Molecular Formulae and Stereodescriptors: How to describe molecular structures and their stereochemistry

- There are several ways of describing a molecular structure using formulae, each with increasing levels of refinement.
- Take the carbohydrate glucose for example [or strictly D-(+)-glucose to be precise]:

**Composition:** The number and kinds of atoms that make up a molecule. This information is supplied by a molecular formula.

**Constitution:** The bonding pattern of the atoms in a molecule (i.e., which atoms are connected to which other atoms and by what kind of bonds). Different bonding constitutions are interconverted only by breaking and reforming covalent bonds. This information is supplied by a structural formula, and is implicit in the IUPAC name.

**Configuration:** The permanent spatial relationship of the atoms of a molecule to each other. Different configurations are interconverted only by breaking and reforming covalent bonds. This information is given in a stereochemical formula, and is also provided by a configurational stereodescriptor(s) as a prefix to the IUPAC name (e.g., cis/trans-, (E/Z)-, syn/anti-, (R/S)-, d/l-, d/d-, (+)/(-)-, threo/erythro-...).

**Conformation:** The variable spatial orientation of the atoms in a molecule to each other that occurs by rotation or twisting of bonds. Different conformations are interconverted without breaking covalent bonds. This information is supplied by a conformational formula, and sometimes also by a conformational stereodescriptor (e.g., gauche, anti).
Molecular Isomerism: Non-identical molecules with the same molecular formula

- Molecules with the same composition (molecular formula), but differing in their constitution, configuration, or conformation are called **isomers** (from Greek: *isos* = 'equal', *méros* = 'parts'). Such molecules are said to be **isomeric** to one another (as opposed to 'homomeric', meaning the same).

- **Constitutional isomers** (sometimes called "structural isomers") differ in their constitution (connectivity), whereas **stereoisomers** differ in their stereochemistry* (spatial arrangement of their atoms, i.e., configuration and/or conformation).

- Stereoisomers can be subdivided into two types: **configurational** and **conformational stereoisomers**, which can be further subdivided into **enantiomers** and **diastereomers**** (more on all of this soon).

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*The word "stereochemistry" is derived from the Greek word "stereós (στρεός)" meaning "solid"

**This term is synonymous with "diastereoisomers" but is often preferred because its shorter!
Conformational Stereoisomers: Bond-rotation and lone-pair inversion isomers

- Conformational stereoisomers can be defined as a set of stereoisomers for which interconversion between the different stereoisomers only requires the rotation of covalent bonds (or, in some cases, the inversion of a stereogenic lone electron pair - see below).

- This includes partial double bonds with single bond character, as in esters or amides.

- A subset of conformational stereoisomers are invertomers - trigonal pyramidal compounds that can interconvert by inversion of a lone pair (through a trigonal planar transition state), much like an umbrella turning inside out. Amines are the most common example.

- Differences in bond lengths or angles during stretching/bending vibrations also lead to differing spatial arrays of atoms, but these are not considered stereoisomers because such deformations are many orders of magnitude faster than bond rotations, and lead to much less pronounced geometrical change.

- Depending on the energy barrier to interconversion versus the energy available to the molecule, the interconversion between the conformational isomers can be either very fast or immeasurably slow, and so the rate of interconversion is also irrelevant to the definition of conformational stereoisomers.
Conformations, Molecular Projections, and Conformers

- A **conformation** is any spatial (3D) arrangement of atoms in a molecule. This is conveyed in visual form by a **molecular projection**, which is a formal 2D representation of a 3D molecular structure obtained by projection of bonds. There are several types in use:

  ![Molecular Projections](image)

  - **'zig-zag' projections**
  - **sawhorse projections**
  - **Newman projections**

  Note that (C–H) hydrogen atoms are often omitted from 'zig-zag' projections, but it is useful when you are still learning to draw them in!

  - Sawhorse and Newman projections are used interchangeably — they are useful for 'looking down' the rotating C–C bond.

- A **conformer** is one of several conformations that corresponds to a local/global energy minimum (i.e., a conformation that is not at an energy minimum is by definition not a conformer).

- Stereochemical properties of individual conformers are normally **time-averaged** due to rapid conformational interconversion, such that samples of conformationally-diverse compounds are **homogeneous** from a macroscopic viewpoint.

- In other words, different conformers are considered to be the same chemical compound, because they generally can't be separated and isolated as separate species.

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*Note that chemists often use the term “stereoisomers” to refer exclusively to *configurational* isomers, and “conformers” to refer to *conformational* isomers.*
**Nomenclature for Torsion (Dihedral) Angles and Rotamers**

- For **torsion (dihedral) angles** between two bonds in organic molecules, a number of terms are used:

  - For torsion (dihedral) angles between two bonds in organic molecules, a number of terms are used:

  - **Rotamers** are conformers that differ by rotation about only a single σ bond. Both **staggered** and **eclipsed** rotamers are possible, but only the former are "conformers" (i.e., energy minima). The special term "gauche"** is used for conformers with a 60° torsion angle.

  - **torsion angle (\(\psi\))**
    - 0° (syn-coplanar)
    - +60° (synclinal)
    - +120° (anticlinal)
    - 180° (anti-coplanar)

  - **conformation**
    - eclipsed
    - staggered (gauche)
    - eclipsed
    - staggered

*The term "periplanar" was coined by Klyne and Prelog in 1960 to define a flexible torsional angle of 0 ± 30° (syn) or 180 ± 30° (anti). The prefix "peri", derived from the Greek for "near", was chosen to make the meaning "approximately planar". However, current common usage of syn- and antiperiplanar is planar, which is incorrect. Thus, it is recommended to use "syn-coplanar" and "anti-coplanar" (see: J. Chem. Educ. 2000, 77, 1366)*

**“Gauche” literally means "left" in French, but its usage in this context may derive from the Middle French word "gauchir", meaning "turn aside, swerve"**
Conformations of Ethane: Hyperconjugation and torsional strain as stabilising/destabilising effects

- We can use Newman projections to show the two main conformations of ethane: the **staggered** and **eclipsed** conformations.
- Weak hyperconjugative interactions ($6 \times \sigma_{C-H} \rightarrow \sigma^*_{C-H}$) are responsible* for the lowest energy conformation of ethane being staggered (see F. Weinhold, *Nature* 2001, 539). The eclipsed conformation is also destabilised by repulsive overlap of the filled $\sigma_{C-H}$ orbitals.

The $2.9 \text{ kcal mol}^{-1}$ of extra energy** in the eclipsed conformation of ethane is called **torsional strain**.

The eclipsed conformation is actually the **transition state** for C–C bond rotation.

The staggered conformation is the only **conformer** for ethane.

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*The activation barrier in ethane is not accounted for by steric repulsion between H atoms, as the van der Waals radii of hydrogen is too small for this to be significant. However, in higher homologues (propane, butane, etc.) steric repulsions become the dominating factor (see later).

**It is common to find energies in organic chemistry quoted in kcal as opposed to kJ, despite it not being an SI unit. This is typically because the former unit is more widely used by American chemists, and the numbers (being smaller) tend to be easier to memorise! $1 \text{ kcal} = 4.184 \text{ kJ}$ (i.e., a kcal is ~25% of a kJ)
Conformations of Butane: The introduction of non-bonded steric interactions as a conformation-controlling factor

- The conformational energy profile of butane is more complex than that for ethane.
- It has two staggered conformers: the anti-coplanar* and synclinal (gauche) conformers. The syn-coplanar and anticinal conformations are not classified as conformers because they are transition states (energy maxima) for bond rotations.

The extra energy in the eclipsed conformations of butane is due to a combination of torsional strain (i.e., bonding orbital repulsion, as in ethane) and steric strain (i.e., atoms/groups forced closer than their van der Waals radii allow). The gauche conformations are destabilised (by 0.9 kcal mol\(^{-1}\)) solely by steric strain, as torsional strain is by definition zero for staggered conformations.

*Note that the 'anti-coplanar' conformer will often be referred to in textbooks as the 'antiperiplanar' conformer, and the 'syn-coplanar' as the 'synperiplanar' conformer. This is acceptable usage of the terminology, but strictly speaking the term 'periplanar' defines a spread of conformations that can differ from coplanarity by up to \(\pm 30^\circ\) (see: J. Chem. Educ. 2000, 77, 1366)
Conformations of Pentane: The syn-pentane interaction, and its use by Nature to control acyclic chain conformations

- The conformations of pentane are more complex, but the take-home message is that the syn-pentane interaction (steric hindrance between the two terminal methyl groups) is highly destabilising.

The symbols $g^+$ and $g^-$ refer to +60° and –60° respectively.

- In many polyketide natural products, Nature uses 1,3-dimethyl stereodiads to control the folding of the acyclic chain, by reducing the number of available conformations that do not suffer from syn-pentane interactions.

Conformations of Cyclohexane: The most important ring in organic chemistry

- Cyclohexane rings can access a number of well-defined conformations, the most important of which is the chair conformation.

  ![Cyclohexane Conformations](image)

  - chair (lowest in energy)
  - twist-boat
  - boat
  - half-chair

- The scheme below shows how to accurately draw a cyclohexane ring (and also how not to draw it!)

  ![Cyclohexane Drawing Scheme](image)

  - draw the ring bonds first...
  - ...then the axial bonds...
  - ...and finally the equatorial bonds

  ![Cyclohexane Drawing Observations](image)

  - each corner atom should be level with its horizontal neighbour
  - every bond is parallel to the bond opposite on the ring

For a discussion on nomenclature of cyclohexane conformations, see: J. Chem. Educ. 2011, 88, 292
**Ring-Flipping of Cyclohexane: Interconversion of chair conformations by C–C bond rotations within the ring**

- The conformational interconversion of a cyclohexane chair conformer to its mirror-image form* proceeds by rotations of C–C bonds within the ring, and is known as a **ring-flip**.
- During a ring-flip, all of the equatorial substituents (just hydrogens on cyclohexane itself) are converted into axial ones (and **vice versa**).
- The ring-flipping proceeds via twist-boat conformers as intermediates, with half-chair and boat conformations being transition states.

*As the (unsubstituted) cyclohexane chair is achiral (it has internal mirror planes), the mirror-image chair conformer is homomeric - it is not an enantiomer!
Ring-Flipping Substituted Cyclohexanes: Taking care not to accidentally permute substituents

Whenever you ring-flip a chair, you need to be careful that you do not inadvertently permute substituents in a way that would require bond breaking and reforming. If the ring carbon in question happens to be stereogenic, this would actually change the configuration!

There are basically two ring-flipping methods, shown as option 1 and option 2 below. They are completely equivalent to one another.

In option 1, you draw the 'other' chair form and keep the blue atom in the same place (i.e., one atom away from the 'pointy' end). Notice how the R substituent is still pointing 'up' (towards the top of the slide) – it is still on the same face of the ring structure (as it should be!).

In option 2, you draw the same chair form and move the blue atom one position along, to either the left or the right. Again, the R substituent is still projecting from the same face of the cyclohexane ring.

There is zero difference in outcome for either of these methods – they only look different because you are viewing the final structure from different angles. Which option you use tends to depend on what is easiest to draw, or it might just be arbitrary!

When more than one substituent is present, the method of ring-flipping is exactly the same as above - just apply everything to both the red and the blue atoms this time.

if you're struggling to understand this, build a model!

- option 1
- option 2
- wrong!
- can't just permute R and H, as this would require bond breaking and reforming!
Configurational Stereoisomers: The concepts of absolute and relative configuration

- **Configurational stereoisomers** are stereoisomers for which interconversion between the different stereoisomers would require the breaking and reforming of covalent bonds.
- The term **configuration** describes the spatial array of atoms that defines a particular configurational isomer.
- Configurational **enantiomers** (mirror-image stereoisomers) are said to differ in their **absolute** configuration, whereas **diastereomers** (non-mirror-image stereoisomers) differ in their **relative** configuration.

Next, we will discuss the concepts of **chirality** and **enantiomorphism** in more detail, followed by properties of enantiomers, and stereodescriptors to define absolute configuration.

After that, we will discuss **diastereomorphism**, properties of diastereomers, and stereodescriptors to define relative configuration.
**Molecular Symmetry: A prelude to chirality and enantiomorphism...**

- A basic understanding of **molecular symmetry** is needed before we can properly discuss chirality and enantiomorphism.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Symmetry Element</th>
<th>Symmetry Operation</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_n$</td>
<td>proper rotation axis</td>
<td>rotation by $(360/n)\degree$</td>
<td><img src="image" alt="Example" /></td>
</tr>
<tr>
<td>$S_n$</td>
<td>improper rotation axis (alternating axis or rotation-reflection axis)</td>
<td>rotation by $(360/n)\degree$ then reflection perpendicular to the rotation axis</td>
<td><img src="image" alt="Example" /></td>
</tr>
<tr>
<td>$\sigma (S_1)$</td>
<td>reflection plane (mirror plane)</td>
<td>reflection in the plane</td>
<td><img src="image" alt="Example" /></td>
</tr>
<tr>
<td>$i (S_2)$</td>
<td>inversion centre</td>
<td>inversion of a point $x,y,z$ to $-x,-y,-z$</td>
<td><img src="image" alt="Example" /></td>
</tr>
</tbody>
</table>

- Note that improper rotations are ‘compound’ operations – they consist of two discrete operations carried out in sequence.
- Mirror planes ($\sigma$) and centres of inversion ($i$) can also be considered as improper rotations ($S_n$) with $n = 1$ and $n = 2$, respectively.
**Chirality**: The property of non-superimposability of an object on its mirror image

- **Chirality** is the geometric property of a molecule (or rigid object) of being non-superimposable on its mirror image. In the language of symmetry theory, chiral objects contain no rotation-reflection ($S_n$) axes, including mirror planes ($\sigma = S_1$) or centres of inversion ($i = S_2$).

![Achiral (mirror plane)](image)

![Achiral but no mirror plane (centre of inversion)](image)

- The term **chiral** (from Greek: 'hand' = χερί) is applied to a molecule (or rigid object) possessing the property of chirality. Never use the term 'chiral' to mean 'enantiomerically pure', as the property of chirality is unrelated to enantiomeric composition.

- **Asymmetric** is a term used for a molecule (or rigid object) devoid of any symmetry elements, such as a tetrahedral carbon atom surrounded by four different substituents. It is not synonymous with 'chiral', as chiral molecules can still possess $C_n$ axes, even when they are non-superimposable on their mirror image ('dissymmetric' molecules*).

- "Dissymmetric" means "lacking one particular symmetry element", and for chiral dissymmetric molecules this is an $S_n$ axis. Thus, a dissymmetric chiral molecule has one or more $C_n$ axes ($n > 1$) as the only symmetry operations.
Enantiomorphism and Stereogenic Centres

- A molecule that possesses the property of chirality will by definition have two possible mirror-image, non-superimposable stereoisomers known as **enantiomers** (from Greek: ‘opposite’ = *énanti*). This type of stereoisomerism is called **enantiomorphism**.

- ‘Optical isomers’ is sometimes used as a synonym of ‘enantiomers’, but it is a redundant term and its use is strongly discouraged.*

- A **stereogenic centre** (stereocentre) is an atom (usually, but not always, carbon) for which permutation of any two ligands generates a stereoisomer. We can see that the carbon atom below is stereogenic, because permuting any two ligands gives the enantiomer.

![Stereogenic Centre Diagram]

- Enantiomers show **identical scalar** physical properties (properties invariant to reflection) in an achiral environment. However, in a chiral environment (e.g., enzyme interior, chiral stationary phase) individual enantiomers may show different scalar physical properties.

- A commonly used term is **chiral centre**, to refer to a stereogenic centre in a chiral molecule. However, this term is redundant, because chirality is a property of the molecule as a whole, not the atoms within it.

- You should simply say ‘stereogenic centre’, regardless if the molecule overall is chiral or not. The example on the right illustrates the pitfalls of unnecessarily using the term ‘chiral centre’...

![Stereogenic Centre Examples]

*Also, not all chiral, non-racemic compounds have measurable optical rotations, so basing a definition on this property is inadvisable

**This includes microscopic properties such as energy, bond angles, torsional angles, and interatomic distances, as well as macroscopic (bulk) properties such as solubility, density, mp, bp, spectroscopic properties, and chromatographic retention times
**Chiral Conformations of Achiral Compounds:** Racemic distributions of chiral conformations lead to macroscopic achirality

- It is perfectly possible for an achiral molecule, if it is sufficiently flexible, to have one or more enantiomeric pairs of chiral conformations.

- Butane is a good example - it is clearly an achiral compound but it does have chiral conformations, in addition to the two achiral co-planar conformations (syn and anti). However, the enantiomeric chiral conformations — being rapidly interconvertible and equal in energy — are always present in a 50:50 ratio (racemic distribution).

- So, from a macroscopic perspective, butane is an achiral compound, because its enantiomeric forms are far too short-lived for separation of its enantiomeric conformers to be possible.*

- Whilst an achiral molecule can have (a racemic distribution of) chiral conformations, it is not possible for a chiral molecule to have any achiral conformations whatsoever. If it did, it would 'forget' which enantiomer it came from and have a 50:50 chance of then converting to the opposite enantiomeric conformation.

- A good example of this is **meso-tartaric acid** (we will explain the "meso" stereodescriptor later on). When drawn as it is on the far left, it 'looks' like a chiral molecule; indeed, this precise conformation is actually chiral. However, a simple bond rotation converts this into an achiral conformation, from which the opposite enantiomer of the original conformation (see far right) can be accessed.

*We will soon meet molecules (so-called atropisomers) where restricted rotation can give chiral conformations with lifetimes of minutes or even years!
To specify the absolute configuration of a particular stereocentre, chemists use (R/S) stereodescriptors as a prefix to the chemical name of a compound.

For an atom (usually carbon) bound to four different groups, specification of the configuration requires that we rank the groups bound to the stereocentre in order of their priority (and we'll explain shortly how one determines the priority!).

(R) and (S) are used to label the absolute configuration in each case: \( R = \text{rectus} \) (Latin for 'right') and \( S = \text{sinister} \) (Latin for 'left').

**Assigning (R) or (S) to a stereocentre**

1. Ensure the lowest priority atom (usually H) is pointing away from you.

2. Rank the three higher priority substituents according to their priority.

3. From highest to lowest priority:
   - Clockwise rotation \( \Rightarrow (R) \)
   - Anticlockwise rotation \( \Rightarrow (S) \)

IUPAC name = \((R)\)-butan-2-ol
Determining Substituent Priorities: Cahn-Ingold-Prelog (CIP) priority rules

- The Cahn-Ingold-Prelog (CIP) priority rules (named after Robert Cahn, Christopher Ingold and Vladimir Prelog) are a set of rules used to allocate priorities to substituents when assigning stereodescriptors.*

1. In the first coordination sphere, assign atom priorities 1 to 4 based on atomic weights, with atom 1 being the highest priority and highest atomic weight.**

2. When two atoms are the same (designated A and B in the diagram), consider the atoms directly attached to them (in the second coordination sphere) and assign priorities 1 to 3. This is the principle of outward exploration.

3. Compare the highest priority atoms A1 and B1. If A1 is higher priority then B1, then A is higher priority than B.

4. If A1 and B1 are identical, move onto A2 versus B2 (and then A3 versus B3 if necessary).

5. If there is still no decision, consider the atoms in the third coordination sphere on A1 and B1. If no decision can be made, move on to the atoms attached to A2 versus B2 (and then A3 versus B3 if required).

6. If there is still no decision, consider the atoms in the fourth coordination sphere on A11 and B11, and so on. Thus, if we are forced to explore higher coordination spheres, we always follow the path of highest precedence.

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**For trigonal pyramidal molecules such as phosphines, the lone pair at the fourth site is assigned an atomic number of zero, and automatically takes the lowest priority. Although not discussed here, there are further rules dealing with scenarios in which a decision cannot be reached using atomic number alone (e.g., assignments between groups differing only by isotopic substitution, double bond configurations, or stereocentre configurations)
In the case of **multiply-bonded groups** (e.g., -CH=O), a convention is applied whereby each atom in the multiple bond is regarded as being associated with a *phantom* (duplicate) atom(s) at the other end of the double bond (see below). By this logic, -CH=O would be higher priority than -CH₂OH (i.e., two O atoms versus one).

![Diagram of carbonyl groups, alkenes, alkynes, and aromatic rings]

**Cyclic compounds** are a little more cumbersome. Strictly speaking, the actual structure is converted into an acyclic tree diagram by turning the ring into two separate chains that each terminate in a *phantom* atom (which represents the other ring atom attached to the stereocentre).

This sounds more complicated than it actually is - we basically just use the principle of outward exploration, going around the ring from both ends, until we can make a decision on which of the initial ring atoms is higher priority. In the example below, we have both a cyclic compound and a multiple bond, so we must combine both of the above conventions.

![Diagram of cyclic structures and acyclic tree diagram]
Optical Activity of Enantoienriched Compounds: Enantiomers rotate plane-polarised light in equal but opposite directions

- When a beam of plane-polarised light passes through a solution of chiral organic molecules, the plane of polarisation is rotated. This phenomenon is referred to as optical activity.
- The amount of rotation can be measured with a device called a polarimeter. By rotating the analyser until the light passes through it, we can find the new plane of polarisation and determine the amount of rotation, $\alpha$, in degrees.

As well as the amount of rotation, we also need to consider the direction. From the observer's viewpoint, one enantiomer will rotate the plane of polarised light to the left (anticlockwise) and is said to be laevorotary (−), whereas the opposite enantiomer will rotate it to the right and is said to be dextrorotary (+).

To express optical rotations in a meaningful way, we have to specify standard conditions. The specific rotation, $[\alpha]_D$, of a compound is defined as the observed rotation when:

- The sample pathlength, $l$, is equal to 1 dm (10 cm)
- The sample concentration, $c$, is equal to 1 g per 100 mL (or $c = 1$ if neat)
- Light of 589 nm wavelength is used (corresponds to sodium "D" line)
- The temperature (usually 298 K) is specified (as a superscript on $[\alpha]_D$)

$$[\alpha]_D^T = \frac{\alpha}{c \times l} \quad \text{[units} = 10^{-1} \text{deg cm}^2 \text{g}^{-1}]$$

For the history of optical activity and an account of blunders in the literature, see:

"Optical activity in small molecules, nonenantiomorphous crystals, and nematic liquid crystals" Chem. Rev. 1980, 80, 41 (O’Loane)
Only samples of chiral compounds in which one enantiomer is in excess rotate plane-polarised light. Such a sample is called enantiomerically pure (or enantiopure) if it consists of only one enantiomer. It is called enantiomerically-enriched (or enantioenriched) if it consists of both enantiomers, but one predominates.*

If a 50:50 mixture of enantiomers is present, the rotation effects due to each will cancel out and the mixture will appear to have no optical activity. Such a mixture is called a racemic mixture (or a racemate). The prefix "(±)" or "rac-" is often used in the chemical name to indicate that it is a racemate [or "(RS)-" for a compound with a single stereocentre, using CIP stereodescriptors].

There is no simple connection between structure and specific rotation. In other words, you cannot guess from the structure whether a molecule will be laevorotary (−) or dextrorotary (+).

Often very similar molecules with the same absolute configuration can have opposite optical rotations to one another.

Optical rotation is an example of a pseudoscalar property (i.e., changes sign, but not magnitude, on reflection).

Other pseudoscalar properties include optical rotary dispersion** (ORD), circular dichroism*** (CD), vibrational circular dichroism (VCD). These are often collectively referred to as chiroptical properties, and are not used especially routinely for small organic molecules.

*The terms "scalemic" or "non-racemic" can be applied a mixture that is neither enantiopure nor racemic, but somewhere inbetween

**Optical rotatory dispersion is the variation in the optical rotation of a substance with a change in the wavelength of light

***Circular dichroism (CD) is an absorption spectroscopy method based on the differential absorption of left and right circularly-polarised light. Optically active chiral molecules will preferentially absorb one direction of the circularly polarised light
**D and L Stereodecriptors for Absolute Configuration: The Fischer-Rosanoff convention**

- The first stereochemical descriptor notation for specifying absolute configuration was actually the D/L system devised by Fischer and Rosanoff around 1900.

- It was based on a (now defunct) method of drawing molecules known as a Fischer projection (see right).

- The (+)-enantiomer of glyceraldehyde (i.e., the enantiomer which rotates plane-polarised light to the right) was selected by Rosanoff as an arbitrary reference compound because of its structural analogy to carbohydrates and \(\alpha\)-amino acids.

- For the Fischer projections as drawn, the (+)-enantiomer was assigned the descriptor "D" (dextro) because the OH group attached to C(2) is on the right-hand side of the molecule as drawn, and the (−)-enantiomer was assigned the descriptor "L" (levo) because the OH group attached to C(2) is on the left side as drawn.

- This method of allocating D or L descriptors to glyceraldehyde is often referred to as the Fischer-Rosanoff convention.*

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*The absolute configuration of (+)-glyceraldehyde was unknown at the time, so the configurations in the Fischer projections above were arbitrarily assigned by Rosanoff to each enantiomer. Luckily, it was determined by Bijvoet in 1951, using anomalous X-ray scattering, that this assignment of (+) and (−) signs to the two glyceraldehydes enantiomers as drawn was in fact correct!
With D-(-)-glyceraldehyde as a reference compound, other enantiopure compounds could be related to it by a series of reactions or degradations. Compounds that could be correlated, either directly or indirectly, to D-(-)-glyceraldehyde, using chemical reactions that do not lead to racemisation at the chiral centre, were labelled D [or L if they related to L-(-)-glyceraldehyde].

For instance, all 20 proteinogenic α-amino acids possess the L configuration, and almost all biologically important carbohydrates (sugars) have the D configuration (at the highest-numbered stereocentre).

It is important to be aware that there is no link between the D or L descriptor of a compound and the direction in which it rotates plane-polarised light, (+) or (−). This confusion is compounded by the fact that lowercase d and l descriptors are sometimes used in place of (+) or (−) symbols, respectively, to denote dextrorotatory or levorotatory enantiomers, based on their optical rotation.

However, it has emerged that the D/L notation has severe failings as a general stereochemical descriptor system:

- It only allows specification of the absolute configuration of a single stereocentre in a molecule. For α-amino acids and carbohydrates conventions dictate which stereocentre is described, but what about other compounds with multiple chiral centres?
- It is restricted to molecules that can be unambiguously drawn as Fischer projections and which obey all relevant rules.
- As organic compounds increase in complexity, it becomes more and more impractical to chemically correlate them to glyceraldehyde.
- Some organic compounds can be equally well correlated to either (+) or (−)-glyceraldehyde by comparison to different secondary standards! Dextrorotatory tartaric acid was specified D by European chemists and L by Americans, because it can be chemically correlated by different reactions with either D- or L-glyceraldehyde!

Despite these deficiencies, the D/L system is still widely used in the biochemical community for carbohydrates and α-amino acids, though for other compounds it has been superseded by the R/S system based on the CIP priority rules.
Quantifying Enantiomeric Composition: Enantiomeric excess (%ee) versus enantiomeric ratio (er)

- **Enantiomeric excess (ee)** is the classical way of reporting the enantiomeric composition of a chiral compound. A racemic mixture has an ee of 0%, while a compound containing only one enantiomer has an ee of 100%.

\[
\text{ee}_R = \frac{R-S}{R+S} \times 100\% \quad \text{or} \quad \text{ee}_S = \frac{S-R}{S+R} \times 100\% 
\]

A good way to think of %ee is that it tells you what percentage of the mixture is not a racemate.

- The **optical purity** of a compound \(\frac{[\alpha\text{measured}]}{[\alpha\text{enantiopure}]}\) as measured by polarimetry can be equated with %ee, provided that these two quantities are linearly related (which is not always the case). Indeed, the historical use of polarimetry to measure enantiomeric composition is why chemists defined %ee in the above way.

- The phrase ‘optically pure’ for ‘enantiopure’ compounds is strongly discouraged, because polarimetry is no longer used to measure %ee and not all enantiopure compounds exhibit measurable optical activity.

- **Enantiomeric ratio (er)** is a more modern, though still not universally used, way of reporting enantiomeric composition. It is simply the ratio of one enantiomer to the other, typically written as a ratio xx:yy normalised to 100 (e.g. 97:3 er).

\[
er = \frac{R}{S} \quad \text{or} \quad er = \frac{S}{R}
\]

- There are compelling arguments for replacing %ee with er as the standard measure of enantiomeric composition.

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*Diastereomeric ratio (dr) is analogous to 'er', but used instead to report relative amounts of diastereomers. Again it is usually normalised to 100, and can include any number of diastereomers (e.g. 80:15:5 dr for three diastereomers)

***Do the Terms "%ee" and "%de" Make Sense as Expressions of Stereoisomer Composition or Stereoselectivity?" J. Org. Chem. 2006, 71, 2411 (Gawley)*
Stereogenicity at Non-Carbon Atoms: Tetrahedral stereocentres at silicon, phosphorus, sulfur, and nitrogen

- Heteroelements from Groups IV–VI with tetrahedral geometries are also stereogenic if the four ligands are all different.
- For example, chiral@Si compounds are known, and have even been prepared in enantiopure form.
- However, this is more commonly encountered for oxides of organic phosphorus or sulfur compounds in their P(V) or S(VI) oxidation states, and is also known for N-oxides or ammonium salts of amines.

- An exciting recent development has been the invention of a practical chiral@P(V) reagent for stereospecific synthesis of methylphosphate oligonucleotides, which have significant pharmaceutical potential.*

\[ \text{(+)-limonene} \quad \$0.06 \text{ per gram} \]

**Stereogenicity at Non-Carbon Atoms:** Trigonal pyramidal stereocentres at nitrogen, phosphorus, and sulfur

- Heteroatoms with **trigonal pyramidal** geometries are stereogenic if the three ligands are different.

- **Amines** that are stereogenic **only at nitrogen** are usually subject to **rapid pyramidal inversion** (i.e., **invertomers**) and are macroscopically achiral on a time average. If there is another stereocentre within the molecule, such that the nitrogen invertomers are diastereomeric, the amine will generally adopt the most thermodynamically-stable configuration (i.e., least strained option). In suitably constrained amines, lone pair inversion can become impossible on account of structural rigidity.

- Also, the inversion process can be slowed dramatically by increasing the **s-character of the N lone pair**, either by: (1) increasing the electronegativity of the ligand(s) or (2) ring-strain. Both effects are present in chiral oxaziridines, for example (see below).

- Inversion is extremely slow for heavier atoms like phosphorus and sulfur, so simple **phosphines** and **sulfoxides** are configurationally-stable and their enantiomers can be resolved. They find use in chiral ligands and auxiliaries for stereoselective synthesis.

<table>
<thead>
<tr>
<th>Lone Pair</th>
<th>$\Delta G_{\text{inv}}$</th>
<th>34% $s$ ($sp^{1.9}$)</th>
<th>0% $s$ ($p$)</th>
<th>34% $s$ ($sp^{1.9}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNMeEt</td>
<td>5 kcal mol$^{-1}$</td>
<td>HNMeEt</td>
<td>HNMeEt</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lone Pair</th>
<th>$\Delta G_{\text{inv}}$</th>
<th>81% $s$ ($sp^{0.2}$)</th>
<th>0% $s$ ($p$)</th>
<th>81% $s$ ($sp^{0.2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNMeEt</td>
<td>35 kcal mol$^{-1}$</td>
<td>HNMeEt</td>
<td>HNMeEt</td>
<td></td>
</tr>
</tbody>
</table>

- An oxaziridine  
- TangPHOS (chiral ligand)  
- Ellman’s chiral auxiliary for imines

**all configurationally-stable at the heteroatom(s)**
**Diastereomers**: Stereoisomers related as non-mirror images, and differing in relative configuration

- **Diastereomers** are defined as stereoisomers that are related as **non-mirror images**. Includes E/Z isomers (for which the term ‘geometrical isomers’ is discouraged).

- They differ in **relative configuration**, whereas enantiomers differ in **absolute** configuration.

- A molecule must contain **at least two stereocentres** to exhibit diastereoisomerism.

- A molecule containing **n stereocentres** will have a maximum of $2^n$ **stereoisomers** (including enantiomers), but the actual number can be lower if achiral (meso) diastereomers are possible.

- A **meso compound** is defined as an achiral diastereomer that also has one or more chiral diastereomers (e.g., tartaric acid - see below).

**Paclitaxel (Taxol®)**

Widely-used chemotherapy for various cancers. Over 1,000 possible stereoisomers, but Nature prepares just one!*

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*For a recent total synthesis of Taxol that mimics Nature’s biosynthetic strategy, see: "Two-Phase Synthesis of Taxol®" *J. Am. Chem. Soc.* **2020**, **142**, 10526 (Baran *et al.*).
**Drawing Stereochemistry:** Conventions for the representation of racemic versus enantiopure compounds, or stereoisomer mixtures

- There are several conventions that you need to be aware of when representing stereochemistry:

### Compounds with a single stereocentre

**Racemic (or scalemic)**

- **What we draw...**
- **Correct but unnecessary!**

**Enantiopure (or highly enantioenriched)**

- **What we draw and what we mean are identical**

### Compounds with two stereocentres

**Racemic (or scalemic)**

- **What we draw...**
- **...and what we mean**

**Enantiopure (or highly enantioenriched)**

- **What we draw and what we mean are identical**

*The earliest known use of bold and hashed bonds to depict stereochemical information is attributed to the late UK organic chemist (and Nobel prize winner) Sir Derek Barton (see "The principles of conformational analysis" Q. Rev. Chem. Soc. 1956, 10, 44)*
But how do we distinguish an enantiopure diastereomer from a racemic diastereomer if they are both drawn the same?

It may surprise (and disappoint?) you that organic chemists haven't actually devised a universal solution to this! The best option is to use **stereodescriptors** to denote enantiomeric composition (see in blue below).

Simple bonds (i.e., not bold or hashed) are also used to denote mixtures of stereoisomers or, in some circumstances, unknown configuration (it depends on the context). Note that **wavy bonds** are also used by some chemists for these purposes, but they are actually redundant.*

**Relative Stereodescriptors:** Specifying relative configurations with a variety of different descriptors

- **(R,R), (S,S), (R,S), (S,R):** For *enantiopure* diastereomers of defined absolute configuration, we can simply list the relevant $R$ and/or $S$ stereodescriptors for each stereocentre, using locants to specify the atoms. We can have as many descriptors as there are stereocentres - it is not limited to two. For racemic compounds, it is possible to add the prefix *rel-* in front of the name, to indicate that the compound is racemic (but there is a better option than this - see below).

- **(RS,RS), (RS,SR) or (R*,R*), (R*,S*):** For *racemic* diastereomers, we can use "RS" in place of "R" and "SR" in place of "S", to denote that the other enantiomer is also present. Locants can be used as before, and we can do this for multiple stereocentres. Alternatively, one can use "R*" in place of "R" and "S*" in place of "S" to imply a racemate.

- **l, u:** When two stereocentres are both $R$ or both $S$, the molecule is designated an *l* ("like") stereodescriptor, and is said to be *u* ("unlike") when one stereocentre is $R$ and the other $S$. The notation can be extended to molecules with more than two stereocentres by considering them in pairs [see: *Angew. Chem. Int. Ed. Engl.* 1982, 21, 567 (Prelog, Helmchen)]. Unfortunately there is no way of indicating whether the compound is racemic or enantiopure without a second descriptor. This system is not in widespread use.
"Soft" Stereodescriptors: Stereodescriptors that can be ambiguous without a structure alongside

- Some stereodescriptors may be ambiguous without a structural drawing - these are called "soft" stereodescriptors.

- **syn, anti:** This notation* is used to specify the relative orientation of substituents attached to a carbon chain, with "syn" meaning the "same side" and "anti" meaning "opposite sides". For acyclic molecules, it must be used in conjunction with a diagram to avoid any ambiguity, and the carbon chain should be drawn as a zig-zag. It is also used for cyclic molecules, as an alternative to cis and trans.

```
\[ \text{Me}CO_2\text{Me} \quad \text{Me}CO_2\text{Me} \quad \text{HO} \quad \text{HO} \quad \text{HO} \quad \text{HO} \]
```

syn    anti

- **erythro, threo:** This notation is derived from carbohydrate nomenclature (from the names of the tetroses erythrose and threose - see below), and is only applicable to acyclic molecules bearing two adjacent stereocentres that can be drawn as Fischer projections. In the threo diastereomer the two substituents are on opposite sides of the Fischer projection, and in the erythro diastereomer they are on the same side. This nomenclature has historically been used heavily in the literature for stereoselective aldol reactions, but it is recommended now to use syn and anti instead.

```
\[ \text{HOH}_2\text{C} \quad \text{CHO} \quad \text{CHO} \quad \text{H} \quad \text{OH} \quad \text{OH} \quad \text{CH}_2\text{OH} \]
```

threo  erythro

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The **Masamune convention** denotes that we draw the 'main' carbon chain of an acyclic molecule as an extended zig-zag.

Satoru Masamune (1928–2003)

**Cis, Trans and E, Z Stereodecriptors**

- **cis, trans**: Describes the relative spatial disposition of two ligands attached to separate atoms, which are either connected by a double bond or contained within a ring. Their spatial relationship is taken relative to a reference plane which lies perpendicular to a plane passing through both ligands. For ring systems, the ligand-bearing atoms need not be neighbouring one another. For double bonds only, (E/Z) descriptors are an alternative to cis/trans and take precedent for tri- or tetrasubstituted double bonds when the terms cis or trans may be ambiguous.

- **(E), (Z)**: The approved stereochemical descriptors for double bonds (or odd-cumulenes, imines). The group of highest CIP priority attached to one of the terminal doubly-bonded atoms (i.e., R\(^1\) or R\(^2\)) is compared with the group of highest precedence attached to the other (i.e., R\(^3\) or R\(^4\)). The stereoisomer is designated as Z (zusammen = together) if the groups lie in a cis relationship and E (entgegen = opposite) if they lie trans. The descriptors are placed in brackets: (Z)- or (E)-.

If there are also stereocentres in the molecule, the Z or E descriptor is placed into brackets after the necessary R/S descriptor(s).
A reaction is **stereoselective** when there is preferential formation of one product stereoisomer (enantiomer or diastereoisomer) over another (see right for an example).

A reaction is **stereospecific** when two different stereoisomeric starting materials (enantiomers or diastereoisomers) react to give two different stereoisomeric (major) products.

A stereospecific reaction need not be 100% stereoselective; the E2 elimination reaction shown below left, for example, is only 84% anti-stereospecific.

A reaction is **stereoconvergent** when two different stereoisomeric starting materials react to give the same stereoisomer of the product (or the same stereoisomeric mixture if the stereoselectivity is imperfect). Some reactions proceeding via carbocation intermediates, for example, are stereoconvergent (see below right).

Note that stereospecific and stereoconvergent reactions are stereoselective by definition – the terms ‘selectivity’ and ‘specificity’ are not mutually exclusive.
Revision Checklist

Revised?

☐ Molecular formulae and descriptors

☐ Molecular isomerism; constitutional isomers, configurational isomers, and conformational isomers

☐ Molecular projections; conformations and conformers; torsion angles

☐ Conformational analysis of ethane, butane, and pentane; torsional strain; steric strain; syn-pentane interactions

☐ Conformational analysis of cyclohexane; the chair conformer; axial and equatorial bonds; ring-flipping

☐ Molecular symmetry and chirality; distinction between the terms "chiral" and "asymmetric" (not synonymous)

☐ Enantiomers and the concept of stereogenic centres (avoid the term "chiral centres", which is redundant)

☐ Chiral conformations of some achiral molecules; time-averaged achirality

☐ Optical activity and specific rotations of chiral, non-racemic compounds

☐ Stereodescriptors for absolute configuration: the R/S system and the (obsolete) D/L system (still in use for amino acids, sugars)

☐ Measures of enantiomeric composition (%ee, er)

☐ Non-carbon stereogenicity, both for tetrahedral and trigonal pyramidal heteroatoms; lone-pair inversion for amines

☐ Diastereomers, including meso compounds that can arise for compounds of high symmetry

☐ Drawing conventions for indicating absolute and relative configurations, or unspecified/unknown stereochemistry

☐ Stereoselective and stereospecific reactions