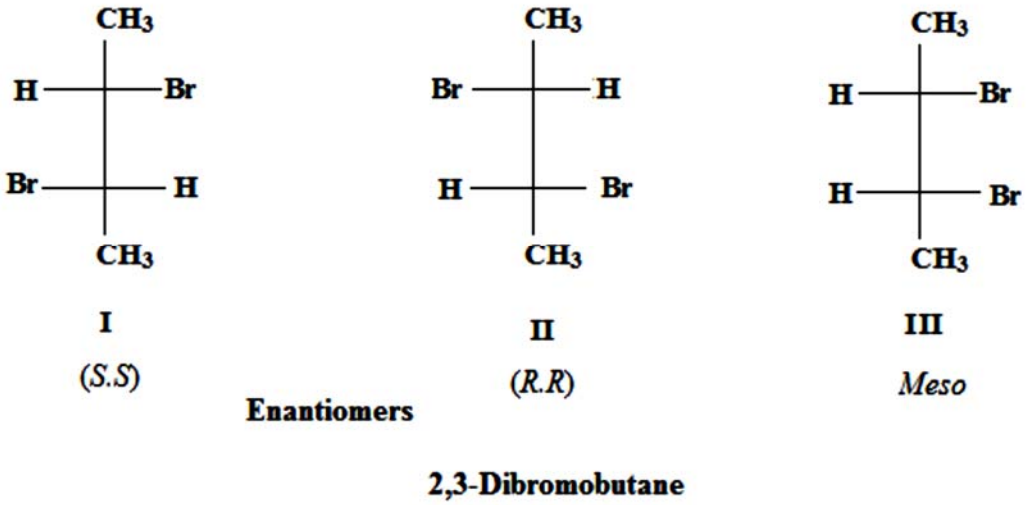
Stereochemistry II

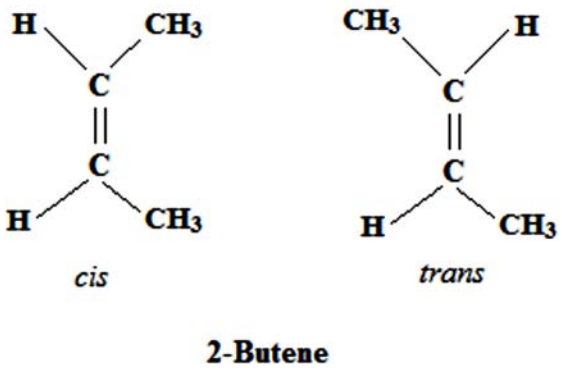
Stereochemistry of Addition of Halogens to alkenes. syn- and anti-Addition

Let us begin with the stereochemistry of *addition*, using as our example a familiar reaction: addition of halogens to alkenes. Addition of bromine to 2-butene yields 2,3-dibromobutane.

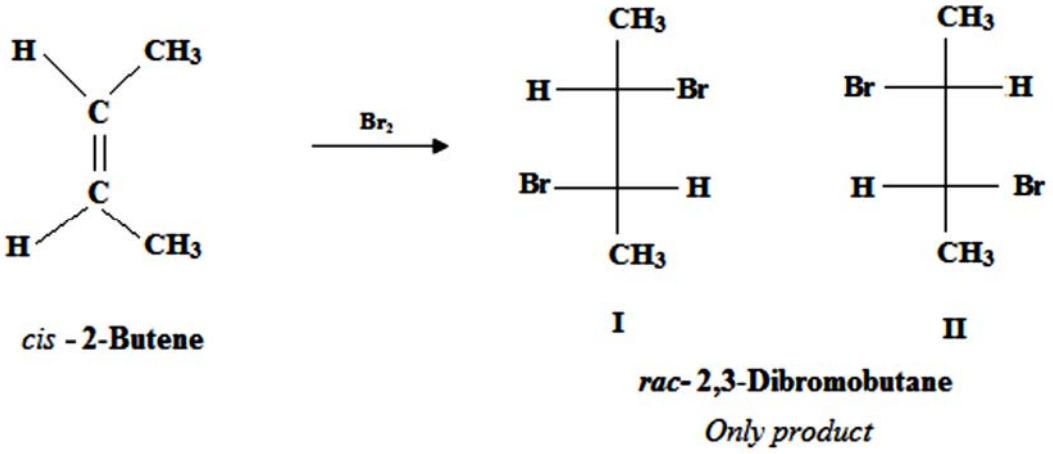
Two chiral centers are generated in the reaction, and the product, can exist as a pair of enantiomers (I and II) and a *meso* compound (III).



The reactants, too, exist as stereoisomers: a pair of geometric isomers, *cis* and *trans*.



If we start with, say, *cis*-2-butene, we get only racemic 2,3-dibromobutane, I and II.



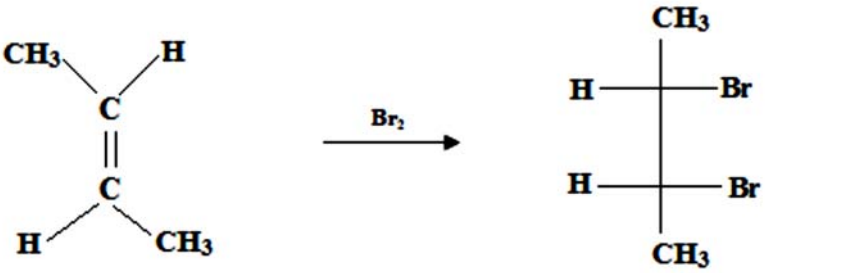
cis - **2-Butene**

***rac*- 2,3-Dibromobutane**

Only product

A reaction that yields predominantly one stereoisomer (or one pair of enantiomers) of several possible diastereomers is called a **stereoselective reaction.**

Now, suppose we start with *trans*-2-butene. Does this, too, yield the racemic dibromide? No. The *trans* alkene yield only *meso*-2,3-dibromobutane.



trans - **2-Butene**

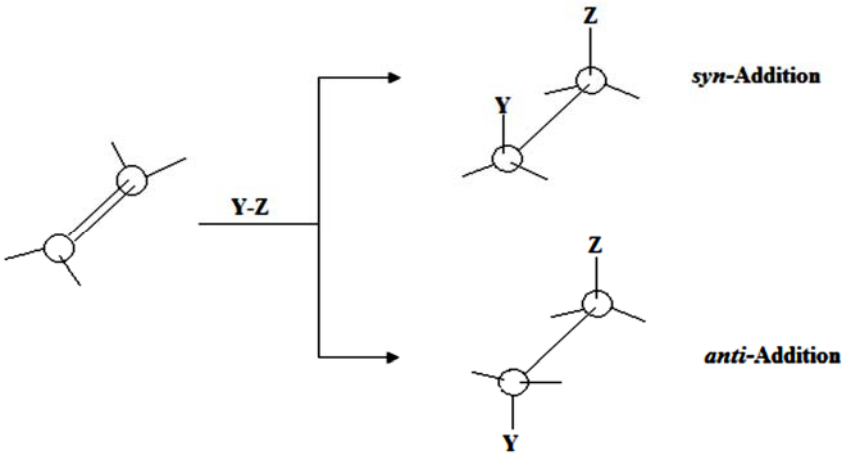
***meso* - 2,3-Dibromobutane**

Only product

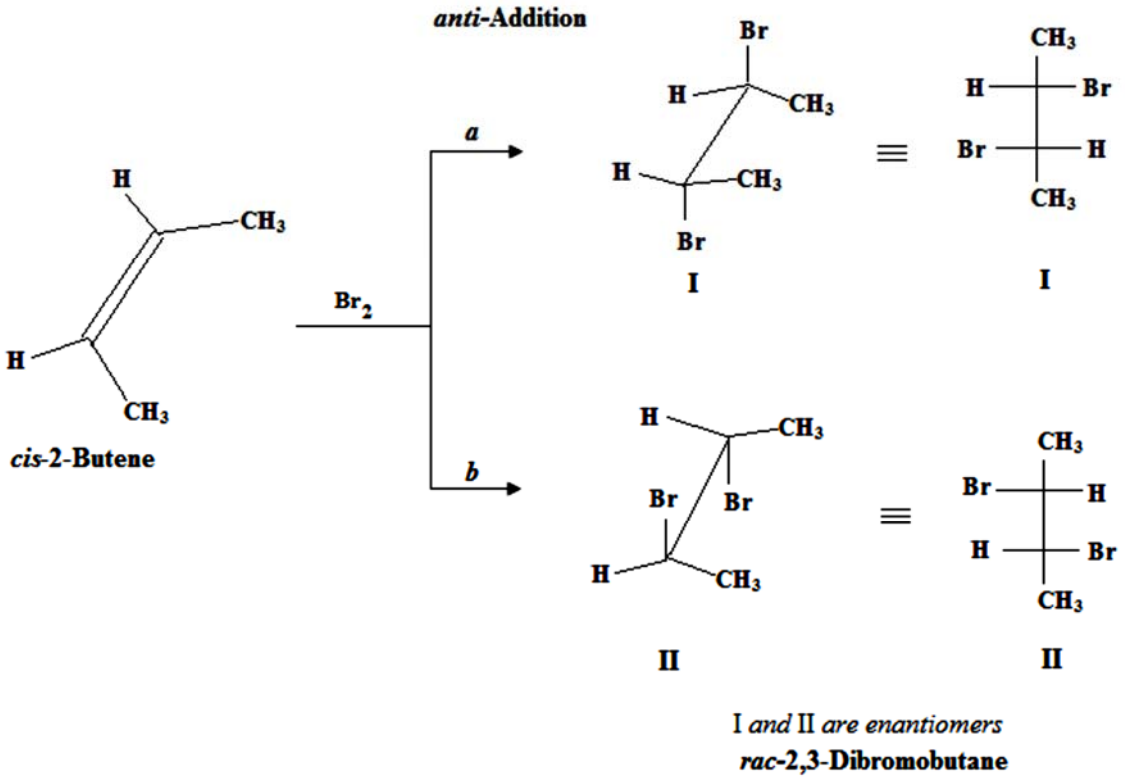
Just which product we obtain depends upon which stereoisomer we start with. *A reaction in which stereochemically different molecules react differently is called a* **stereospecific reaction**.

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 stereospecificity in addition reactions, the concept of ***syn***-addition and ***anti***-addition

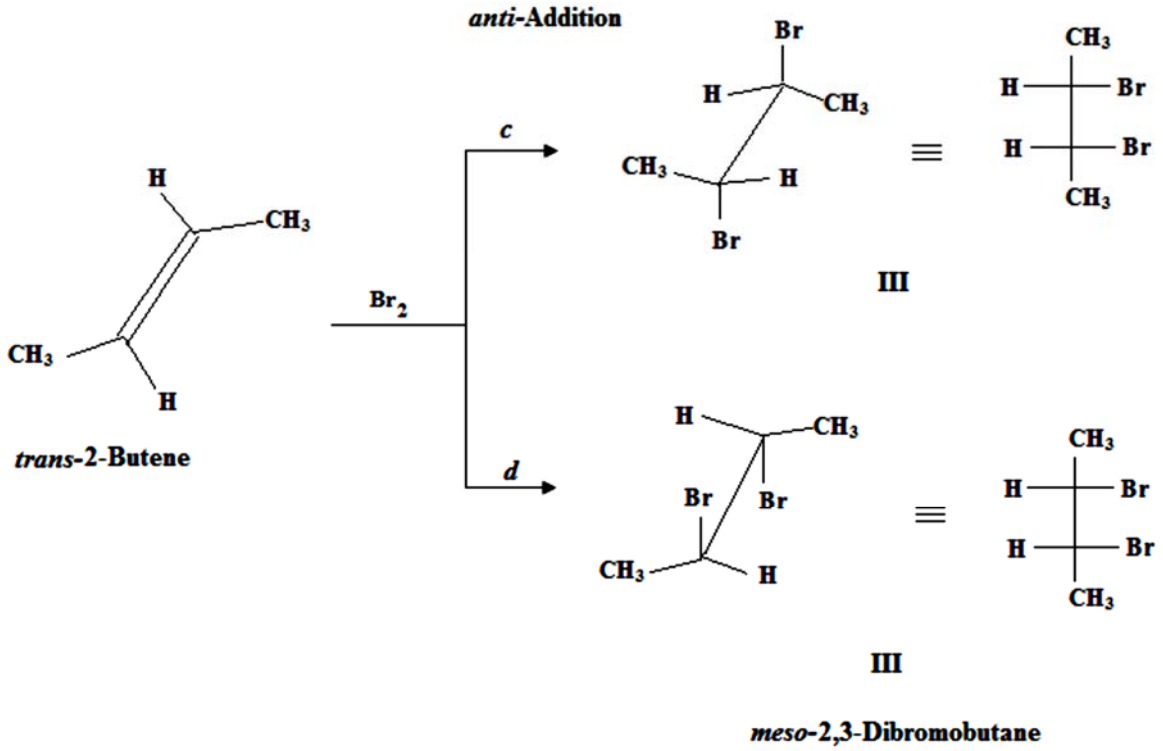
are used. These terms indicate the stereochemical fact: that the added groups become attached to the same face (***syn***) or to opposite face (***anti***) of the double bond.



Addition of bromine to the 2-butenes involves *anti*-addition. Let us see that this so. If we start with *cis*-2-butene, we can attach the bromines 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.



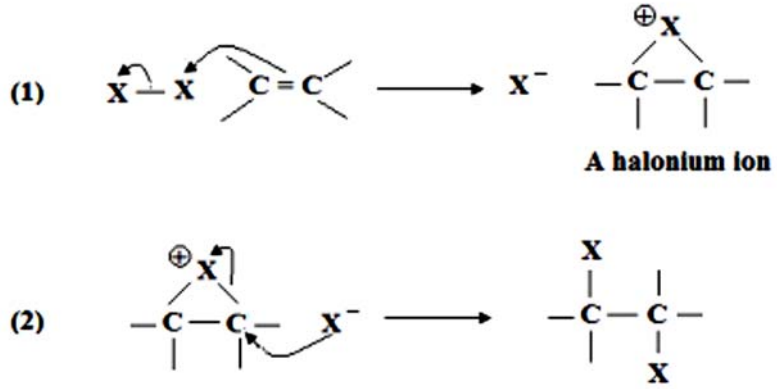
Starting with *trans*-2-butene, we can again attach the bromines to opposite faces of the double bond in two ways: as in (*c*) or in (*d*). Whichever way we choose, we obtain III, which we recognize as the *meso* dibromide.



Anti-Addition is the general rule for the reaction of bromine or chlorine with simple alkenes.

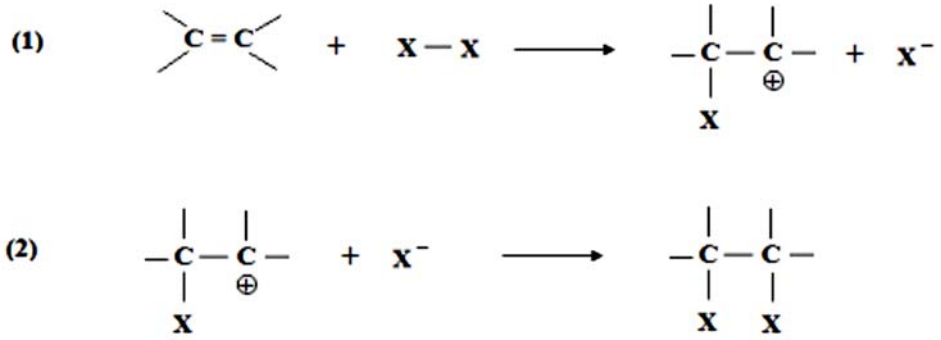
Mechanism of Addition of Halogens to Alkenes

We saw that the addition of halogens to alkenes proceed by two steps. In step (1) a halogen is transferred, without a pair of electrons, from a halogen molecule to the carbon-carbon double bond; there is formed a halide ion and organic cation. In step (2) this cation reacts with a halide ion to yield the addition product.

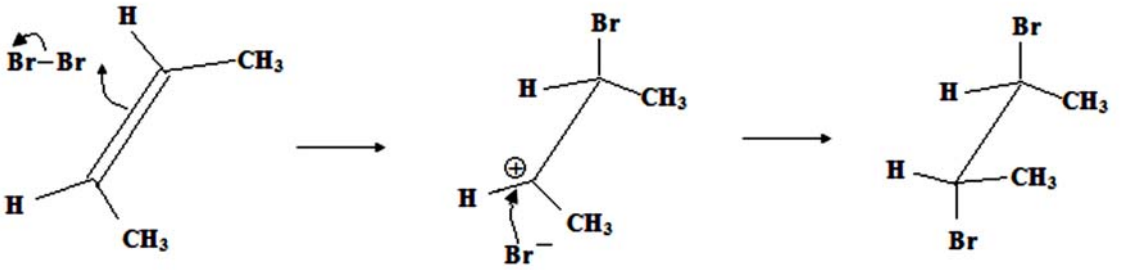


The nature of the intermediate cation that is our chief concern here, it is the halonium ion: a cyclic ion in which halogen is attached to both carbons and carries a positive charge.

Halogens add with complete stereoselectivity and in the anti-sense. What does this stereochemistry tell us about the nature of the intermediate? Assume first that reaction proceeds via an open carbocation.

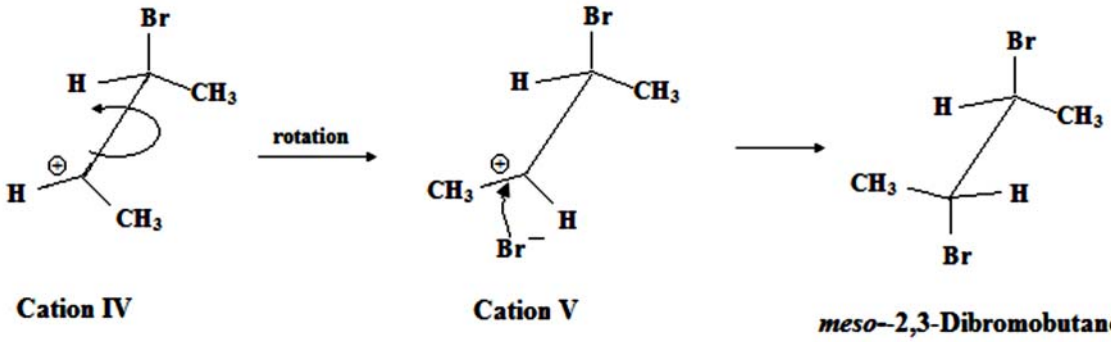


Is the observed stereochemistry consistent with a mechanism involving such an intermediate? Let us use addition of bromine to *cis*-2-butene as an example. A positive bromine ion is transferred to, the top face of the alkene to form carbocation IV. Then, a bromide ion attacks the bottom face of the positively charged carbon to complete the *anti*-addition; attack at this face preferred, we might say, because it permits the two bromines to be as far apart as possible in the transition state. (We obtain the racemic product: the *S,S*-dibromide as shown; the *R,R*-dibromide through attachment of positive bromine to the near end of the alkene molecule).



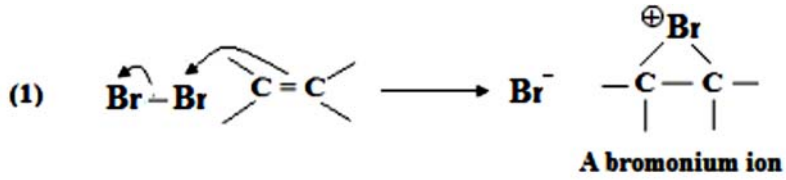
cis-2-Butene Cation IV (*S*,*S*)-2,3-Dibromobutane

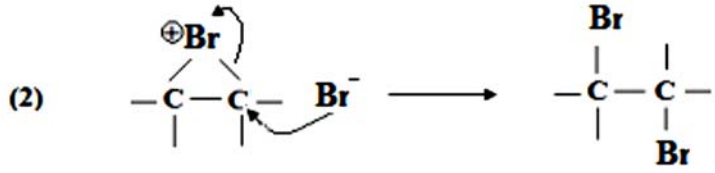
But this picture of the reaction is not satisfactory, and for two reasons. First, to account for the complete stereospecificity of addition, we must assume that attack at the bottom face of the cation is not just preferred, but is the only line of attack: conceivable, but especially in view of other reactions of carbocations not likely. Then, even 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.



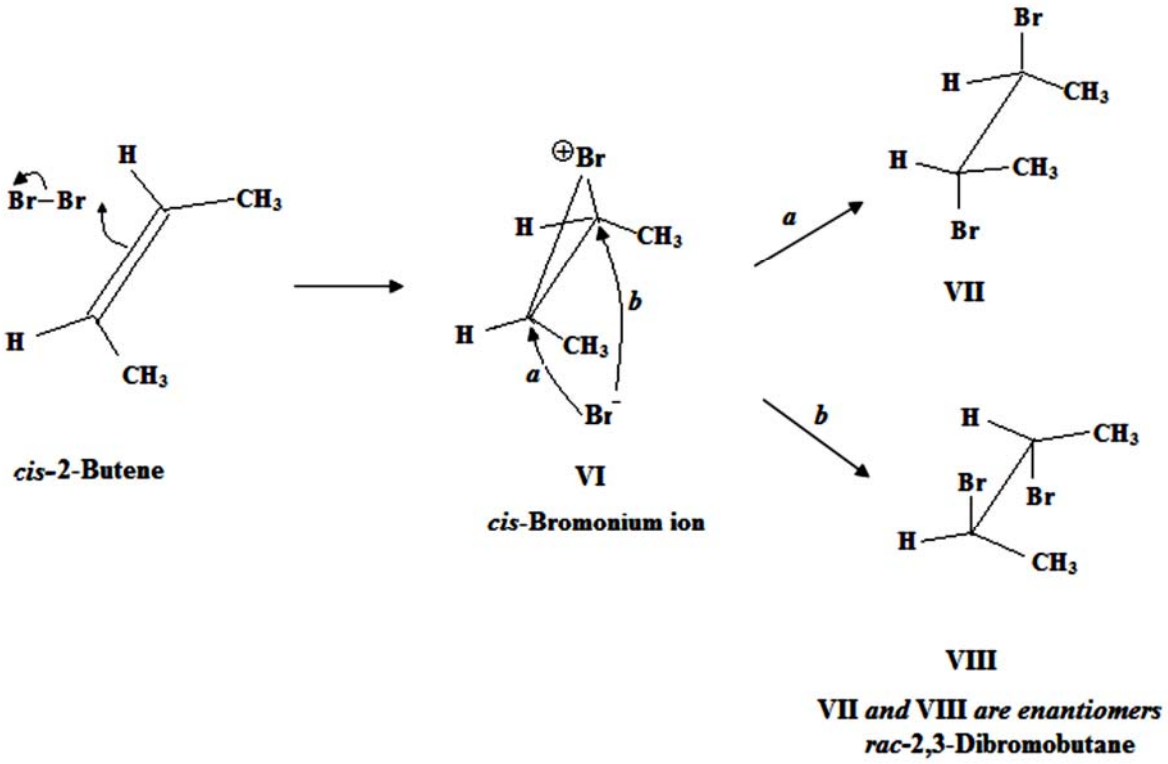
Cation IV Cation V *meso*–2,3-Dibromobutane

To accommodate the stereochemical facts, then, we would have to make two assumptions about halogen addition: after the carbocation is formed, it is attacked by bromide ion (*a*) before rotation about the single bond can occur, and (*b*) exclusively from the face away from the halogen already in the cation. Neither of these assumptions is very likely; together, they make the idea of an open carbocation intermediate hard to accept. It was to account better for the observed stereochemistry that proposed the bromonium ion mechanism that we have given.





Now, how does the bromonium ion mechanism account for *anti*-addition? Using models, let us first consider addition of bromine to *cis*-2-butene.

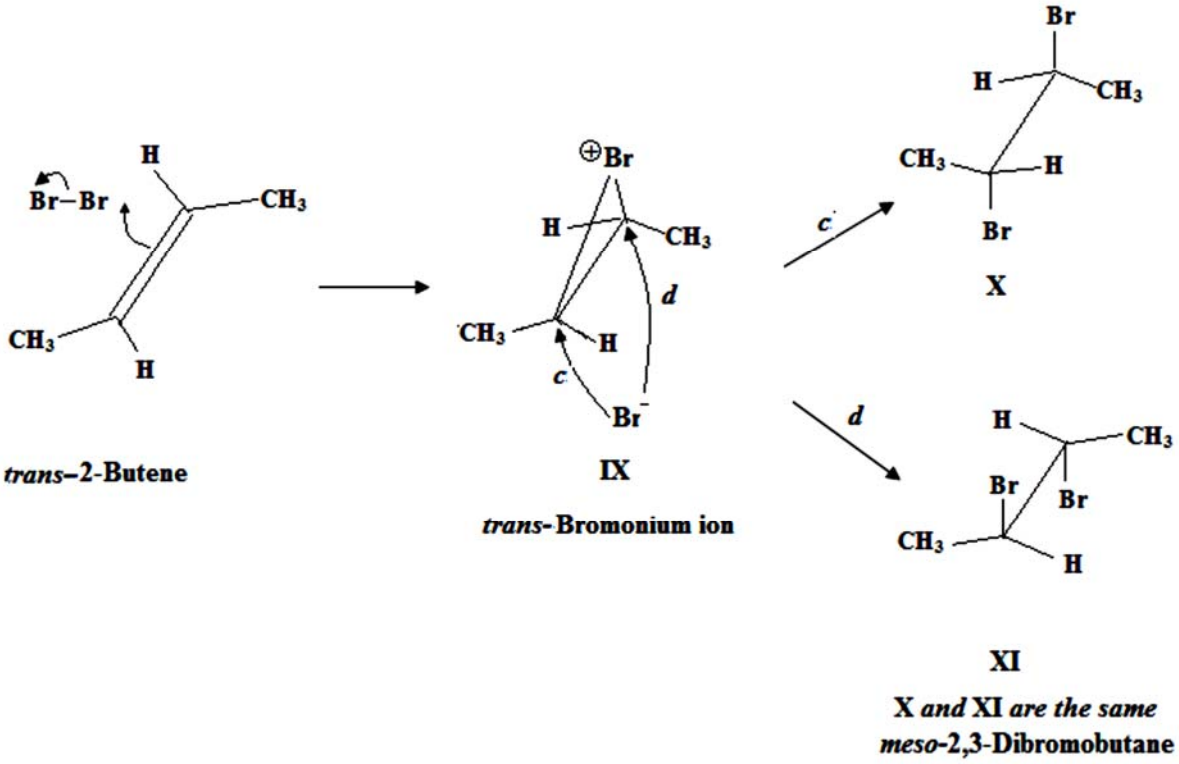


In the first step, positive bromine becomes attached to either the top or bottom face of the alkene. Let us see what we get if bromine becomes attached to the top face. When this happens, the carbon atom of the double bond tends to become tetrahedral, and the hydrogens and methyls are displaced downward. The methyl groups are still located across from each other, however, as they were in the alkene. In this way, bromonium ion VI is formed.

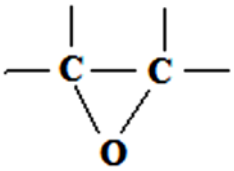
Now bromonium ion VI is attacked by bromide ion. A new carbon-bromine bond is formed, and an old carbon-bromine bond is broken. This is a familiar reaction, nucleophilic substitution; bromide ion is the nucleophile, and the positive bromine is the leaving group. As we might expect, then, attack by bromide ion is from the back side; on the bottom face of VI, so that the bond being formed is on the opposite side of carbon from the bond being broken. There is inversion of configuration about the carbon being attacked.

Attack on VI can occur by path (*a*) to yield structure VII or by path (*b*) to yield structure VIII. We recognize VII and VIII as enantiomers. Since attack by either (*a*) or (*b*) is equally likely, the enantiomers are formed in equal amounts, and thus we obtain the racemic modification. The same results are obtained if positive bromine initially becomes attached to the bottom face of *cis*-2-butene.

Now, 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. The same results are obtained if positive bromine is initially attached to the bottom face of *trans*-2-butene. The concept of a halonium ion solves both of the problems associated with an open carbocation: a halogen bridge prevents rotation about the carbon-carbon bond, and at the same time restricts attack by bromide ion exclusively to the opposite face of the intermediate. The stereochemistry of halogen addition thus not only gives powerful support for a two-step mechanism, but it shows, in a way no other evidence could, just what those two steps almost certainly are.

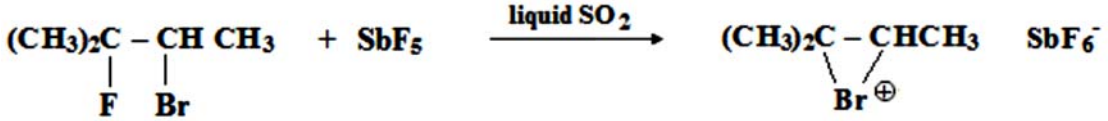


That such cyclic intermediates can give rise to *anti*-addition is demonstrated by hydroxylation with peroxy acids: there, analogous intermediates, perfectly respectable compounds called epoxides, can be isolated and studied.



An epoxide

Cyclic halonium ions were first proposed, then, simply as the most reasonable explanation for the observed stereochemistry. Since that time, however, more direct evidence has been discovered.



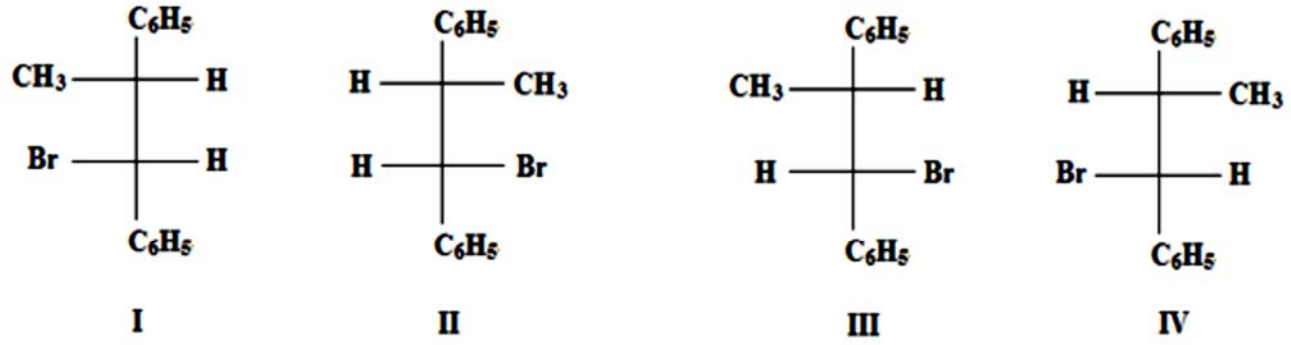
Stereochemistry of the E2 Reaction. Syn- and Anti-Elimination

Let us look at the stereochemistry of elimination, using as our example another familiar reaction: dehydrohalogenation under E2 conditions.

Consider dehydrohalogenation of the alkyl halide 1-bromo-1,2-diphenylpropane. (Phenyl, - C_6H_5, is an aromatic hydrocarbon group that is inert under these reaction conditions).

1-Bromo-1,2-diphenylpropane **1,2-Diphenylpropene**

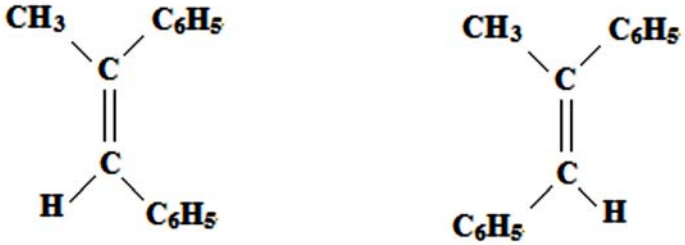
This compound contains two chiral centers, and we can easily show that it can exist as two pairs of enantiomers: I and II, called *erythro*; and III and IV, called *threo*. Each pair is diastereomeric with the other pair.



Erythro *Threo*

1-Bromo-1,2-diphenylpropane

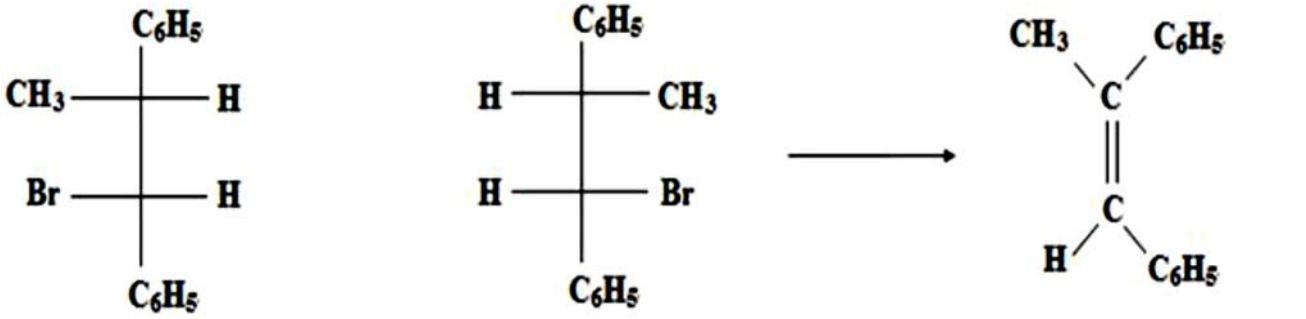
The product, too, exists as stereoisomers: a pair of geometric isomers, *Z* and *E*.



(*Z*) (*E*)

1,2-Diphenyl-1-propene

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

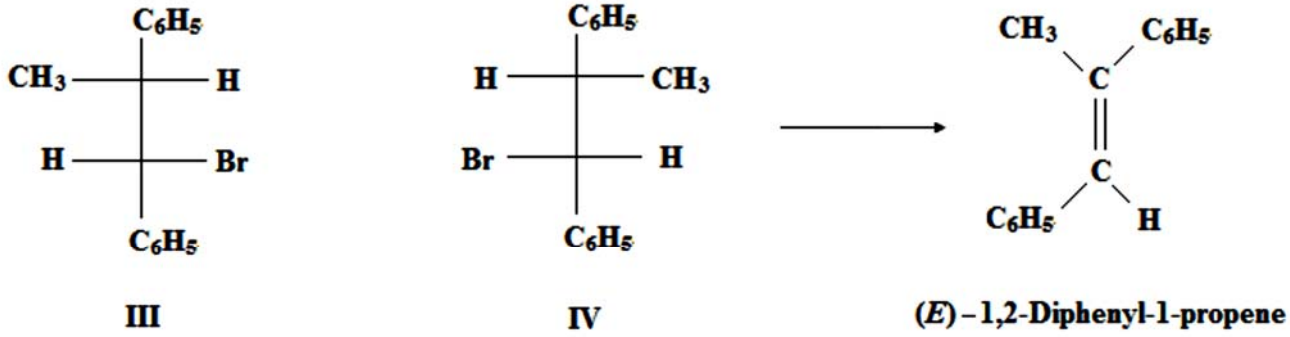


I **II** **(*Z*)–1,2-Diphenyl-1-propene**

Erythro

1-Bromo-1,2-diphenylpropane

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



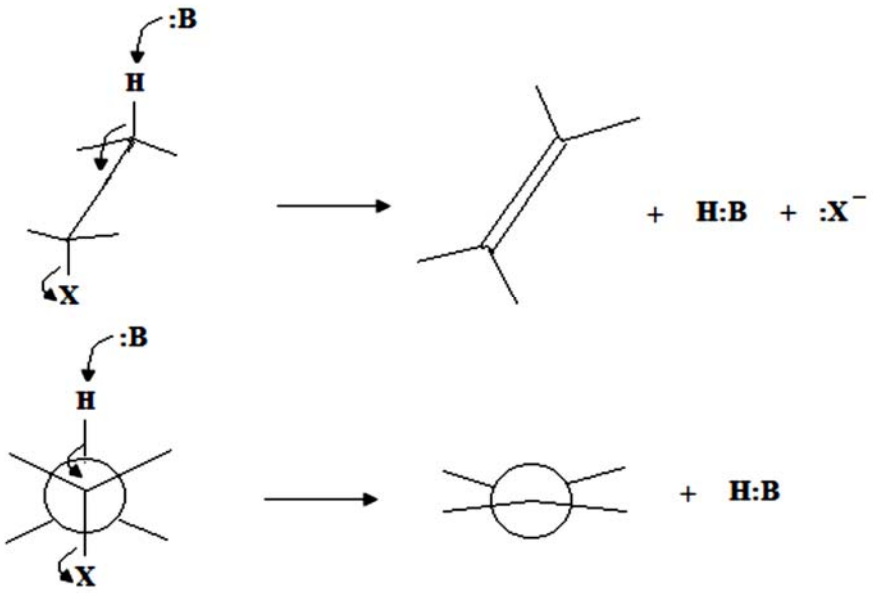
III **IV** **(*E*)–1,2-Diphenyl-1-propene**

Threo

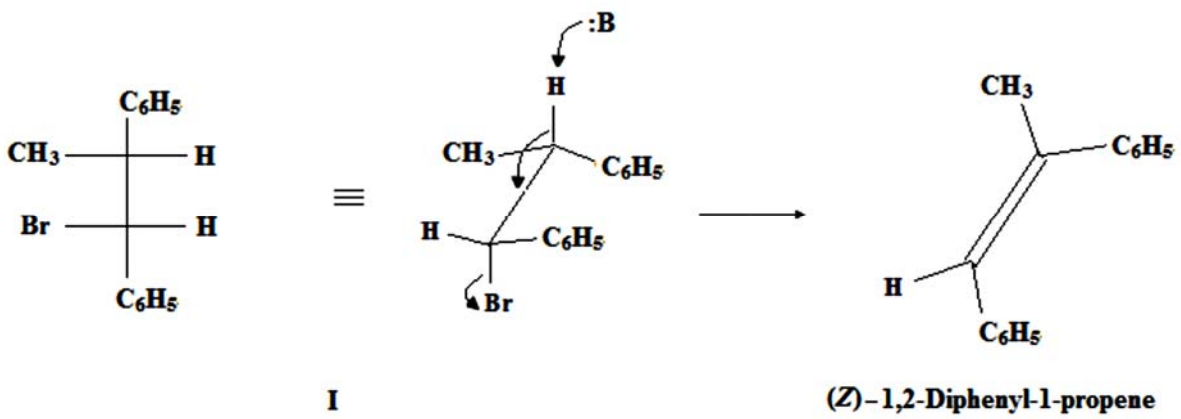
1-Bromo-1,2-diphenylpropane

Other studies have shown that these results are typical: *E2 elimination is both stereoselective and stereospecific.* To describe the kinds of stereoselectivity that may be observed in elimination reactions, the concept of ***syn**-elimination* and ***anti**-*elimination are used. These terms are not the names of specific mechanisms. They simply indicate the stereochemical facts: that the eliminated groups are lost from the same face (***syn***) or opposite face (***anti***) of the developing double bond.

As this example and many others show, E2 elimination typically involves *anti*-elimination: in the transition state the hydrogen and the leaving group are located in the *anti*-relationship as contrasted to *gauche* or *eclipsed*.

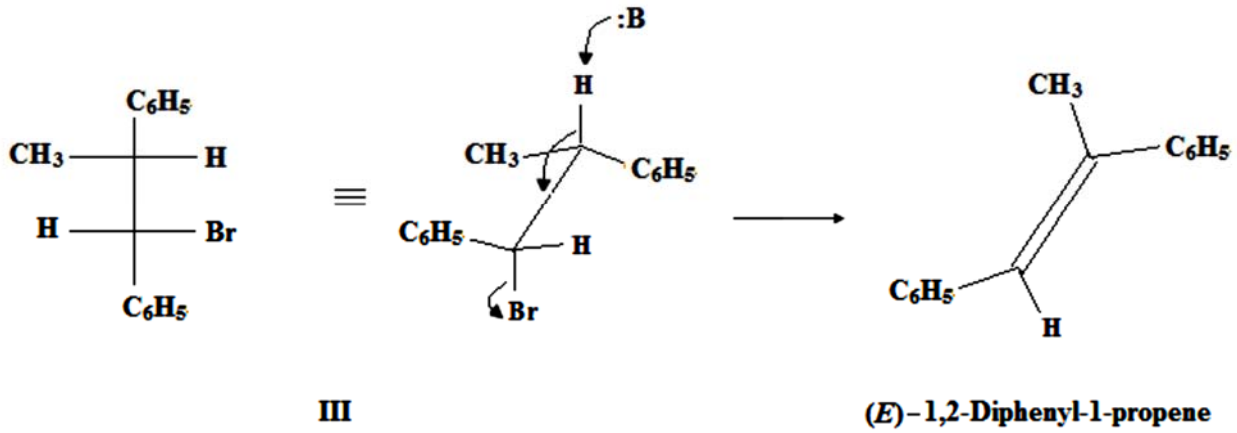


Thus, diastereomer I (or its enantiomer, II) gives the *Z* alkene:



I **(*Z*)-1,2-Diphenyl-1-propene**

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



III **(*E*)–1,2-Diphenyl-1-propene**

Stereospecific Reactions

We have defined a stereospecific reaction as one in which stereochemically different molecules react differently. Let us look more closely at what is meant by this definition. By "stereochemically different molecules" is meant stereoisomers: enantiomers or diastereomers. To "react differently" means to show any difference whatsoever in chemical behavior. In a stereospecific reaction, stereoisomers can:

(a) yield different stereoisomers as product;

(b) react at different rates, in some cases to such an extent that, while one stereoisomer reacts readily, the other does not react at all;

(c) react by different paths to yield quite different kinds of compounds as products.

Stereospecificity toward enantiomers is called **enantiospecificity**. In reactions with achiral reagents, enantiomers can show only difference (a): they can yield different stereoisomers as products, as in the SN2 reaction, but in all other respects they must react identically, at identical rates to yield products that are identical except for their stereochemistry. On the other hand, in reaction with optically active reagents, or in a chiral medium of any sort, enantiomers may show all the differences in behavior that we have listed. We have already encountered enantiospecificity in the resolution of

racemic modifications by use of optically active reagents. There, they yielded stereochemistry different products, not enantiomers, as in the SN2 reaction, but diastereomers. Biological systems generally discriminate sharply between stereoisomers. The organism responds to only one enantiomer of a pair, or responds differently to the two; only one is metabolized, or serves as a hormone or drug, tastes sweet, and so on. Now, biological activity, in the final analysis, depends upon chemical reactions in the organism, in this case, reactions with one enantiomer or the other. The discrimination is the result of virtually complete enantiospecificity in these reactions. Such enantiospecificity is the rule for the countless reactions taking place in the chiral medium provided by the optically active enzymes of living organisms.

Stereospecificity toward diastereomers is called **diastereospecificty**. Diastereomers can differ in all the ways that we have listed above, whether the reagent is optically active or inactive. A different in rate of reaction is the rule for diastereomers; in this respect at least, diastereomers will always react stereospecifically, although often to only a modest degree.

Stereoselectivity vs. Stereospecificity

Many reactions are, like the addition of bromine, both stereoselective and stereospecific. But this is not always true. 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. Some reactions are stereospecific but not stereoselective. Stereoisomers may react at widely different rates, but yield the same stereoisomers as the product, or yield products that differ in ways other than in their stereochemistry. Sometimes one stereoisomer reacts readily, and another does not react at all, as in the biological reactions. The quality of **stereoselectivity** is focused on the **reactants** and their stereochemistry; it is concerned with the products, too, but only as they provide evidence of a difference in behavior between reactants. Of stereoisomeric reactants, each behaves in its own specific way. The stereospecificity of biological reactants has

given a powerful impetus to the development of synthetic methods that are highly stereoselective. In synthesizing a drug, for example or a hormone, a chemist wants to use (stereoselective) reactions that produce just the correct stereoisomer, since only that stereoisomer will show (stereospecific) activity in a biological system.