

Assigning Stereochemistry I

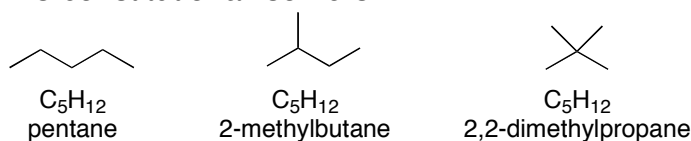
What is stereochemistry?

Types of isomers

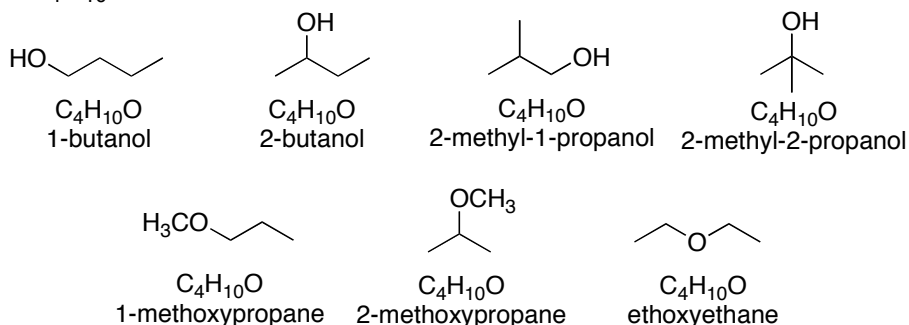
As organic molecules get larger (more than two central atoms) there are often multiple ways to bond the atoms in a given formula. The resulting substances are entirely different molecules, which are called isomers and have widely different properties.

- *Isomers* – Molecules with the same chemical formula.
- *Constitutional Isomers* – Molecules with the same atoms (chemical formula), but different bonds. Constitutional isomers have different shapes, functional groups and properties and are typically treated as completely different substances with completely different names.

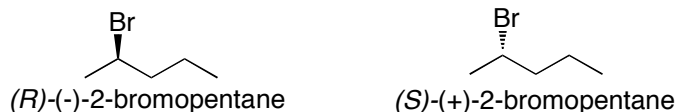
- C_5H_{12} – 3 constitutional isomers



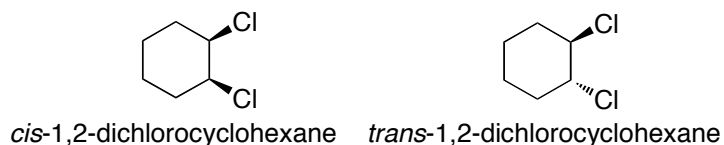
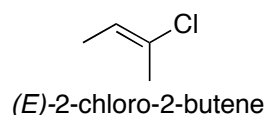
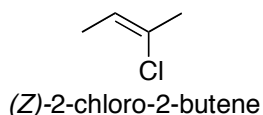
- $C_4H_{10}O$ – 7 constitutional isomers



- *Stereoisomers* – Molecules with the same atoms (chemical formula) and same bonds/connectivity, but different shapes. Stereoisomers are not superimposable, if laid on top of one another they would not be the same. Stereoisomers have different shapes and different physical properties, but will have the same functional groups and the same name in IUPAC nomenclature. Stereoisomers can be classified into two groups: enantiomers and diastereomers.
 - *Enantiomers* – Non-superimposable stereoisomers that are exact mirror images. Enantiomers have identical physical properties except for rotation of plane-polarized light. Molecules that have enantiomers are chiral molecules.



- *Diastereomers* – Non-superimposable stereoisomers that are not mirror images. Diastereomers have distinct physical properties and may or may not be chiral molecules.



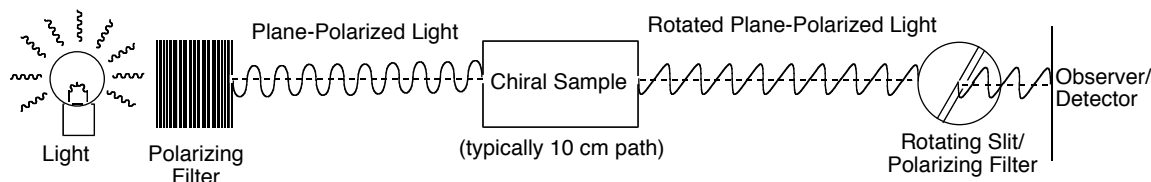
Finding Stereoisomers

Molecules with stereoisomerism will contain either:

- *A stereocenter* – A stereocenter (a.k.a chiral center or chiral carbon) is an sp^3 -hybridized carbon that has four different substituents attached. Chiral centers have no planes of symmetry.
 - Look for CH or quaternary carbons.
 - Check each of these to see if they have four different groups attached.
 - It doesn't matter how far away the difference is, any difference counts.
 - CH_3 and CH_2 cannot be stereocenters as they have at least two of the same group (hydrogen) attached.
 - sp^2 and sp hybridized carbons cannot be stereocenters as they cannot have four different groups attached.
- *An alkene* – Alkenes where the two carbons that make up the alkene each have two different substituents attached will have stereoisomers.
 - Look for an alkene.
 - For both carbons of the alkene, check to make sure the two substituents on that carbon are different.
 - It doesn't matter how far away the difference is, any difference counts.
 - Alkenes are inherently planar (symmetrical) so will not be able to make enantiomers unless a stereocenter is also present.
- *Overall asymmetry* – Molecules where steric hindrance causes a permanent twist may display stereoisomerism without a stereocenter or asymmetrical alkene, these are relatively few and do not tend to show up in the Chemistry 8 or 118 series, but they do exist. (e.g. helicene)

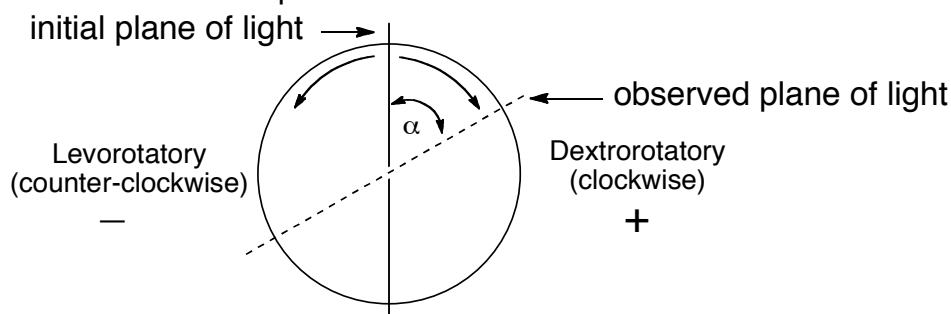
Polarimetry / Optical Rotation:

Polarimeter Schematic



Enantiomers have nearly identical physical properties; the major exception is the rotation of plane-polarized light where one enantiomer will rotate light clockwise and the other will rotate light an equal amount counter-clockwise. Molecules that rotate plane-polarized light are said to be optically active. The process of measuring the rotation of plane-polarized light is called polarimetry.

- All chiral molecules (molecules with a nonsuperimposable mirror image) are optically active and all optically active molecules are chiral. Thus the terms chiral and optically active are functionally synonymous and can be used interchangeably.
- The amount a compound turns plane-polarized light measured as an angle α . The $[\alpha]_D$ is a physical constant that can be calculated from α , pathlength, and concentration of the sample.



- Molecules that rotate plane polarized light clockwise (rightwards) from the point of view of an observer looking at the light through the sample are said to be dextrorotatory (D) and are given a positive (+) sign.
- Molecules that rotate plane polarized light counterclockwise (leftwards) are said to be levorotatory (L) and are given a negative (-) sign.
- For any given pair of enantiomers one molecule will be levorotatory (-) and the other will be an equal amount dextrorotatory (+), however which is which cannot be predicted from just observing the structure or R/S assignments.
- A racemic mixture is a 1:1 mixture of enantiomers and will have an optical rotation of 0 degrees (equal amounts levorotatory and dextrorotatory).

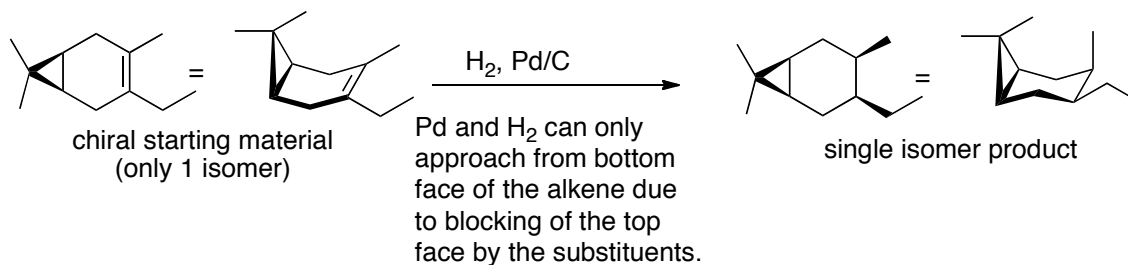
Absolute vs. Relative Stereochemistry

Absolute Stereochemistry – The exact stereoisomer with ALL relationships between atoms determined for molecules with either single or multiple stereocenters. Determining absolute stereochemistry requires the assignment of R vs. S or dextrorotatory vs. levorotatory. A molecule where absolute stereochemistry is known is a particular enantiomer.

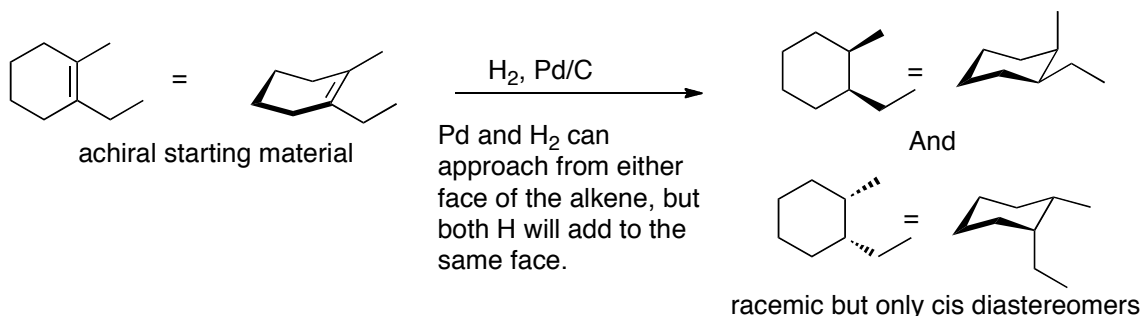
Relative Stereochemistry – The relative positioning of multiple stereocenters within a molecule. Giving relative stereochemistry determines the diastereomer, but not which of the two possible enantiomers. Requires the assignment or anti/syn, cis/trans, or erythro/threo etc., but does not require R/S assignments. A molecule where only relative stereochemistry is known can be differentiated from its diastereomers, but is usually racemic.

Stereochemistry in Reactions

- Reactions that start with a single isomer (or use a single isomer chiral reagent) will tend to give a preference for a single isomer.



- Reactions that start with a racemic mixture or achiral molecule will tend to give racemic products, though they may still give particular relative stereochemistry (e.g. bromination of alkenes gives *anti* relative stereochemistry as a mixture of enantiomers).



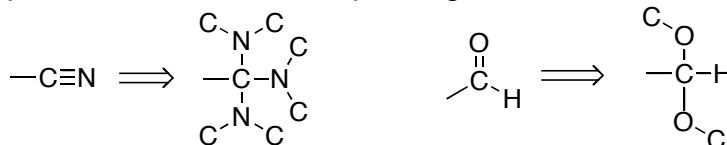
Assigning Stereochemistry II

Assigning Priority (Cahn-Ingold-Prelog Rules)

To describe the orientation of substituents around a stereocenter or an alkene each substituent is assigned priority through the Cahn-Ingold-Prelog rules.

Cahn-Ingold-Prelog Rules

- 1) Priority is primarily assigned by atomic number, higher atomic number get first priority
 - a. In order 1st Br then Cl then C and lastly H 4th
 - i. H always has lowest priority.
 - ii. CH₃ is typically next lowest after H.
 - iii. Heteroatoms typically get high priority.
- 2) If isotopes are encountered the heavier isotope gets priority
 - a. ¹⁴C has priority over ¹³C, which has priority over ¹²C
- 3) If two of the same atom are encountered priority is assigned by the *first difference* in bonded atoms
 - a. -CH(CH₃)CH₂CH₂CH₃ has priority over -CH₂CH₂CH₂Br
- 4) Multiple bonds count as multiple single bonds to the same atom

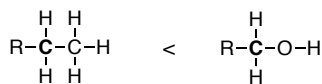


Assigning Priority

- 1) Look at the atoms attached directly to the stereocenter/alkene.
- 2) If any have clearly different atomic numbers this is the first difference, use the atomic number to assign priority.
- 3) If any have the same atomic number (typically C), determine what atoms are attached (2 bonds from the stereocenter/alkene).
 - a. List the attached atoms in order of atomic number and look for a higher atomic number.
 - i. A C attached to C, C, and H is higher priority than a C attached to C, H, and H.
- 4) Continue following the attached atoms away from the stereocenter/alkene until a difference is found.
 - a. The first difference is the only one that matters.
 - b. If no difference is found then the two substituents are the same and the carbon is not a stereocenter or the alkene is symmetrical.

Cahn-Ingold-Prelog Examples:

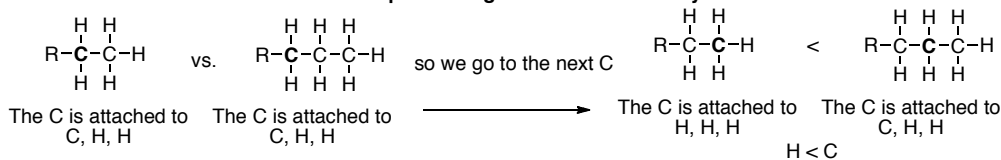
Example 1: Larger Atomic Number gets Priority



The C is attached to C, H, H The C is attached to O, H, H
C < O

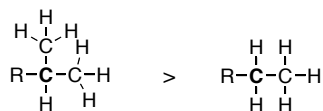
Oxygen is larger than carbon so the alcohol gets priority, functional groups usually get priority as they tend to have larger atoms.

Example 2: Longer Chains Get Priority



Longer chains will get priority as any atom will win over H.

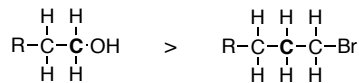
Example 3: Branched Chains get Priority



The C is attached to C, C, H The C is attached to C, H, H
C > H

The first C attached to each is the same, but the second C is larger than H. Branched chains will usually get priority.

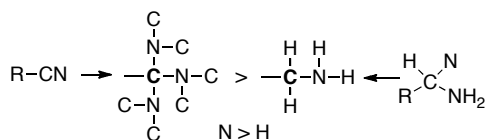
Example 4: First Difference gets Priority



The C is attached to O, H, H The C is attached to C, H, H
O > C

The Br is too far away, it is not the first difference. Closer differences take priority not the ultimately largest atom.

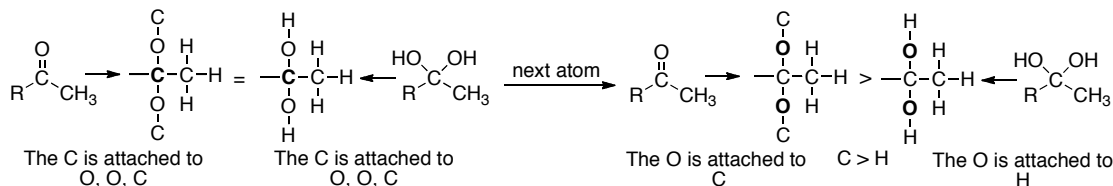
Example 5: Multiple Bonds Count Multiple Times



The C is attached to N, N, N The C is attached to N, H, H

The triple bond counts as 3 bonds to N so N is larger than H.

Example 6: Multiple Bonds Count Extra for Both Atoms

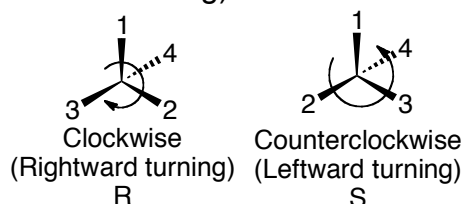


The carbonyl counts as two C-O bonds from the carbons perspective so we need to go on to the next atom. The O is attached to H in the diol and back through the second bond to the C in the carbonyl.

Assigning Stereochemistry III

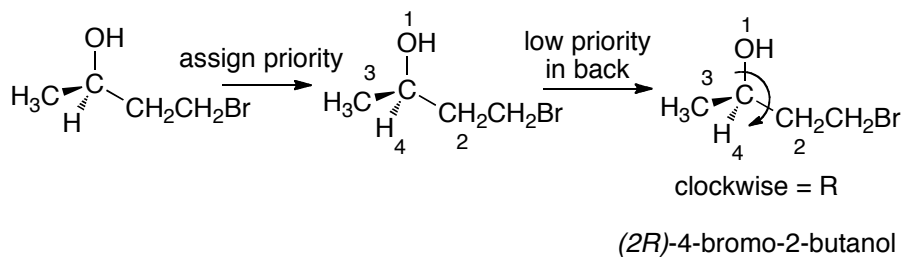
R and S in Alkanes

- A chiral carbon has four different groups attached to it, the differences may be several bonds away, but so long as they are different in any way the groups are considered different.
 - Stereocenters are chiral carbons and vice versa
- Chiral molecules are asymmetric molecules
 - They do not have an internal mirror plane
 - They nearly always have at least one stereocenter
 - Chiral molecules may lack a mirror plane *and* have no chiral centers, they exist but are beyond the scope of this course (i.e. helicene)
 - They are optically active and rotate plane-polarized light
 - Left (counterclockwise) rotation is (-) and levorotory
 - Right (clockwise) rotation is (+) and dextrorotory
- Individual chiral centers are classified as either R or S.
 - R/S designation is completely unrelated to the direction of rotation of plane polarized light.
 - If no dashes/wedges are given the stereocenter is unassignable and considered to be racemic.
- Assigning R vs. S stereocenters – The Absolute Configuration:
 - Working outward from the chiral carbon assign priority to each attached group. (Cahn-Ingold-Prelog Priority Rules)
 - See Assigning Stereochemistry II
 - Once priority is assigned rotate the lowest priority to the back
 - If 1 → 2 → 3 proceeds clockwise the center is R (right turning)
 - If 1 → 2 → 3 proceeds counterclockwise the center is S (left/sinister turning)

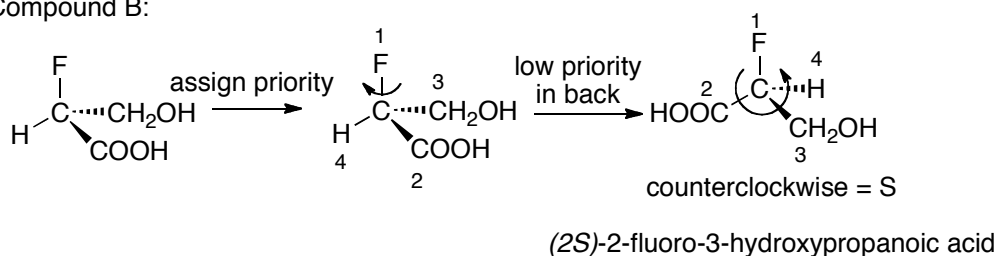


Examples:

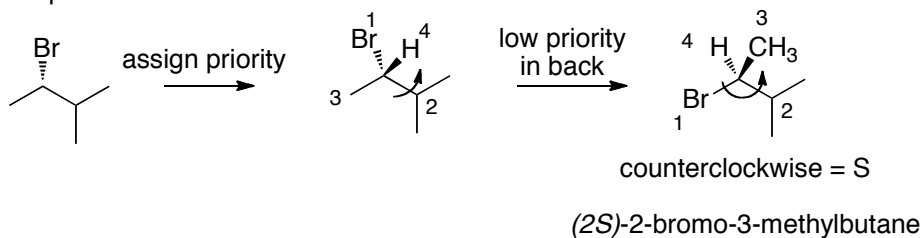
Compound A:



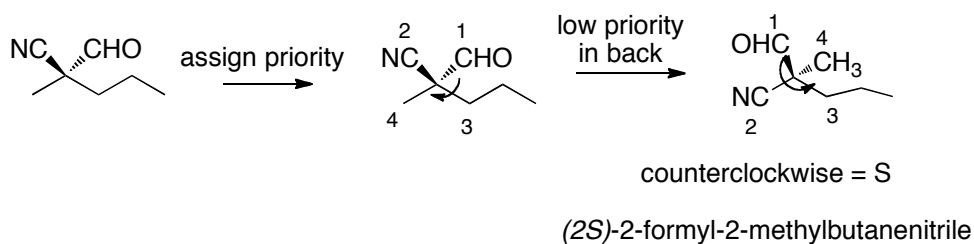
Compound B:



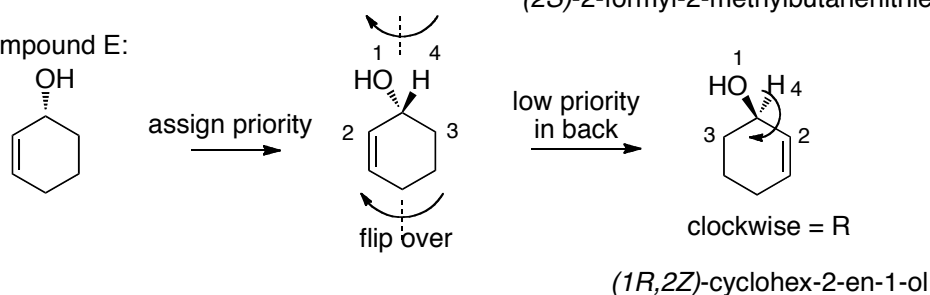
Compound C:



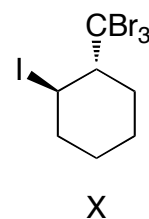
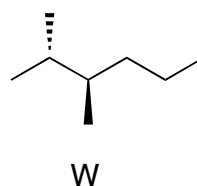
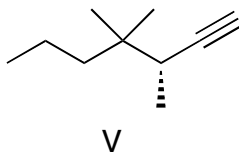
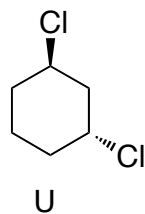
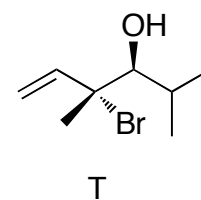
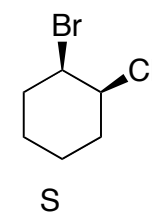
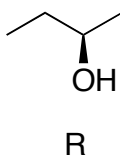
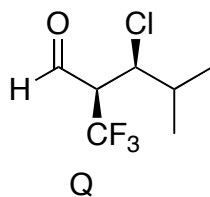
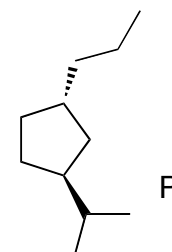
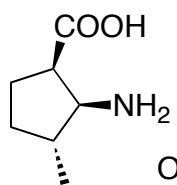
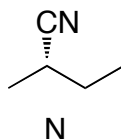
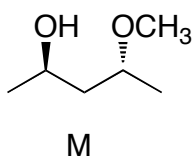
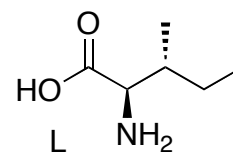
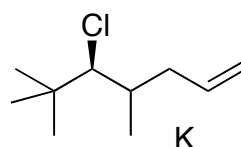
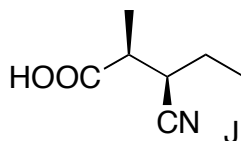
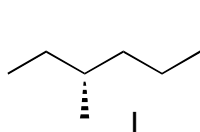
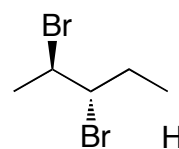
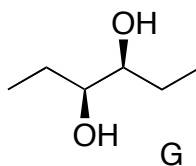
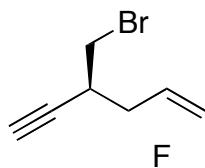
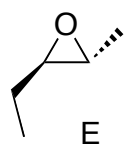
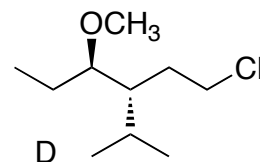
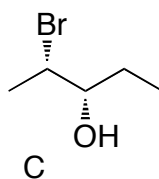
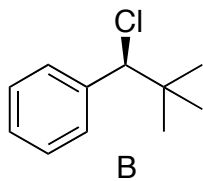
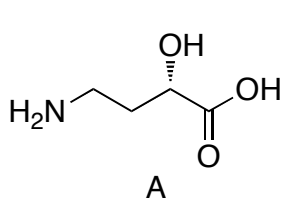
Compound D:



Compound E:



Practice R/S Assignments:



Practice R/S Assignments KEY:

