

Rearrangements and Reactive Intermediates in Organic Synthesis

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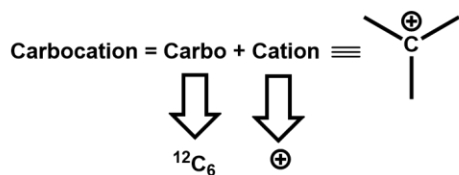
Lecture 01: Carbocation

Welcome back to my course on reactive intermediates and molecular rearrangement and in the today's class I am going to talk about carbocation and the first question arises into our mind that why you have to learn carbocation because there are many organic transformations which goes via formation of carbocation intermediate. So, if we not able to understand the carbocation then you cannot able to predict the product which is going to form, first and then you cannot able to compare that which product will be form faster and which will be slower. So, for that reason I am going to go through carbocation in really details to make sure you understand the fundamental of carbocation, what are the different type of reactivity and stability parameters. So, let us start with that. In this course, first thing we are going to learn about the electronic structures, their geometry, molecular orbitals, and then we are going to learn their different classification, what are the different type of carbocations. We are going to learn about the primary, secondary, tertiary, benzylic, allylic and all the different classes.

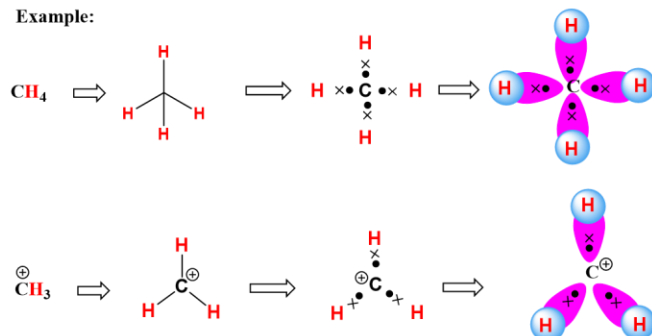
We are going to compare their stability. So, that is very important as you will know slowly, that is going to dictate some of the reaction rate. So, there are different parameters like hybridization and then there will be inductive effect, there will be resonance effect, there will be the hyperconjugation. So, those are the things going to play a role to compare their stability.

So, first things, I think if you try to define what is carbocation? In this term itself there is a carbo and there is a cation. So, the carbo comes from the carbon and then the cation is the positive charge. So, if you look into the first example, I have a simple molecule is methane. If you see about methane this has a sp^3 hybridized carbon having the carbon attached with the four hydrogens. Now, as soon as we abstract one hydrogen as H- from methane, then it will generate a carbocation here.

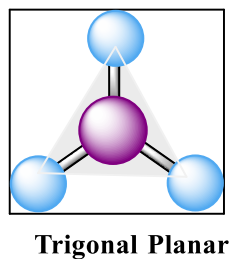
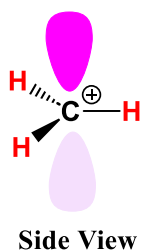
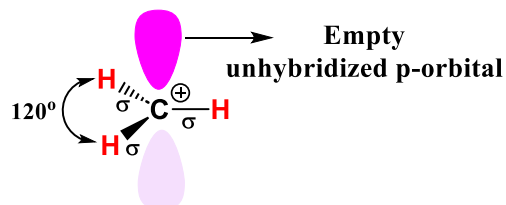
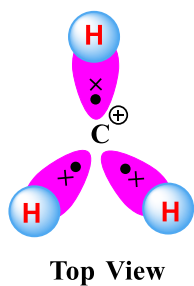
Structure:



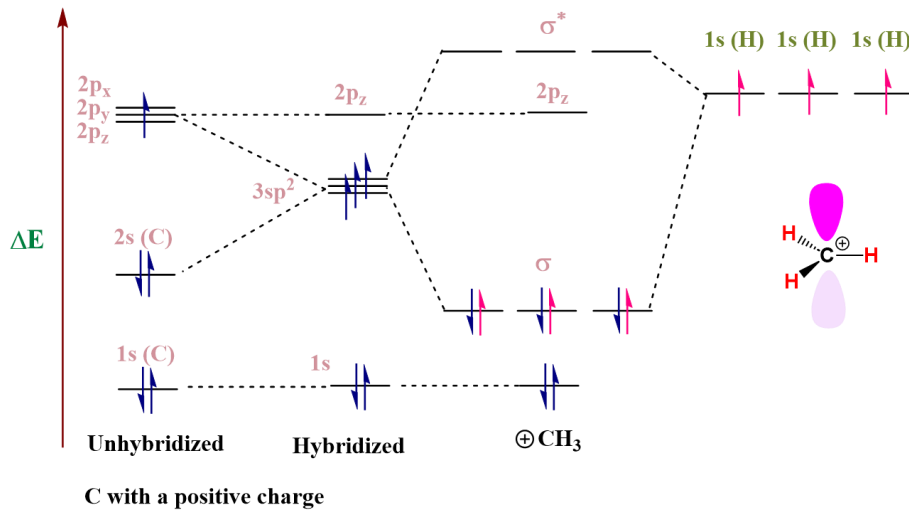
Example:



So, you can see now it will generate a CH_3^+ . So, it will generate a CH_3^+ now if you see if you compare them a CH_3^+ and a methane (CH_4) they have lot of difference not only their structure but in their reactivity also. If you try to understand the structure of this compound then you can see that we have carbon attached with three hydrogen and it is a trigonal planar structure that means the carbon here is sp^2 hybridized, which was sp^3 when it was methane.

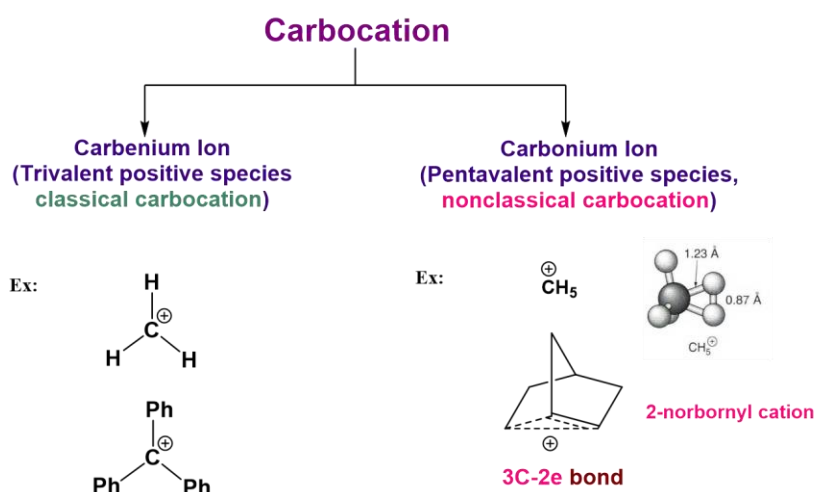


So, not only that, now if you try to understand their bonding through the molecular orbital you can see that in the terms of carbon with a positive charge in unhybridized state you have five electrons here.



you can see there are two in the 1s orbital, two in the 2s and one in the p-orbital. The electron in the 2s and the p-orbital forms the hybridized sp^2 orbital. So, you can see there are three sp^2 orbital here and then you have an empty p-orbital. So, you have a three sp^2 orbital here and then you have another p-orbital which remain empty. Now, there are the the 1s orbital of hydrogen which going to form the σ -bond with this sp^2 orbital. So, we will have a three σ -bond. So, that is going to be the molecular structure for a methyl carbocation.

Now, we are quickly trying to understand that in the next slide that what are the different type of carbocation. Again, I think, the definition of carbenium versus carbonium actually proposed by Professor George Olah. Professor George Olah, received Nobel Prize in Chemistry in 1994 for his contribution to the carbocation chemistry. So, he defines that carbocation can be classified with carbenium ion and carbonium ion.



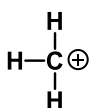
Prof. George A. Olah
1994 Nobel Prize in
Chemistry

So, the carbenium ion will be the one which the one in the beginning which is going to be the very similar to the carbocation the classical carbocation which I am going to discuss in the class, but the other class is the carbonium ion. In the carbonium ion the first thing is the pentavalent positive species that means, he reported in his publication that formation of this CH_5^+ . So, this CH_5^+ can only form if you take methane with a very strong acid which can even protonate methane and the structure going to look like there is a trigonal pyramidal with this the $-\text{CH}_3$ which is attached with this hydrogen here. The other class of this type of carbonium ion is the nonclassical carbocation. So, here is an example of norbornyl cation where you can see the formation of three-centre and two-electron bonds and we are going to talk about a lot in the future classes. what is the different method for their formation and what are the importance of the nonclassical carbocation.

So, now I am going to talk about mostly in the first class which is the carbenium ion? So, first I am going to start with the different classification of carbocations. So, I am going to start with the first classification where you have a methyl carbocation. So, what I have done in this classification you can see I have classified carbocation based on the number of hydrogen atom attached. If there are three hydrogen atoms attached, we call it methyl. If there is two hydrogen atoms attached, we call it the primary carbocation. If there is a single hydrogen attached, we call it a secondary carbocation. And if there is no hydrogen atom attached, we call it a tertiary carbocation, which is this last class. And there are other class of carbocation as well.

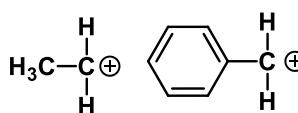
Methyl Carbocation

Three hydrogens attached to the C^{\oplus}



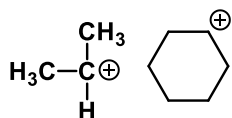
Primary Carbocation

Two hydrogens attached to the C^{\oplus}



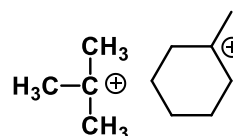
Secondary Carbocation

One hydrogens attached to the C^{\oplus}



Tertiary Carbocation

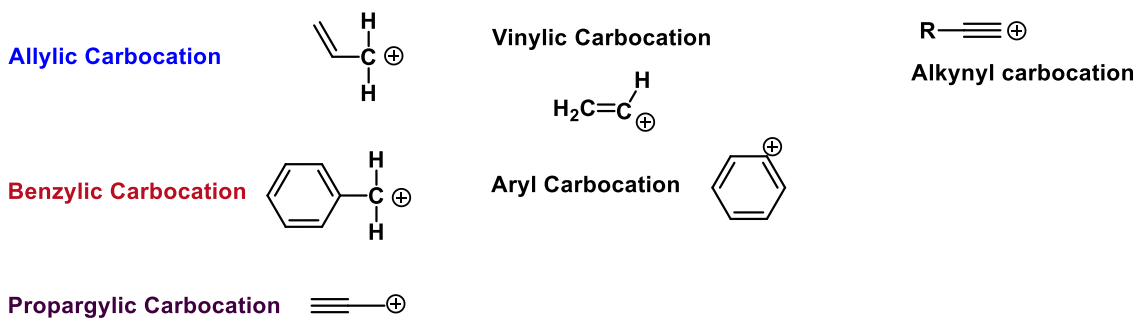
No hydrogens attached to the C^{\oplus}



We are going to talk about the allylic carbocation here, where you have a double bond which is attached with this carbocation. Then if there is a phenyl ring we call it a benzylic

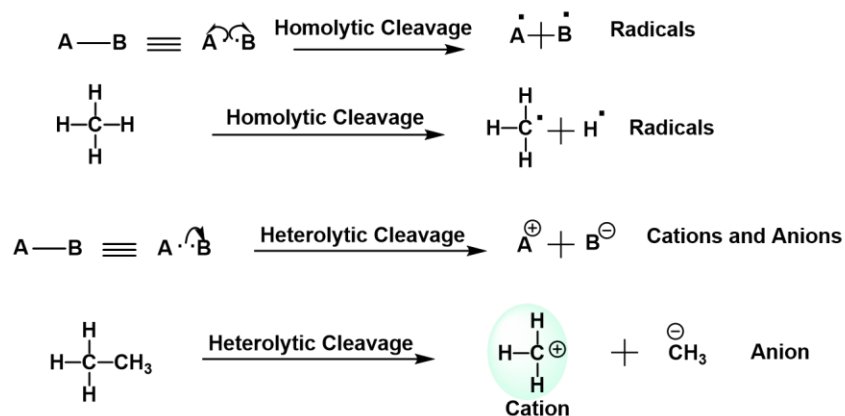
carbocation and then if it is on the top of the double bond we call it a vinyl carbocation when the carbocation is forming on the sp^2 carbon. Then, if it is next to alkyne we call it a propargylic carbocation. If it is formed the aryl ring itself, we call it aryl carbocation and then we have alkynyl carbocation here.

Positive charge on Csp^3 center *Positive charge on Csp^2 center* *Positive charge on Csp center*



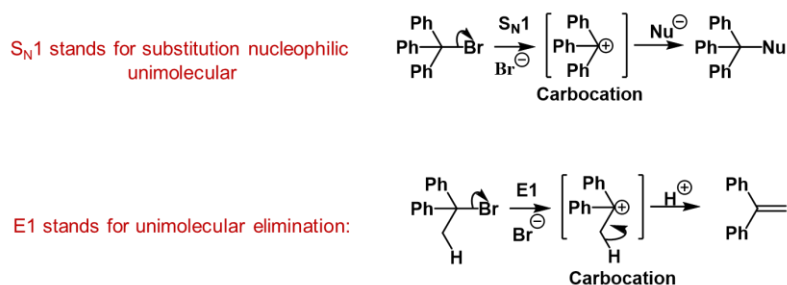
So, after learning, different classification of this, carbocation, what we are going to learn slowly about formation of carbocation. So, one of the methods to form carbocation has to be some sort of a heterolytic cleavage. That means that you have to cleave a bond heterolytically so that the one part will take these two electrons form a negative charge and the other part will be a positive charge which you call it as a carbocation. And the other type of cleavage of this bond is the homolytic cleavage, I am going to talk about during the radical chemistry where the after the homolytic cleavage you can form these radicals.

The synthesis of carbocation via the heterolytic fusion of a chemical bond



Now, we are going to talk about the different synthesis method for carbocation generation. And one of the elementary reactions in the organic chemistry which you must have learned in the organic chemistry is the S_N1 reaction. It is a very important reaction here the first step is the you can see first step there is a leaving group here there is a carbon bromine bond we are talking about what is going to happen. So, there will be the bromine will come out from this C–Br bond there will be some sort of ionization going to happen it will generate a Br^- and a C^+ which will generate a carbocation, and in the S_N1 reaction the first step is the dissociation of this C–Br bond is the rate determining step. That means, the formation of carbocation is very important here and the stability of carbocation is also important as that going to play important role into the reactivity. After the carbocation forms the nucleophile attacks to form the product.

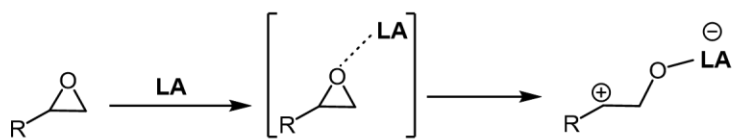
We have two mechanisms that encompass the carbocations as the key intermediate



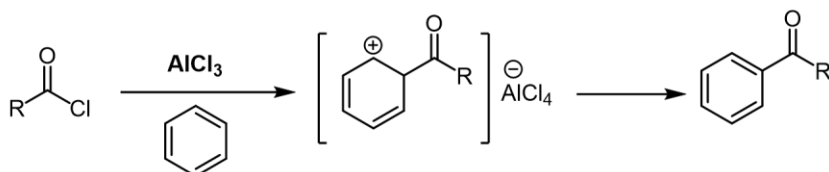
The other important reaction is the E1 elimination, which is a unimolecular elimination reaction, where the first step is also the dissociation of carbon bromine bond to form the carbocation. But now if you have a carbon which has a carbon hydrogen bond then this hydrogen will be abstracted as a H^+ to form this olefin here, through E1 elimination.

So, these are the methods for generation of the carbocation and then there are other method like the epoxide ring opening, where you can see that if you have epoxide and once you put a Lewis acid, what is going to happen? It is going to make a carbocation as well. The other important elementary reaction is the Friedel-Crafts reaction. We all know about that when an electrophilic Lewis acid like $AlCl_3$ with acid chloride with a benzene ring, it goes via electrophilic aromatic substitution to generate a carbocation again here. after that, the hydrogen getting abstracted to form the corresponding acylated benzenes.

Epoxide ring opening:

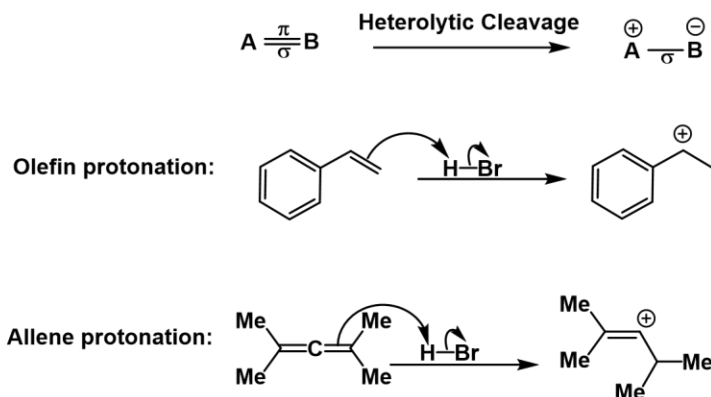


Friedel-Crafts reactions :



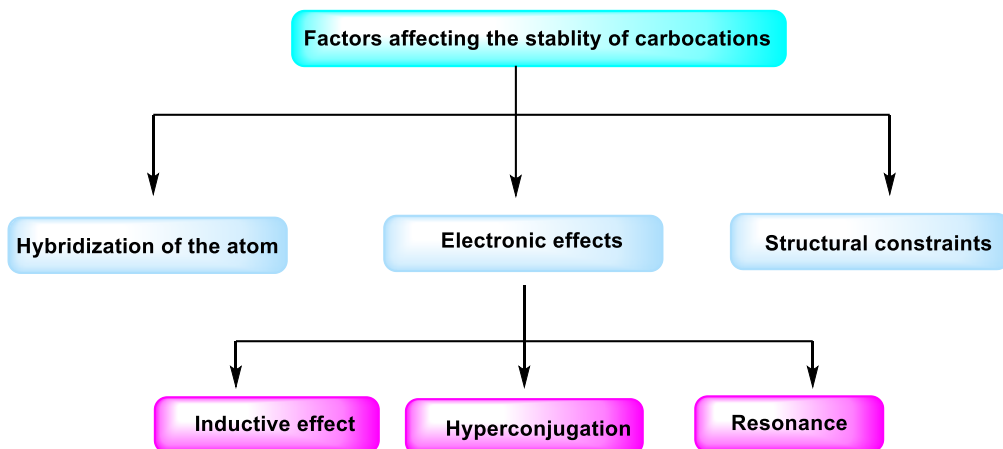
The other type of reaction where the carbocation form is if you can protonate an olefin or alkyne or allene. That means, if you take an acid with the olefin it will take the π -electron cloud and generate a carbocation. It can form the benzylic carbocation if it is styrene, if you start with an alkyne then it will form a vinyl carbocation. And if it is happening from the allene it can also form a vinyl carbocation as well. So, why I am talking about this vinyl carbocation and benzylic carbocation. And so, now what we are going to learn that among these all these different types of carbocation we have classified which one of them is more stable. So, that the reaction if you are performing a different chemical reaction that will if the carbocation formation will be the rate-determining step, then that will be the reaction that will be faster.

π -electron shifting to an electrophile :



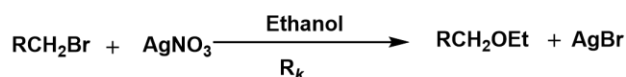
So, there are different factors to compare their stability. One of the important factors is that we go for the hybridization of the carbon where it is forming, then there are

lot of electronic effects, we are going to talk about this inductive, hyperconjugation and resonance effect throughout my lecture.



One of the things about this carbocation formation is this S_N1 reaction which I was trying to mention in couple of slides back. that if you are performing this S_N1 reaction with a primary versus secondary versus tertiary alkyl halides What is going to happen? The reaction rate increases once you go from primary to secondary to tertiary you can see the difference here. So, why there is a rate increase? Because, as I said, the carbocation formation is the rate determining step, now the stability of the carbocation makes a difference. If it is a more stable it will be much more reactive. So, that is why for tertiary the reaction rate is much higher compared to the primary.

Carbocation stabilization controlling the S_N1 rate:



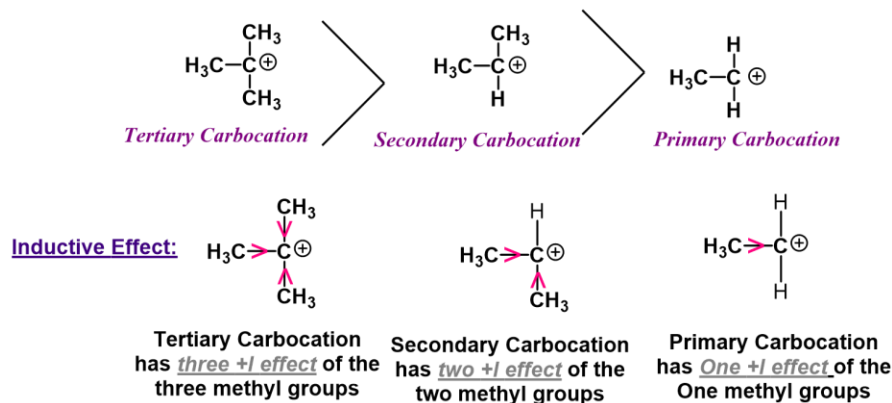
R_k : Rate of the forward reaction

	R	Formed carbocation	R_k	
Carbocation stability increase ↓	Et		0.07	Reaction rate also increase ↓
	ⁱ Pr		0.12	
	^t Bu		2100	

And now, I am going to compare them why the tertiary carbocation is more stable compared to a secondary versus a primary? You can see here in case of tertiary carbocation, now I am going to talk about a inductive effect. We all know the methyl

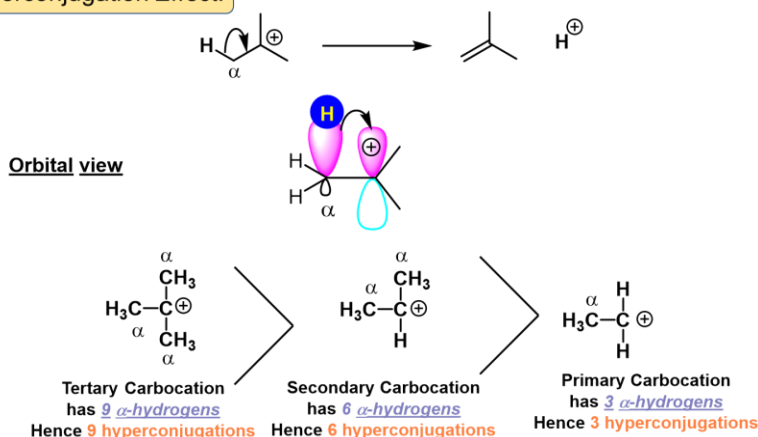
group has a +I effect, through +I effect it can stabilize a carbocation. Now, you can see for tertiary carbocation you have three methyl group. participating in the inductive effect, but once you come to secondary there is two methyl group participating in inductive effect and once you come to primary there is only one methyl group which is participating.

Why dose the 3° carbocation is more stable over 2° and 1°?



We can explain this result also via the hyperconjugation, we all know about the hyperconjugation what happened there? A σ -bond try to give electron density to the corresponding empty orbital. So, what is happening here? This σ - of this C-H bond giving electron density to this empty p orbital here in the carbocation. So, now this electron donation tendency if you come to the tertiary carbocation, you can see there are three CH_3 group are attached with this. That means, it has total 9 α -hydrogen which can participate in the hyperconjugation compared to the secondary there will be 6 and 3. As the number of hyperconjugation decreases the stability getting decreased. So, this is all about the hyperconjugations and the inductive effect.

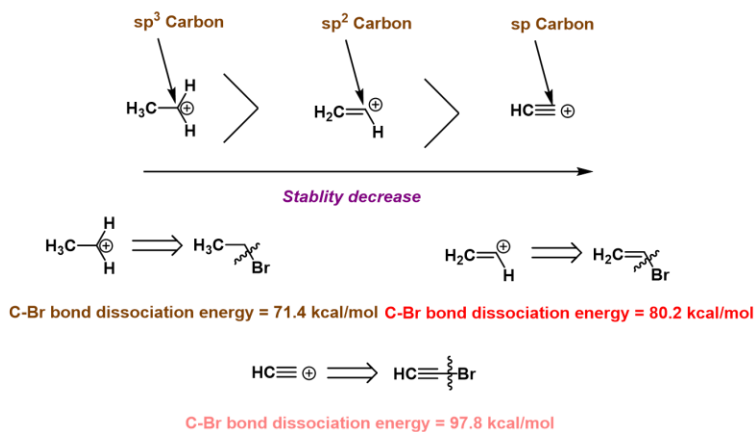
Hyperconjugation Effect:



Now, we are going to learn about that, what will happen if the carbocation is forming in a

sp^3 carbon versus sp^2 carbon versus a sp carbon. So, you can see from this bond dissociation energy that for sp^3 carbon it is 71.4 kcal/mol, for sp^2 carbon is 80 kcal/mol, but for sp it is close to 100 kcal/mol. So, you can see there is a huge difference in this bond dissociation energy. One of the things is that, once you go from sp^3 to sp^2 to sp , the percentage of s character getting increased.

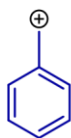
Higher s-character leads to unstable carbocation



As the percent of s character getting increased, the carbon is become more electronegative and it has tendency to withdraw or attract more electron density. And now, if that is happening it is getting hungrier for electron and getting more and more destabilization. So, that is why you will see that the formation of the carbocation in a sp^3 carbon is very common with sp^2 it is less common and with sp it is very rare.

So, now I am going to move to the other type of effect which is called the resonance effect. So, how this resonance effect is important? Now, I am going to show you two different type of carbocation one is benzylic and one is allylic.

Resonance effect:

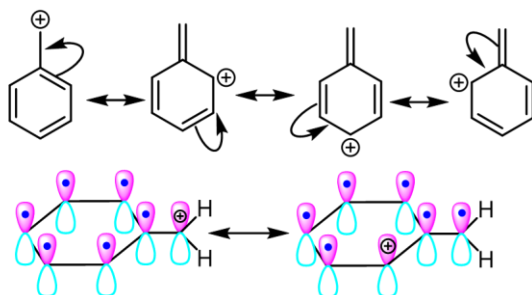


Benzylic carbocation

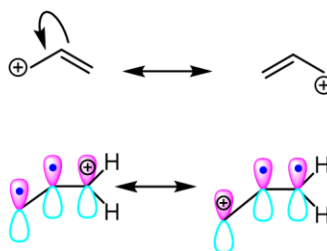


Allylic carbocation

Four resonating structures:



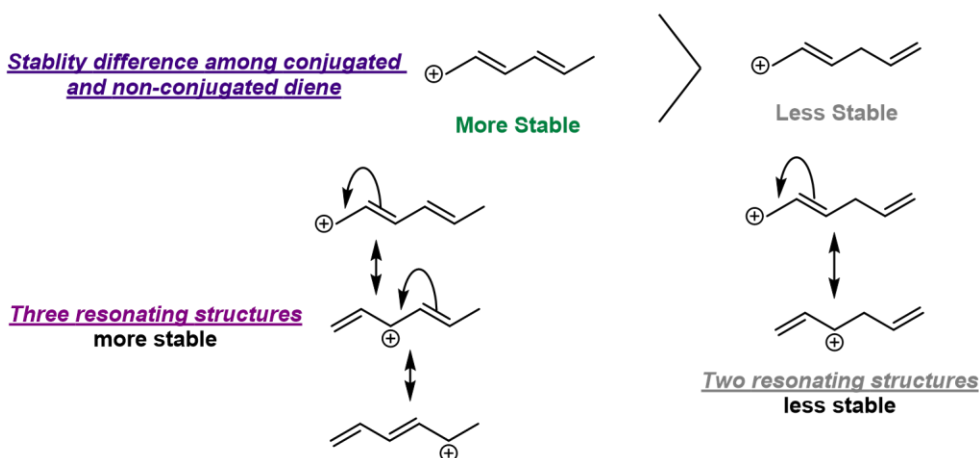
Two resonating structures:



Just looking into them you might think they are just primary carbocation. because the carbon is primary, but then it is attached with a double bond here in case of allylic, and it is attached with a phenyl that makes a huge difference because now that can have a resonance structure. We have learned about this canonical structure; we have drawn this canonical structure here which you must have drawn in your organic chemistry. You can see there are four resonating structures here and, but there are only two resonating structures here. So, this resonance structure really makes this carbocation stable compared to a primary. That means, if you are performing a S_N2 or S_N1 reaction versus with a benzylic bromide, allylic bromide with a simple alkyl bromide your reaction rate for benzylic will be more compared to allylic and then compared to the primary alkyl halide because of this resonance stabilization. So, this actually play a very important role.

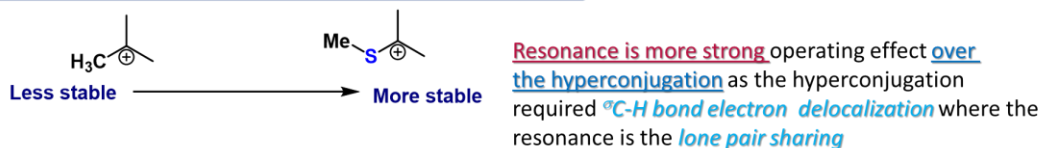
Then the other thing is in the previous slide what we have learnt only about allylic. Now, the question comes after allylic, if you have another double bond that means if you have a 1,3-diene type of conjugated system. Now, if you have a conjugated versus you have a non-conjugated means there is a break here. So, there is a break, we call it non-conjugated. Then the conjugated structures will have more number of resonance structures you can see here compared to the non-conjugated and the conjugation gives this carbocation even more stability. So, that is why this carbocation will be more stable compared to the others.

Stability increase with the number of resonating structures:

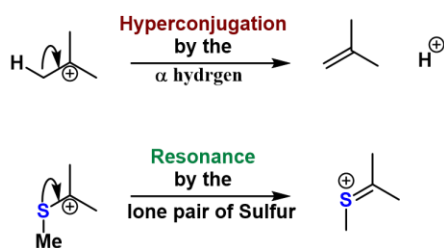


And then that the next another important aspect is we have learned about the hyperconjugation and now we are trying to learn about the resonance effect. So, if there is a carbocation like $-\text{CH}_3$ versus $-\text{SMe}$, now which one will be more stable? Now, this resonance effect will be more stable compared to the hyperconjugation.

Resonance predominant over hyperconjugation



Mode of stabilization via +R effect:



In case of resonance effect, the lone pair of the sulfur which is actually donating to this carbocation compared to the $\sigma\text{-C-H}$ bond electron delocalization. So, that is why this resonance effect going to be the prominent one which will be the most stable compared to the hyperconjugation. We can also explain this very same thing using inductive effect versus the resonance effect. You can see the resonance effect will be always winner compared to the inductive effect of this group.

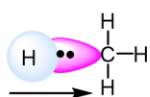
Now what about if you have F, Cl, Br, I, O all these different atoms. Now, all these different atoms have a different electronegativity. We know from the electronegativity definition that is a atom electronegativity of atom indicates the tendency to hold the bonding electron and the lone pair tightly. That means depending on this electronegativity the tendency to donate this lone pair will be getting decreased.

Electronegativity:

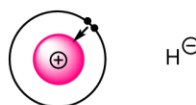
Electronegativity of any atom indicate the tendency to hold the bonding electrons and the lone pair tightly

More electronegativity of an atom
Tightly hold the lone pair
Less tendency to lone pair donation for resonance

Atom	EN (Pauling scale)
F	4.0
Cl	3.0
Br	2.8
I	2.5



The attraction of bonding electron towards electronegative atom



The attraction of outer shell electron towards nucleus

So, we are going to see clearly here in this example that if we have nitrogen versus oxygen versus fluorine. What is happen? We are seeing the electronegativity getting increased from this direction, but at the same time the stability of the carbocation getting decreased, because the lone pair donation capacity getting decreased from nitrogen to oxygen to fluorine. So, that is going to be the deciding factor here for the stability.

Attachment of the electronegative/electropositive atoms

Electronegativity of the attached atom:

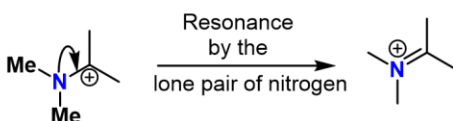
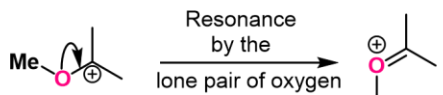


Electronegativity **N** = 3.0 in Pauling scale

Electronegativity **O** = 3.44 in Pauling scale

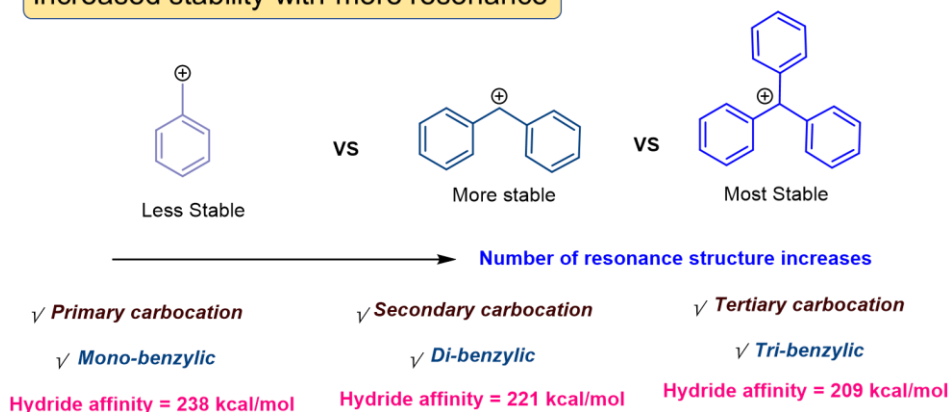
Electronegativity **F** = 4.0 in Pauling scale

Mode of stabilization via +R effect:



So, previously we have learned about the benzylic and allylic systems, where we have learned about mostly about this monobenzylic system, where there is a phenyl ring with a carbocation here in the benzylic position. Now, if there is di-benzylic or there is tri-benzylic. So, if you happen by looking into that it is looks like this is a primary, secondary, tertiary it is not like that. There is another effect we have to consider which is the resonance effect. So, once you go from the mono- to di- to tri-, the number of resonance structure getting increased. And that is why the tribenzylic carbocation can be isolated and stored. So, I told at the beginning the carbocations are not able to isolate, but this carbocation because of this stability it can be able to isolate.

Increased stability with more resonance

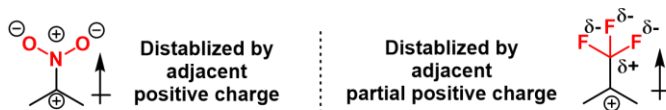


Beside we also can correlate with the hydride affinity of the carbocations

And then we are going to learn about some other effect like if you have a electron withdrawing group. Suppose you have a carbocation where electron withdrawing group is attached. So, what is going to happen if there is a withdrawing group there. that going to destabilize the carbocation. And now there are different type of electron withdrawing group. Now, if I am going to compare $-NO_2$ versus $-CF_3$ both are electron withdrawing, but $-NO_2$ you have a positive charge on nitrogen so that is very strong electron withdrawing. Now if you have a very strong electron withdrawing group there it will even destabilize the carbocation more. That means, if you have a $-NO_2$ versus $-CF_3$, the $-NO_2$ will be more destabilizing.

The nature of the attached functional groups:

Carbocations are destabilized by the neighboring electron-withdrawing groups

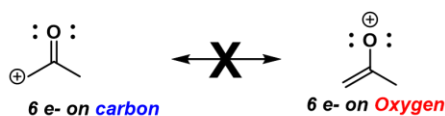
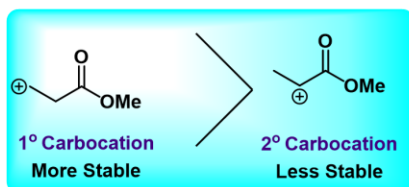


Higher distabilization by nitro group

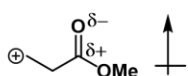
Now, the other example is by looking into this example that you have a 1° carbocation versus a 2°, but one of the differences here this 2° carbocation is attached with next to an ester group. Although, it is a 2°, but the problem is it attached to electron withdrawing group and the carbonyl carbon is electron deficient. So, it cannot able to participate, it cannot able to form a resonance structure by making oxygen positive, that is not possible.

So, that is why this carbocation will be unstable carbocation here, although it looks like a secondary, but it is an unstable carbocation.

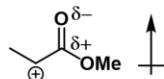
Position of carbocation:



This resonance is forbidden as the more electronegative atom must have a full octet



Although it is a primary carbocation
But no distbalization effect operates



Although it is a secondary carbocation
But distbalization effect operates due to the presence of electron withdrawing group

So, in this particular topic what we have learned, we have learned that carbocations are very highly reactive intermediates. We have learned that it having a 6 electron when it forms bond with these 3 hydrogens and we talk about there is a vacant p orbital in this which is electron deficient which can take electron density from another nucleophile. I have talked about different classification like primary, secondary, tertiary,

allylic, benzylic, vinylic, propargylic and I have talked about different type of effect like inductive effect, hyper conjugation, resonance effect and how you generate different type of carbocation we also talk about them and then we have compared their stability which is very important once you compare their different type of reactions. So, these are the books you have to follow Clayden organic chemistry books which also talk about carbocation, then there is Carey-sundberg books, then the organic chemistry books by Smith and then there is a modern physical organic chemistry book.

Also there is a books on the carbocations chemistry by Olah which is little more advanced if you want to know even more about that. And thank you all for the listening and thank you.