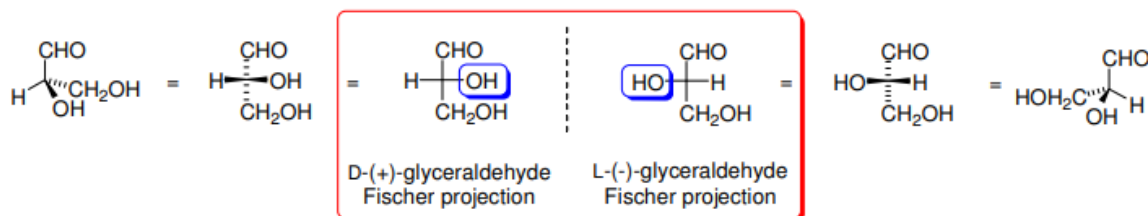


Stereochemical Naming of Chiral Molecule

It is obviously necessary, as a matter of convenience, to be able to describe the configuration of a chiral molecule by an unambiguous symbol rather than have to draw a three-dimensional perspective figure.

A. D,L –Naming System:

The first system for doing this was developed by Fischer and Rosanoff around 1900. Fischer first developed a method for drawing carbohydrates in two-dimensions, and a convention with respect to orientation, so as to indicate their three dimensional structures, so-called Fischer projections (see below). Fischer and Rosanoff then devised a notation for designating the configurations of stereogenic centres, depicted in Fischer projections, as either D or L. Totally arbitrarily, (+)-glyceraldehyde was defined as being D because the OH group attached to the C-2 is on the right hand side (RHS) of the molecules when drawn in its correct Fischer projection (in which the CHO group appears at the top). Its enantiomer [(-)-glyceraldehyde] was defined as L because the OH group is on the left hand side (LHS).

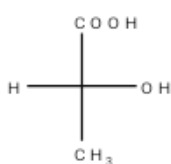


The source of the D,L descriptors was the Latin word *Dexter* (meaning on the right) and *Leavus* (meaning on the left). The naming system is explained by following process:

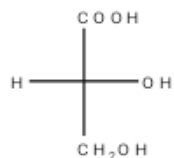
1. The molecule of the type RCHXR' is written in Fischer projection with the main longest chain, R-C-R' as vertical chain with C-1 carbon (according to IUPAC) at the top, then if X is on the right hand side (RHS) of the molecules, the designation used as D and when X- is on the left hand side (LHS) of the molecules, the designation used as L. here X is taken to be an electronegative atom/group.



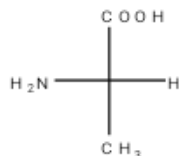
For example,



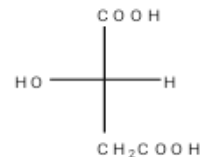
D-Lactic acid



D-Glyceric acid

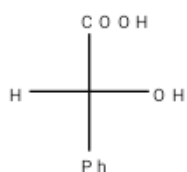


L-Alanine

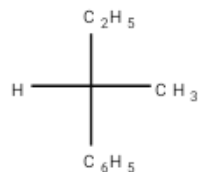


L-Malic acid

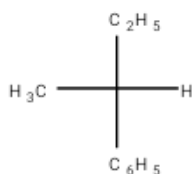
2. When the chiral centre contain a ring stem, then total number of carbon atoms including the ring are taken into consideration to write down the main chain in Fischer projection (vertical chain). For example when Ph-group is attached to the chiral centre then it is generally placed at the lower vertical bond in Fischer projection.



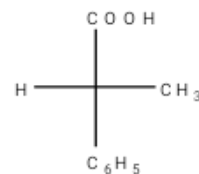
D-Mandelic acid



D-2-Phenylbutane

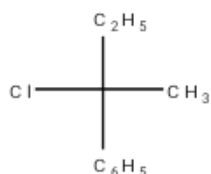


L-2-Phenylbutane

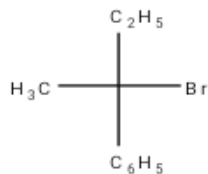


D-2-Phenylpropanoic acid
(Hydratropic acid)

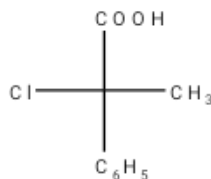
3. When the chiral centre does not contain H atom as one of the ligands and the two attached ligand on chiral centre has apparently different electronegativity, then D,L-naming depends on the orientation of the more electronegative group. For example



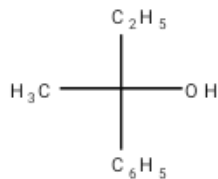
L-2-Chloro-2-Phenylbutane



D-2-Bromo-2-Phenylbutane

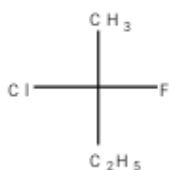


L-2-Chloro-2-Phenylpropanoic acid

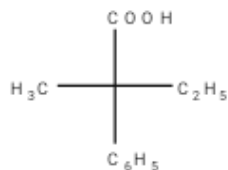


D-2-Phenylbutan-2-ol

4. When the chiral centre contain two different substituent of comparable electronegativity, then D,L-naming may be done separately for each ligand of chiral centre to state the configuration, for example

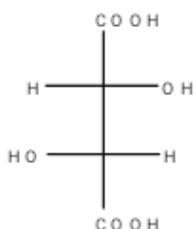


2L-Chloro-2D-fluorobutane

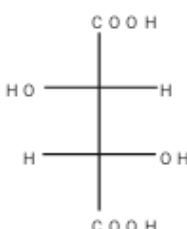


D-2-Ethyl-L-2-methyl-2-phenyl-2-butanoic acid

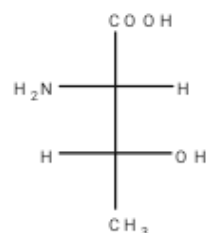
5. It is noted that there is a convention that for α -amino acids and α -hydroxy acid the D,L-naming is used taking the first chiral centre from the top in FPF as the key. Other chiral centre(s) are not taken into consideration, e.g.



D-Tartaric acid

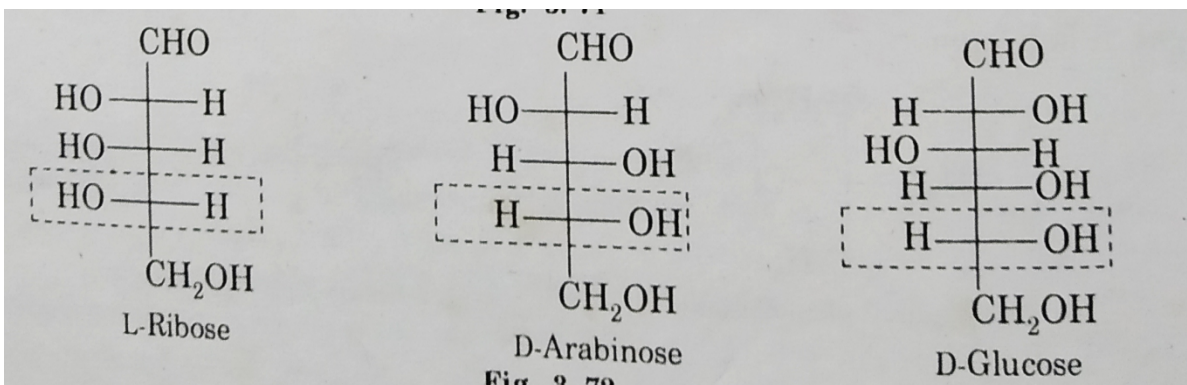
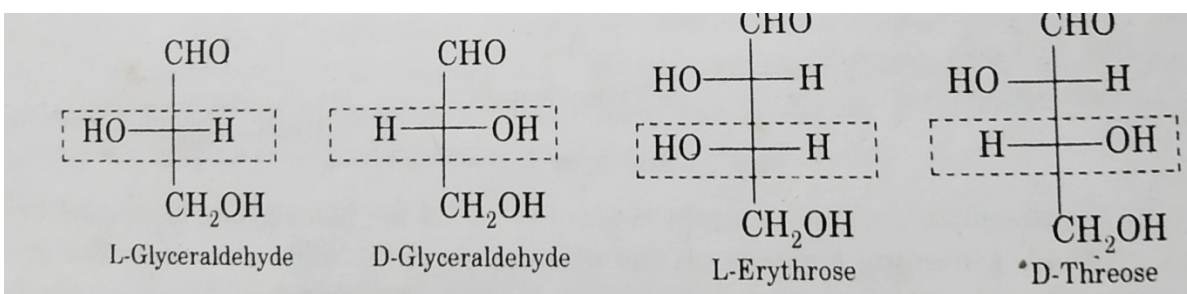


L-Tartaric acid



L-Threonine

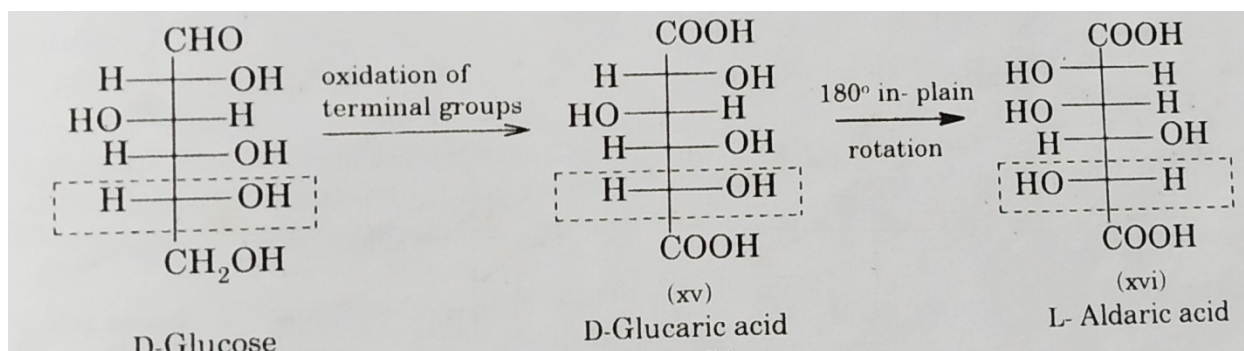
6. However in carbohydrate chemistry, the OH group attached to the bottom most chiral carbon atom in the chain determines the assignment of D or L. Thus (+)-glucose has the D-configuration and (+)-ribose has the L-configuration.



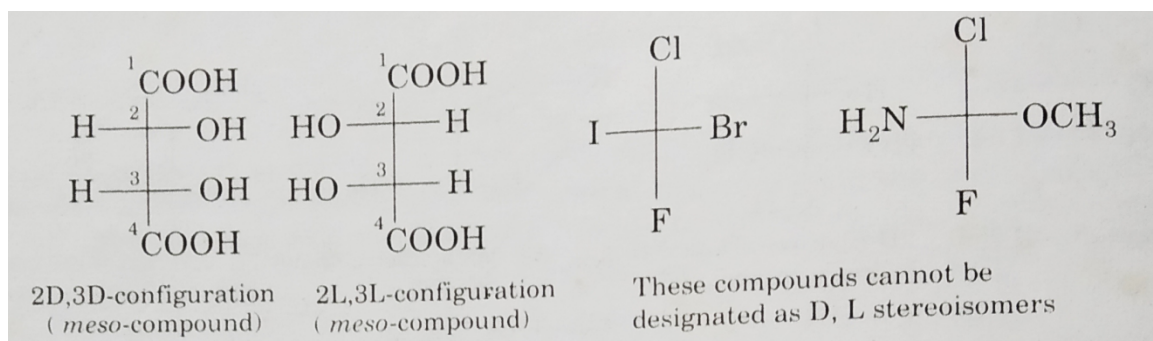
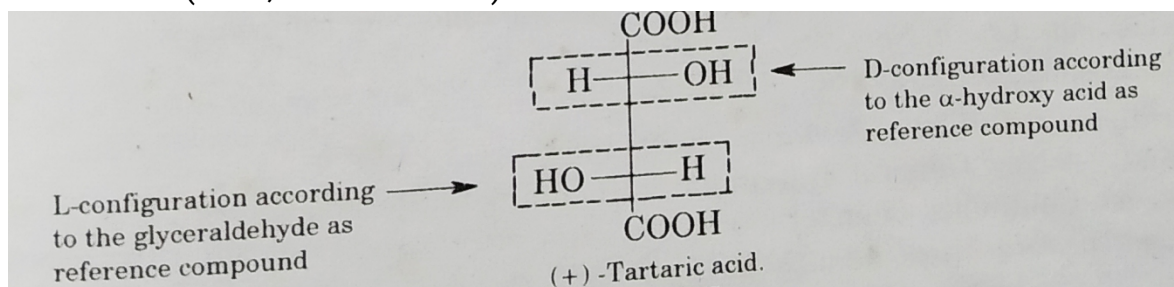
Drawback of D,L Naming:

The major defect of D,L-naming systems of specifying configuration of stereoisomers is revealed when the system is applied on sugar. In sugar, the symbol D or L specified the configuration of bottom most chiral centre only, while the configuration of the remaining chiral centres are to be memorized from the trivial name of the concerned sugar.

Another drawback is observed when D-glucose is oxidized to glucaric acid. This glucaric acid can be written in two different Fischer projections. According to convention of naming of sugar, the same glucaric acid may be designated either as D-compound or as L-compound.

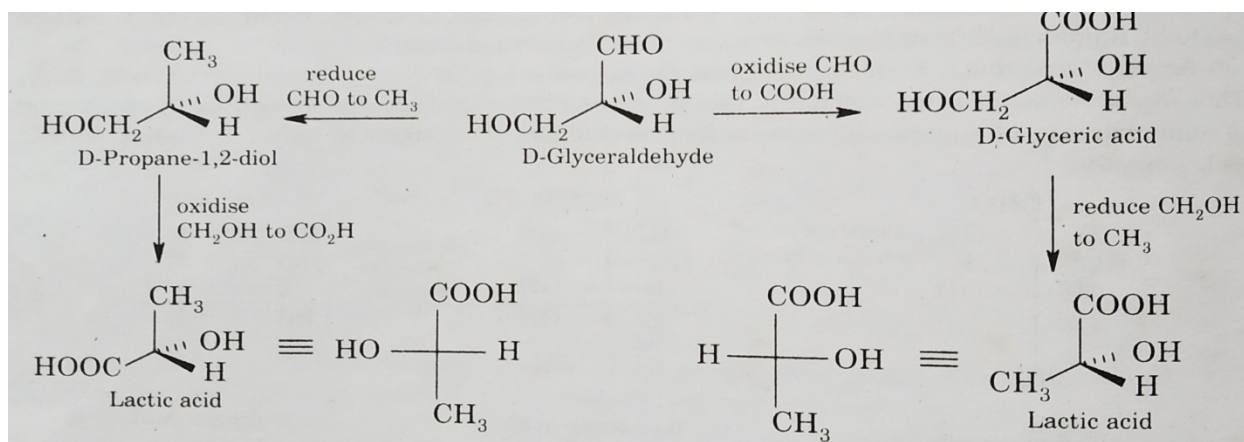


Ambiguity also arises to designate isomeric tartaric acids following Rosanoff method of keeping most oxidized group at the top. Following this technique, meso-tartaric acid would be 2D,3D-tartaric acid (or 2L,3L-tartaric acid) and active isomers are 2D,3L-tartaric acid (or 2L,3D-tartaric acid).



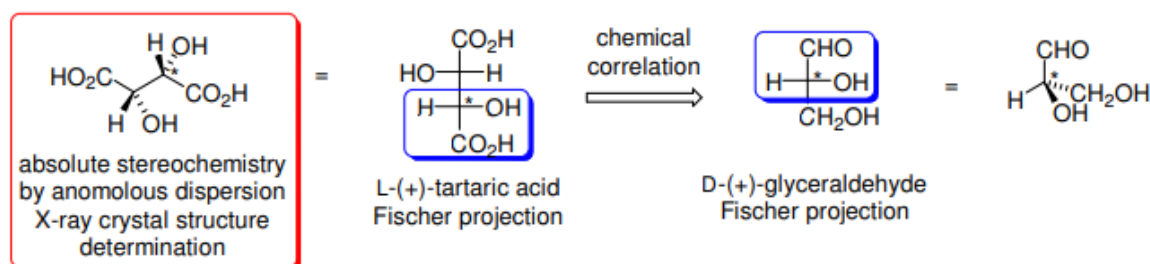
Serious ambiguity of the D,L system is revealed from the sequences of reaction outlined

below:



Bijvoet's Determination of the Absolute Configuration of (+)-Tartaric:

As explained above, Rosanoff **arbitrarily** assigned (+)-glyceraldehyde as having the D configuration. It was not until 50 years later that this arbitrary assignment was able to be tested experimentally. In 1951, **Bijvoet** performed a structure determination on the sodium rubidium double salt of (+)-tartaric acid using **anomalous dispersion X-ray crystallography**.



Although X-ray crystal structure determination will NOT normally distinguish between enantiomers the incorporation of a heavy atom (in this case rubidium) results in an anomalous dispersion of the X-rays which allows the **absolute three-dimensional structure** to be determined. Since chemical synthesis had already been carried out to correlate one of the stereogenic centres in (+)-tartaric acid with that in (+)-glyceraldehyde it was therefore possible to verify Rosanoff's assignment. **Fortunately, the configuration was the same as that arbitrarily assigned!**

Nowadays, anomalous dispersion X-ray crystallography can be carried out fairly routinely on crystalline molecules provided >6 or so atoms with atomic number >12 (e.g. typically, Ns and Os) are present. Absolute configurations can also be obtained by **circular dichroism** (CD) and certain other techniques.

Bijvoet's breakthrough provided the impetus for the development of a totally

unambiguous notation for defining absolute configuration: the (R)/(S) notation.

(R)/(S) Notation:

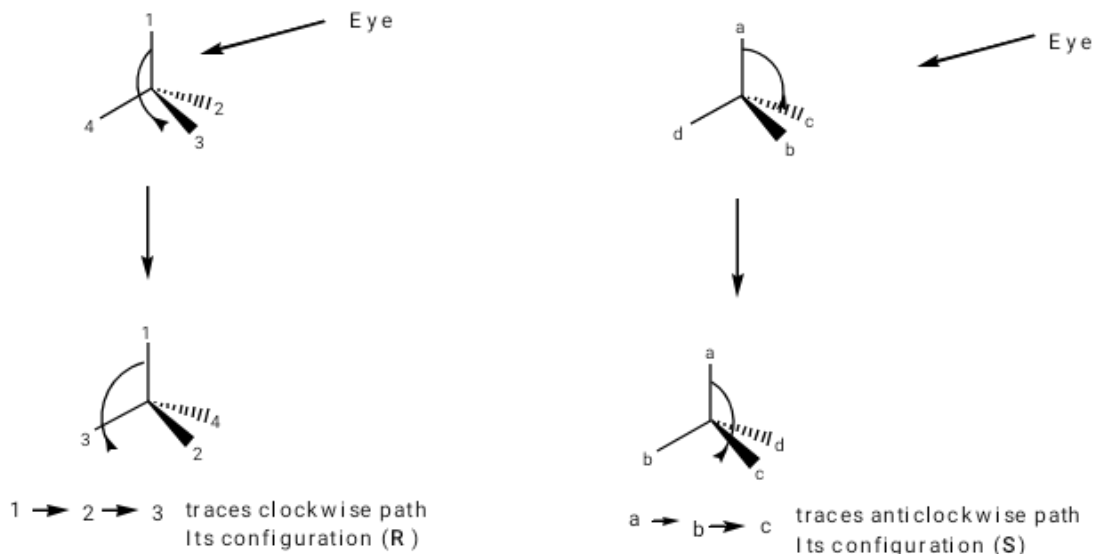
The Cahn Ingold Prelog (CIP) Sequence Rules:

Configurational isomers contain carbon atoms with four different substituents. The carbon atoms are called **stereogenic centers** or **chiral centers**. A naming system has been devised so that we can distinguish one enantiomer from the other based on the orientation of those substituents.

Cahn, Ingold and *Prelog* introduced this systematic notation during the period 1951-1956. The notation allows us to define in an unambiguous manner the absolute configuration of a drawn stereogenic centre by assigning it as either (R) or (S). Correlation with an arbitrary standard is not involved.

For assigning R/S naming of any chiral centre some procedure must be followed, and they are:

1. Identify the chiral centre(s) of the molecule consider.
2. Identify the four different atom(s) and or group(s) attached to each chiral centre. Assign to each of the substituents on a chiral centre with a priority symbol 1, 2, 3, 4 or a, b, c, d based on **CIP sequence** (discuss latter) rule, such that decreasing order of priority is $1 > 2 > 3 > 4$ or $a > b > c > d$, where ' $>$ ' denotes 'has priority over'.
3. Then the molecule is viewed from the position remotest from the lowest priority group (4 or d) and a hypothetical path is drawn moving from 1 to 2 to 3 or a to b to c ($1 \rightarrow 2 \rightarrow 3$ or $a \rightarrow b \rightarrow c$). If this path describe a clockwise motion then the stereocentre is said to have *R* configuration (*R* from *rectus*, Latin for *right*). If the said path describe a anticlockwise motion then the stereocentre is said to have *S* configuration (*S* from *Sinister*, Latin for *left*).



In order to use this notation the first thing to do is to assign an **order of priority** to the atoms of the groups directly attached to a stereogenic centre. In order to make this the sequence rule were formulated by **Cahn, Ingold** and **Prelog** in 1966 as listed below:

1. **Rule 1:** is that atoms of higher atomic number take precedence over those of lower atomic number. Lone pairs of electrons are assigned the lowest priority.

order of priority: I > Br > Cl > F > O > N > C > H > lone pair of electrons

2. **Rule 2:** is that isotopes of higher atomic weight take precedence. (if rule 1 invalid)

order of priority: ^3H (tritium) > ^2H (deuterium) > ^1H (hydrogen)

3. **Rule 3:** *seqcis* stereogenic unit precedes *seqtrans* unit and those precede *nonstereogenic* units (*seqcis* > *seqtrans* > *nonstereogenic*).

4. **Rule 4:** a). Chiral stereogenic unit precede pseudoasymmetric stereogenic unit and these precede nonstereogenic unit.

b). When two groups have different descriptor pair, then likewise descriptor pair precedes than unlike pair:

e.g. likewise pair RR or SS precedes over unlike RS or SR;

MM or PP precedes over MP or PM

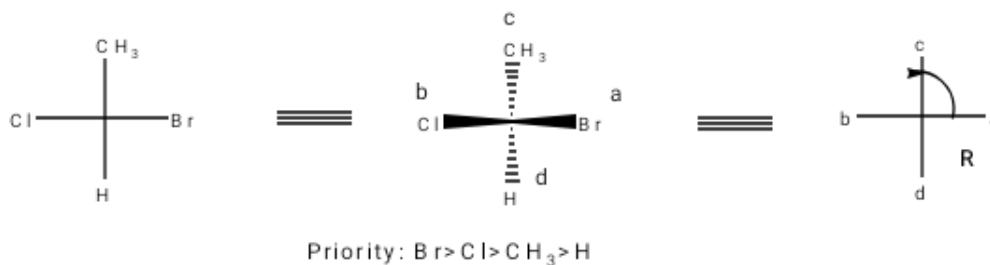
seqcis/ seqcis or seqtrans/seqtrans Precedes over seqcis/seqtrans or seqtrans/seqcis

for pseudoasymmetric centre, R precedes S

5. **Rule 5:** A group with descriptor R, M, *seqCis* has priority over its enantiomeric S, P or *seqTrans*.
6. **Rule 0:** Nearer end of chiral axis or side of chiral plane precedes further.

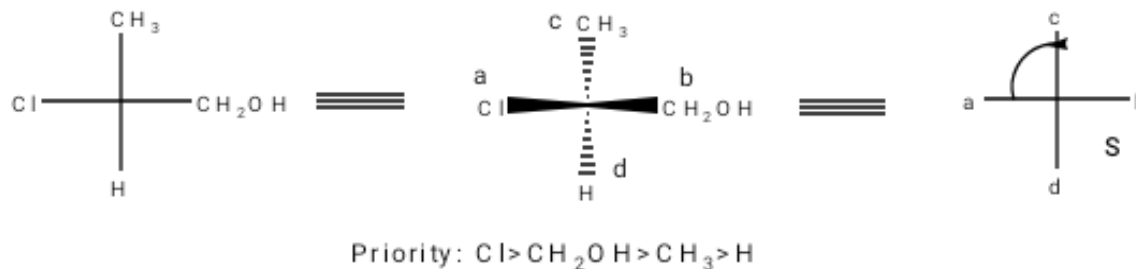
If the molecule is written in FPF and the lowest prior group/atom is in vertical position, then the molecule is viewed from the normal position which will be remotest (as the vertical line is below the plane) then moving from 1 to 2 to 3 or a to b to c ($1 \rightarrow 2 \rightarrow 3$ or $a \rightarrow b \rightarrow c$) is clockwise motion then the stereocentre is said to have *R* configuration (*R* from *rectus*, Latin for *right*). If the said path describe a anticlockwise motion then the stereocentre is said to have *S* configuration (*S* from *Sinister*, Latin for *left*).

Example 1:



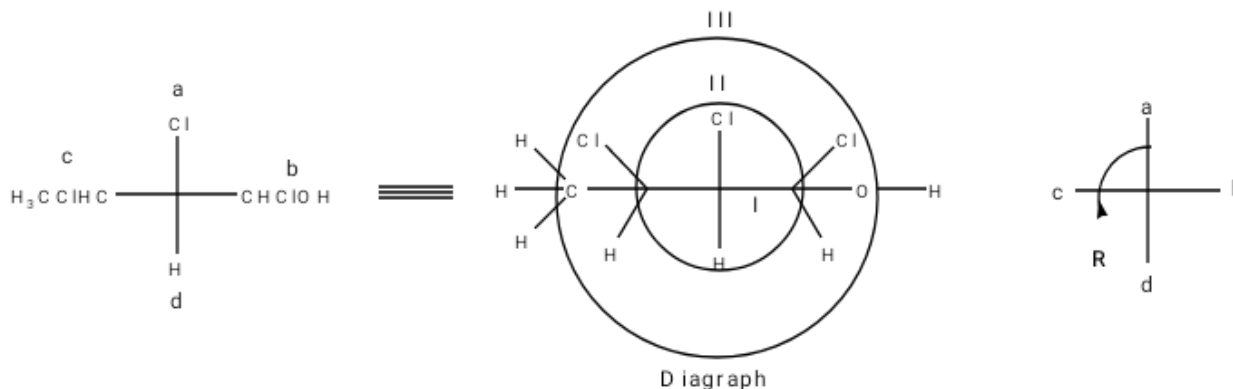
As the atomic number of Br > Cl > C > H, so its sequence is done by atomic number rule and as the movement $a \rightarrow b \rightarrow c$ is clockwise and d is on vertical line, so its configuration is **R**.

Example 2: CH₃-CHCl-CH₂OH

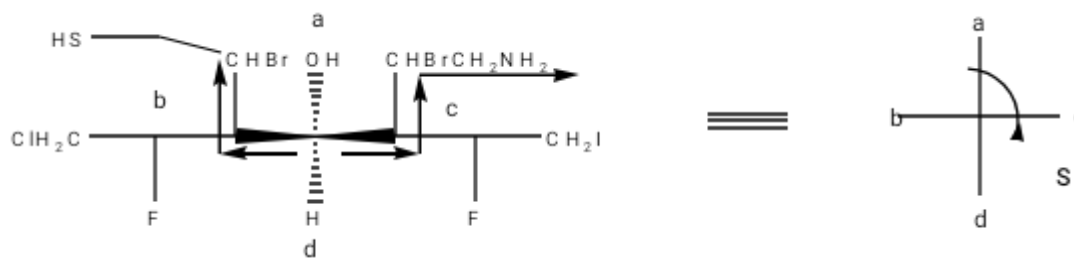


In the above example, the order of seniority is done based upon rule-1 and rule-0, according to rule-1 the atomic number priority is Cl > C > H, so more prior and least prior is confirmed, for the second and third priority we have to move to the next atom where the priority is O > H. so the chiral centre atom/groups sequence is Cl > CH₂OH > CH₃ > H and we get its configuration S.

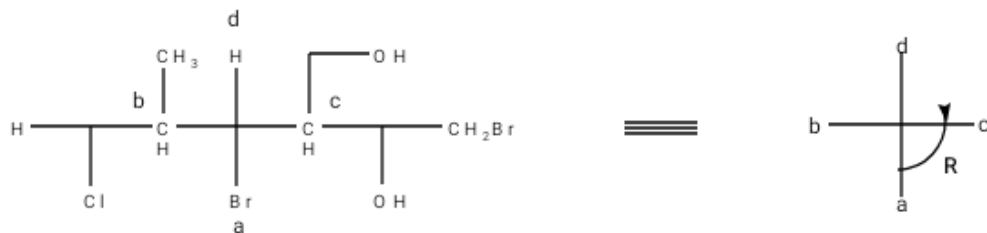
Example 3: in this example, sequence rule 1 establishes the seniority order of proximal atoms as Cl > C > C > H in circle 1: but no decision between b and c could be reached. However, in circle-II, the atoms attached to the carbon atoms 1 and 3 are (Cl, O, H) and (Cl, C, H) respectively. The comparison of the two senior atoms in each set, Cl atom, does not permit a choice to be made, but, comparison of the two second atoms in the set O and C, respectively, establishes the precedence O > C and thus the group -CHCl(OH) is get b > -CHClCH₃ is get c.



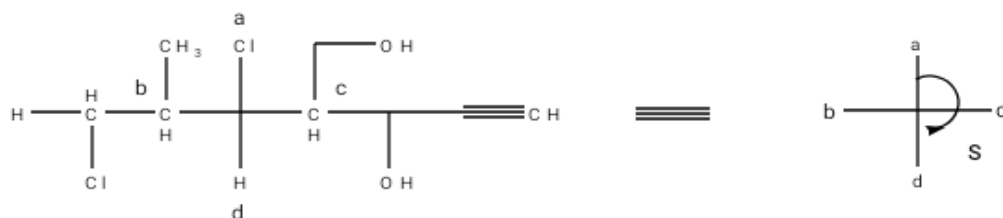
Considering the following example:



In this example, the OH group has highest priority and H has the lowest priority but between the other two ligands containing carbon chain, the priority according to CIP sequence rule should be decided by the hierarchy of path denoted by groups, -CHCHBrCH₂NH₂ and -CHCHBrCH₂SH and not by the groups -CHFCH₂I and -CHFCH₂Cl because -CHCHBr- has the higher priority over -CHCHF-. Therefore, the group on the left side will get higher priority over the group on the right side, i.e., -CHCHBrCH₂SH has the higher priority over CHCHBrCH₂NH₂ and the absolute configuration of the molecule is (S). More example;



Another example;

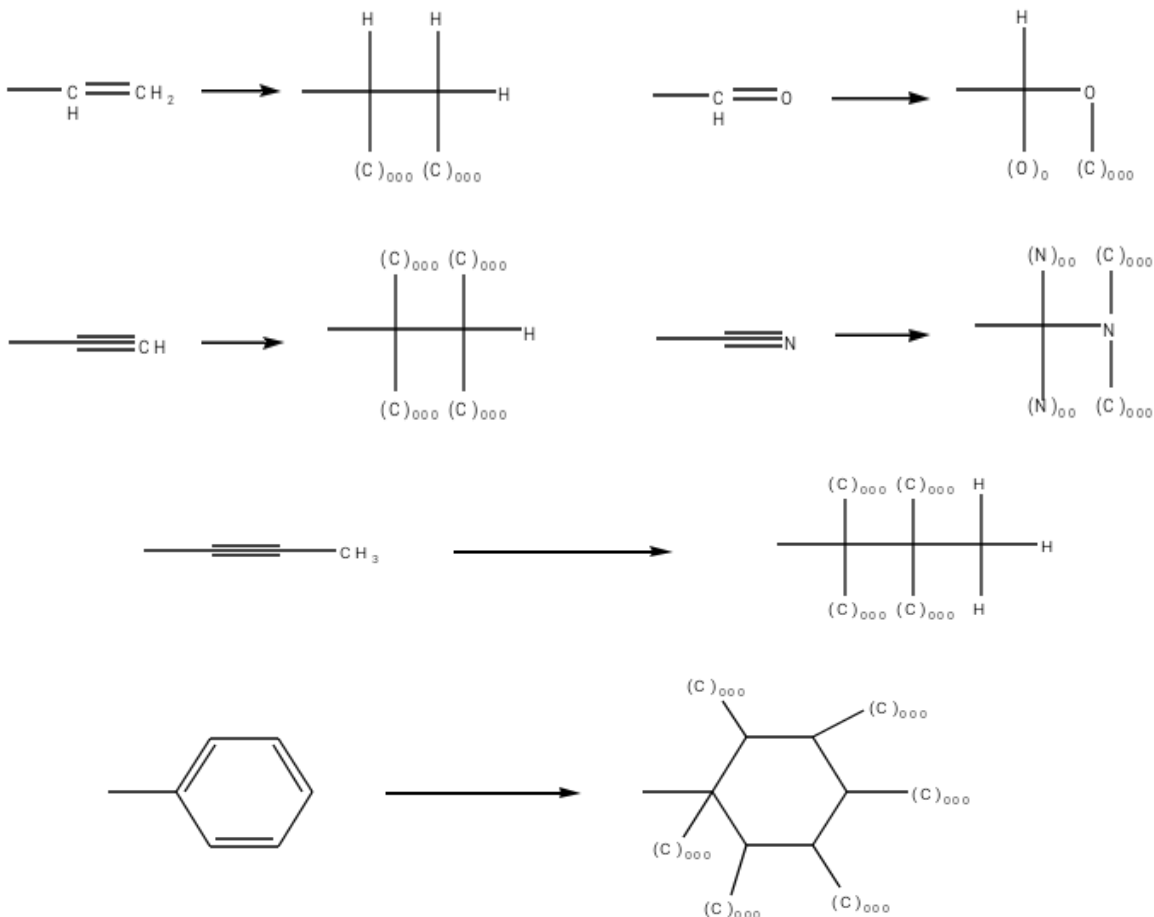


More Example:



Priority order CH₂OH > CH₃ > D > H, by rule 1 and rule 2

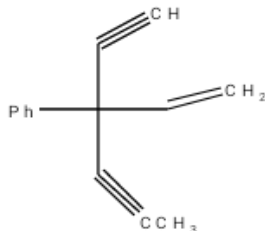
For the purpose of assigning the priority of multiple bond (double, triple bond and ring), the multiple bond or ring are split into two or three single bonds by replication of the atom(s) at the other end of the multiple bond. Replicated atom(s) enclosed in parenthesis in the expanded form of the group. Each replicated atom, except H, is converted to single bond tetravalency by adding so called phantom atoms. Phantom atoms are imaginary having an atomic number which is never extend its valency.



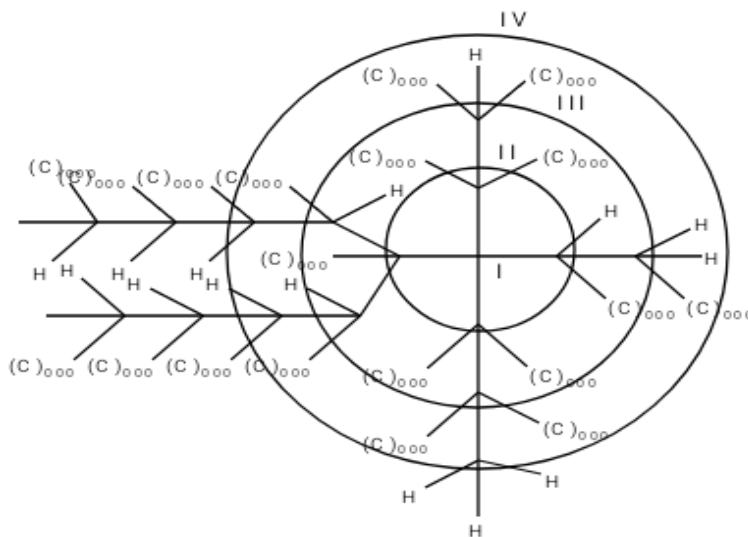
So priority order will be

COX>CO₂R>COOH>CONH₂>COR>CH(OMe)₂>CHO>CH(OH)₂>CR₂OH> -CH(OH)R> -CH₂OH> -C≡C-R> -Ph> -C≡CH> -C(R)=CR₂> -CR₃> -CH=CHR> -CH=CH₂> -CHR₂> -CH₂C₆H₅> -CH₂C≡CH> -CH₂C=CH₂> -CH₂CH₃> -CH₃> -D> -H.

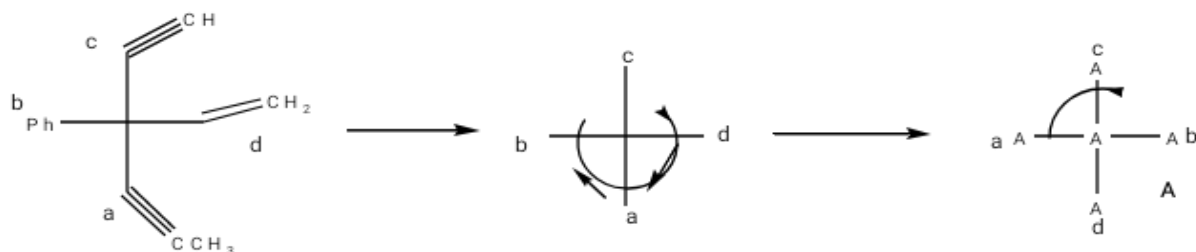
Q1: Give the R/S Naming of the following compound:



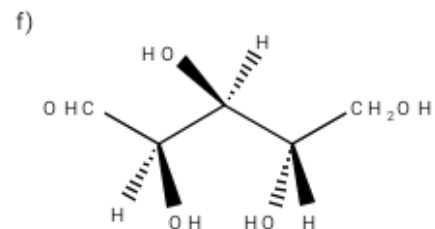
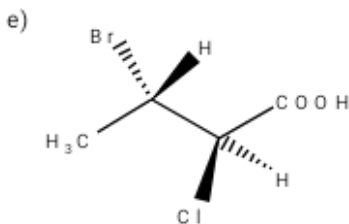
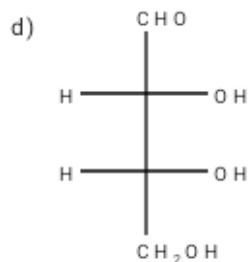
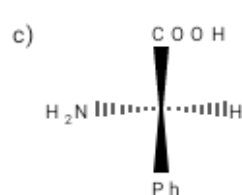
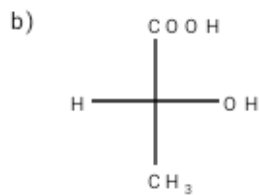
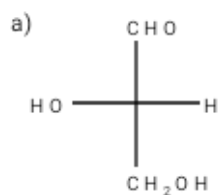
Ans: Before R/S Naming we have to arrange the group according to CIP sequence. Considering the phantom atoms of the molecule, it can be rewrite as follows



In circle II, the atoms are, (C,C,H); (C,C,C); (C,C,C); (C,C,C) as CCH has lowest priority so $-\text{CH}=\text{CH}_2$ get least priority, considering circle III, (C,C,C) > (C,C,H) > (C,H,H) as (C)₀₀₀ has no valency so its priority will be less than C atom. So the CIP sequence order will be $-\text{C}\equiv\text{CCH}_3 > -\text{Ph} > -\text{C}\equiv\text{CH} > -\text{CH}=\text{CH}_2$, so its chiral centre configuration will be **S**.

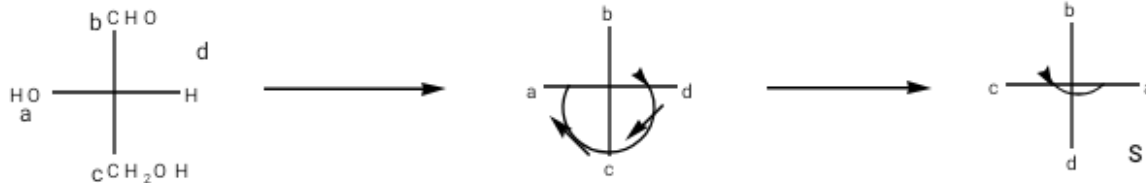


Assign the R/S notation of the following compounds:

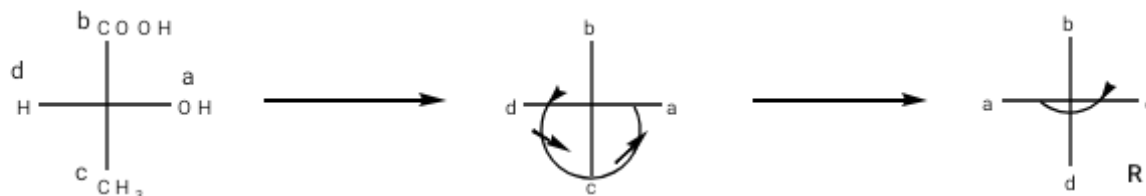


Answer:

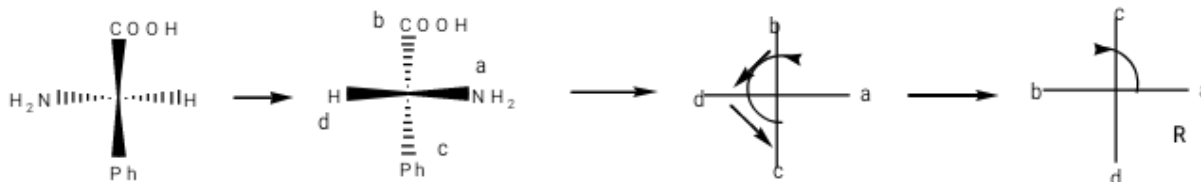
a).



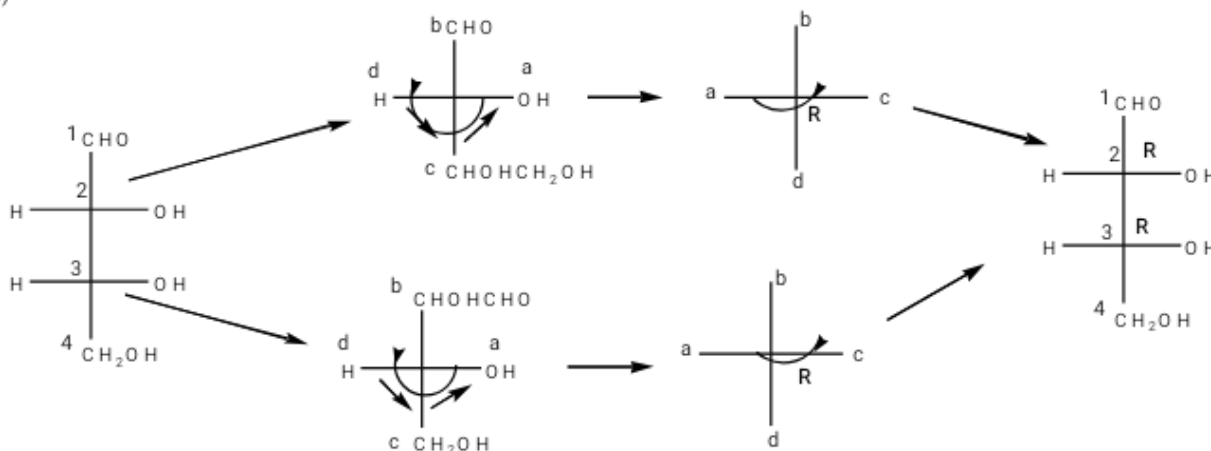
b).



c).



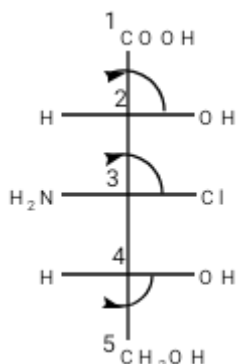
d).



Very good (mnemonic) method of assigning absolute configuration:

Another alternative method for quickly assigning absolute (R/S) naming to a chiral centre is due to Eplig (1982). The procedure is known as *very good method*. *Very good stands for vertical good*. The method is applicable in Fischer Projections only and makes use of the sequence rule introduced by **Cahn, Ingold and Prelog**. If in a Fischer Projection, priority order of group(s) and or atom(s) are $a > b > c$, then path traced from $a \rightarrow b \rightarrow c$ (without d) gives the correct descriptor (R) for clockwise and (S) for

anticlockwise if d (lowest priority group) is on either of the vertical bonds. But if 'd' remain on the horizontal bond then anticlockwise path indicate (R) and clockwise path indicate (S) configuration. This method is helpful for assigning absolute configurations rapidly to the chiral centres in a molecule. e.g.,



Priority of groups in different chiral centres of the compound are as follows:

C-2: $-\text{OH} > -\text{C}(\text{NH}_2)\text{Cl} > -\text{COOH} > -\text{H}$

C-3: $-\text{Cl} > -\text{NH}_2 > \text{CH}(\text{OH})\text{COOH} > \text{CH}(\text{OH})\text{CH}_2\text{OH}$

C-4: $\text{OH} > \text{C}(\text{NH}_2)\text{Cl} > \text{CH}_2\text{OH} > \text{H}$

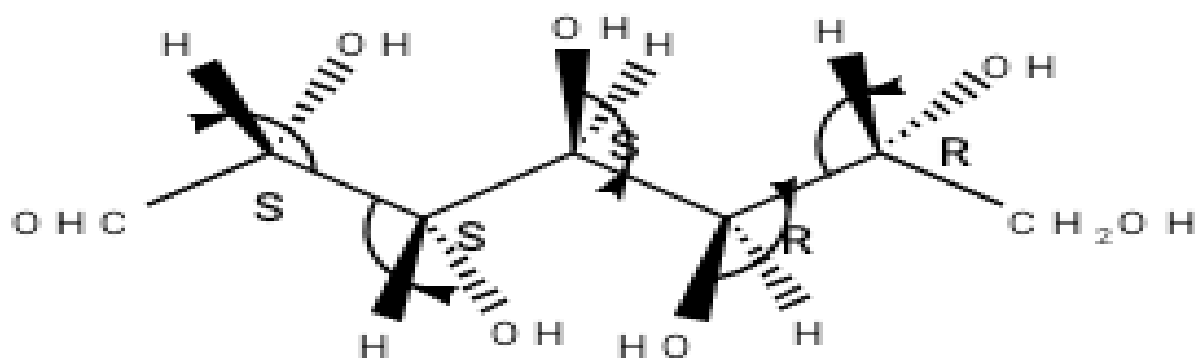
At C-2 and C-4 lowest priority group (H) is on horizontal position, therefore, the absolute configuration at C-2 is (S), because a \rightarrow b \rightarrow c traces a clockwise path. On similar ground, the absolute configuration at C-4 is (R). Absolute configuration at C-3 is also (R) because the lowest prior group (CHOHCH_2OH) is on vertical position and the prior group traces a $a \rightarrow b \rightarrow c$ to a clockwise path.

4-Back Rule:

Another very popular rule is 4-Back Rule, according to this rule if the lowest priority group is on the below the plane i.e., below the plane in wedge projection then if the movement of a \rightarrow b \rightarrow c traces a clockwise path then its configuration is (R), and if a \rightarrow b \rightarrow c a anticlockwise path then its configuration is (S). This rule is simplified as follows:

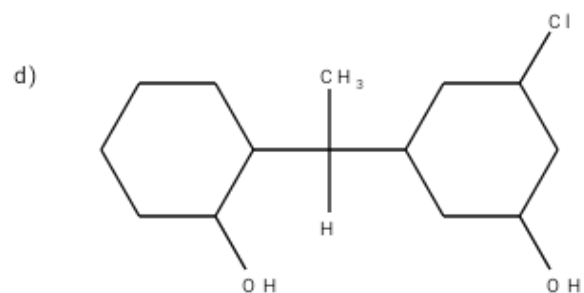
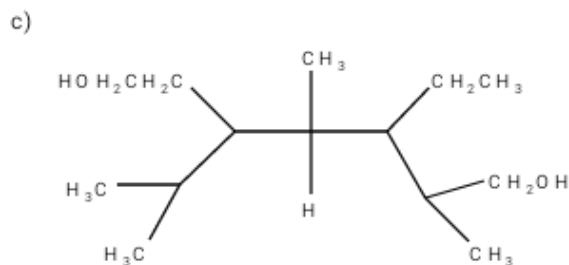
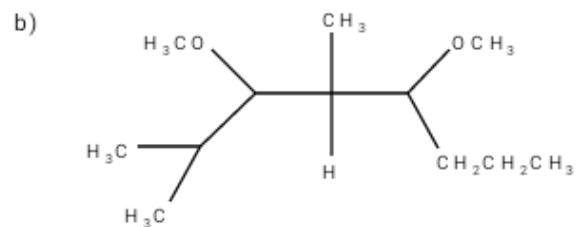
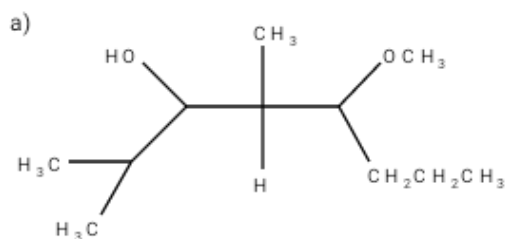
Group is on back (Flying wedge and zigzag)	Path traces	Rotation and Configuration
4-Back/d-back	1 \rightarrow 2 \rightarrow 3 or a \rightarrow b \rightarrow c	Clockwise : R
		Anticlockwise : S
3-Back/c-back	1 \rightarrow 2 \rightarrow 4 or a \rightarrow b \rightarrow d	Clockwise : S
		Anticlockwise : R

2-Back/b-back	1 → 3 → 4 or a → c → d	Clockwise : R
		Anticlockwise : S
1-Back/a-back	2 → 3 → 4 or b → c → d	Clockwise : S
		Anticlockwise : R

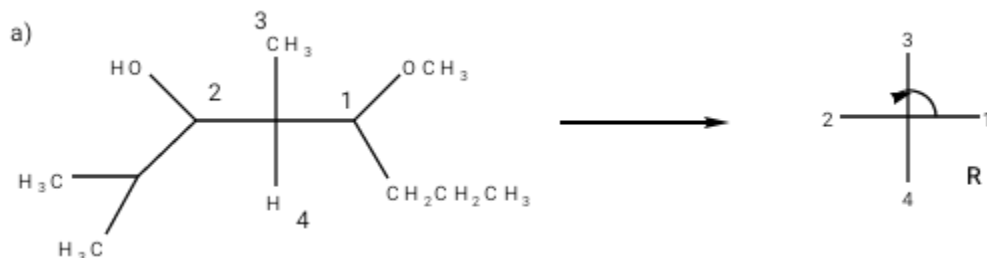


More R/S nomenclature:

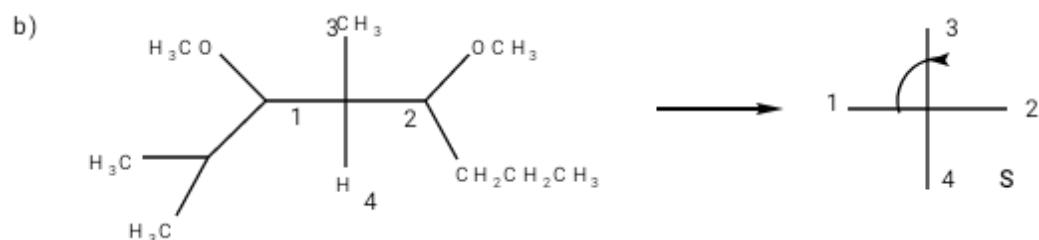
1. Give the R/S Naming of the following compounds



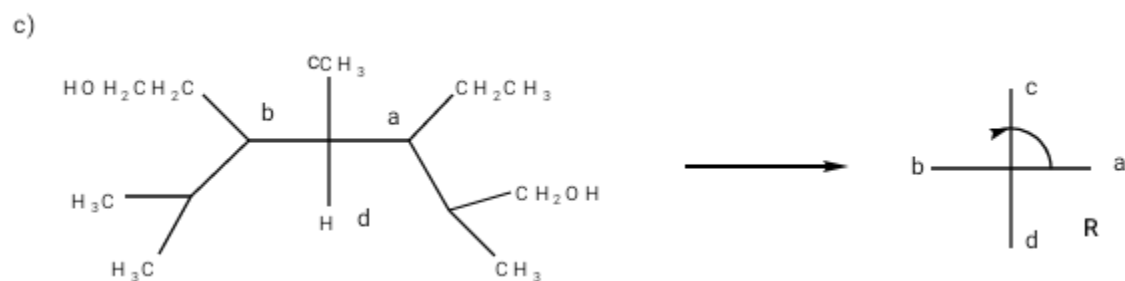
Answer:



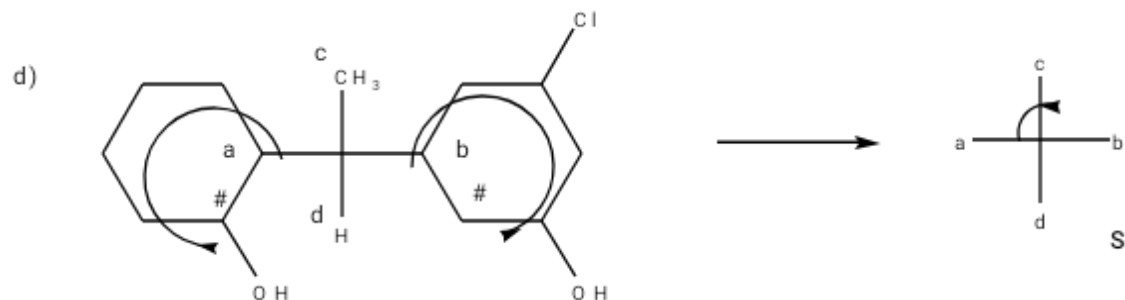
From the branch point, one should proceed first along with the prior branch. In this case, along with the oxygen branch. For this reason, $-(\text{CH})\text{-O-C}$ on the right hand side has the priority over $-(\text{CH})\text{-O-H}$ on the left. Only if the prior branches do not differ, one should proceed along the other. This is shown in the next example.



In the above example, the two oxygen branches ($-\text{OCH}_3$) are the same and therefore, one should consider the other branches and in this case priorities are $-\text{C}(\text{C},\text{C},\text{H}) > -\text{C}(\text{C},\text{H},\text{H}) > -\text{CH}_3 > -\text{H}$ and the configuration is (S).

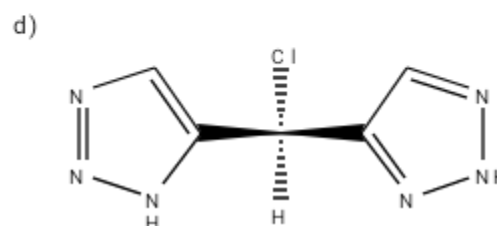
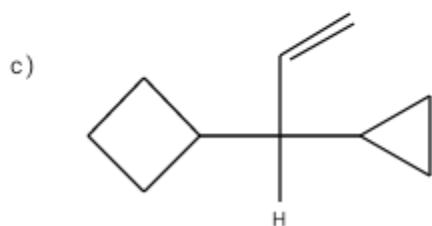
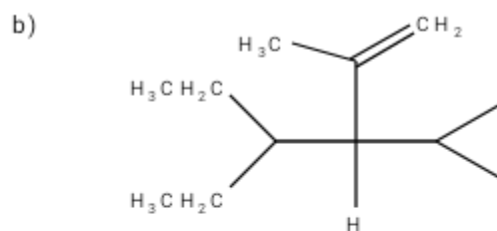
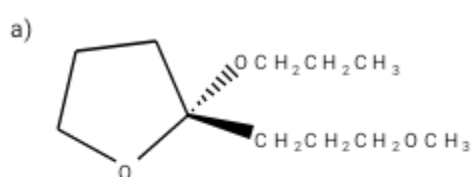


In the above example secondary carbon chain get priority over the primary carbon chain because $-\text{C}(\text{C},\text{C},\text{H}) > -\text{C}(\text{C},\text{H},\text{H})$. For this reason we have to move towards secondary carbon and $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$ is prior over $-\text{CH}(\text{CH}_3)_2$, and the configuration will be **R**.

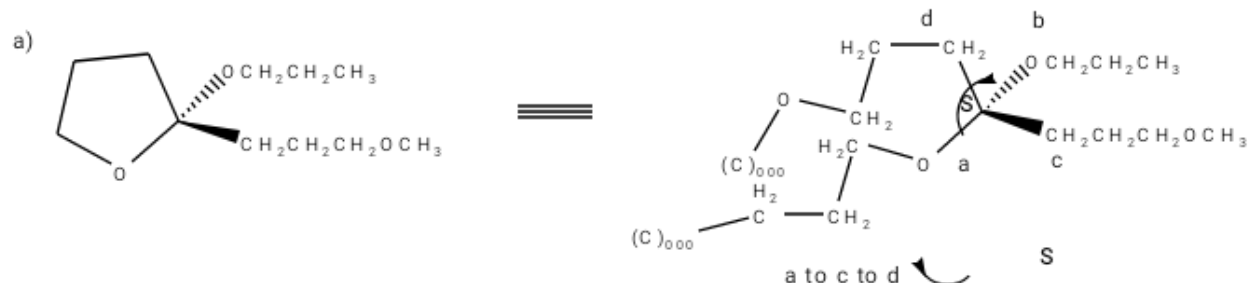


In the above case, the left handed ring get priority over the right handed ring because working out towards first difference is met on the marked positions where $-C(C,H,O) > -C(C,H,H)$ and the configuration is (S).

Example: Give the R/S notation of the following molecules

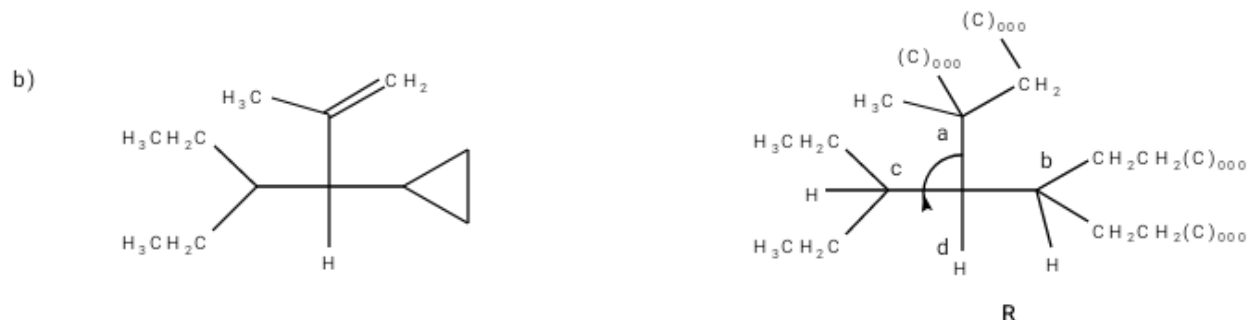


The answers will be done by considering the phantom atom and their configuration will be as follows

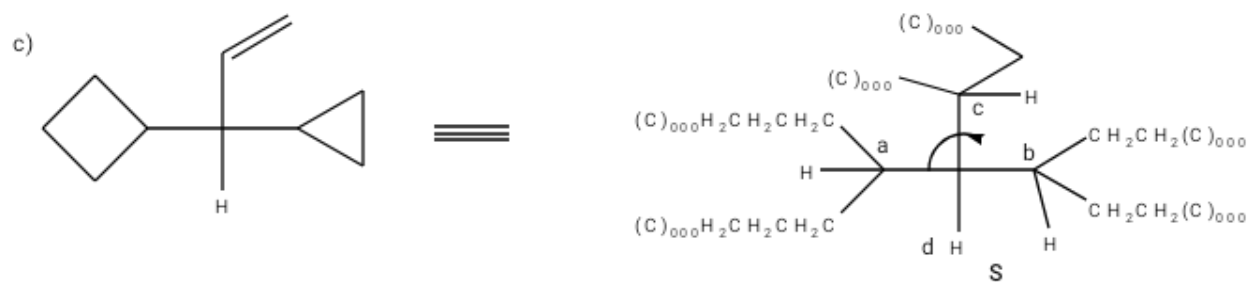


In the above example the connected atoms to the chiral centre are $-O, -O, -C, -C$, so $-O$ and $-O$ will be first and second prior and $-C, -C$, will be third and fourth prior. For considering first and second priority (a and b) the groups $-O-CH_2CH_2CH_2(C)_{000}$ and are

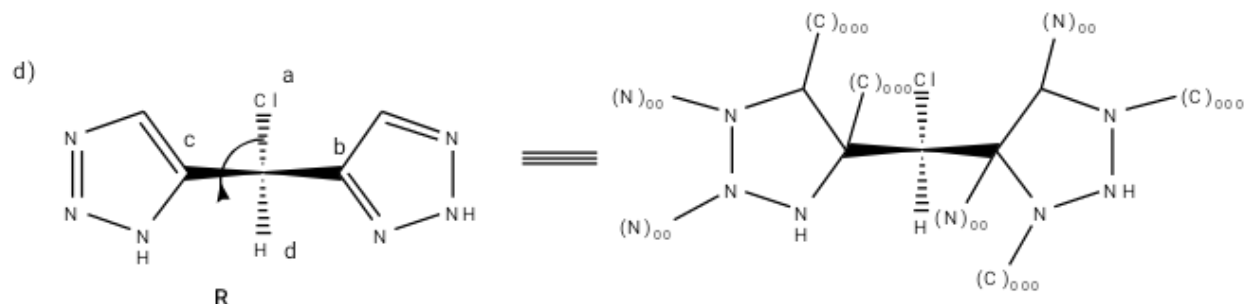
$-O-CH_2CH_2CH_2-H$ respectively. Phantom Carbon $(C)_{000}$ has higher priority than H, so $-O-CH_2CH_2CH_2(C)_{000}$ is more prior than $-O-CH_2CH_2CH_2-H$. For considering third and fourth priority (c and d) the groups $-CH_2CH_2CH_2O-CH_3$ and are $-CH_2CH_2CH_2-O-(C)_{000}$ respectively. Phantom Carbon $(C)_{000}$ has no valency, so it has lower priority than H, so $-CH_2CH_2CH_2O-CH_3$ is more prior than $-CH_2CH_2CH_2-O-(C)_{000}$. Considering 2-Back rule and the path is counterclockwise, its configuration is S.



The above example can be explained by taking the phantom atoms. The priority order is $-C(C,C,C) > -C(C,C,H) \approx -C(C,C,H) > H$. So, first and fourth prior group and atom already decided. For the second and third priority of groups we have to consider the phantom atom, $-CH_2CH_2(C)_{000}$ is prior over than $-CH_2CH_2-H$. So its configuration is R.



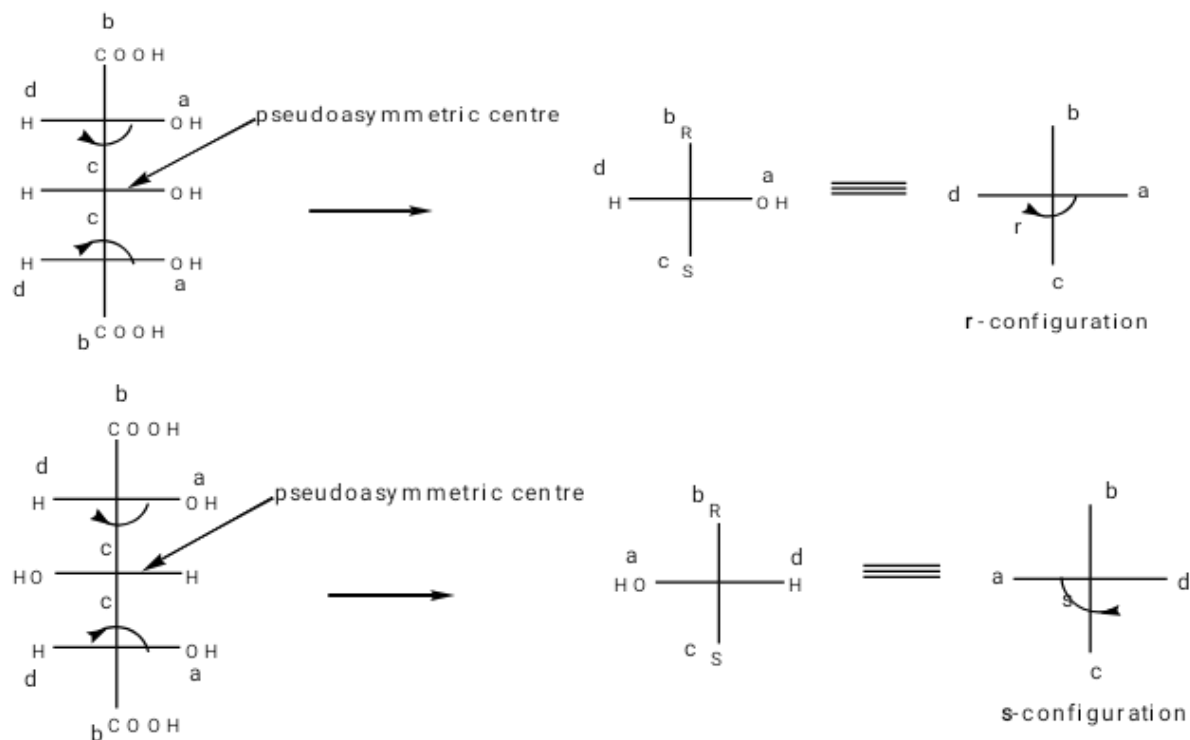
The above example can be explained by taking the phantom atoms. The priority order is $-C(C,C,H) \approx -C(C,C,H) \approx -C(C,C,H) > H$. So, the fourth prior atom is already decided. For the first, second and third priority of groups we have to consider the phantom atom, we know that phantom atom has no valency as well as no priority on extension, so the priority order is $-CH_2CH_2CH_2(C)_{000} > -CH_2CH_2(C)_{000} > -CH_2(C)_{000}$. So its configuration is R.



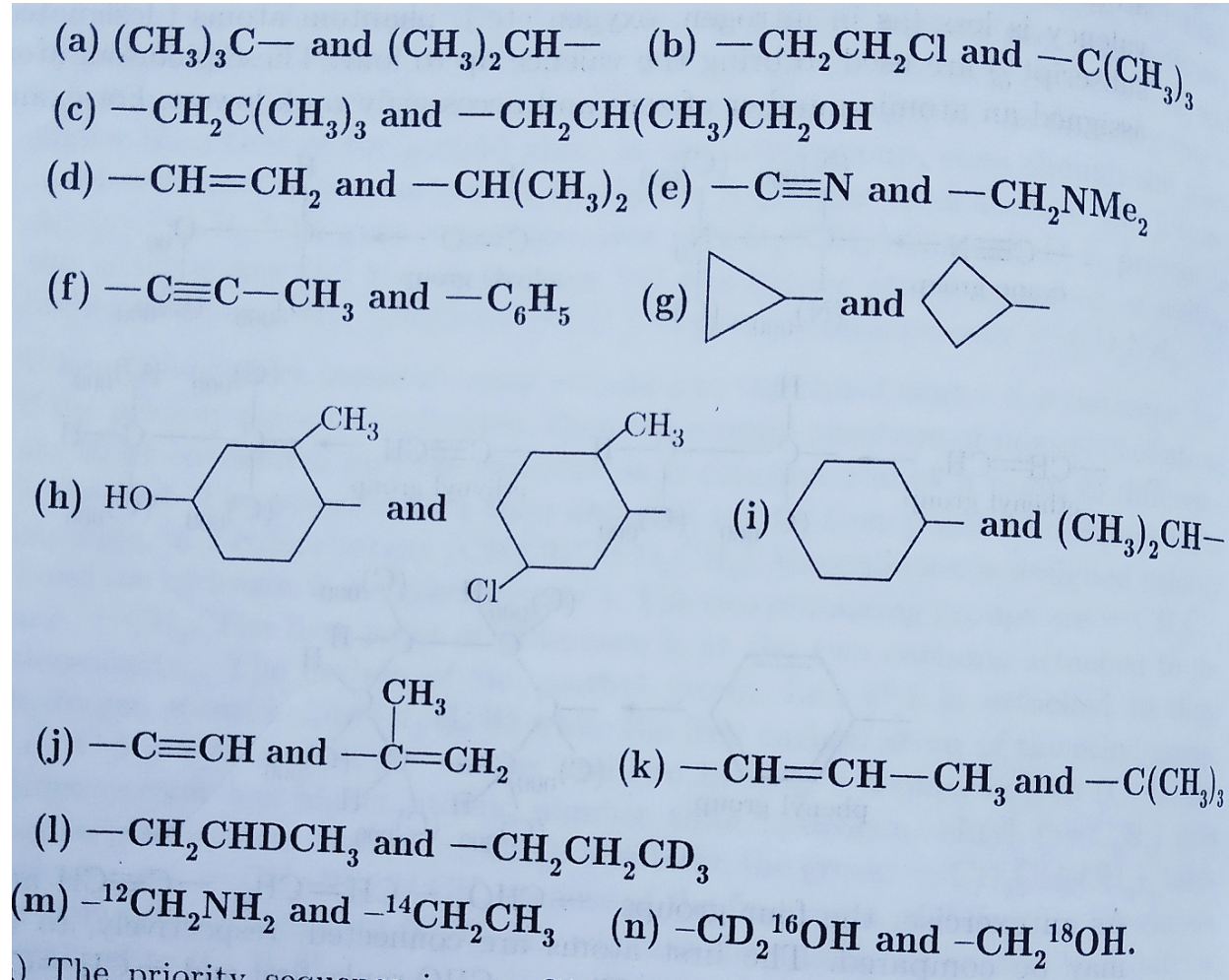
In the above example the two rings are tautomers. Considering their phantom atom concept the priority order is $-Cl > -C(N,N,C) > -C(N,C,C) > -H$. Applying very good rule its configuration is R.

Naming at Pseudoasymmetric Centre:

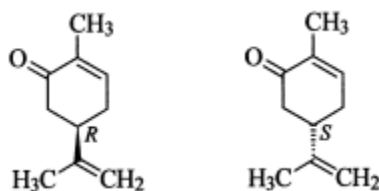
The centre which belong to stereogenic but achirotopic, due to presence of plane or centre of symmetry, is known as Pseudoasymmetric centre. As they contain two enantiomorphous group its absolute configuration will be 'r' or 's' following the same sequence rule of R/S naming. Examples are:



Problem 1: Assign the priority of the following pair using CIP sequence rule

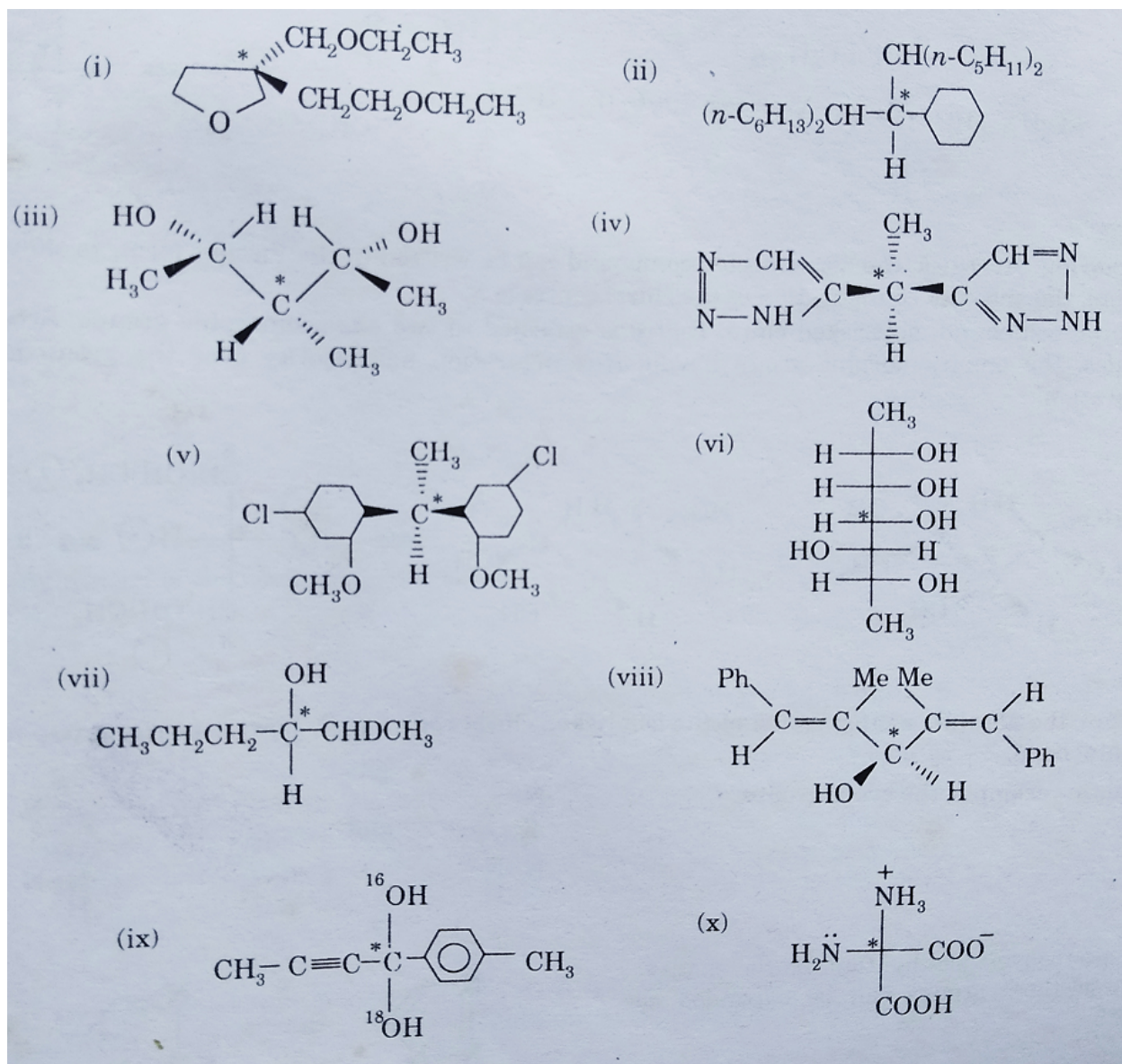


Problem 2: Which of the following properties or methods can be used to distinguish between (R)-carvone and (S)-carvone?

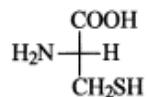


- a) boiling point b) UV spectroscopy c) refractive index d) melting point e) smell
 f) optical rotation g) dipole moment h) circular dichroism
 i) NMR spectroscopy j) IR spectroscopy

Problem 3: Find out the absolute configuration of the following marked chiral centre.

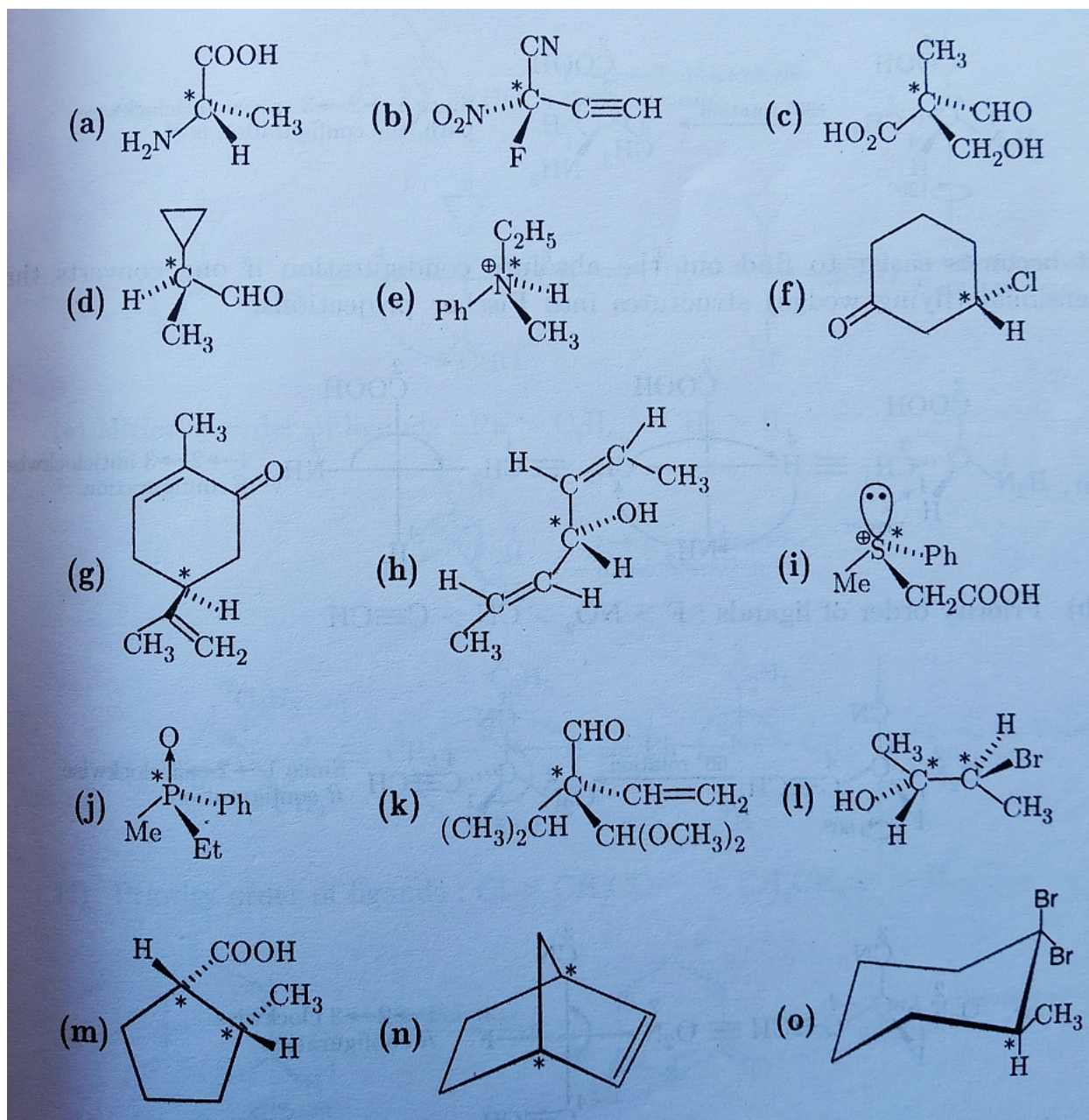


Problem 4: Deduce the absolute configuration of l-cysteine according to the R/S nomenclature.



Problem 5: Draw the structural formulae for both (RS,RS)- and (RS,SR)-2-phenyl2-(piperidin-2-yl)acetic acid methyl ester

Problem 6: Find out the absolute configuration of the following marked chiral centre.



The Isomers of C₃H₄Cl₂,

