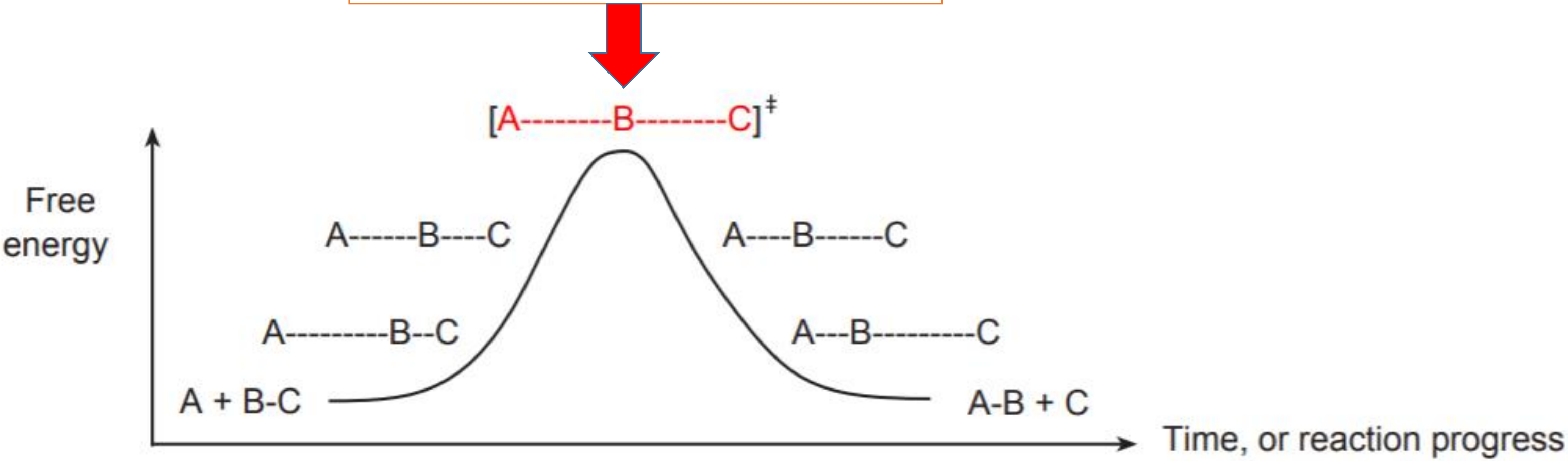
Reaction Intermediates in Organic reactions

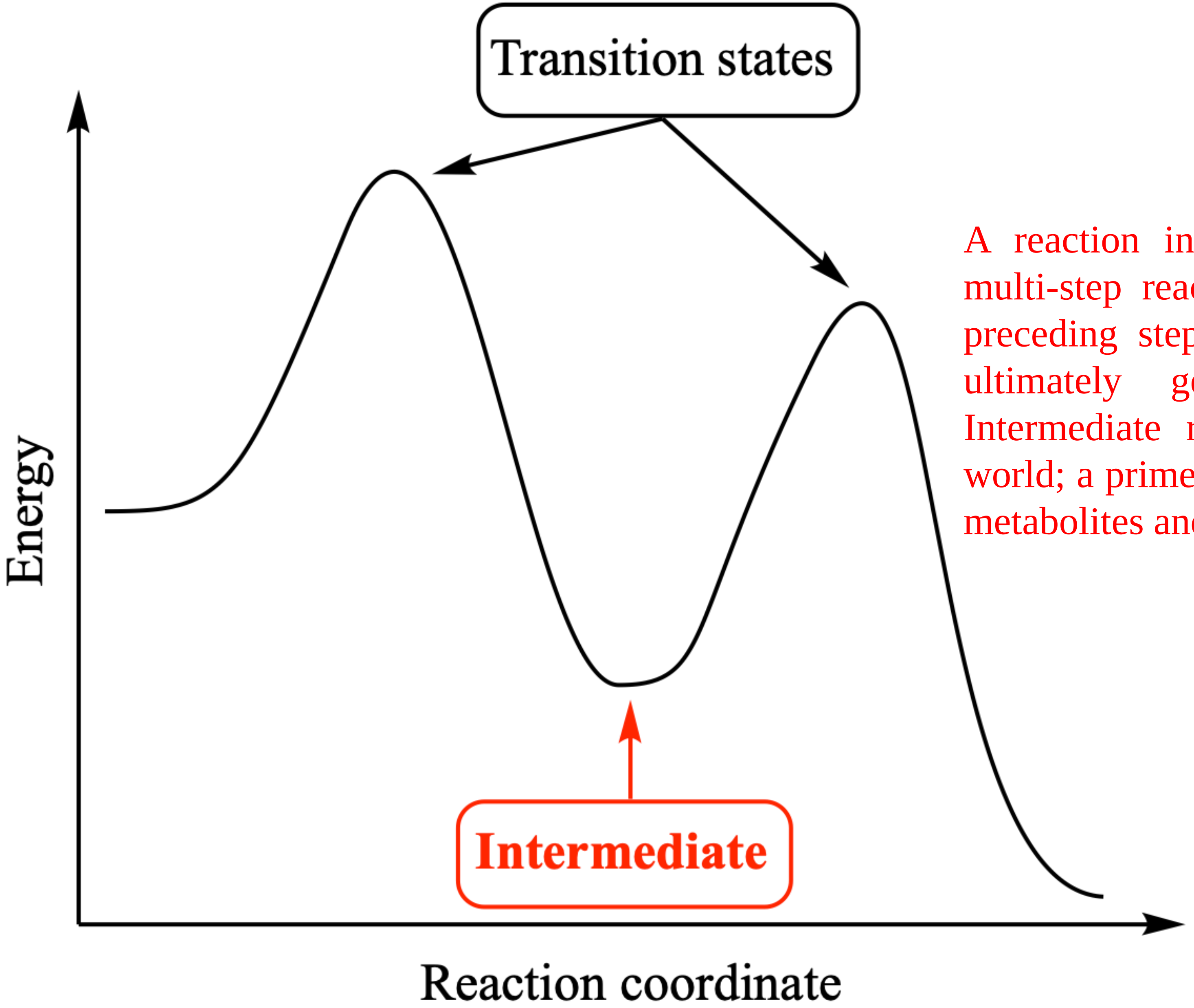
Passang Tshering Lepcha
Ananda Chandra College
Jalpaiguri

Progression of Reaction

A point of particular interest in this reaction profile is the **energy maximum**. The structural species that exists at this point is called a **transition state**

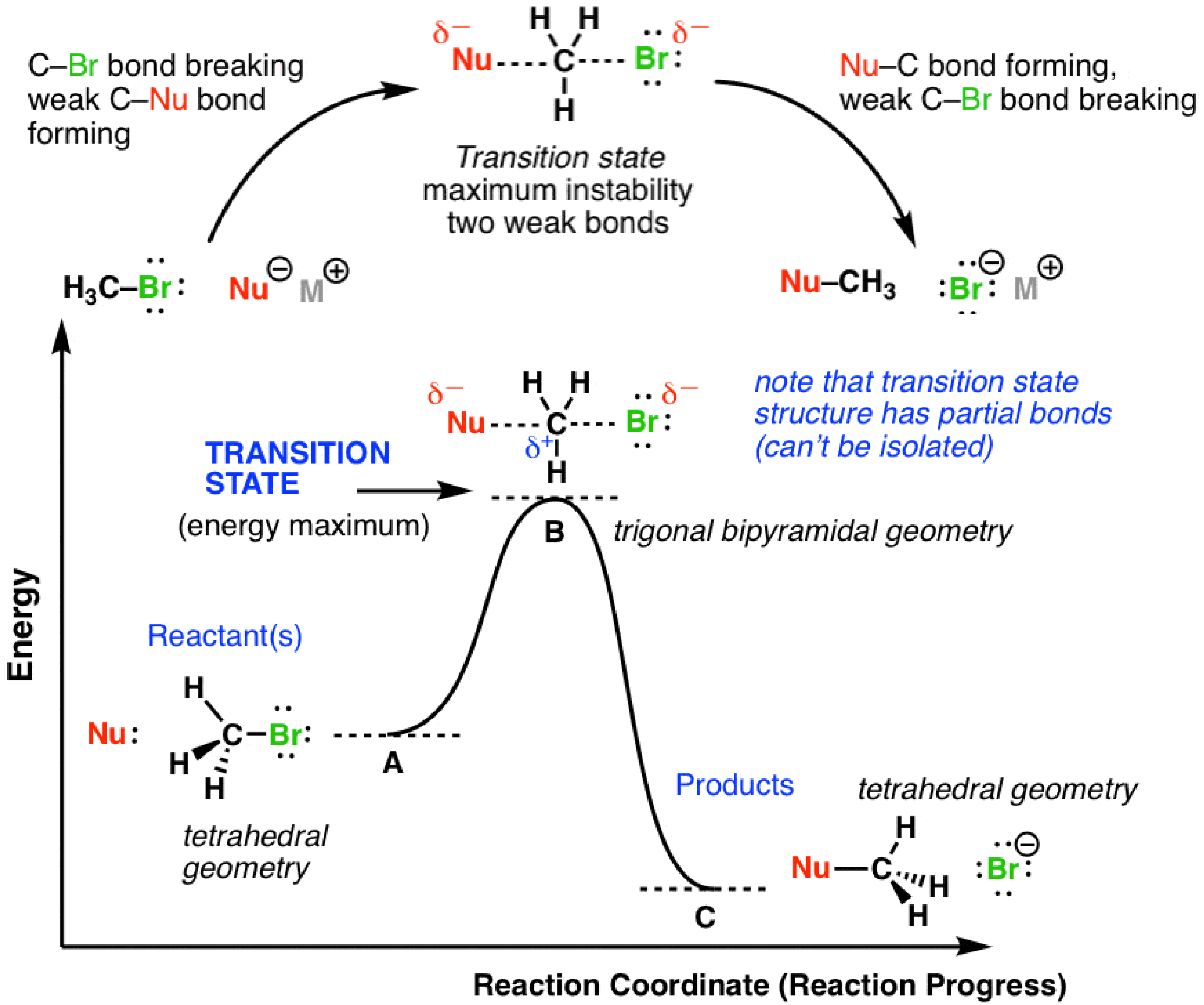


We Know this isn't it?



A reaction intermediate is transient species within a multi-step reaction mechanism that is produced in the preceding step and consumed in a subsequent step to ultimately generate the final reaction product. Intermediate reactions are common in the biological world; a prime example can be seen in the metabolism of metabolites and nutrients.

Example of nucleophilic substitution (S_N2):



C–Br bond breaking weak C–Nu bond forming

Transition state maximum instability two weak bonds

Nu–C bond forming, weak C–Br bond breaking

note that transition state structure has partial bonds (can't be isolated)

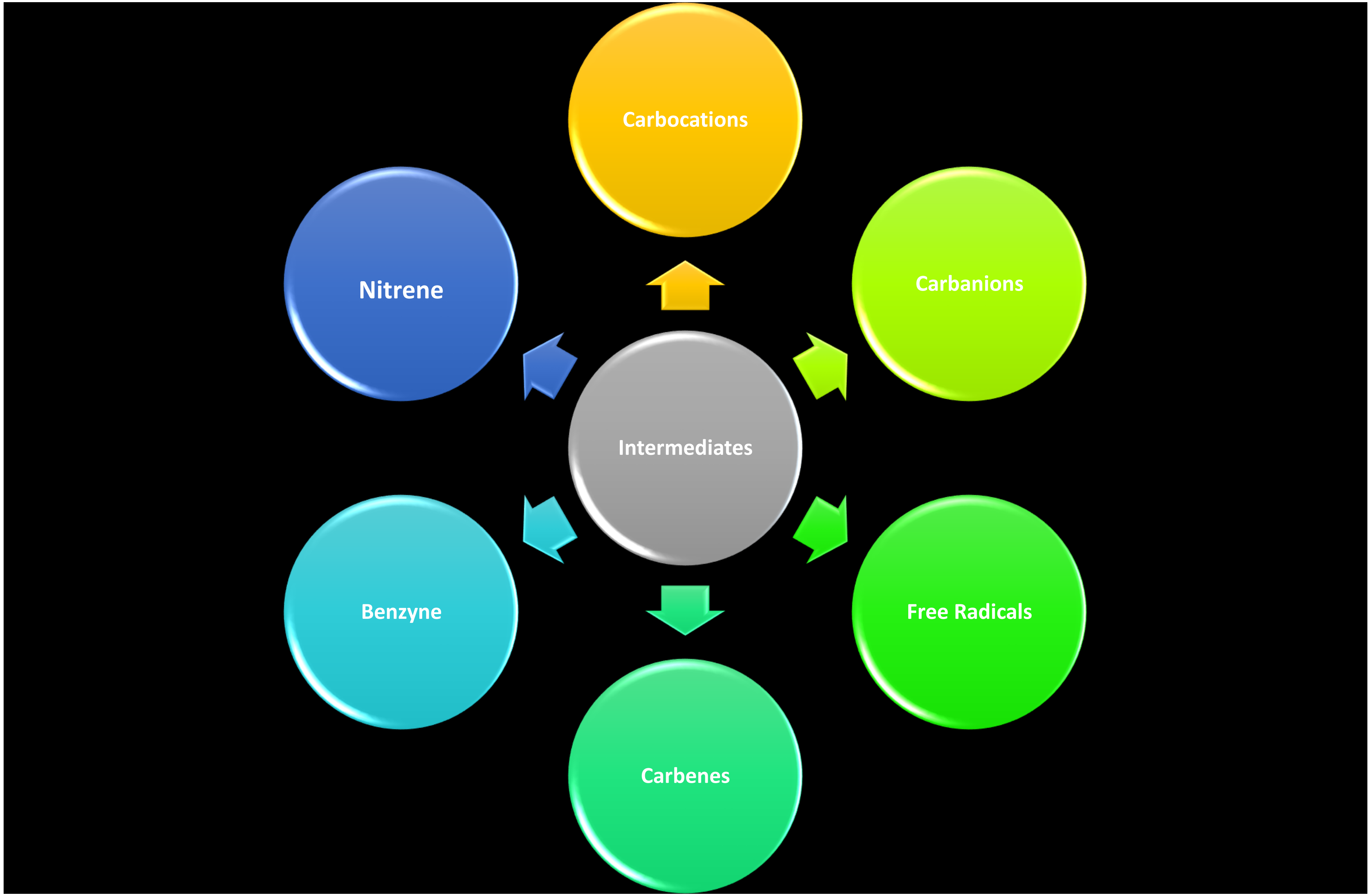
TRANSITION STATE (energy maximum)

trigonal bipyramidal geometry

tetrahedral geometry

tetrahedral geometry

Types of Reactive intermediates



Reactive intermediates have several features in common

- **low concentration** with respect to reaction substrate and final reaction product
- often generated on **chemical decomposition** of a chemical compound
- it is often possible to prove the **existence** of this species by **spectroscopic** means
- cage effects have to be taken into account
- often **stabilization** by conjugation or resonance
- often difficult to distinguish from a transition state
- prove existence by means of **chemical trapping**

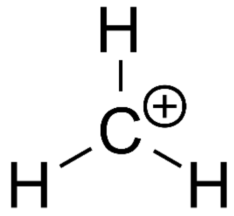
Carbocations

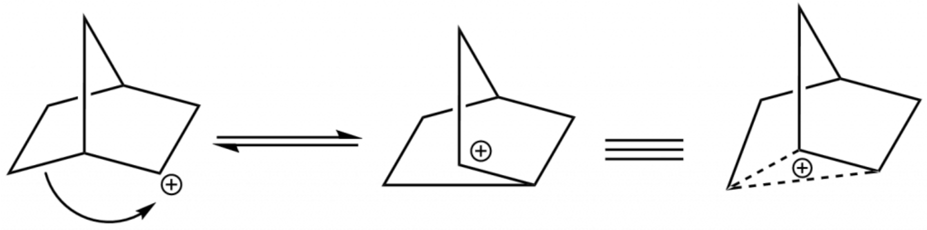
Carbocations are positively charges reactive intermediates

Carbocations

- Trivalent-tricoordinate (Hypocoordinate) carbenium ions "Classical" ions CH_3^+
- Hypercoordinate carbonium ions "Non-Classical" ions CH_5^+

Property	CH_3^+	CH_5^+
Number of bonds to C^+	3	5
Electrons in outer shell	6	8
Empty orbital	Yes, a p orbital	No
Electron-deficient	Yes	No

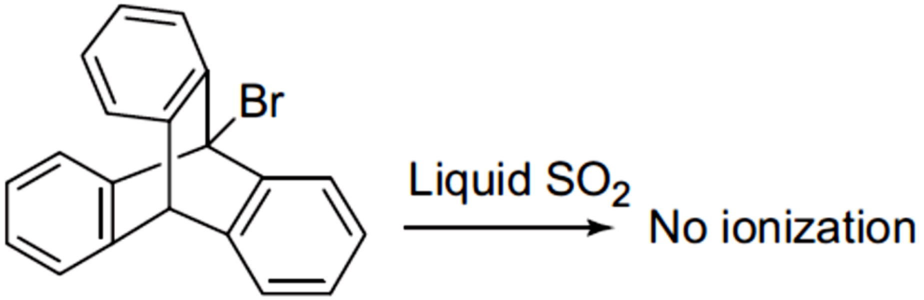




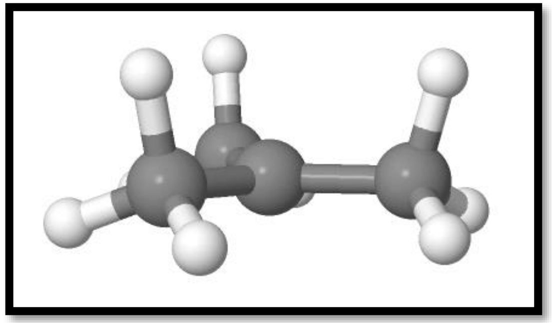
Norbornyl cation

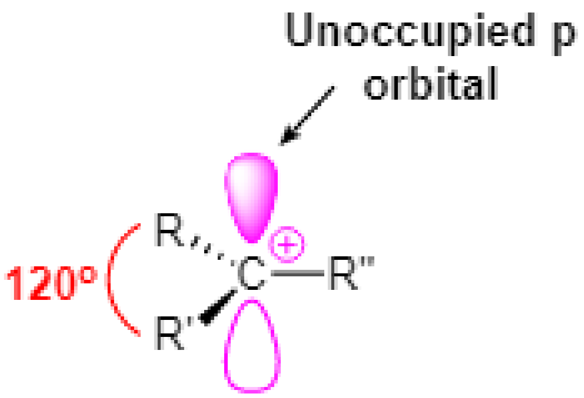
Structure of Carbocations

$$Ph_3CCl \xrightarrow{SO_2} Ph_3C^{\oplus} + Cl^{\ominus}$$



Central Carbon is sp2 hybridised
It means that the structure assumes planar geometry

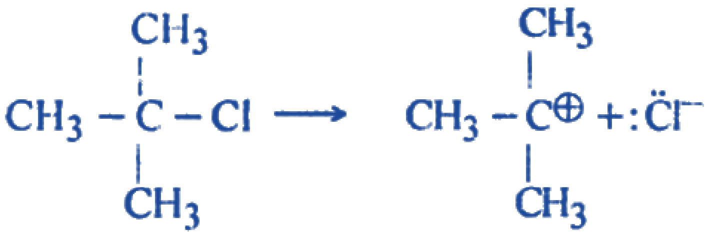




- empty **p-orbital** ✓
- **trigonal planar** geometry ✓
- **Lewis acidic** (i.e. accepts a pair of electrons) ✓
- **6** valence electrons ✓
- sp^2 hybridization ✓

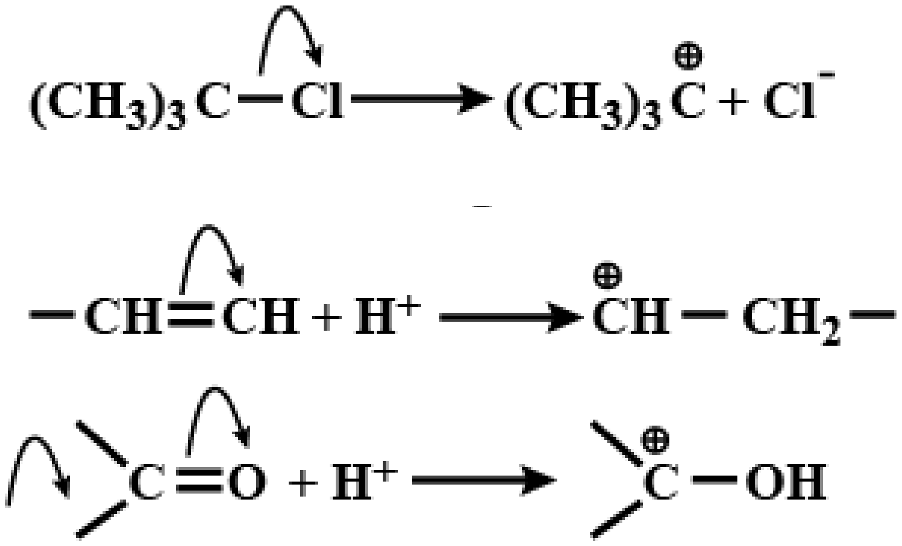
Methods of Forming Carbocations

1. Heterolytic Fission of neutral species

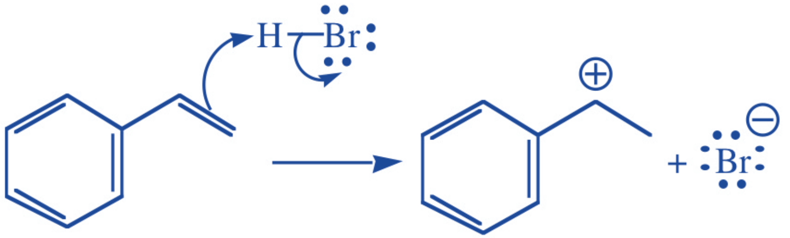


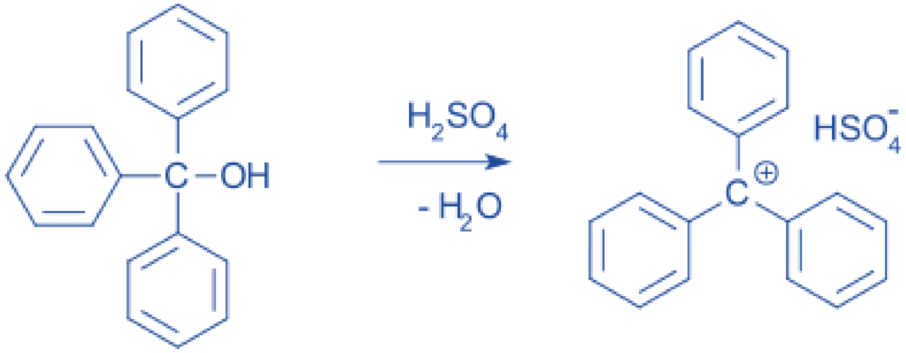
tert. butyl chloride

tert. butyl cation



2. Addition of cation to neutral species

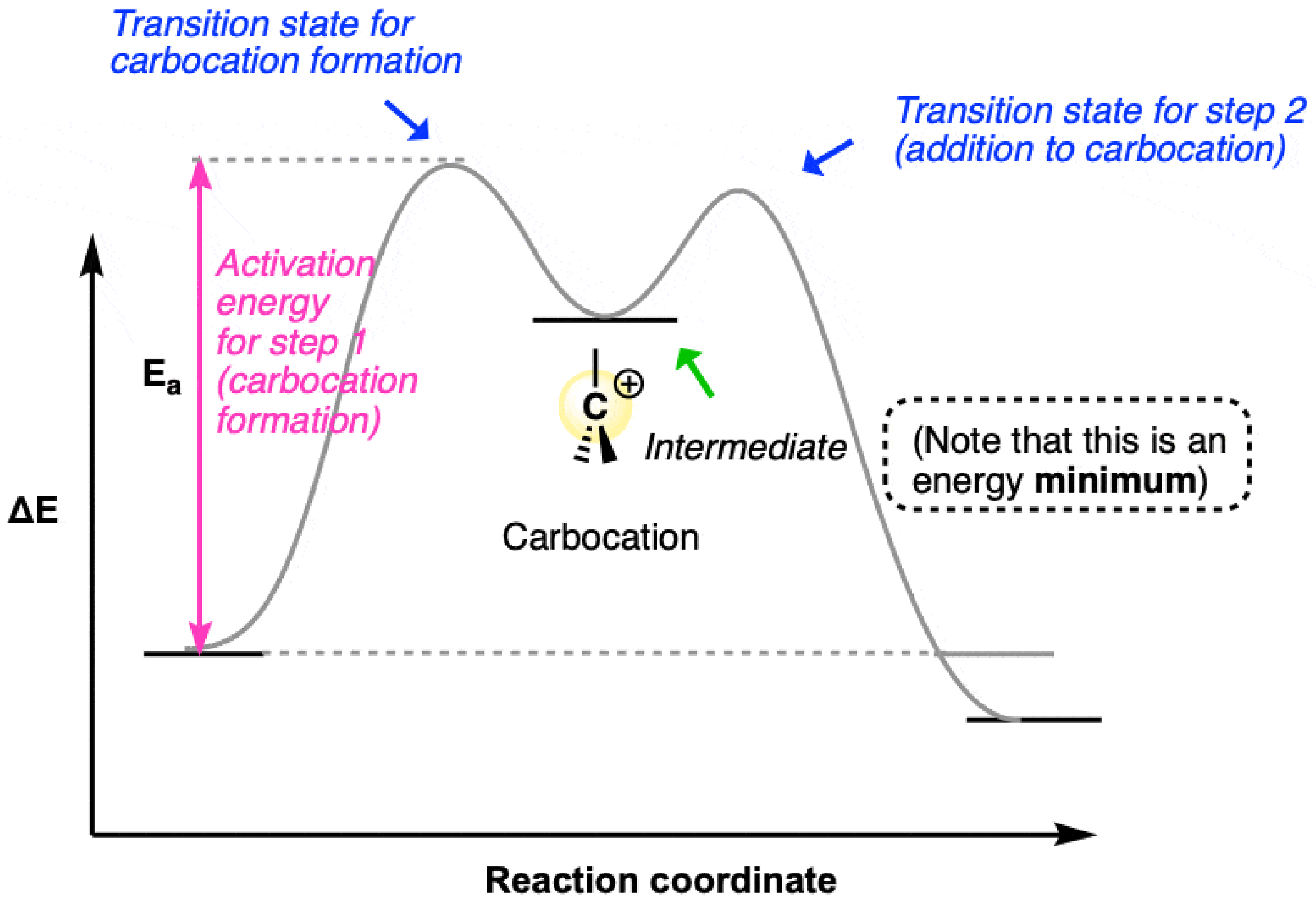




Stability of Carbocations

Reaction Coordinate Diagrams For Carbocation Formation

- Carbocations are reactive **intermediates** in many reactions
- One way to distinguish an **intermediate** from a transition state is that intermediates are local **minima**, whereas transition states are local maxima



Because the ***rate-determining*** step for each of these reactions is formation of the carbocation intermediate.

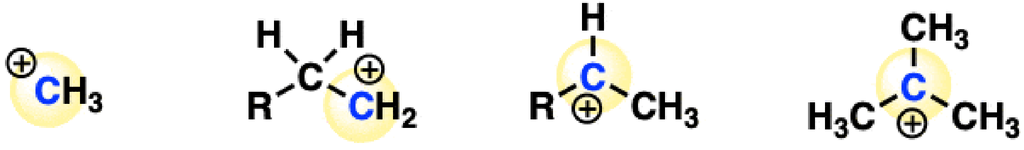
The more ***stable the carbocation*** intermediate, the ***lower in energy*** the transition state that leads to that carbocation, which translates into a **lower activation** energy and a ***faster reaction***.

Therefore, if we understand the factors that govern the stability of carbocations, then it will also help us understand why certain reactions happen quickly whereas others do not!

Factors effecting stability of carbocations

1. Substitution

Carbocation **stability increases** as the number of adjacent alkyl groups is **increased**



Number of carbons attached to carbocation: 0, 1, 2, 3

"methyl" "primary" "secondary" "tertiary"

Least stable → **Most stable**

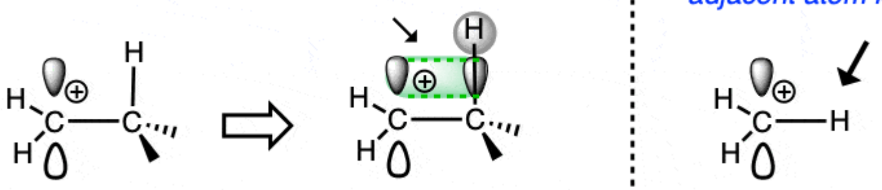
- **primary** carbocation
- less donation of electron density
- more electron-poor
- less stable

- **tertiary** carbocation
- more donation of electron density
- more electron-rich
- more stable

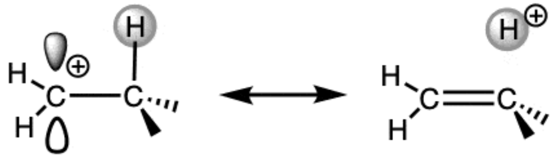
Inductive Effect

orbital overlap between p-orbital and C–H bond

not possible when the adjacent atom is H !

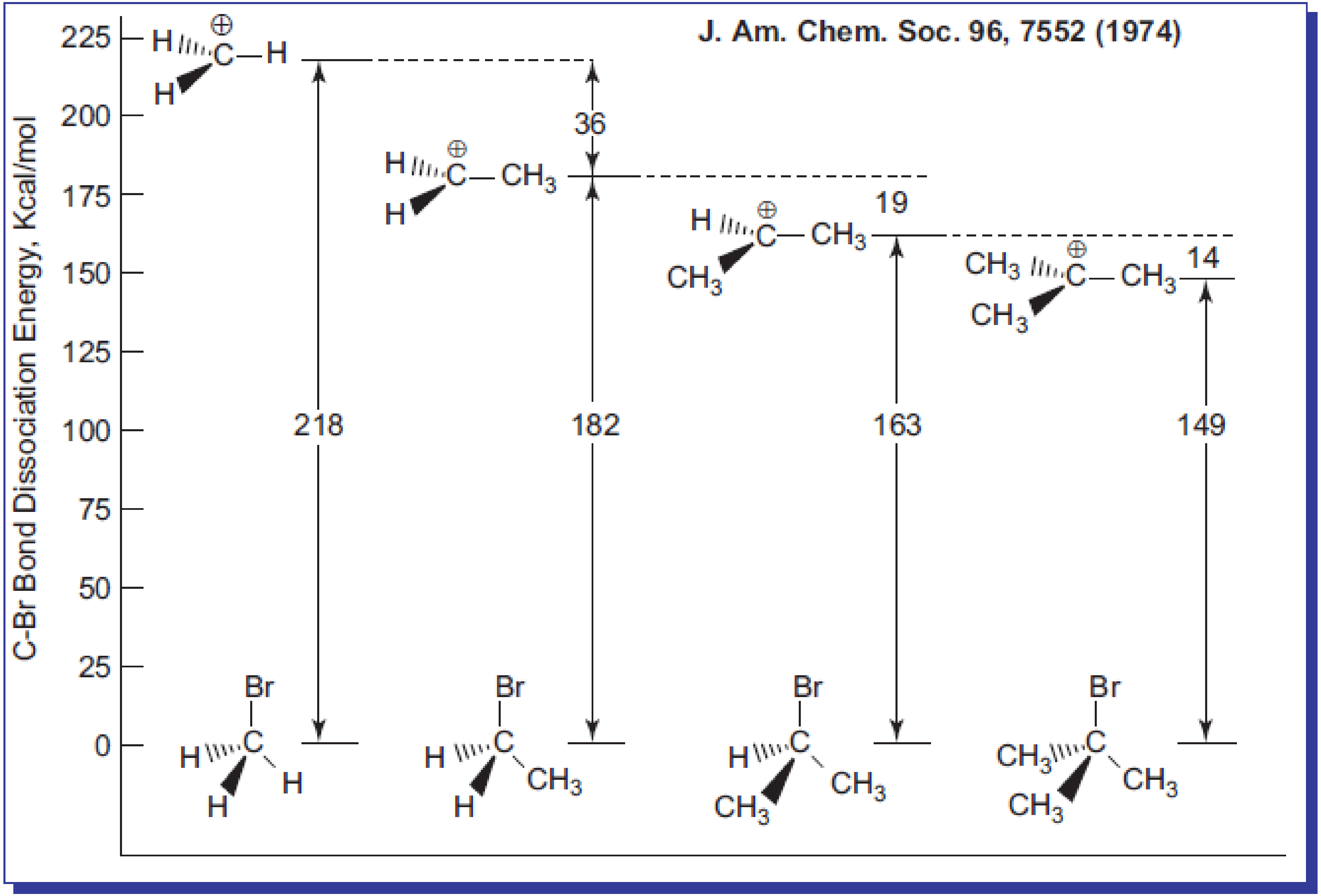


One way to think about this is "**pi-bond** / **no-bond** " resonance



- not an *actual* resonance form!
- just a helpful way of thinking about this interaction

Hyperconjugation



J. Am. Chem. Soc. 96, 7552 (1974)

Factors effecting stability of carbocations

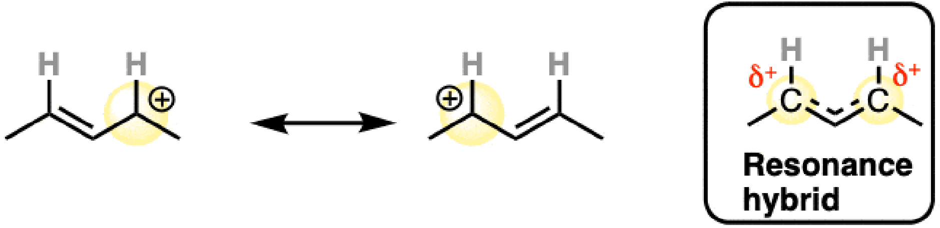
2. Resonance / Delocalization

Resonance stabilization of carbocations

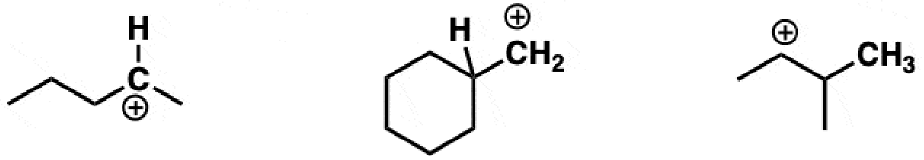
- When a pi bond is adjacent to the carbocation, then the positive charge can be **spread out** over multiple carbons through **resonance**

- This **reduces** the overall charge density of the carbocation, making it more **stable**.

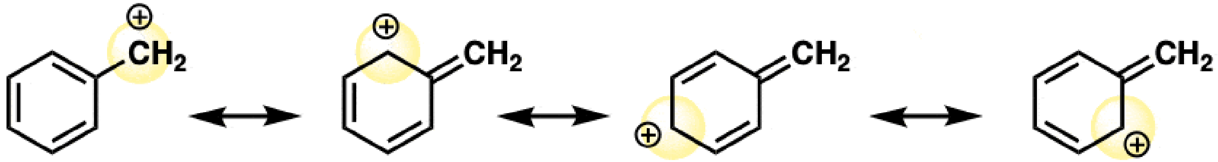
In the case below, each carbon bears a positive charge of +0.5 in the resonance hybrid



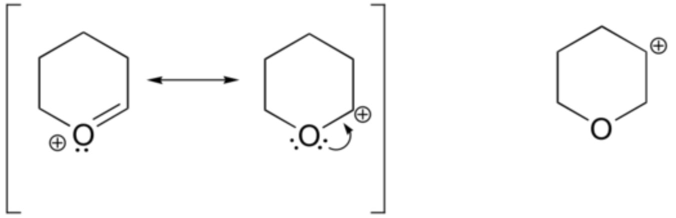
Contrast that to the carbocations below, where the positive charge **cannot** be delocalized through resonance due to the absence of neighboring p-orbitals



Aromatic rings (e.g. benzene) also stabilize positive charge through **resonance**



In order for resonance stabilization to occur, the empty p-orbital of the carbocation must be capable of overlap with the adjacent pi-bond



more stable

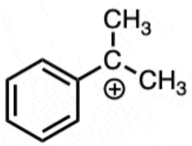
less stable

(no resonance delocalization)

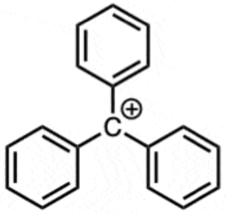
Adjacent Lone Pairs

Let's try ourselves

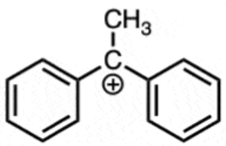
Rank the following carbocations in order of stability (1 = most stable, 4 = least stable)



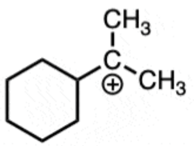
A



B



C

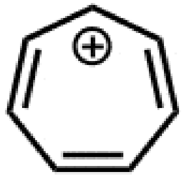


D

Factors effecting stability of carbocations: Special Cases

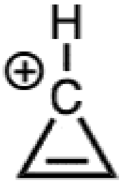
3. Aromaticity

Aromatic carbocations are unusually stable



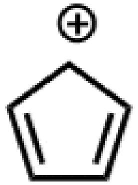
Cycloheptatrienyl cation
“Tropylium ion”

Commercially available



Cyclopropenium ion

Antiaromatic carbocations are unusually unstable

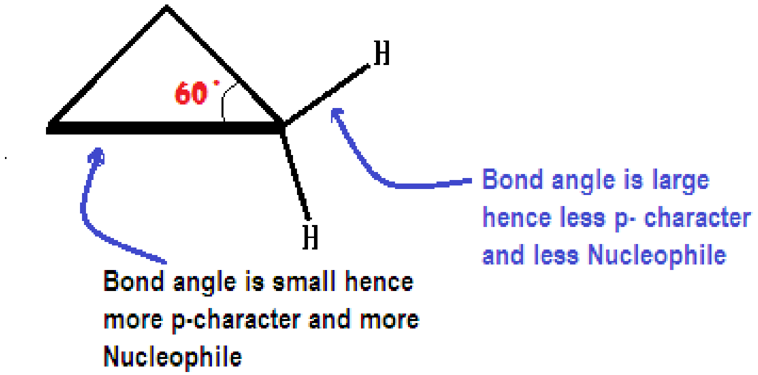


Cyclopentadienyl cation

Unstable even at very low temperatures

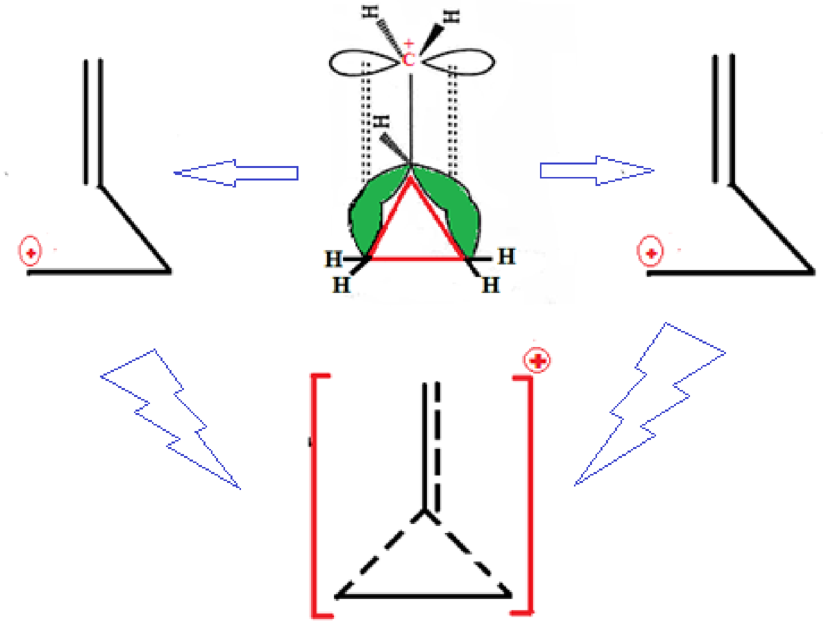
Sigma Bond Resonance or Dancing Resonance

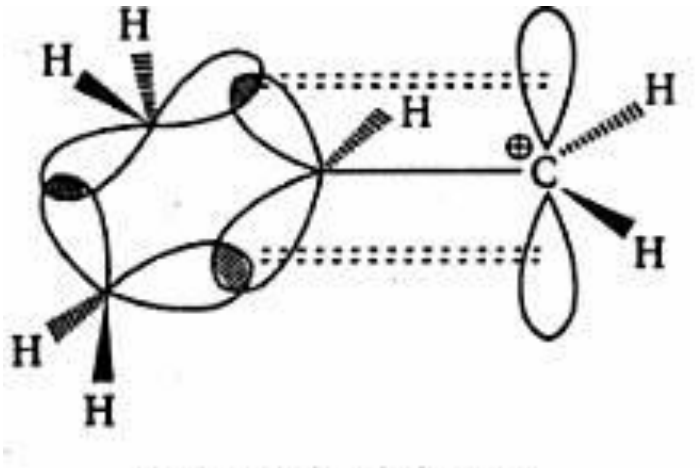
4. Cyclopropylmethyl cation



Bond angle is large hence less p- character and less Nucleophile

Bond angle is small hence more p-character and more Nucleophile





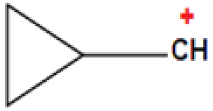
Cyclopropylmethyl cation

In cyclopropane all the carbon is sp3 hybridized and the bond angle for the same should be 109 degree 28′ but the actual bond angle is 60 due to which angle strain develops. So in order to minimize the strain p orbital bents due to which it acquires partial sigma and partial pi bond character which behave like pi bond. And resonance take place between sigma and vacant p-orbitals hence called P-orbitals overlapping or sigma resonance

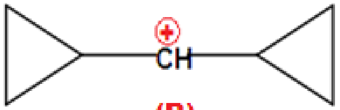
Most Stable Carbocation

Stability order

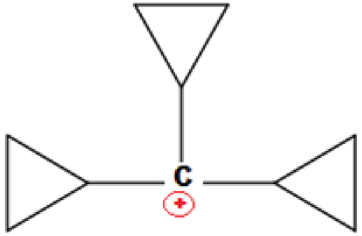
(C) >(B) >(A)



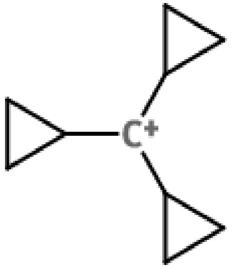
(A)



(B)



(C)



Tricyclopropyl methyl carbocation

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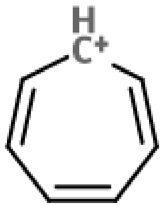
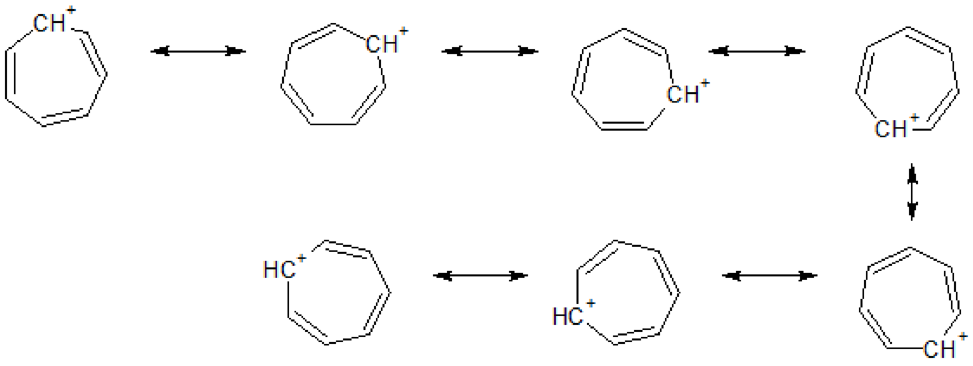
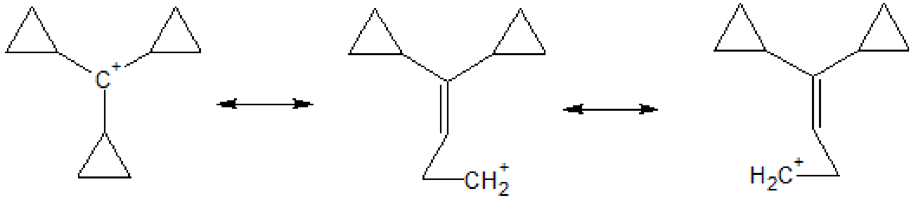


Tropylium Carbocation

7 resonance structures for the tropylium carbocation



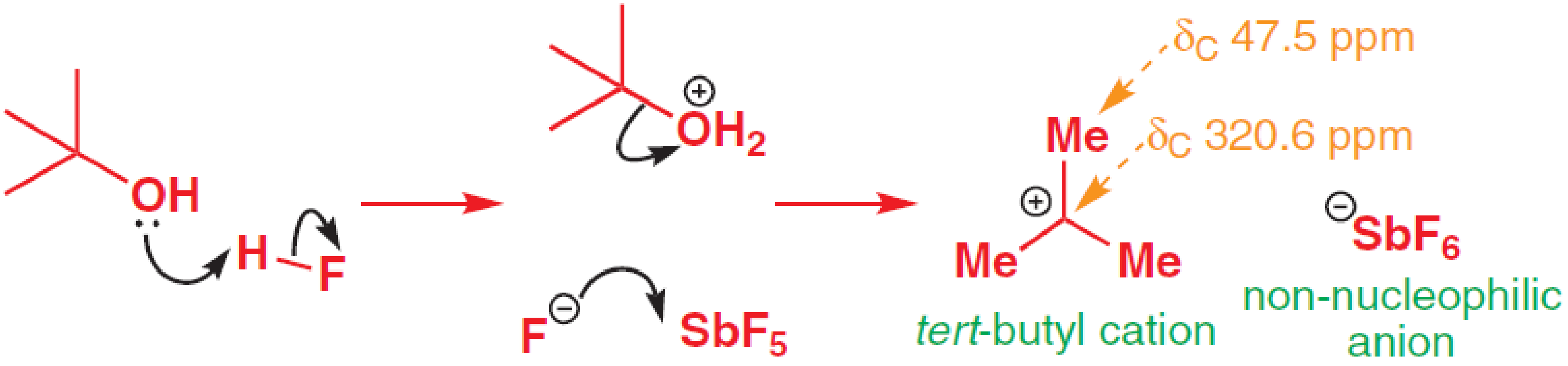
7 resonance structures for the tricyclopropyl carbocation



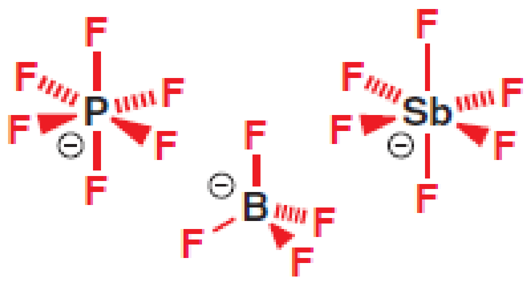
plus 4 more structures, 2 on each of the other 2 cycopropane rings

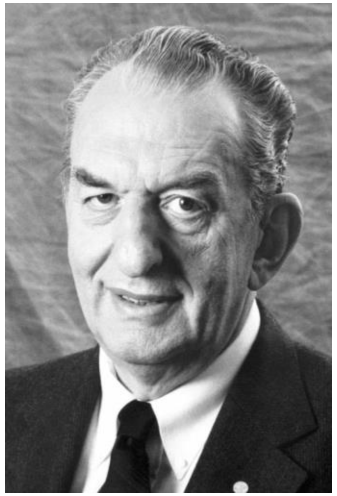
Detection of Carbocations

Olah's preparation of the *t*-butyl cation in liquid SO_2



non-nucleophilic anions



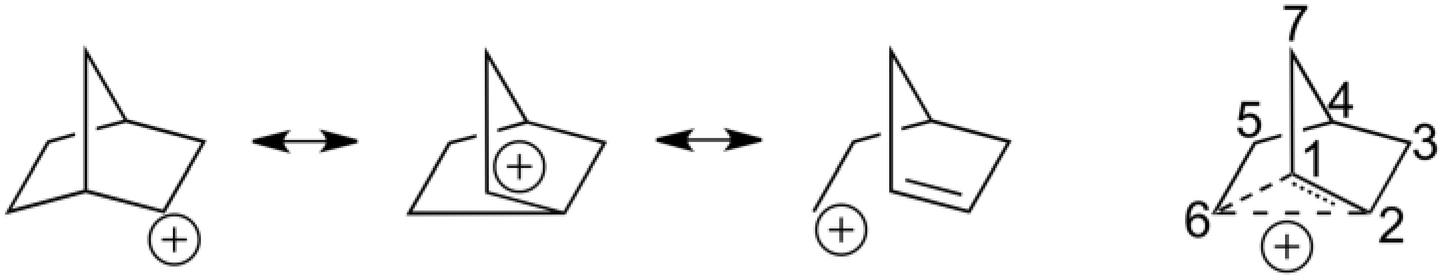


George A. Olah
The Nobel Prize in Chemistry 1994
“for his contribution to carbocation chemistry”

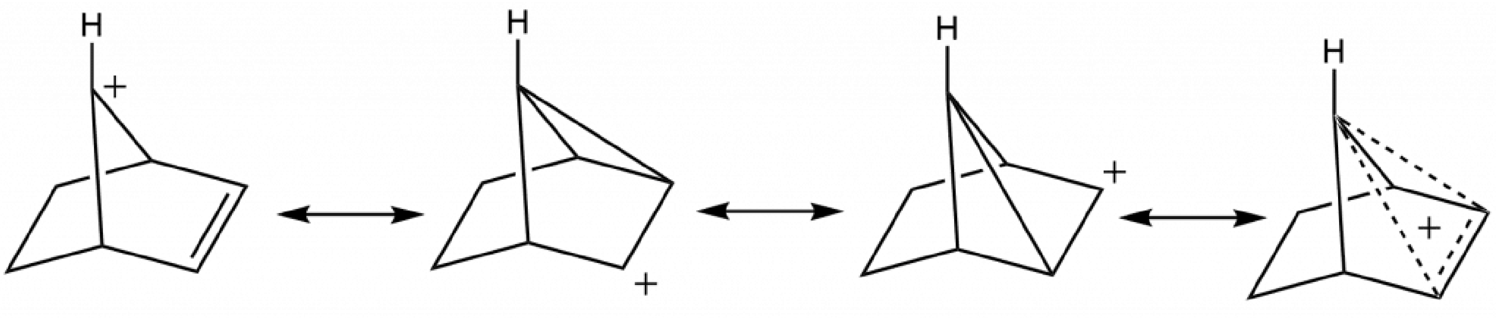
Non-Classical Carbocations

What is Non-classical Carbocation?

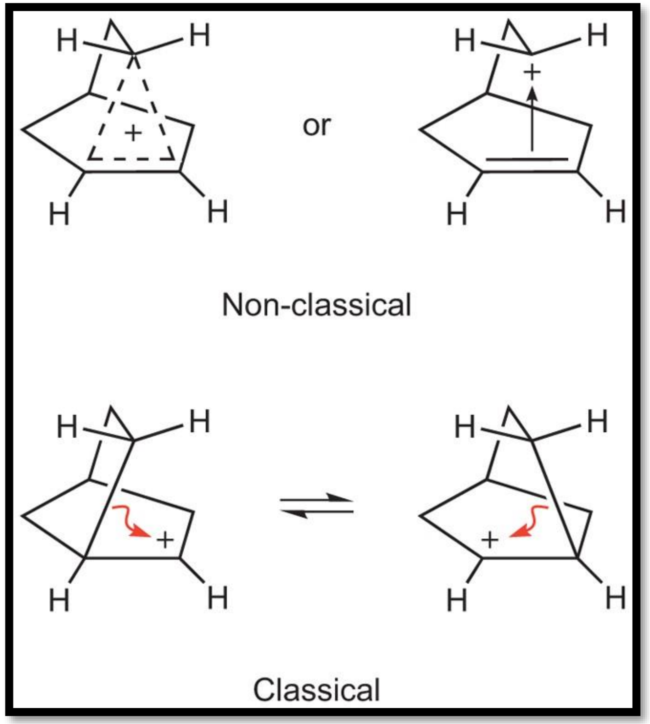
A non-classical carbocation is an ion containing a positively charged carbon in a **three-center two-electron bond**. This means, there are three atoms sharing two electrons in these carbocations. This type of electron sharing is named as delocalization of the electrons.



(a) (b)

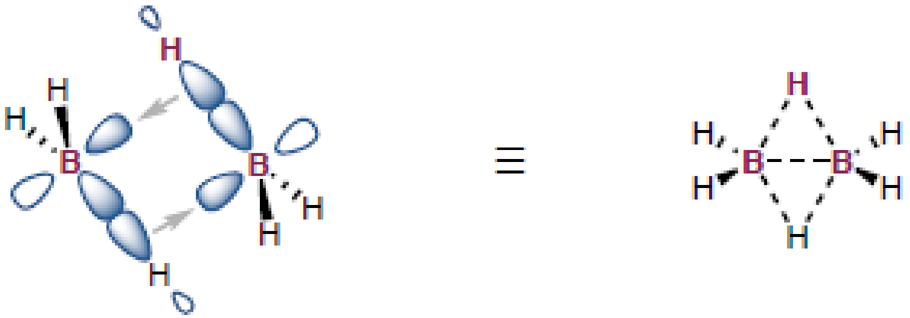


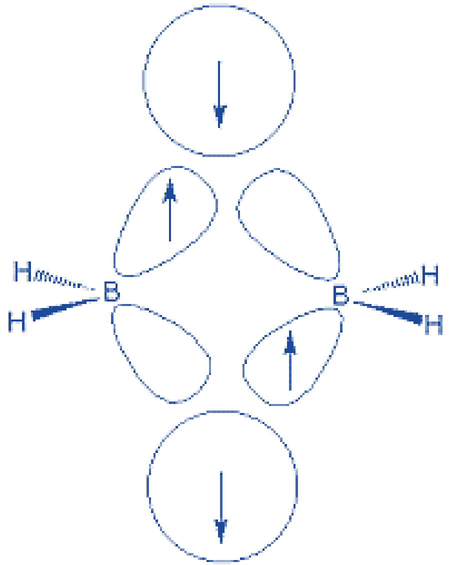
Norbornenyl cation

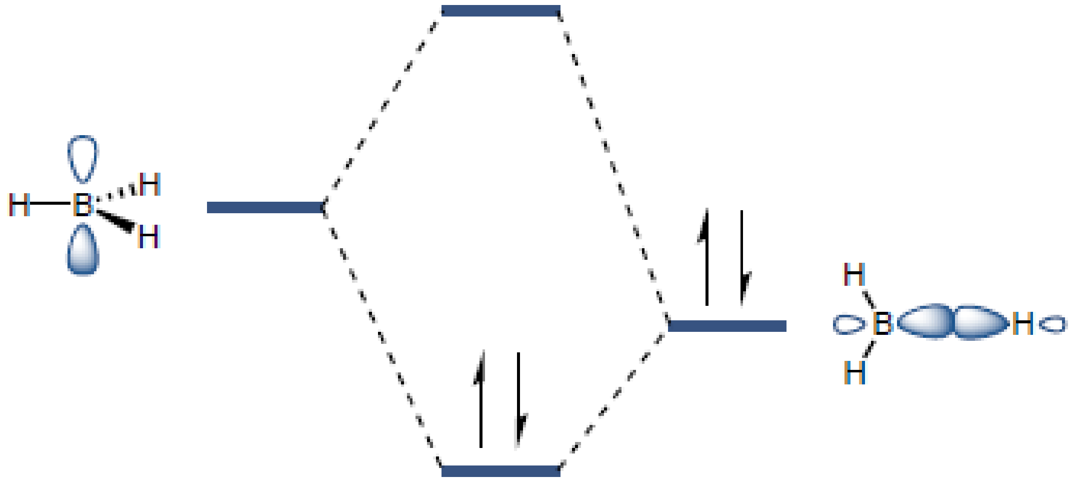


The 3-center, 2-electron bond

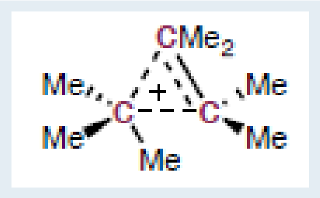
diborane: prototypical example of 3-center, 2-electron bonding

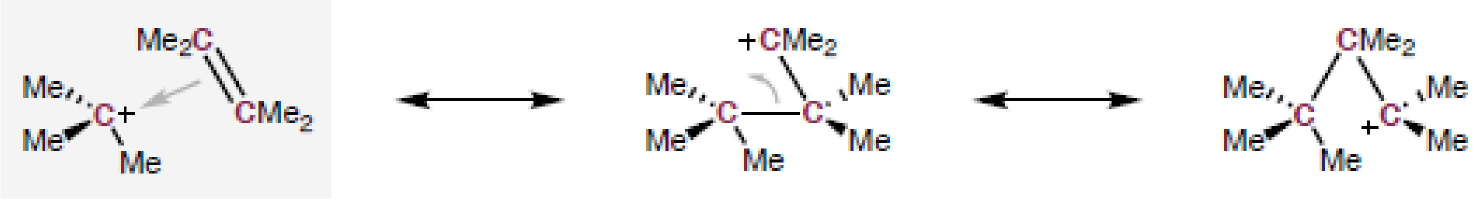


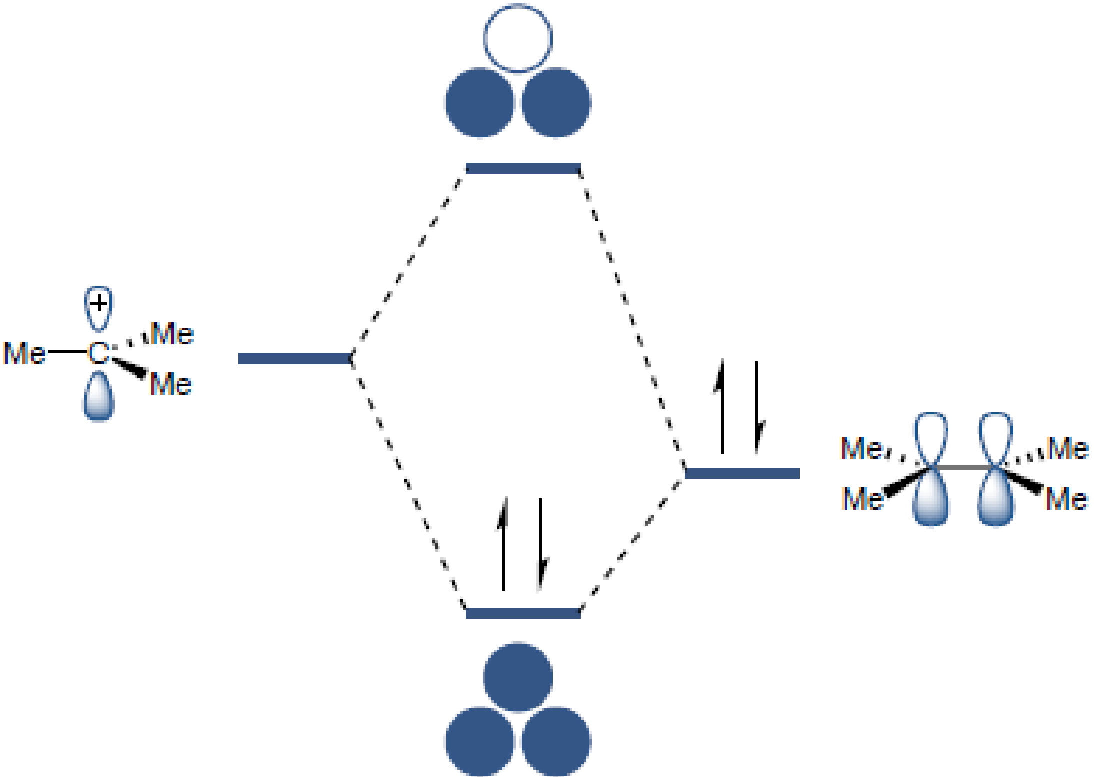




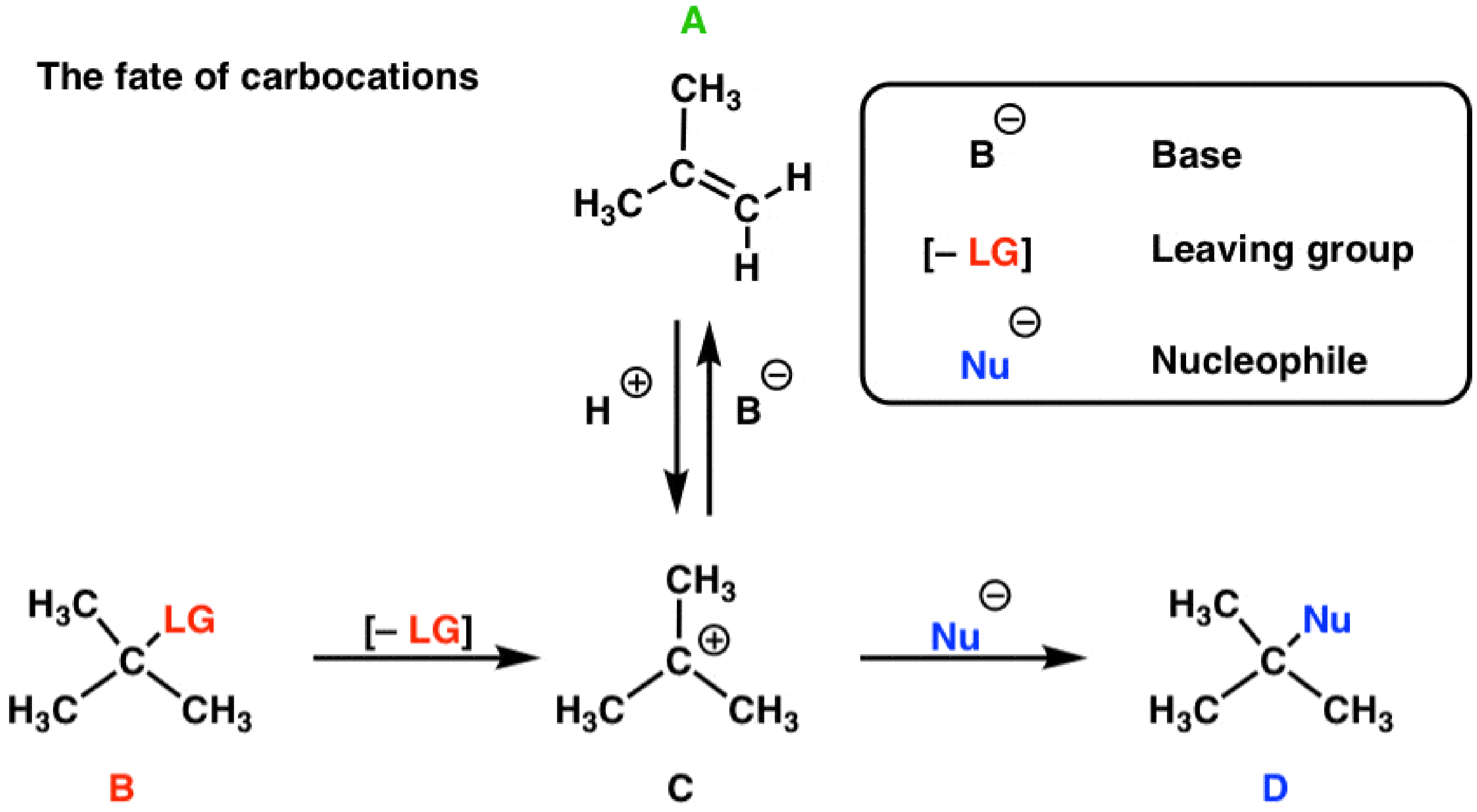
The 3-center, 2-electron bond







The fate of carbocations



Carbocation

$B^{\ominus}$ Base

[– LG] Leaving group

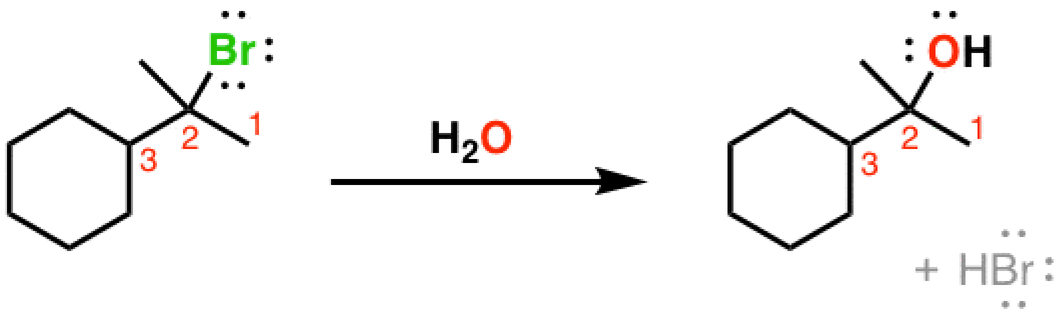
$Nu^{\ominus}$ Nucleophile

A ⟶ C ⟶ D Addition to alkenes with H–X (e.g. H-Br)

B ⟶ C ⟶ D S_N1 Reaction

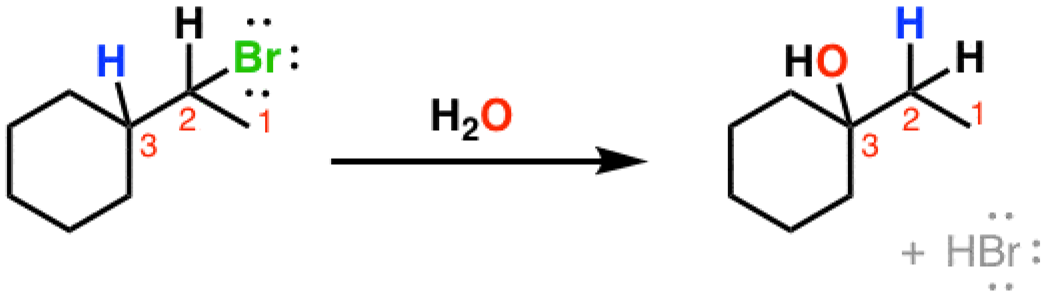
B ⟶ C ⟶ A E1 Reaction

A "normal" substitution reaction



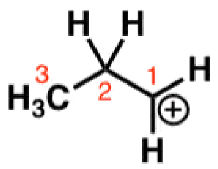
Form	Break
C_2–OH	C_2–Br
H–O	H–Br

Substitution with rearrangement

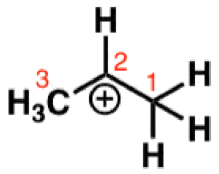


Form	Break
C_2–H	C_2–Br
C_3–OH	C_3–H
H–O	H–Br

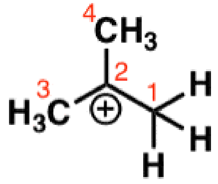
Note extra bond forming/breaking of ***H***



Primary carbocation
(least stable)



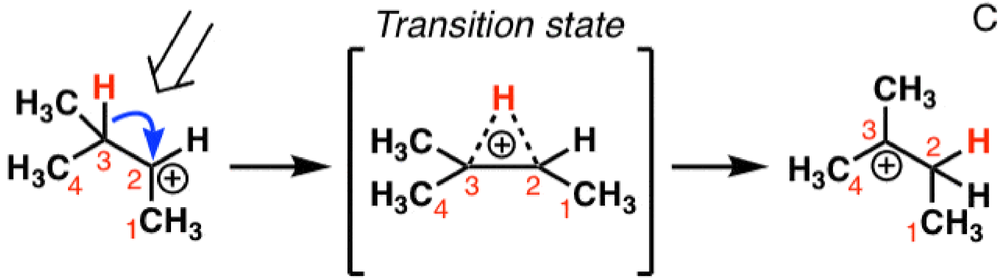
Secondary carbocation



Tertiary carbocation
(most stable)

One pathway rearrangements can occur through is a *hydride shift*.

FOLLOW THIS ARROW



Secondary carbocation

Tertiary carbocation

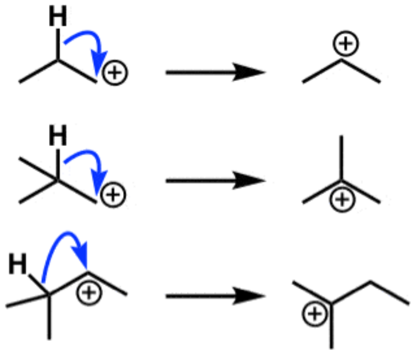
Form	**Break**
C_2–H	C_3–H

Some examples of "allowed" hydrogen rearrangements
(note: "hidden" hydrogens not drawn!)

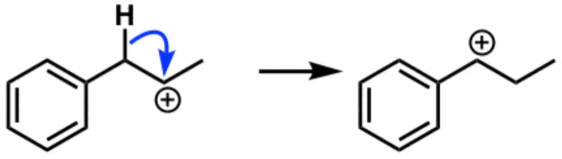
Primary → Secondary

Primary → Tertiary

Secondary → Tertiary



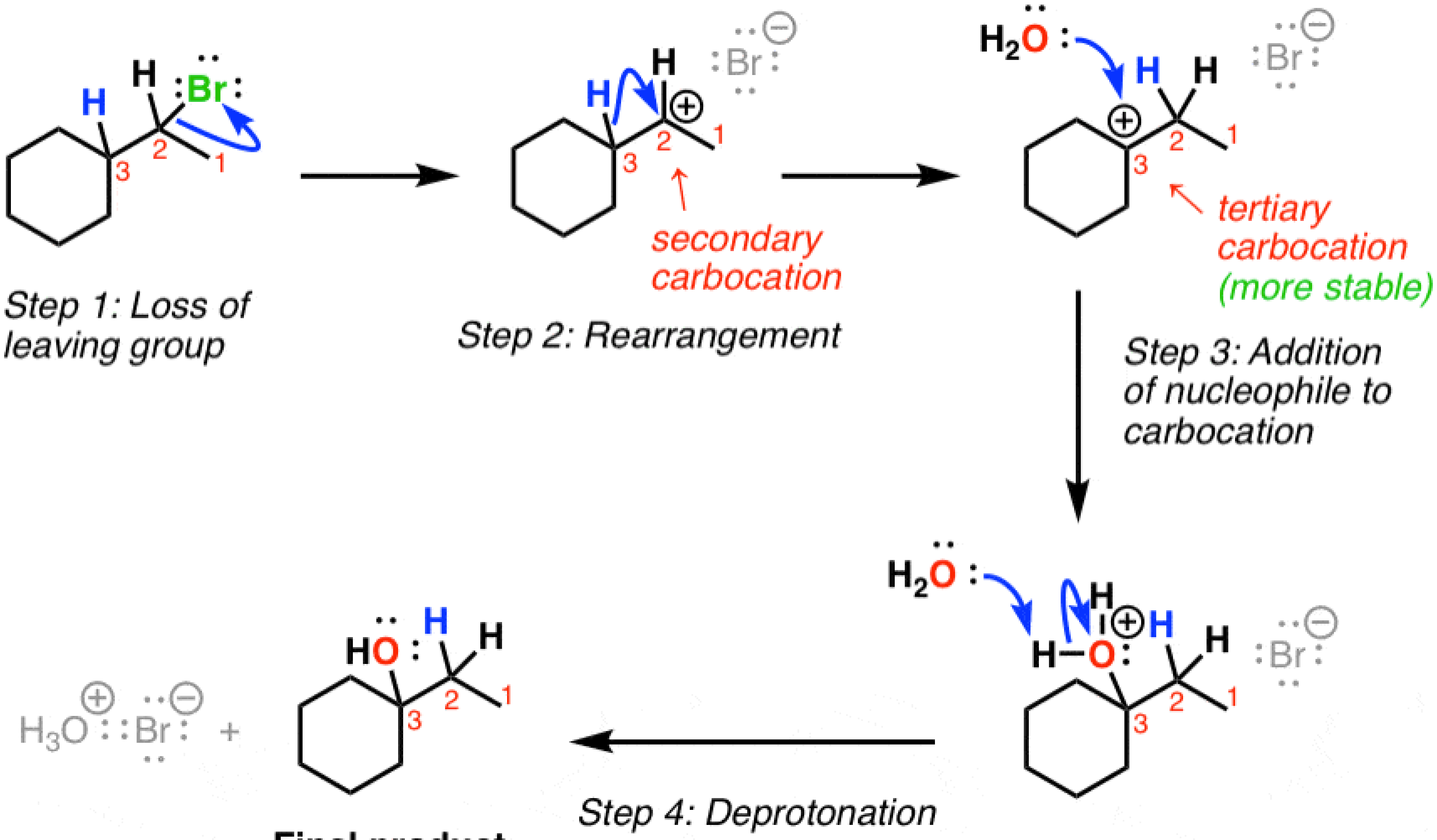
Note: **Carbocations with the same substitution pattern can rearrange if it results in a resonance-stabilized carbocation**



Secondary

Secondary
(resonance stabilized)

Rearrangements can accompany reactions where carbocations are formed, such as in the S_N1 reaction:



Step 1: Loss of leaving group

Step 2: Rearrangement

secondary carbocation

tertiary carbocation

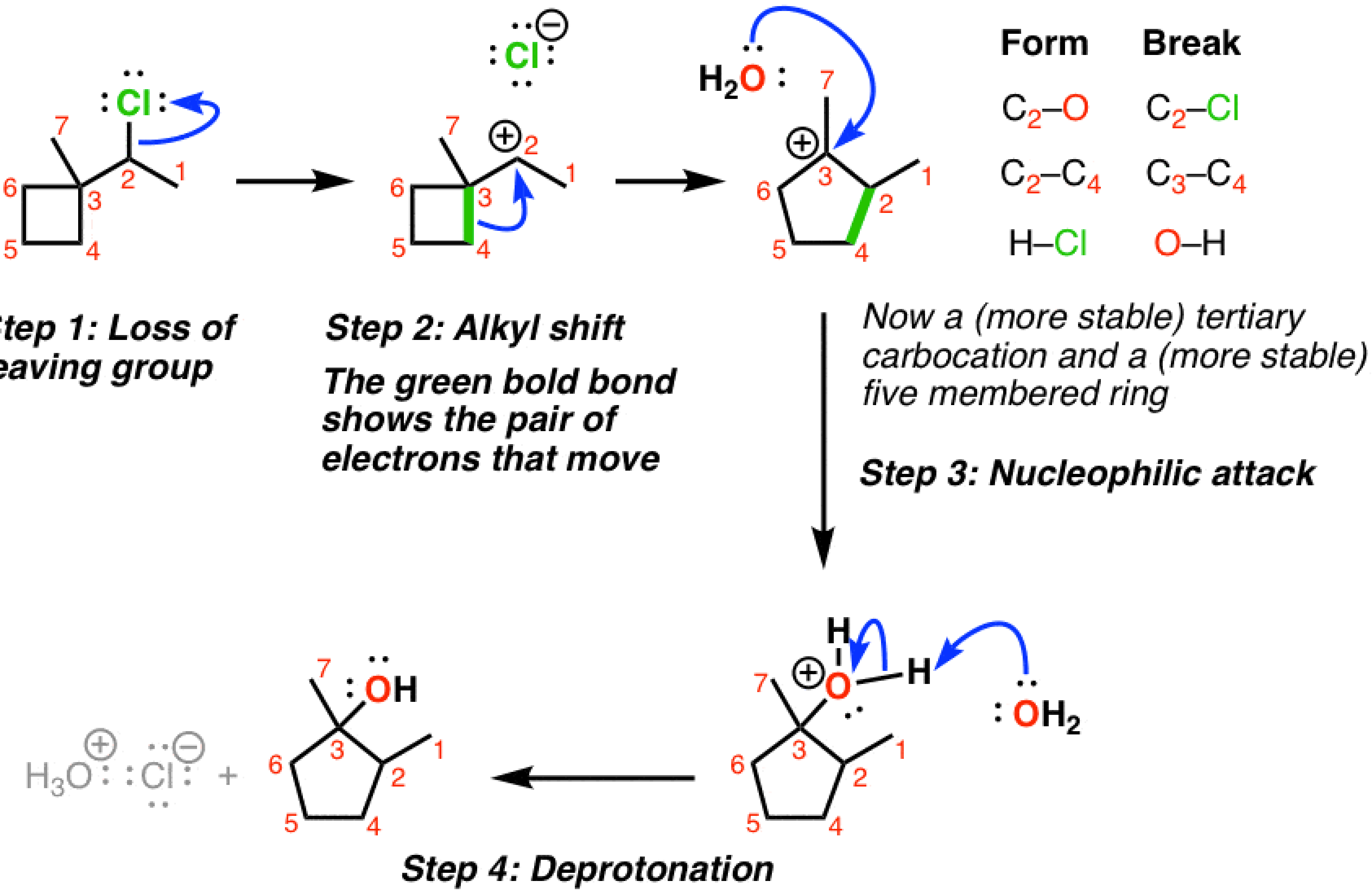
(more stable)

Step 3: Addition of nucleophile to carbocation

Step 4: Deprotonation

Final product

S_N1 with rearrangement



Step 1: Loss of leaving group

Step 2: Alkyl shift

The green bold bond shows the pair of electrons that move

Form	**Break**
C_2–O	C_2–Cl
C_2–C_4	C_3–C_4
H–Cl	O–H

Now a (more stable) tertiary carbocation and a (more stable) five membered ring

Step 3: Nucleophilic attack

Step 4: Deprotonation