



STEREOCHEMISTRY II

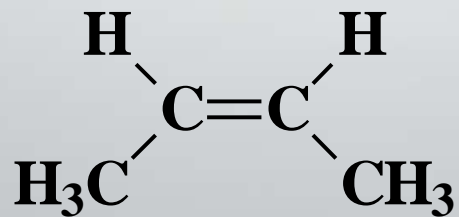
Department of Pharmaceutical Chemistry

Dr. Husam Hamza

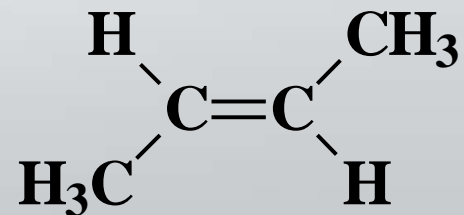
Diastereomers

Stereoisomers that are not mirror images of each other are called diastereomers

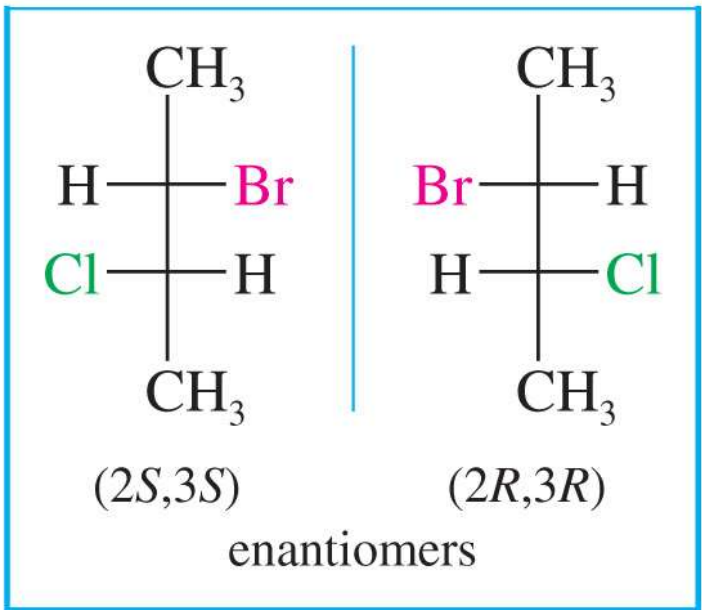
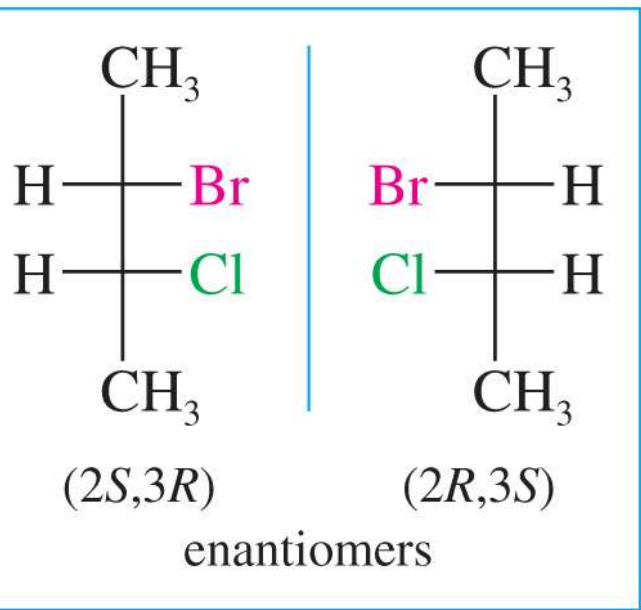
- Stereoisomers that are **not** mirror images.
- Molecules with 2 or more chiral carbons.
- Geometric isomers (*cis-trans*), since they are **not mirror images**.



cis-2-butene



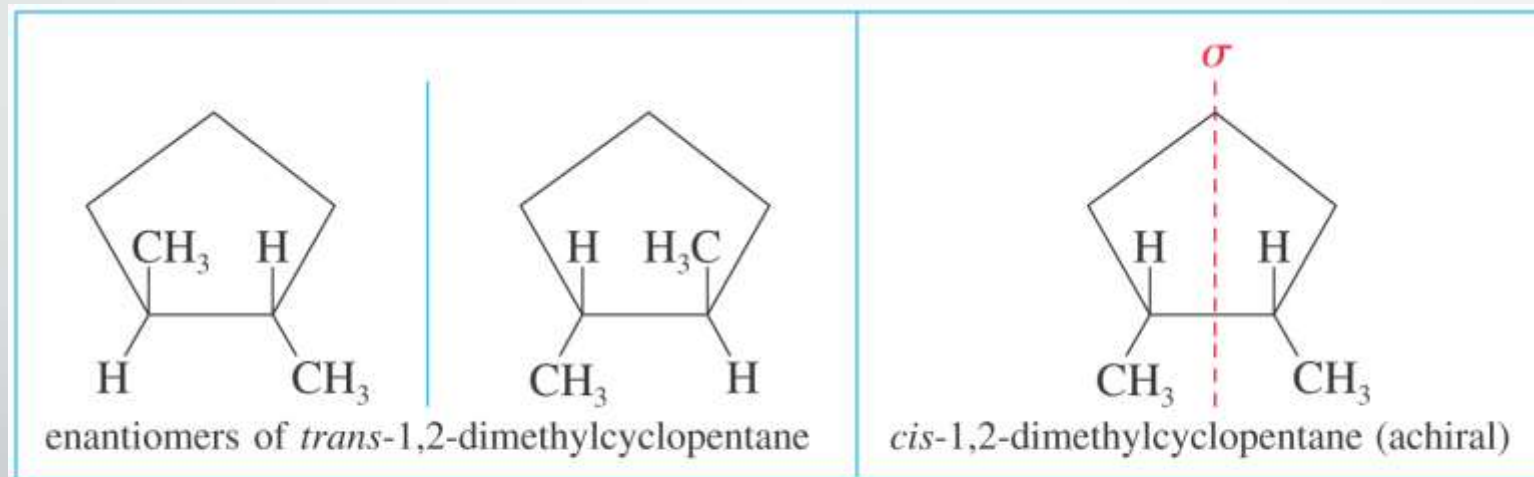
trans-2-butene



diastereomers

Ring Compounds

- **Cis-trans** isomers possible.
- May also have enantiomers.
- Example: *trans*-1,2-dimethylcyclopentane



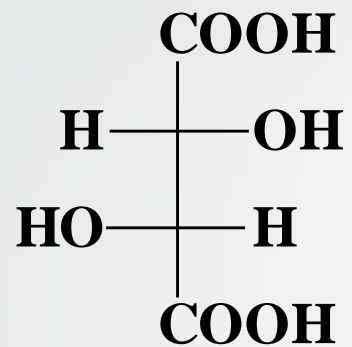
diastereomers

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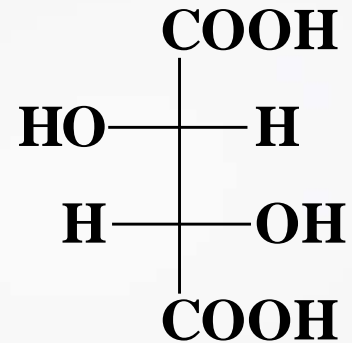
Two or More Chiral Carbons

- Enantiomer? Diastereomer? Meso? Assign (*R*) or (*S*) to each chiral carbon.
- Enantiomers have opposite configurations at each corresponding chiral carbon.
- Diastereomers have some matching, some opposite configurations.
- Meso compounds have internal mirror plane.
- Maximum number is 2^n , where n = the number of chiral carbons.

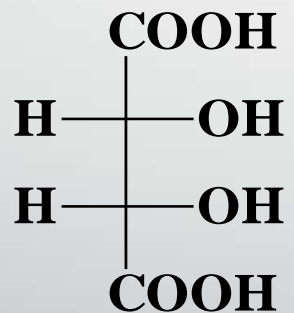
Examples



(2*R*,3*R*)-tartaric acid



(2*S*,3*S*)-tartaric acid

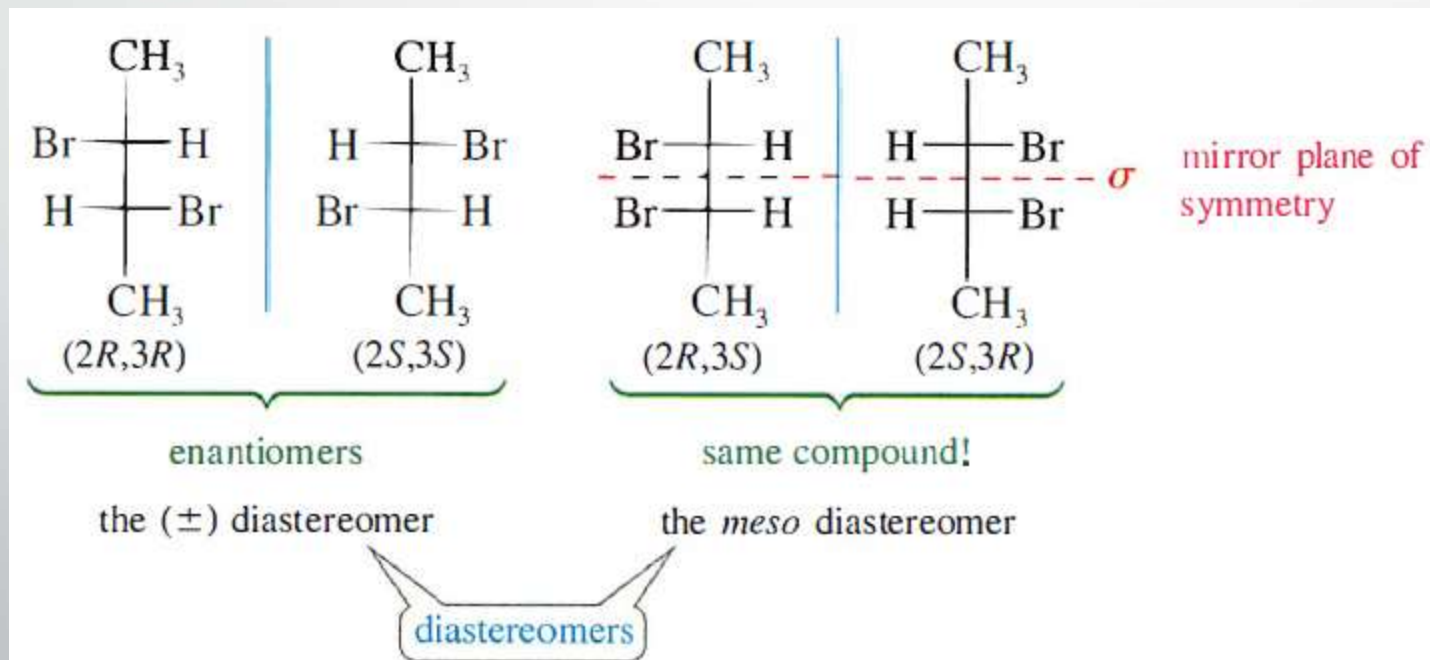


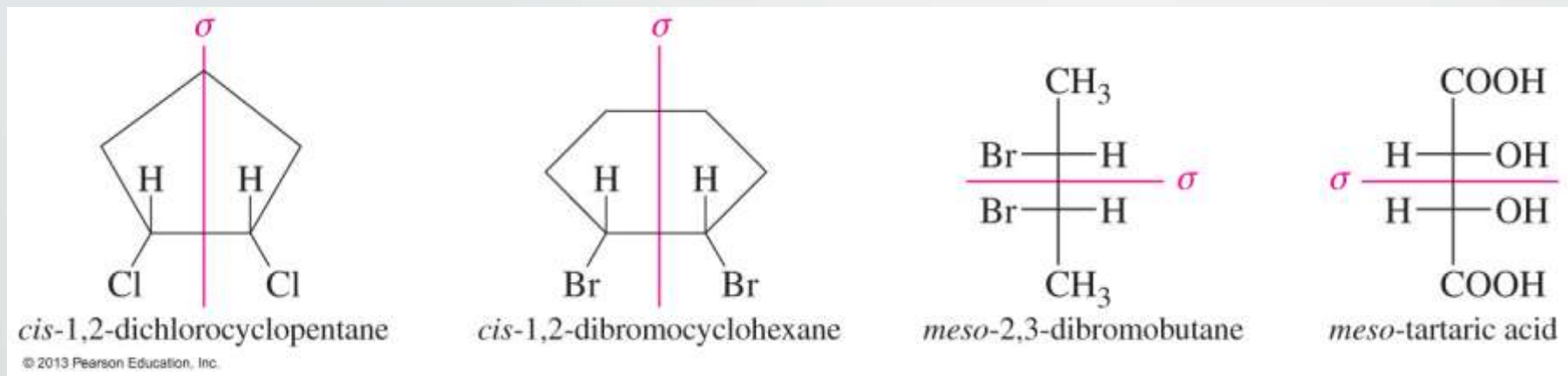
(2*R*,3*S*)-tartaric acid

A meso compound, contains 2 or more stereocenters and a plane of symmetry

Meso Compounds

- Meso compounds have a plane of symmetry.
- If one image was rotated 180°, then it could be superimposed on the other image.
- Meso compounds are achiral even though they have chiral centers.

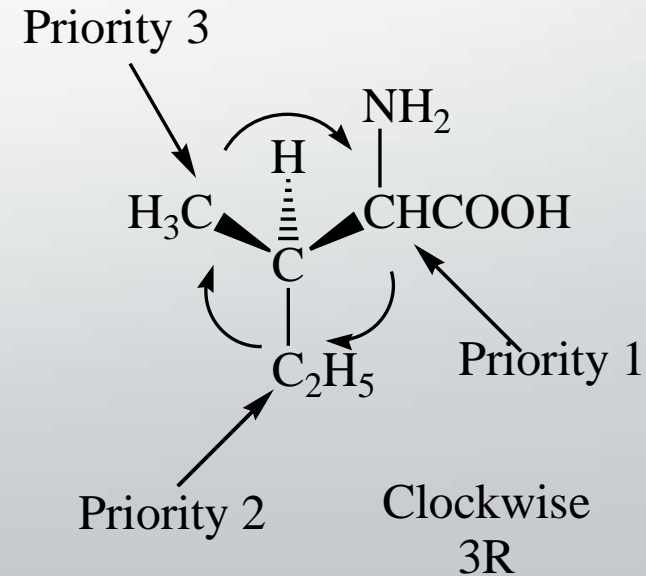
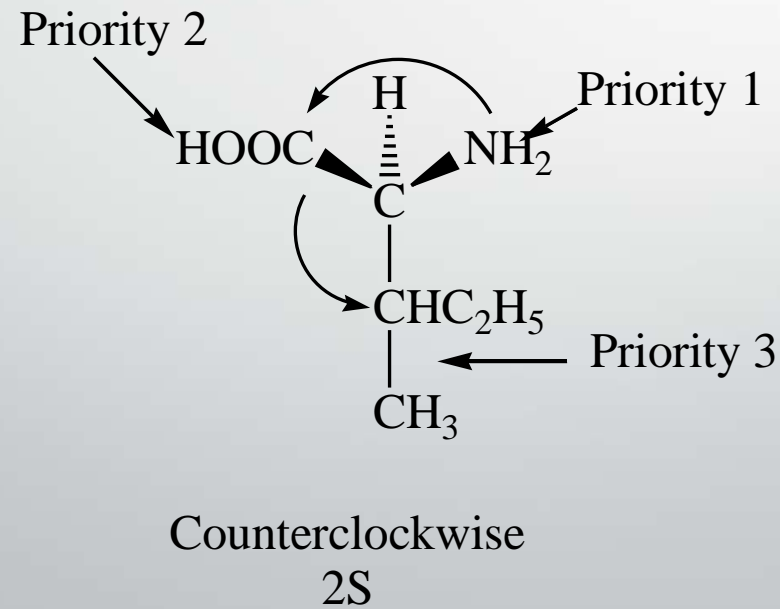
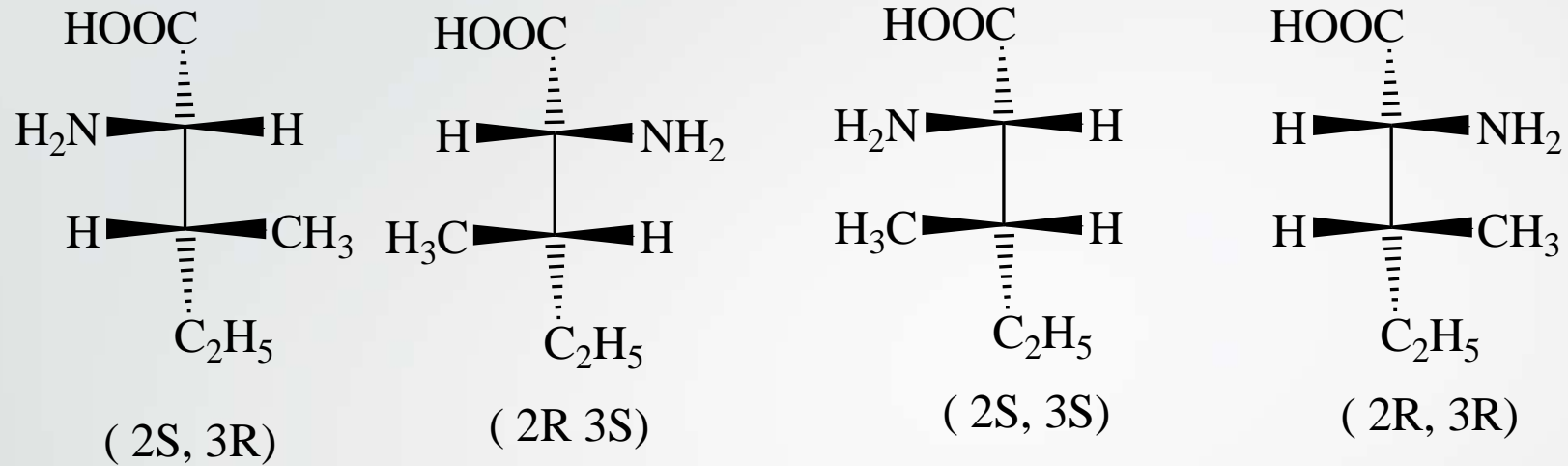


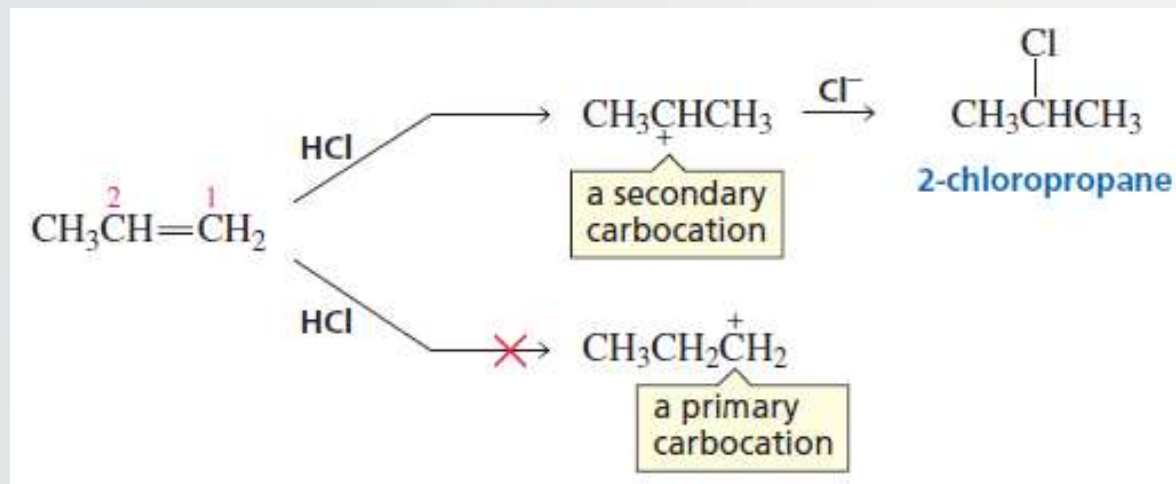


Properties of Diastereomers

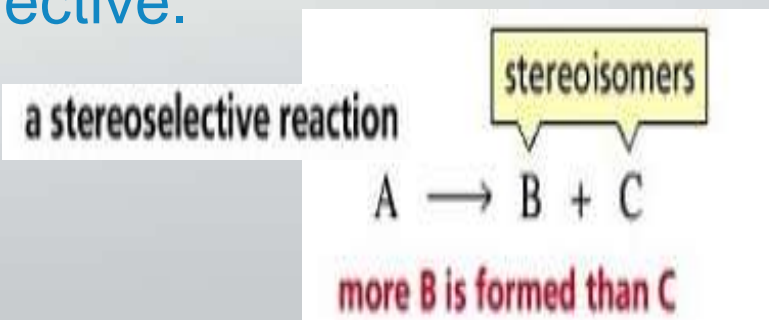
- **Diastereomers** have **different physical properties**, so they can be **easily separated**.
- Enantiomers differ only in reaction with other chiral molecules and the direction in which polarized light is rotated.
- **Enantiomers are difficult to separate**.
- Convert enantiomers into diastereomers to be able to separate them.

Specification of configuration: more than one chiral center



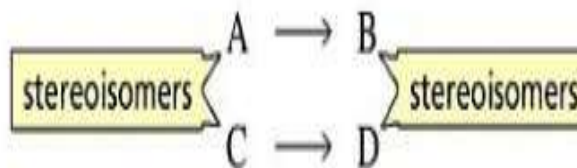


Stereoselective is a similar term, but it refers to the preferential formation of a stereoisomer rather than a constitutional isomer. , it selects for a particular stereoisomer. Depending on the degree of preference for a particular stereoisomer, a reaction can be described as being moderately stereoselective, highly stereoselective, or completely stereoselective.

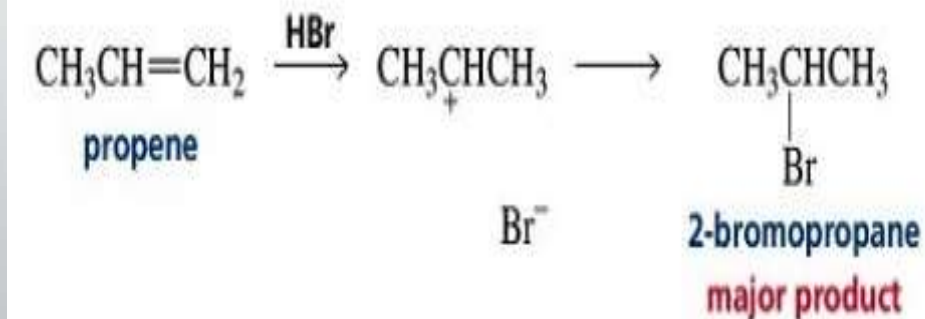


A reaction is **stereospecific** if the reactant can exist as stereoisomers and each stereoisomeric reactant leads to a different stereoisomeric product or a different set of stereoisomeric products. stereoisomer A forms stereoisomer B but does not form D, so the reaction is stereoselective in addition to being stereospecific.

stereospecific reactions



Stereochemistry of Electrophilic Addition Reactions of Alkenes

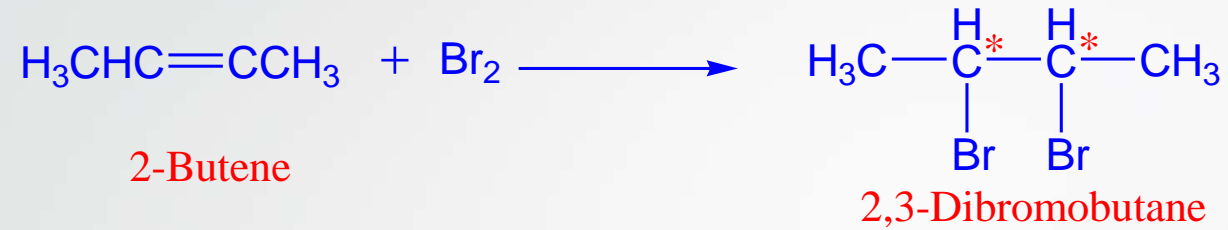


Stereoselective and Stereospecific Reactions

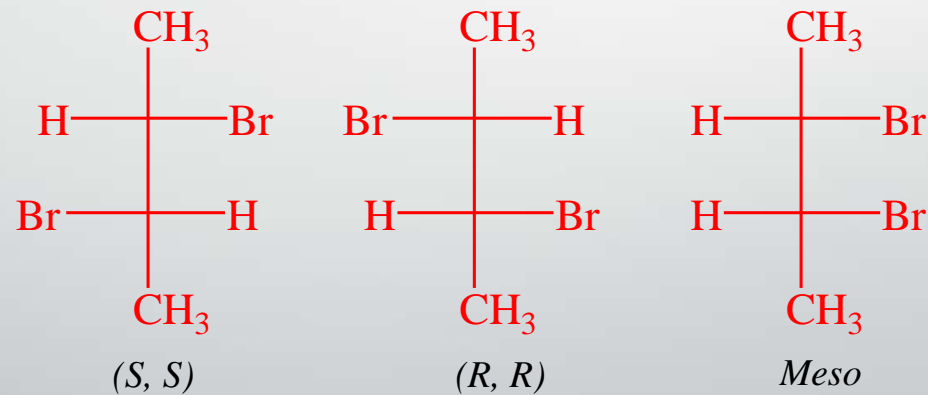
- Stereochemistry can give us a three-dimensional picture of a reaction: the direction of attack; the shape of transition state.
- Reactivity in the **S_N2** reaction is largely determined by crowding about pentavalent carbon in the **transition state**. And stereochemistry can often give, indirectly, other **information** as well: the timing of bond-breaking and bond-making; the nature of an intermediate.
- The **S_N2** reaction proceeds with **complete inversion of configuration**, this not only shows that attack is not from the back side, but is strong evidence that reaction involves a single step, with concerted bond-making and bond-breaking

Stereochemistry of addition of halogens to alkenes. Syn- and anti-addition

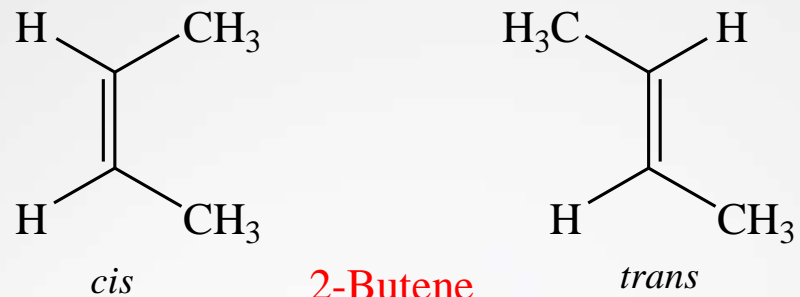
➤ Addition of bromine to 2-butene yields 2,3-dibromobutane



➤ Two chiral centers are generated in the reaction, and the product can exist as a pair of enantiomers (I and II) and a meso compound (III).

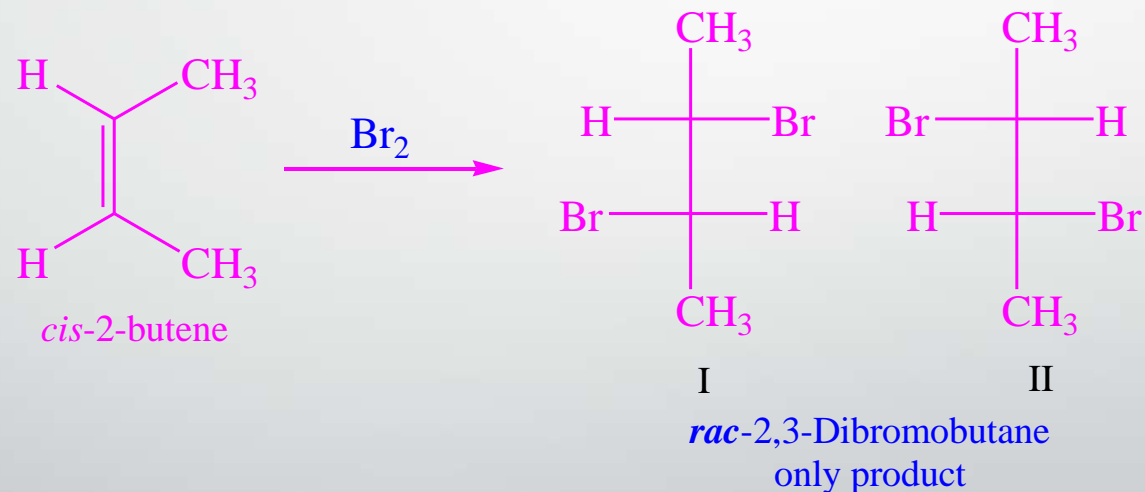


❖ The reactant, too, exists as diastereoisomers: a pair of geometric isomers, *cis* and *trans*.



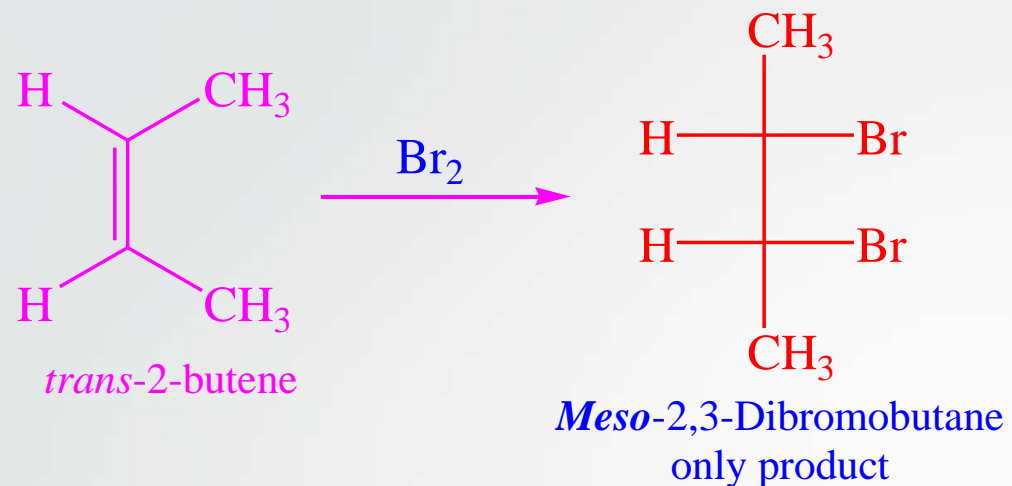
❖ If we start with *cis*-2-butene

➤ A mixture of all of them? *cis*-2-Butene yields only racemic 2,3-dibromobutane; I plus II none of the *meso* compound is obtained.



➤ A reaction that yields predominantly one stereoisomer (or one pair of enantiomers) of several diastereomeric possibilities is called a **Stereoselective reaction**.

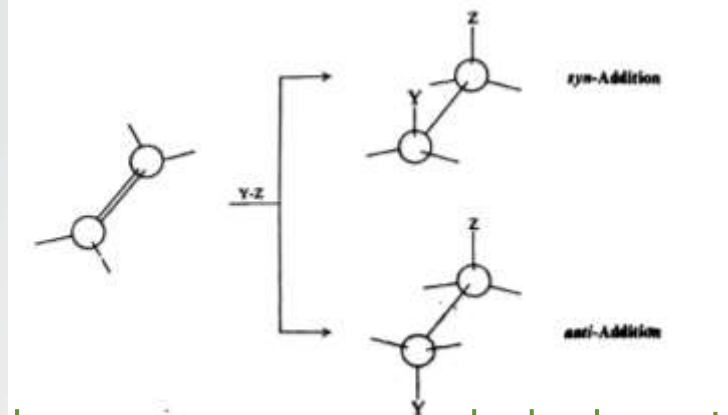
❖ If we start with *trans*-2-butene



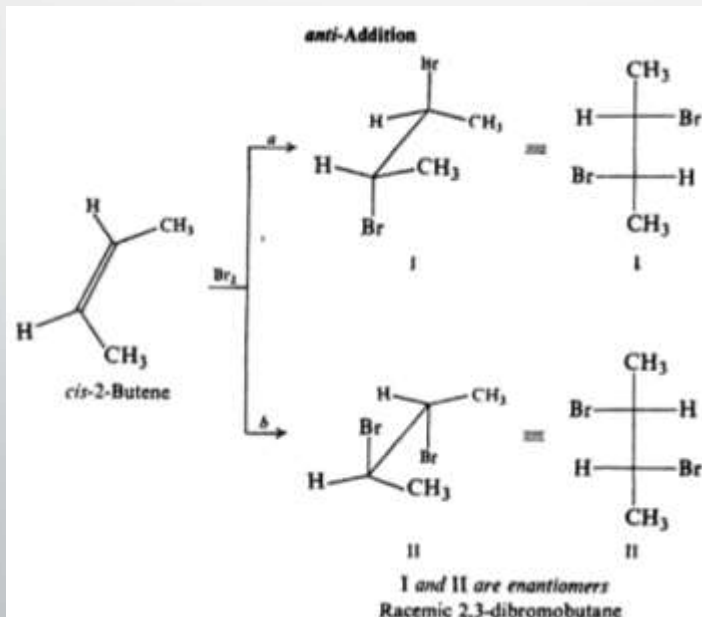
❖ A reaction in which stereochemically different reactants give stereochemically different products is called **a stereospecific reaction**.

➤ Addition of bromine to alkenes is both **stereoselective and stereospecific**. We say it is **completely stereoselective** since, from a given alkene, we obtain only one diastereomer (or one pair of enantiomers). We say it is **stereospecific**, since stereoisomeric alkenes react differently: they give (stereochemically) different products

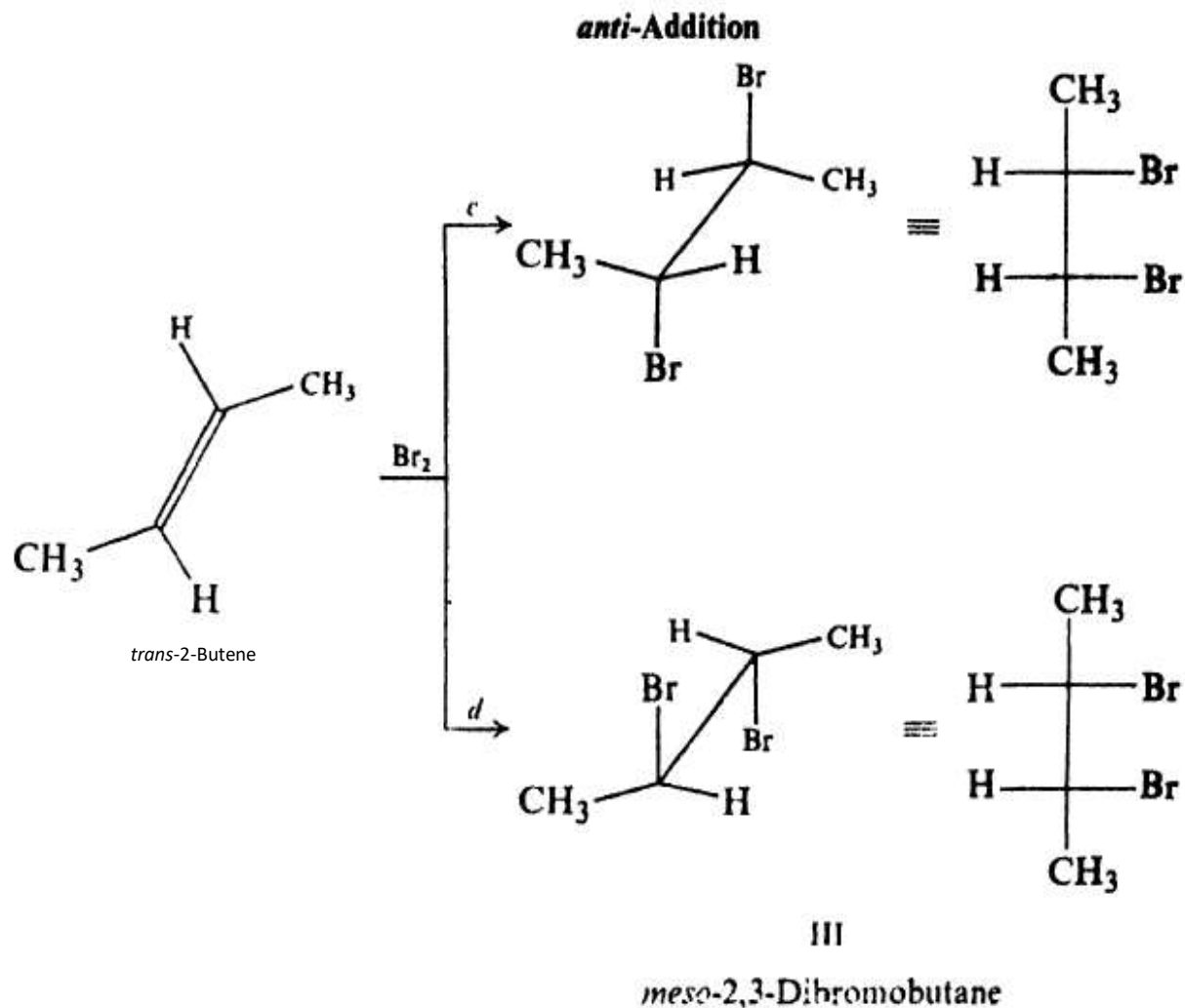
To describe the kind of stereochemistry possible in addition reactions, the concepts of *syn*-addition and *anti*-addition are used.



➤ If we start with *cis*-2-butene, we can attach the bromine atoms to opposite faces of the double bond in two different ways. Attachment as in (a) gives enantiomer I; attachment as in (b) gives enantiomer II. Since, whatever the mechanism, (a) and (b) are equally likely, we obtain the racemic modification.

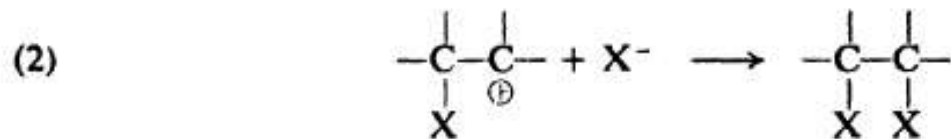
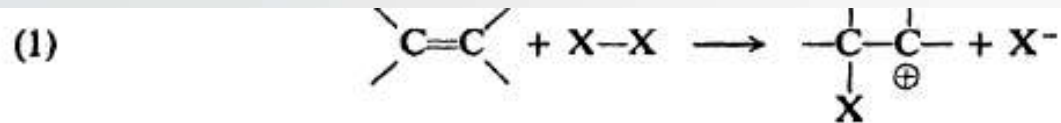


❖ Starting with *trans*-2-butene we can again attach the bromine atoms to opposite faces of the double bond in two ways: as in (c) and (d). Whichever way we choose, we obtain III, which we recognize as the **meso** dibromide.

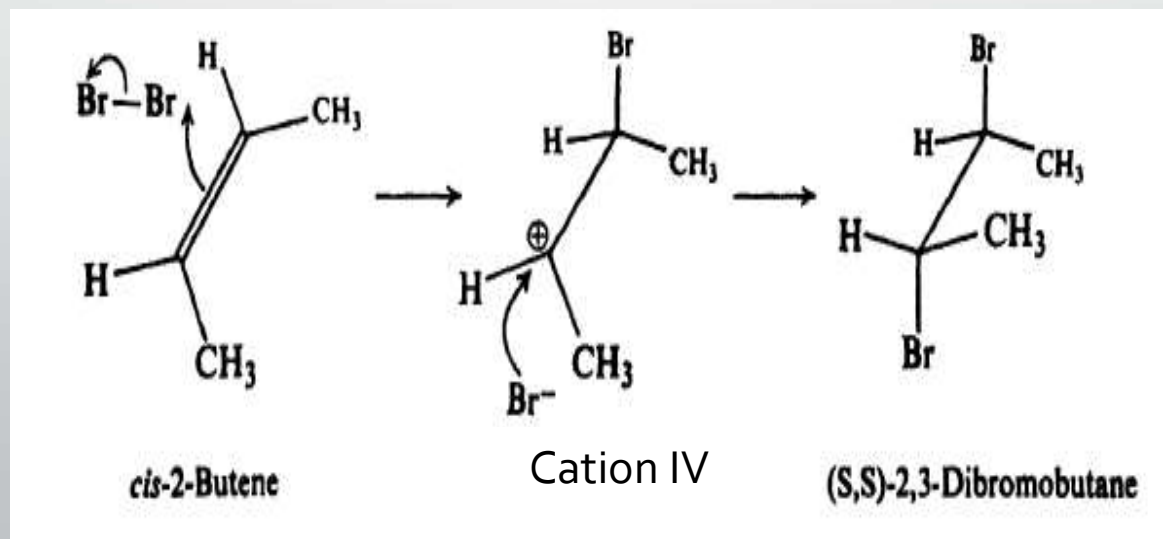


Mechanism of halogen addition to alkene

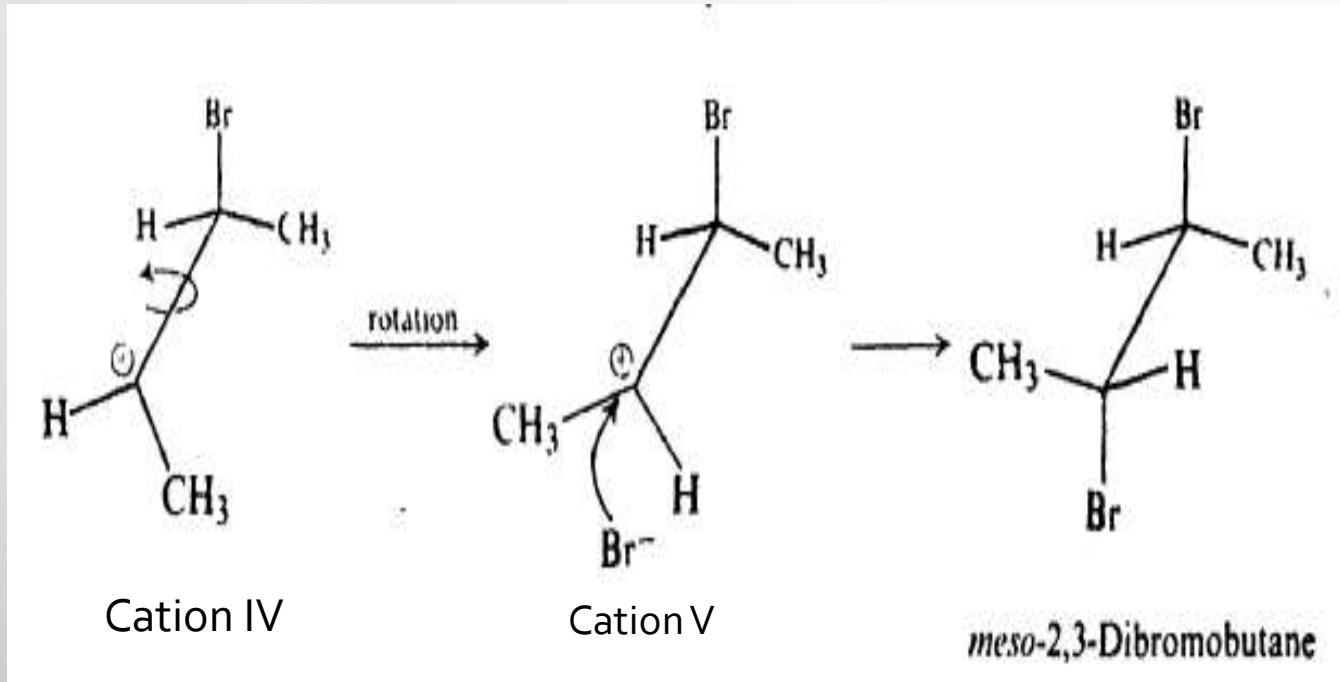
➤ Assume first that reaction proceeds via an open carbocation



Let us use addition of bromine to *cis*-2-butene as an example. A positive bromine ion is transferred to, say, the top face of the alkene to form the carbonium ion I. Then, a bromide ion attacks the *bottom* face of the positively

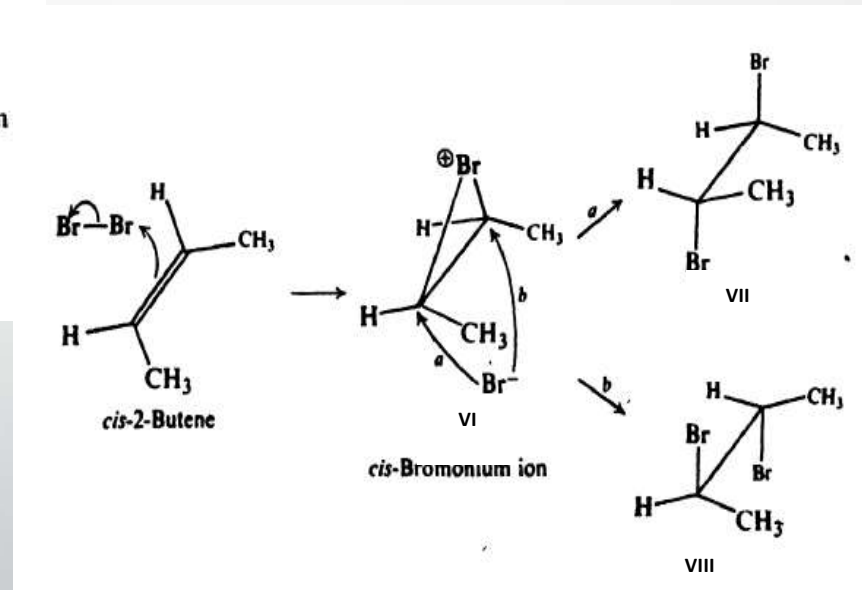
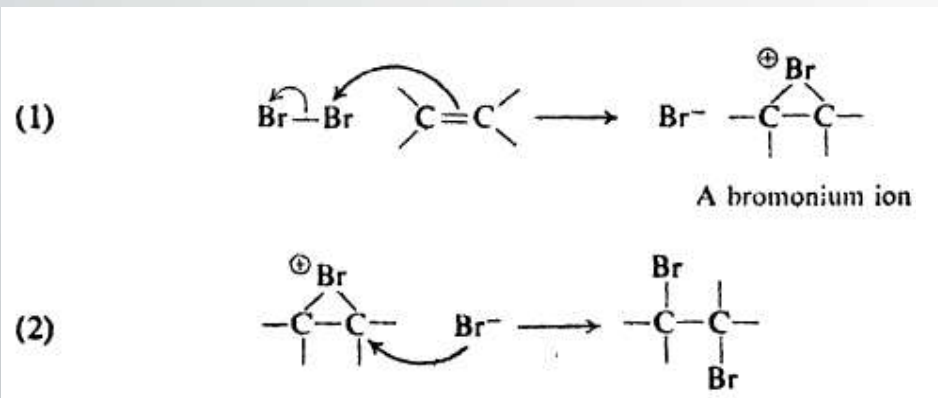


➤ If we accept this exclusively bottom-side attack, we are faced with a second problem. Rotation about the carbon-carbon bond would convert cation IV into cation V; bottom-side attack on cation V would yield not the racemic dibromide but the *meso* dibromide in effect *syn*-addition, and contrary to fact.



❖ To accommodate the stereochemical facts

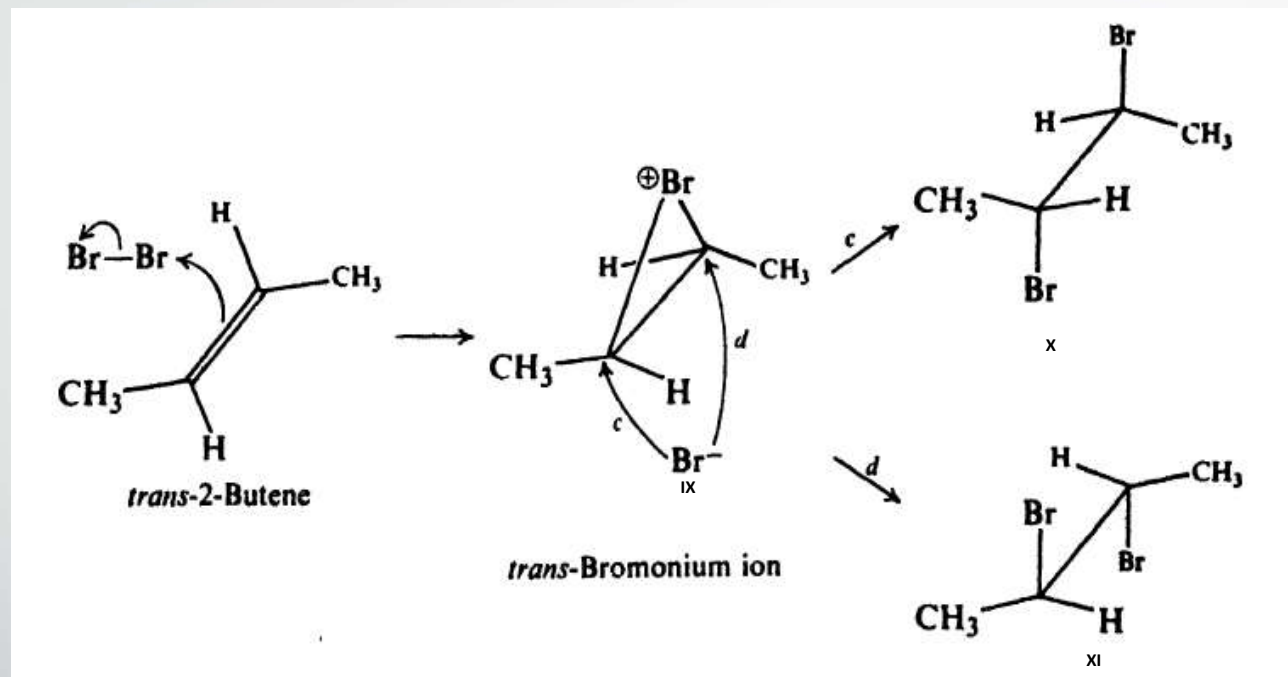
➤ after the carbonium ion is formed, it is attacked by bromide ion (a) before rotation about the single bond can occur, and (b) exclusively from the side away from the halogen already in the cation. Neither of these assumptions is very likely; together, they make the idea of a simple carbonium ion intermediate hard to accept.



VII and VIII are enantiomers

rac-2,3-dibromobutane

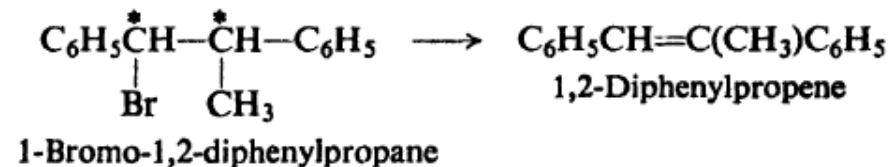
➤ let us carry through the same operation on trans-2-butene. This time, bromonium ion IX is formed. Attack on it by path (c) yields X, attack by (d) yields XI. If we simply rotate either X or XI about the carbon-carbon bond, we readily recognize the symmetry of the compound. It is *meso*-2,3-dibromobutane; X and XI are identical.



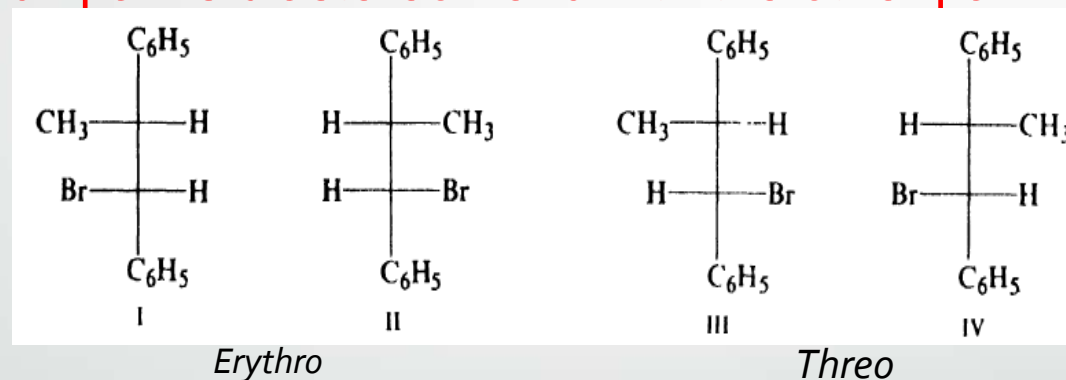
*X and XI are the same
meso*-2,3-Dibromobutane

Stereochemistry of the E2 reaction. *syn*- and *anti*-Elimination

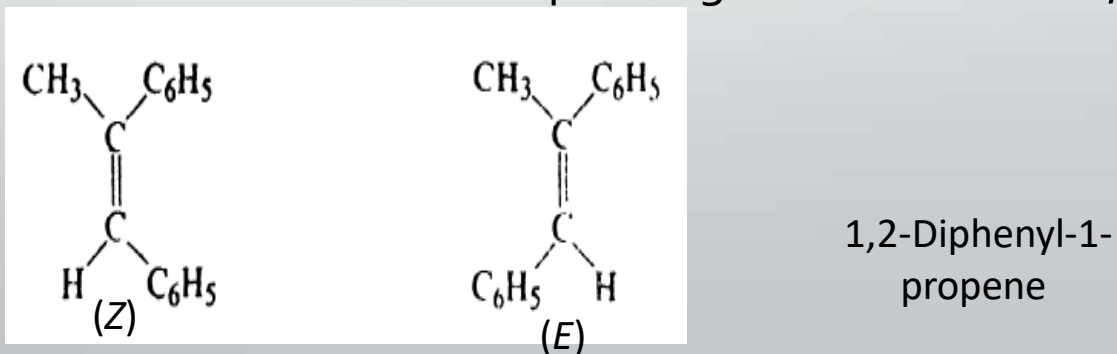
➤ Consider dehydrohalogenation of the alkyl halide 1-bromo-1,2-diphenylpropane. This compound contains two chiral



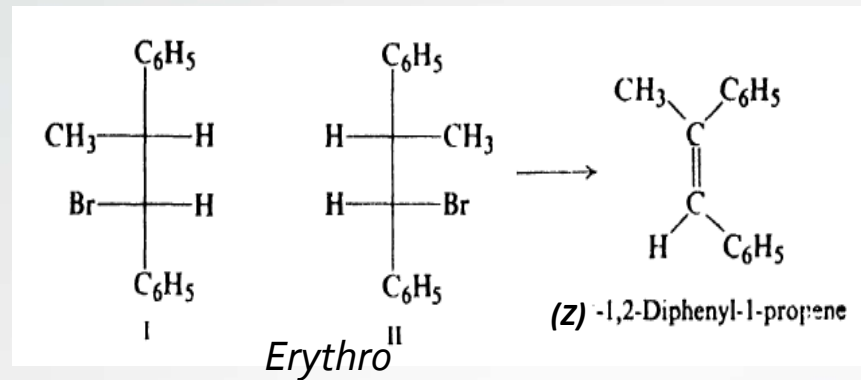
➤ It can exist as two pairs of enantiomers: I and II; called *erythro*; and III and IV, called *threo*. Each pair is diastereomeric with the other pair



✓ The product, too, exists as stereoisomers: a pair of geometric isomers, *Z* and *E*.

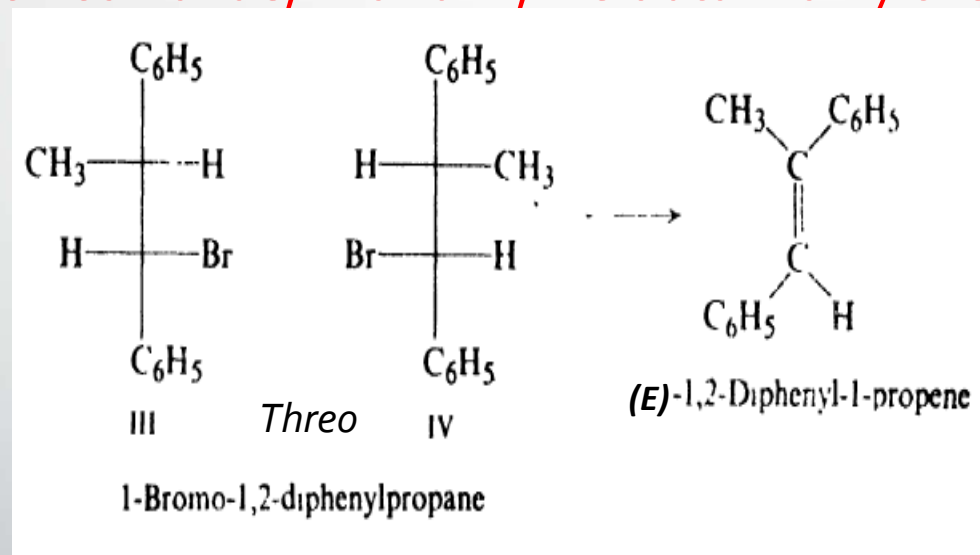


➤ If we start with the *erythro* halide, I and II, we obtain *only* the *Z* alkene.



1-Bromo-1,2-diphenylpropane

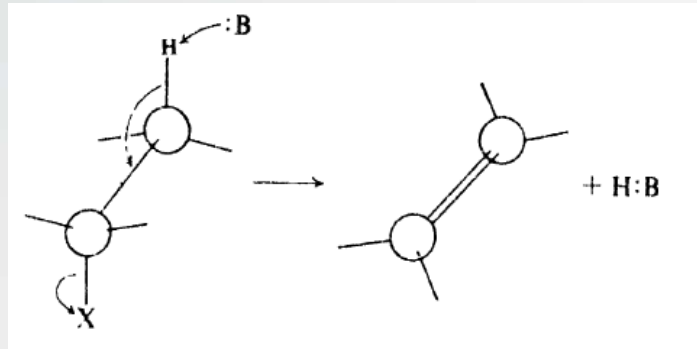
➤ If we start with the *threo* halide, III and IV, we obtain *only* the *E* alkene



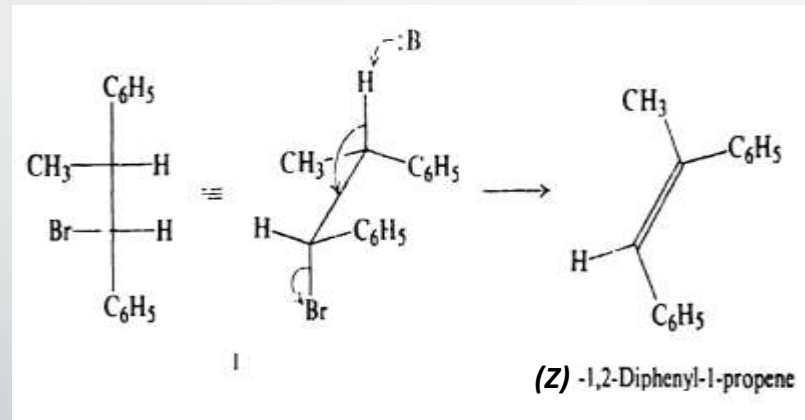
1-Bromo-1,2-diphenylpropane

➤ *E2* elimination is both **stereoselective** and **stereospecific**.

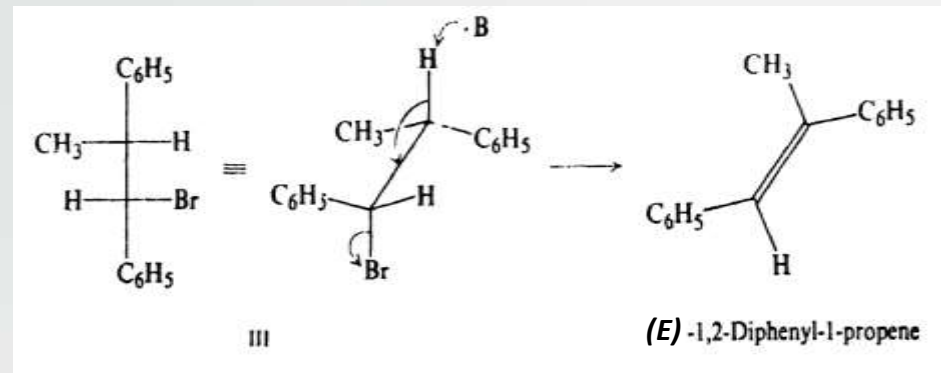
➤ E2 elimination typically involves *anti*-elimination: in the transition state the hydrogen and the leaving group are located in the *anti* relationship



➤ diastereomer I (or its enantiomer, II) gives the *Z* alkene:



- diastereomer III (or its enantiomer, IV) gives the *E* alkene:



Stereospecific reactions

❖ stereospecific reaction as one in which stereochemically different molecules react differently.

➤ Stereospecificity toward enantiomers is called **enantiospecificity**

Stereoselectivity vs Stereospecificity

➤ *Some reactions are stereoselective but not stereospecific: one particular stereoisomer is the predominant product regardless of the stereochemistry of the reactant, or regardless of whether the reactant even exists as stereoisomers.*