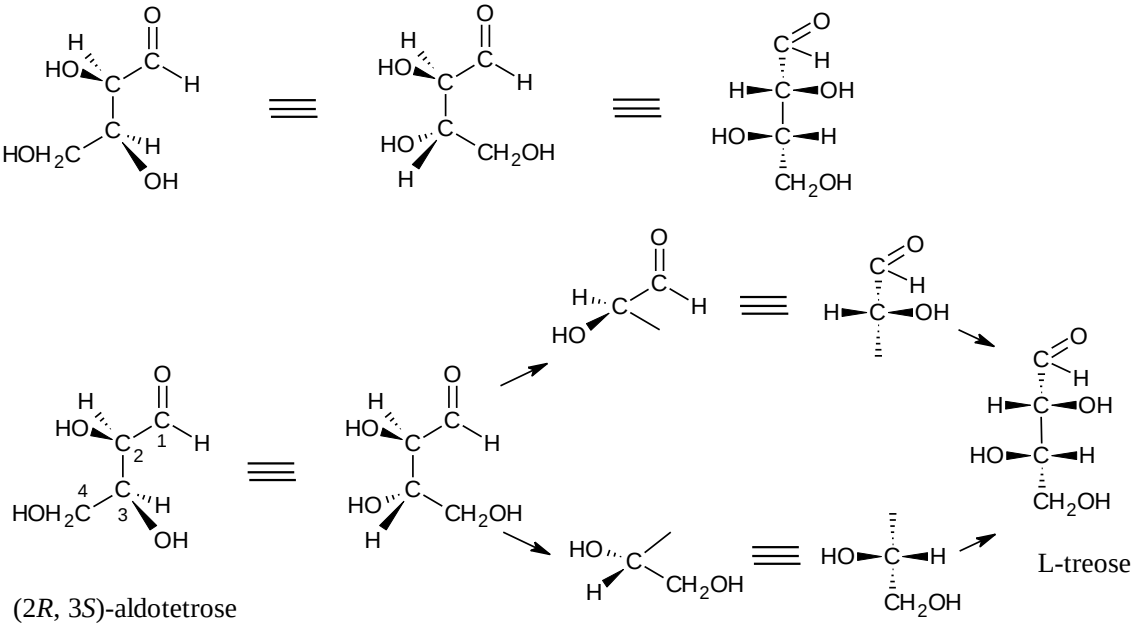
As we mentioned before, enantiomers can be differentiated according to the sign of their optical activity. However, it is important to know that there is no direct relationship among the configurational notations (*R* and *S*, D and L) and sign of the optical activity (+ and −). It means that optical rotation of a compound with *R* or D configuration can be either + or −. Therefore measurement of optical rotation does not provide information on the configuration (spatial structure) of the centre of chirality.

Compounds with many stereogenic centres

If a compound has many centres of chirality, then apply these projection rules for each centre. It does not present any problem for the 3D representation, however, there are problems with the projected formulas. We should follow the following method at projection of carbon chains: rotate the carbon chains having the centres of chirality into syn periplanar conformation (this eclipsed conformation is the least likely), then make a straight chain from it without rotation. Draw this formula in vertical way, then project each centre of chirality to the sheet of paper one by one. See the attached figure. As a consequence, the projected formulas do not present conforma-

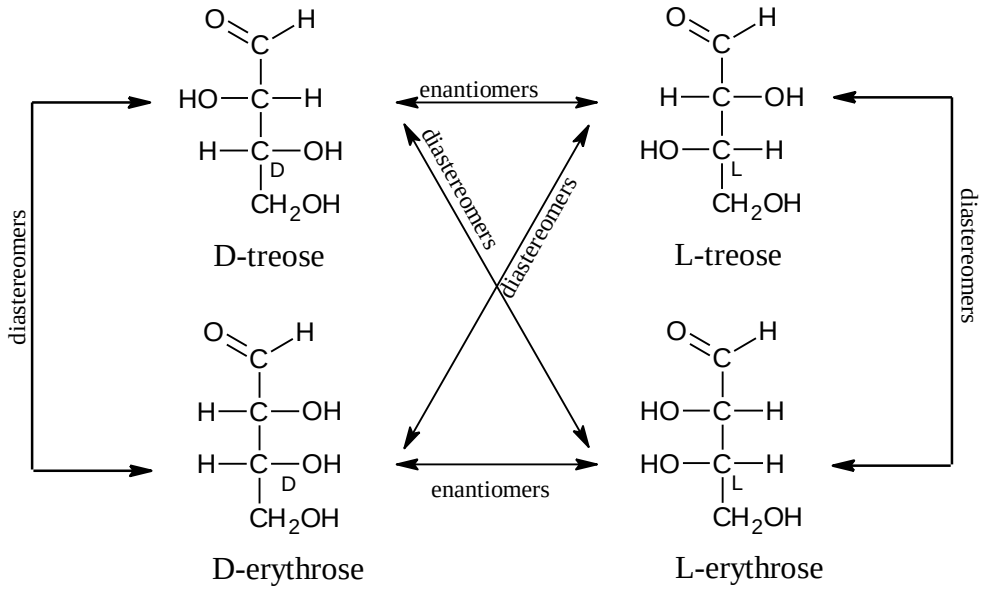
tion of the compound, or relative position of single atoms, or groups realistically, showing only configuration of centres of chirality clearly.

Projecting compounds with two centres of chirality



number of stereoisomers = 2^n
n = number of centres of chirality

Projection of a cyclic compounds can be carried out after a mentally ring opening of the cycle. Number of stereoisomers is increasing exponentially by increasing number of the centres of chirality: $N=2^n$, where N is the number of stereoisomers, n is the number centres of chirality. For example, there are two centres of chirality in the aldotetrose with four carbon atoms, number of stereoisomers is $2^2=4$. Its projected formulas are shown on the following figure.

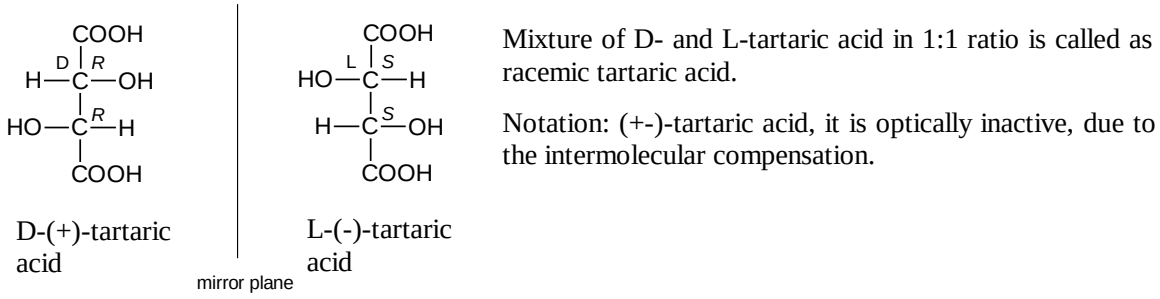


Each compound has a mirror image (enantiomer). They have opposite configuration of every centres of chirality. The physical and chemical properties of these compounds are identical at achiral influence, the absolute values of their optical activity are also identical, but with different signs (chiral effect). Each compound is differing from the other compounds in respect to configuration of one of the centres of chirality (not all of them are different). The bond distances and the bond angles can be identical in these isomers (however not necessarily), but the internuclear atomic distances measured through space are different (it can be easily checked by molecule models). As it was mentioned before, these stereoisomers are called as *diastereomers*, their relationship is *diastereomerism*. The internal energy of diastereomers, as well as their physical and chemical properties are different, although these differences are slight only. Diastereomeric relationship is shown in their names, as well. D-threose has the enantiomer: the L-threose, but their diastereomers are D-erythrose as well as L-erythrose (these are also enantiomers of each other). Since the stereoisomers of aldotetrose are different in the configuration of the centres of chirality, these are configurational isomers of each other. Stereoisomers of aldotetrose, or generally stereoisomers differing from each other in their optical activity are called as *optical isomers*, while this phenomenon is called as *optical isomerism*. Optical isomers can be enantiomers or diastereomers of each other.

Racemic and meso compounds

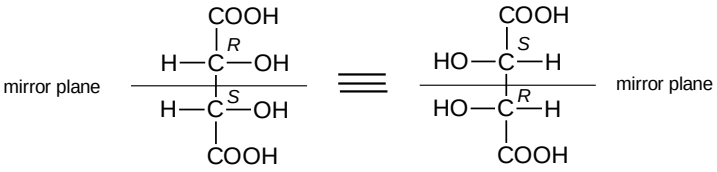
There is an exemption from the rule considering the number of stereoisomers, for example, if the molecule has an internal mirror plane. If we transform both the formyl group (–CHO) and the hydroxymethyl group (–CH_2OH) of aldotetroses to carboxyl group (–COOH) (it can be done in the reality), we get the appropriate tartaric acid.

Meso compounds and racemic mixtures



Mixture of D- and L-tartaric acid in 1:1 ratio is called as racemic tartaric acid.

Notation: (+-)-tartaric acid, it is optically inactive, due to the intermolecular compensation.



The two formulas represents the same structure. It is not chiral, since it has a mirror plane: meso tartaric acid. It is optically inactive, due to the intramolecular compensation.

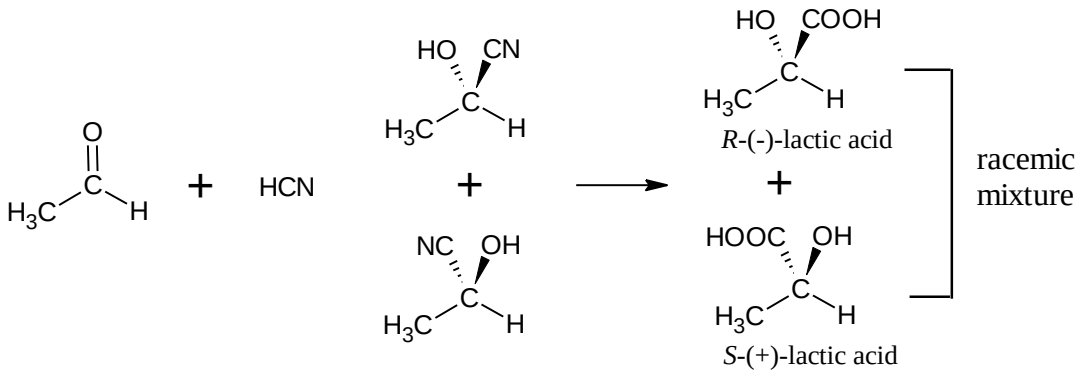
It is clear from the projected formulas, that there is an internal mirror plane, and the two formulas represent the same molecule. It can be easily checked by molecule

models, but is also evident from the projected formulas. We have mentioned before, that projected formulas can be rotated by 180° in the plane of the sheet of paper without changing its configuration. The lower two formulas at the previous figure are interchangeable: we get one from another with rotation by 180° in the sheet of paper. Therefore tartaric acids have only three stereoisomers, not four of them. D- and L-tartaric acid are enantiomers of each other. They rotate the plane of polarised light with the same angle, but with different signs, their mixture in 1:1 ratio is optically inactive (with 0° optical rotation). This mixture is called as racemic pair, or *racemic mixture*. This inactivity is due to *intermolecular* compensation: the net result of the rotation of the two enantiomers is 0°. The third tartaric acid is *meso*-tartaric acid, which is diastereomer of the D-tartaric acid as well as the L-tartaric acid. *Meso*-tartaric acid is also optically inactive, while it has an internal symmetry plane, and having opposite configuration for both centres of chirality. Reason of inactivity in this case is *intramolecular* compensation.

Formation and separation of racemic mixtures

If a chiral compound is prepared in the laboratory from another chiral compound with only one centre of chirality, always racemic mixture is generated. It is due to the fact that internal energy of the enantiomers forming the racemic mixture are identical, therefore probability of their formations are also the same. Reacting the achiral acetaldehyde with achiral hydrogen cyanide, then heating the resulting product with aqueous acid, racemic mixture of D- and L-, or *R* and *S* lactic acid is formed, which is an optically inactive product.

Formation of a racemic mixture



There is always formation of racemic mixtures from achiral reagents in the laboratory. However, chiral enzymes result in one of the enantiomers.

This can be highly different under biological conditions. There is only formation of L-lactic acid from pyruvic acid in muscle cells, D-lactic acid is not formed at all. However, this reaction runs in the presence of lactic acid dehidrogenase enzyme. Enzymes have protein-like nature, and built from L-amino acids. The enzymatic process can be considered as a chiral effect, since it is catalysing transformation of pyruvic acid by a chiral reagent NADH. In such cases, the two enantiomers are not formed neces-

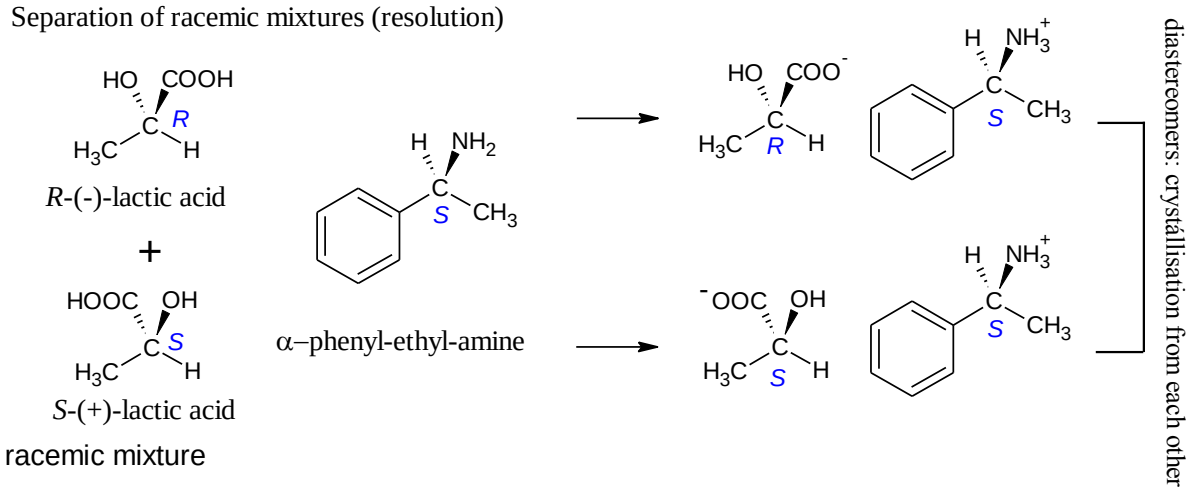
sarily in ratio of 1:1, but in the contrary, *stereoselective* reactions turn to be *stereospecific* reactions, using many enzymes.

Racemic mixture is formed using achiral reagents, while there is formation of one of the enantiomers by using chiral enzymes.

However, stereoselective reactions can be also carried out under chemical conditions, if one of the reagents is chiral. Recently, more and more such methods are applied.

If degree of stereoselectivity of the reaction is not enough high, then resolution of the racemic mixture is needed. The best process for it is preparation of a diastereomeric pair of salts.

Reacting racemic mixture of *R* and *S* lactic acid with one of the enantiomers of α-phenyl ethyl amine, e.g., with the enantiomer of *S* configuration, two salts are formed. Their relationship with each other is diastereomerism, since configurations of the carbon atom with hydroxyl group are opposite, but configurations of the carbon atom with ammonio group are the same.



Since properties of diastereomers are different from each other (but only slightly), it can be expected that their crystallisation properties are also different. There is chance, depending on the chemist's skill, for separation by recrystallisation of these salts. The enantiomeric lactic acids can be liberated by addition of a stronger acid to it, e.g., aqueous HCl.

Separation of racemic mixtures has of great importance. Most of the drug molecules are chiral compounds, but usually only one of the enantiomers is effective. The compounds prepared in laboratories or in factories are usually racemic mixtures. Application of racemic mixtures to the patients directly would present unnecessary addition of the enantiomer without effect (if we are lucky), but it is also possible that the other enantiomer has adverse effects. Therefore recently there is great effort at the drug factories as well as at the health authorities to apply the useful enantiomer only (this is called as eutomer), by separation of racemic mixtures.

Biological importance of chirality

Importance of chirality is obvious looking at the abovementioned Chapters. Life is chiral. Most of the compounds constructing living organisms or taking place in the processing of living organisms are chiral. Chiral compounds are the amino acids and

e peptides and proteins built from them (and such a way, the enzymes, as well), the carbohydrates (monosaccharides, polysaccharides, as well as the ribose and deoxyribose built into nucleic acids), and furthermore, many small molecules and drugs. Consequently, most of the biochemical processes are stereoselective. It is interesting that most of the amino acids built into proteins belong to the L series, while configuration of the farthest centre of chirality from the oxo group is D (these belong to the D series). This selectivity can be found in organisms which phylogenetically show much less specialisation, compared to the current living organisms.

We cannot answer why compounds with given configuration are formed during their biogenesis, or how did form the first chiral compound. But it looks like that these questions depend on the vectorial property of the weak interaction of the components of nuclei. Nature is not mirror symmetric.

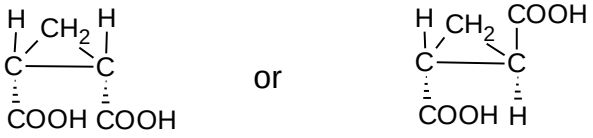
Biological importance of chirality:
- chiral compounds
  - amino acids (presumably with L configuration)
  - peptides, enzymes
  - carbohydrates (presumably with D configuration)
  - drugs
- Life is chiral

How did form the first chiral compound?
- depend on the vectorial property of the weak interaction of the components of nuclei.
- Nature is not mirror symmetric

V. Isomerism of other cyclic compounds

Cyclopropanecarboxylic acids

Cyclopropanedicarboxylic acid has two isomers, having the two carboxyl groups in *cis* or *trans* positions.



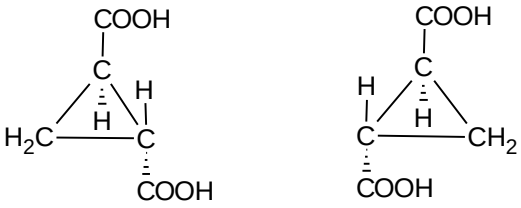
cis *trans*

The same substituents are located on one side of the cycle for the *cis* configuration, while the two carboxyl groups can be found on opposite sides of the cycle for the *trans* configuration.

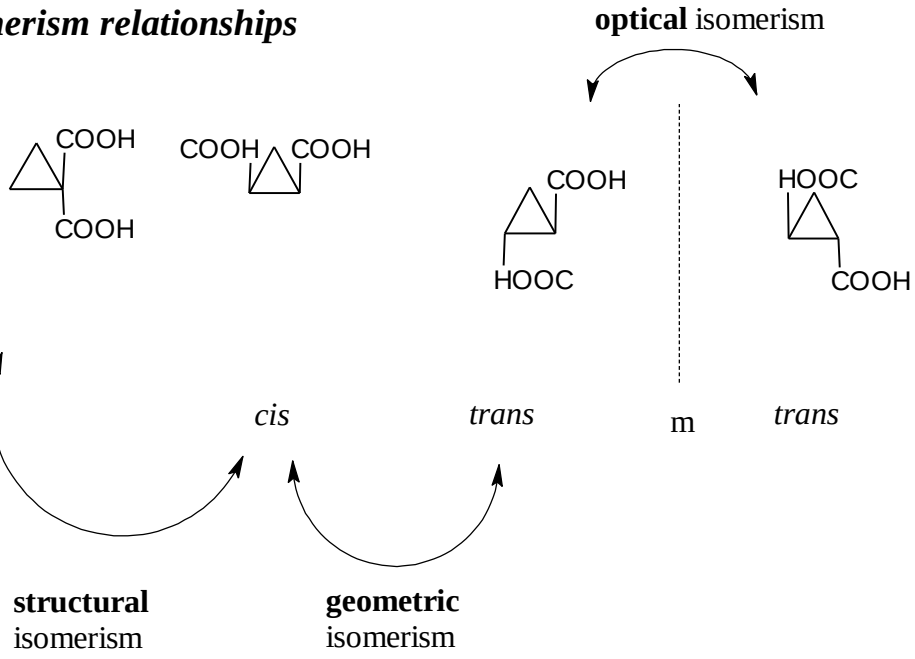
The notation system, that is used for steroids, can also be applied here. If a substituent is located below the plane of the ring system of the compound, then mark with dotted line, if above it, then mark with single solid line.

These isomers can be easily differentiated from each other by chemical methods. *Cis* dicarboxylic acids easily form anhydride due to the advantageous position of the carboxyl groups. However, the *trans* isomer does not result in anhydride, due to its asymmetric substituents. The racemic *trans* compound can be re-

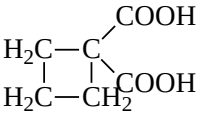
soluted by formation of diastereomeric pair of salts to its active components (1*R*,2*S* and 1*S*,2*R*).



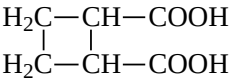
Isomerism relationships



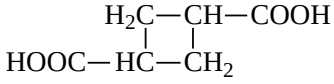
Cyclobutanedicarboxylic acids



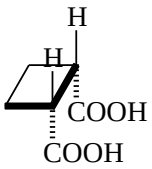
cyclobutane-1,1
-dicarboxylic acid
mp: 155°C

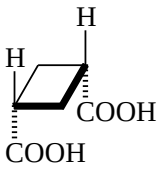


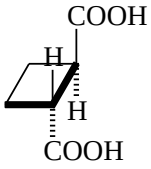
cyclobutane-1,2
-dicarboxylic acid
mp_{cis} 138°C
mp_{trans} 131°C

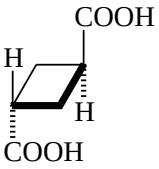


cyclobutane-1,3
-dicarboxylic acid
mp_{cis} 131-2°C
mp_{trans} 190°C

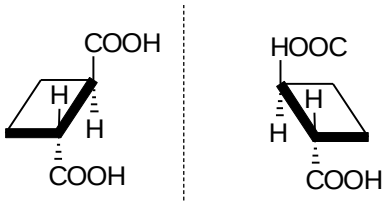






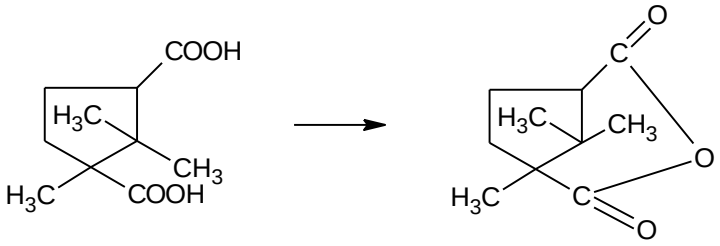


The *trans* cyclobutane-1,2-dicarboxylic acid has asymmetric structure, therefore can be resoluted to optically active forms.



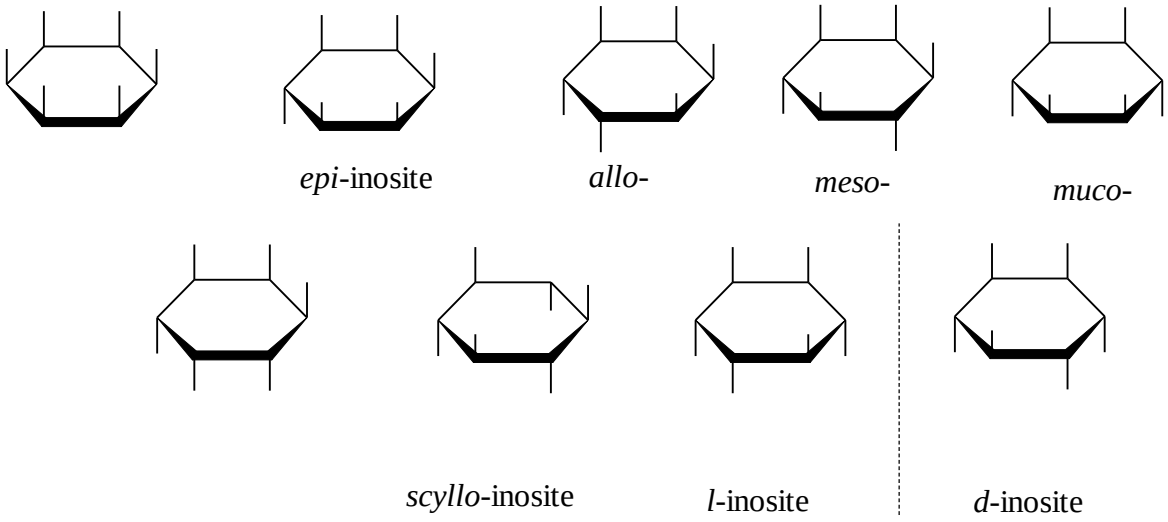
Cyclopentanecarboxylic acids

1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid, which is the metabolite of the monoterpene compound camphor, also belongs to these kind of stereoisomers. The compound has two stereogenic centres, therefore four active stereoisomers are possible. The compound forms anhydride despite of the fact that the two carboxyl groups are not located in the neighbourhood of each other.



Cyclohexanehexols

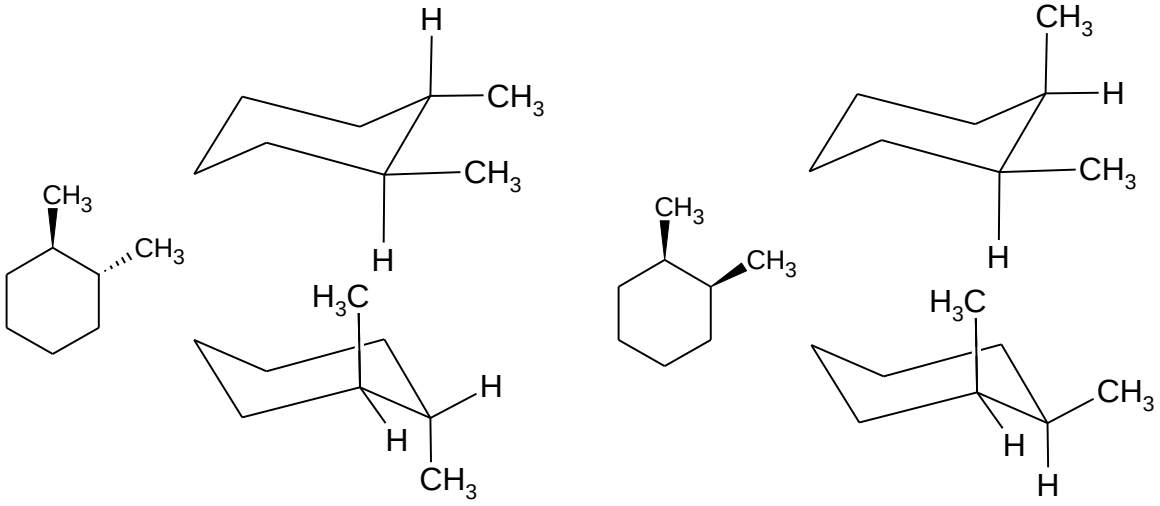
Members of the inosite group belong to it, these are widespread in plants. There are 9 isomers, 4 isomers (*meso*, *scyllo*, *d*- and *l*-inosite) can be found in plants, while further 3 isomers are artificial products.



Disubstituted cyclohexanes

trans *cis*

1,2-dimethylcyclohexane



Decaline

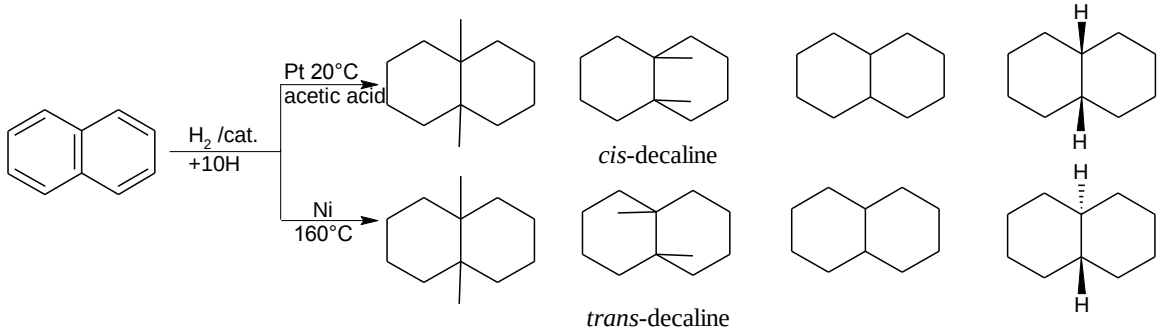
The compound can be also called as decahydronaphthalene or bicyclo [4.4.0] decane. This compound is used as a solvent, but its importance was stressed by the statements in relation to its spatial structure. Leroux stated in 1904 that catalytic hydrogenation of naphthalene at 160 °C resulted in decaline.

Mohr suggested in 1918 reconsideration of the previously discarded Sachse's theory, in order to prepare a model of cyclohexane, without any internal ring strain.

Meanwhile Mohr demonstrated, that two cyclohexanes can be assembled to decaline having two isomers.

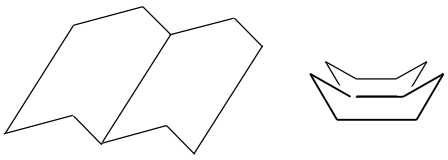
These two isomers was prepared by Hückel in 1925 by the following methods:

1. *cis* decaline was prepared by catalytic hydrogenation of naphthalene, using platinum as catalyst in acetic acid according to Willstätter's method
2. *trans* decaline was prepared by catalytic hydrogenation of naphthalene, in the presence of nickel, at 160 °C according to Sabatier-Senderens's method (1899)

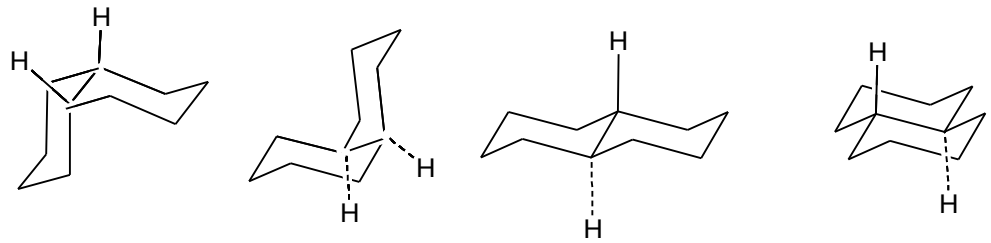


These two isomers are stable products, easily separable from each other. The two stereoisomers of disubstituted cyclohexane cannot be separated from each other, since they are transformed to the other stereoisomer, just applying slight heat.

On the other side, decaline is stable in *cis*, or *trans* configurations or in the corresponding boat, or chair conformations, therefore the two hydrogens in anellation positions are fixed. According to the previous theory, *cis*, or *trans* decaline were drawn in 3 forms, despite of the fact that two cyclohexanes could be put together as many as 8 forms, considering boat, or chair conformations for both rings.



Hassel and Bastiansen found in 1943, that boat-boat conformation was disadvantageous, and they preferred the chair-chair attachment. Energy level of cyclohexane in boat conformation is higher by 5.8 kcal/mol, compared to the chair conformation. Therefore Hassel peferred the following conformations, in the contrary to the Mohr's theory:



cis-decaline
chair-chair

trans-decaline
chair-chair

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