GLOBAL LEARNING ISSUE: STEREOCHEMISTRY
Stereochemistry "Problem Solving"

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This tutorial section is designed solely to introduce a method of "problem solving" involved with determining the stereochemical relationship between a pair of compounds. Additional tutorials have been provided to deal with other important aspects of stereochemistry. Also, prior to attempting to solve the problems in this review tutorial, you are advised to review your notes on stereochemistry from Principles of Drug Action I (PY450). The problems below test your understanding on key stereochemical concepts such as chirality, optical isomerism and enantiomers, diastereomers, geometric isomerism and conformational isomerism, etc.

When attempting to determine the stereochemical relationship between a pair of compounds the following method is recommended using the examples of compounds A and B shown below. For this method to work, you must follow the steps in order!

STEP ONE: Are the compounds positional (regio-) isomers. Is there a difference in the bonding arrangements? Do the compounds have similar functional groups but different positions of attachment on the molecular framework? IF NOT, GO TO STEP TWO!

Example: NO! Compounds A and B above have the same empiric formula, the same groups and the same bonding positions or "attachment" of functional groups. Both consist of cyclohexane rings with a hydroxyl and methyl attached to one carbon and an amino group and methyl group attached to the adjacent carbon. So go to step two.

STEP TWO: If they are not positional isomers, are these compounds geometric isomers? Do they contain a site of hindered bond rotation such as a C=C or cyclic system AND are the atoms (carbons) at this site unsymmetrically substituted? If such a system is present, assign the stereochemistry as "cis" or "trans" or "E" or "Z". IF NOT, GO TO THE THIRD STEP!

Example: Compounds A and B above consist of a cyclic system (restricted bond rotation) AND two of the carbon atoms of this system are unsymmetrically substituted. Thus geometric isomerism is possible!
For these two compounds to be geometric isomers, one must have the "E" configuration, and the other the "Z" configuration. Configuration can be assigned by identifying the highest priority group on EACH unsymmetrically substituted carbon atom and determining the relative spatial relationship of those groups within compound. For example, in compound A the OH group is a higher priority than the CH₃ on one carbon, and the NH₂ group is a higher priority than the CH₃ on the other carbon. Since the highest priority groups on each unsymmetrically substituted ring carbon project upward from the average plane of the cyclohexane ring, thus compound A is the "Z" or "cis-like" isomer. Similar priority assignments can be for compound B. When this is done it is observed that the highest priority groups on each unsymmetrically substituted ring carbon project in opposite directions from the average plane of the cyclohexane ring (one up, one down). Thus compound B is the "E" isomer:

Since the compounds in the example above were geometric isomers, you stop here with this example. If they were not you would proceed to step three.

**STEP THREE:** Are these compounds optical isomers? If they are not positional isomers or geometric isomers AND contain an asymmetric ("chiral") center (sp³ hybridized carbon) they may be optical isomers (enantiomers). If such a system is present, assign the absolute configuration of each enantiomer as R or S. **IF NOT, GO TO STEP FOUR!**
Example: Compounds A and B of this example were already determined to be geometric isomers, therefore THEY CANNOT BE ENANTIOMERS! See additional problems below for possible enantiomers.

**STEP FOUR:** Are these compounds conformational isomers ("confomers" or "rotamers"). If they are not positional, geometric or optical isomers AND they differ only in the spatial orientation of atoms-functional groups as a result of rotation about sp$^3$ hybridized carbons atoms, they may be conformers. If conformational isomerism is present, assign the conformers as "eclipsed", "gauche" or "anti". If you have arrived at this point and the compounds are not positional, geometric, optical or conformation isomers, you have probably made a mistake! Go back to step one and start over.

Example: Compounds A and B of this example were already determined to be geometric isomers, therefore THEY CANNOT BE CONFORMERS! See additional problems below for possible conformers.

**Sample Problems:** Apply the method above in attempting to determine the stereochemical relationship between the following pairs of compounds:

![Problem 1](image1)

![Problem 2](image2)

![Problem 3](image3)

![Problem 4](image4)
**Positional, Configurational (Geometric & Optical) and Conformational Isomers**

**Positional Isomers:**
Same atoms/groups but in a different relative bonding arrangement: Different properties in all environments!

**Geometric Isomers:**
Same atoms/groups in the same relative bonding arrangement, but restricted rotation with asymmetric Cs Different properties in all environments!

**Optical Isomers (Enantiomers):**
Same atoms/groups in the same relative bonding arrangement, but chiral sp³ with different configurations Different properties in chiral environments!

**Conformational Isomers:**
Same atoms/groups in the same relative bonding arrangement, same geometry and chiral configuration, but different rotational forms. Different rotational forms of the same compound!