Principles and Applications of NMR spectroscopy
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Module 2
Lecture No 07

Welcome back, in the last class we looked at how the chemical shifts of a different functional groups in a molecule vary with respect to the ppm values. so we will today look at the different factors which influence these values, why these different functional groups why do they come at different values of ppm and this is how we can understand or assign or interpret the different NMR spectrum.

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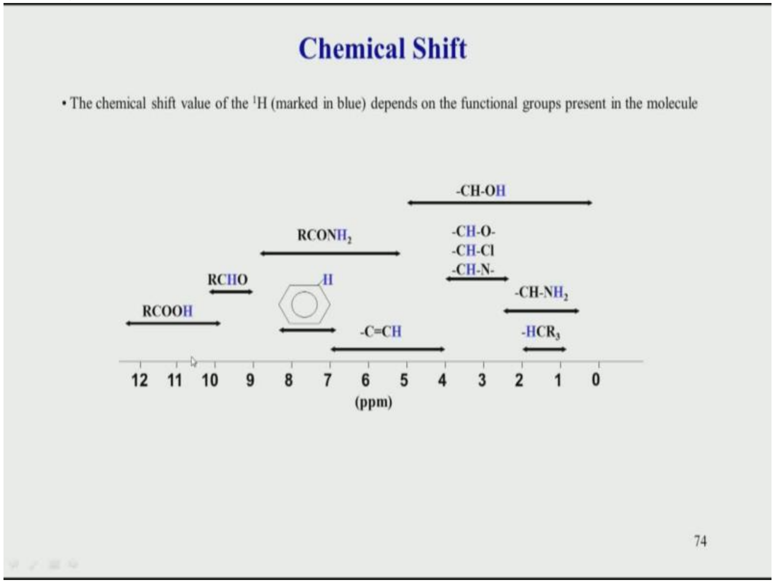

Chemical Shift

- The chemical shift value of the ^1H (marked in blue) depends on the functional groups present in the molecule

So, let us start from the last slide which was shown in the last class. So, we looked at the chemical shift values of different functional groups here which is shown. Yes so we looked at the Methyl groups which comes very up field shifted or many times or always between 0 to 2, 2 .5 ppm then as you add more electronegative atoms like nitrogen, chlorine, oxygen they start going what is called down field. So, to recollect the last time we mentioned that anything which is a on the right side typically towards 0, 1, 2, 3, we use the word up field shifted and the one which is towards a lower values like 7, 8 and so on we call them down field shifted.

So, remember this is just a qualitative notation to decide which is more upfield and downfield. Typically the center of spectrum.. we talk with respect to that. So, you can see that in this aromatic functional groups the hydrogen atom which is attached to an aromatic ring or amide nitrate, an amide proton, that means hydrogen is attached to CONH2 and these kind of functional group they come very much downfield shifted downfield **in the** lower field or lower ppm value, higher ppm value and this carboxylate group very typical it comes there very high chemical shift value.

So, looking from NMR spectrum, looking at these functional groups one looking at the peaks in this from regimes one can very easily identify the different functional groups. This is only a limited set of functional groups which is shown here, as we go further we will see more and more detailed analysis of more different functional groups.

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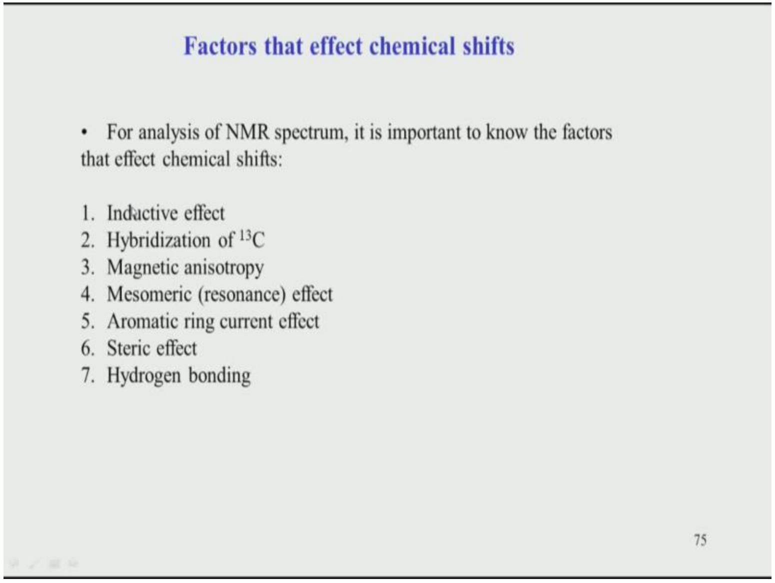

Factors that effect chemical shifts

- For analysis of NMR spectrum, it is important to know the factors that effect chemical shifts:

1. Inductive effect
2. Hybridization of ^{13}C
3. Magnetic anisotropy
4. Mesomeric (resonance) effect
5. Aromatic ring current effect
6. Steric effect
7. Hydrogen bonding

so, the now the question arises is what determines these kind of values? Who how do you decides that a particular hydrogen atom will come in the downfield region, up field region and so on?

So, there are variety of factors **which** affect or influence the chemical shifts and these are listed here some of them the these are the major factors. we will try to go one by one to these affects. So, the most important effect is inductive effect then followed by hybridization and so on.

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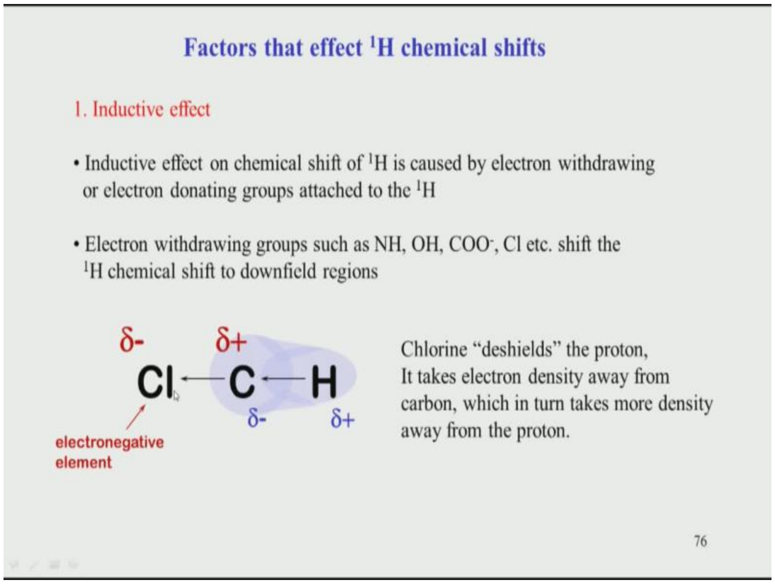

Factors that effect ^{1}H chemical shifts

1. Inductive effect

- Inductive effect on chemical shift of ^{1}H is caused by electron withdrawing or electron donating groups attached to the ^{1}H
- Electron withdrawing groups such as NH, OH, COO^-, Cl etc. shift the ^{1}H chemical shift to downfield regions

Chlorine "deshields" the proton, It takes electron density away from carbon, which in turn takes more density away from the proton.

So, let us start from inductive effect, how does that influence the chemical shift value? So, what is an inductive effect?

Inductive effect is a very simple concept. The idea is that suppose you have an electronegative atoms such as chlorine, oxygen, nitrogen these electronegative atoms they draw the electron cloud towards themselves because they are more electronegative if they are attached to a more electropositive atom. So, for example, here you see carbon is more electropositive compared to chlorine which is electronegative and therefore, **the electron cloud** density around this carbon is removed is less dense because it is been attracted towards the chlorine.

Now, in what happens is if that if the hydrogen electron cloud is attracted towards the chlorine that the electron cloud around this hydrogen also gets pulled towards this chlorine. So, essentially chlorine is acting like a pulling the electron cloud towards itself because of it is strong electronegative nature and if the (elec) electron density around this hydrogen is reduced what happens is thus if you recollect one of the class we discussed that (the elect) the chemical shift comes because the electrons around the hydrogen atoms, they do, they shield this hydrogen nucleus proton from the main magnetic field but now if I remove this electron that is by reducing the electron density the shielding effect is reduced.

So, therefore we use the word de-shielding. So, we say that chlorine de-shields the proton because it takes away the electron density from that carbon which in turn takes away the density from proton. So, this is the electron withdrawing effect and this is typically **observed in** functional groups such as NH,OH, Carboxylate, Chlorine et cetra and they shift because of that this hydrogen now will appear at a chemical shift value where is down field shifted.

So, this is what we saw in the previous slide. There is a Hydrogen attached to a chlorine it comes down field shifted. If there was another hydrogen here instead of a chlorine then this would become a methylene group CH2 group and that would not have so much of de-shielding effect because Hydrogen is not so electronegative compared to carbon and therefore, a CH2 system the Hydrogen will now appear in the regular up field shifted position but because of the attachment of a chlorine atom to a carbon to which hydrogen is attached this hydrogen becomes de-shielded and appears at a low chemical shift or higher chemical shift or relatively higher chemical shift value.

So, this is one of the simple idea of (elect) inductive effect and this can be further extended to more systems.

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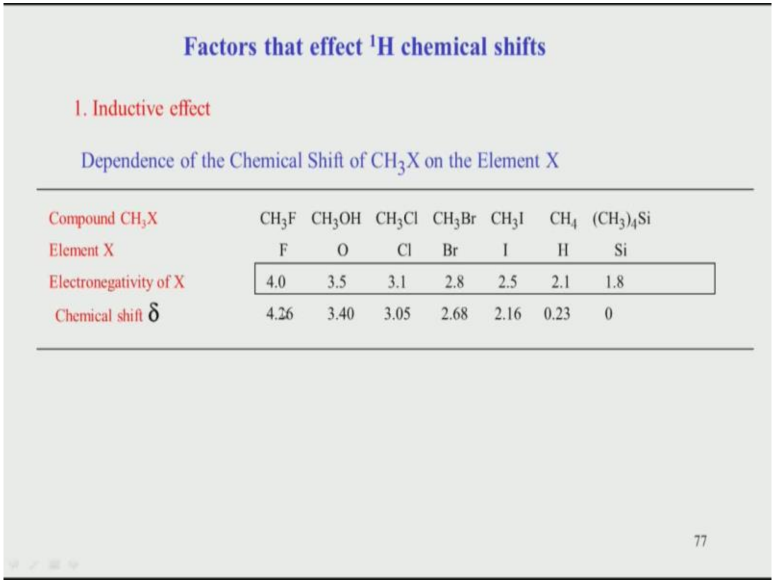

Factors that effect ^1H chemical shifts

1. Inductive effect

Dependence of the Chemical Shift of CH_3X on the Element X

Compound CH_3X	CH_3F	CH_3OH	CH_3Cl	CH_3Br	CH_3I	CH_4	$(CH_3)_4Si$
Element X	F	O	Cl	Br	I	H	Si
Electronegativity of X	4.0	3.5	3.1	2.8	2.5	2.1	1.8
Chemical shift δ	4.26	3.40	3.05	2.68	2.16	0.23	0

So, this is what is shown here for different X atoms. So, this is a simple CH3X system where X can be any other heteroneuclus. it can be electronegative elements such as here. So, this is the most electronegative element in the periodic table fluorine. So, when you have a CH3F system the F withdraws a current electron density from the carbon which in turn withdraws from hydrogen. So, therefore CH3F the hydrogen in CH3F comes at a very down field shifted ppm typically around 4.26 ppm. Okay.

So, if you go to the Oxygen now the next electronegative in the series, we can see here that again oxygen pulls the electron density away from the CH3. So, we are all looking at CH3 and not at OH. So, the CH3H hydrogen atom now becomes de-shielded because of this electronegative nature of oxygen and that comes at a ppm value of around 3.4. So, we can see as nice as linearly as the electronegativity decreases the chemical shift also decreases. So, this is going in hand in hand with our idea that inductive effect is because of the electronegative nature. So, similarly if we go to higher heavier Halogens, we know that the electronegativity decreases.

So, for example, if you look at CH3I system, it is coming at also downfield shifted which is 2.16 compared to methane but it is up field shifted compared to methyl chloride. So, we can see that between these two both are halogens I mean halides but because chlorine is more electronegative than Iodine this the inductive effect of Iodine is less compared to inductive effect of Chlorine and therefore, a CH3I molecule will have a hydrogen coming at up field shifted compared to CH3Cl and Methane which is all hydrogen atom asymmetrical molecule is the most up field shifted and it will come at zero.

So, remember again we are looking at a reference. So, we will, we saw in the previous class how we actually calculate chemical shift values. So, what typically we do is that we take a reference molecule which can be any molecule of our choice typically standard is used which is agreed upon an IU pack standard which is agreed upon by everyone and that is tetramethylesilane This is a tetramethylesilane and what we use word the word TMS. So, this is an organic compound which comes at a field value .We arbitrarily or we forcefully assign this as zero.

So, you have to keep in mind that it is not that the chemical does not have any chemical shift value. This link the Tetramethylesilane and the hydrogen atom in tetramethylesilane is definitely has a chemical shift value but we called we put it as zero. So, when we put that as zero the that becomes our reference and with respect to that all other chemical shifts are calculated. So, chemical shifts are calculated based on this idea. You can choose any other molecule as zero but there are different reasons why we choose this particular as a reference compound.

We will see that again in the later slides in the later classes, one of the reason is this is a very inert sample compound. It will not interact with the compound in your sample. And therefore, and secondly it is independent of the many conditions such as temperature and pH. There is of course slight variation but those variations are very minor compared to what happens in your molecule. Hence therefore, it is and also it has a very strong signal. It has 3 into 4 12 types of hydrogens because all CH3 are equivalent. We will look at equivalence later.

So, the point here is that this tetramethylesilane is ideally suited for a molecule which is away from can from molecules or Hydrogen atom comes at a very up field shifted chemical shift and at the same time it is a inert compound. So, that has been designated used as s reference all over the world and that reference with respect to that you calibrate. So, we use word calibration. Calibration is basically decide first set that chemical shift of the reference to zero and with respect to that you can measure what a any other chemical shift.

So, this is the point to drive here is that chemical shift reference in a way is an arbitrary concept. It is arbitrarily you decide one particular hydrogen atom as reference and we will measure with all respect to that and we also saw in the previous class that chemical shift reference chemical shift value does not depend on the frequency the spectrometer frequency when you measurein ppm scale. So, chemical shift in ppm scale does not change. So, if you say, if I say is 0.23 ppm for CH4 Methane it will be the same in every spectrometer whether it is a 300 MHz whether it is 600 or 900 this value does not change, the reason being we always set in that particular frequency reference as zero ppm. So, everything is with respect to that remains constant.

So, there is a idea which we discussed in the last class and we this will come up again later on.

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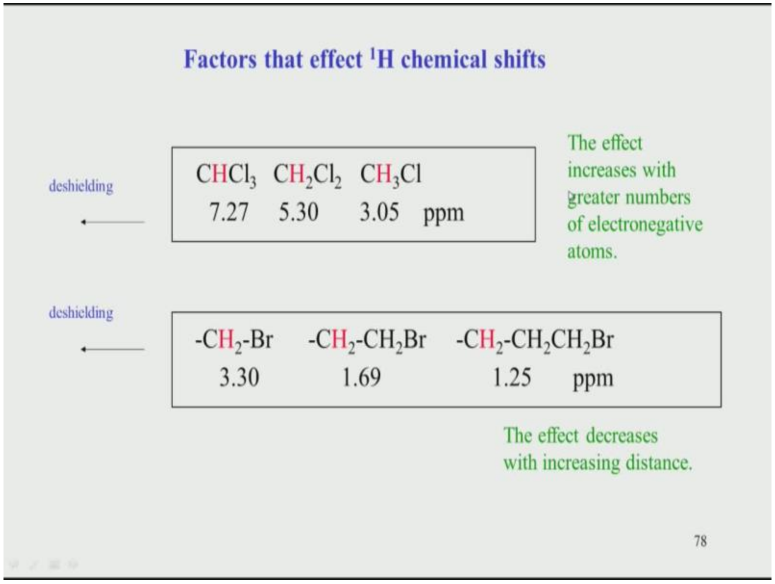

Factors that effect ^{1}H chemical shifts

deshielding ←

$CHCl_3$	CH_2Cl_2	CH_3Cl	
7.27	5.30	3.05	ppm

The effect increases with greater numbers of electronegative atoms.

deshielding ←

$-CH_2-Br$	$-CH_2-CH_2Br$	$-CH_2-CH_2CH_2Br$	
3.30	1.69	1.25	ppm

The effect decreases with increasing distance.

So, now let us look at what happens if there are more a little bit more at the inductive effect. So, you can see now there are Chlorine atom attached compared to methyl chloride. So, you see this is Methyl chloride, Methelenedichloride and Chloroform. So, you see in Chloroform there are three carbon atoms, three chlorine atoms sorry. So, when you have three number of chlorine atoms you expect more electronegative effect because three is more stronger in electro pulling electron density than one Chlorine atom.

So, when you have three Chlorine atoms they very strongly pull the electron density away from the carbon and hydrogen and therefore, this hydrogen has very less electron density around itself and if it has less electron density it is less shielded from the main magnetic field and therefore, it comes in de-shielded. So, shielding is remember shielding is essentially protecting that nucleus from the main magnetic field. So, it pushes that a hydrogen atom up field near zero ppm but if you remove that shielding effect it goes more down field towards 7 or 8 ppm.

So, this is what we are seeing here. Now if I reduce the number of chlorine atoms I make it only two chlorine atoms then there is reduction in the inductive effect because one chlorine atom has gone and has been replaced by hydrogen which is not at all as electronegative as chlorine. So, by reducing one chlorine atom I have actually reduced the de-shielding effect and therefore, this hydrogen is now less de-shielded compared to this original inductive less chloroform.

Now, if I remove one more chlorine this is what we saw in the last slide a simple Methyl Chloride system. Here, there is only one chlorine but still it has a electronegative effect and that create that results in a chemical shift value of 3ppm. So, as I keep adding more and more chlorine it is a simple linear increase in the chemical shift value. So, this is what is written here, the effect increases with greater number of electronegative atoms. Now we can do another look at another molecule where we insert a CH2 between the Hydrogen and the electronegative atom.

so, if you see here there are two CH2s and Bromine is located far away. So, we are looking at this Hydrogen atom keep in mind we are looking at the one which is shown in red color. So, we are now looking at this Hydrogen atom. So, there is one Bromine directly attached to this Carbon and that is the electronegative effect again which we saw in the previous class, previous slide sorry, but now if I insert a Methylene group in between this bromine and CH2. I am reducing the effect of this Bromine on this Hydrogen why because now in between there is a interfering group and this is located further away from this hydrogen.

So, It is effect electronegative effect pulling the electron cloud from this Hydrogen is reduced considerably and that results in this Hydrogen getting back in to the shielded state and therefore, the ppm value is going up field. similar the situation if I insert one more CH2 in between and this Bromine now gets further away from this Hydrogen and therefore, it is much further again shielded. So, if I keep inserting CH2s in between I keep going further an further away from Br bromine and the electronegative effect of the terminal electronegative atom on this hydrogen will reduce and slowly it will move towards the final the most shielded up field shielded chemical shift value that is it will move closer towards Methane.

So, remember in the previous slide we saw that Methane has the most up field shift in a in the CH4 that is 0.3 ppm. So, that is what is shown here that the effect decreases that effect means the electronegative or an de-shielding effect of the electronegative atom decreases with increasing distance from Hydrogen.

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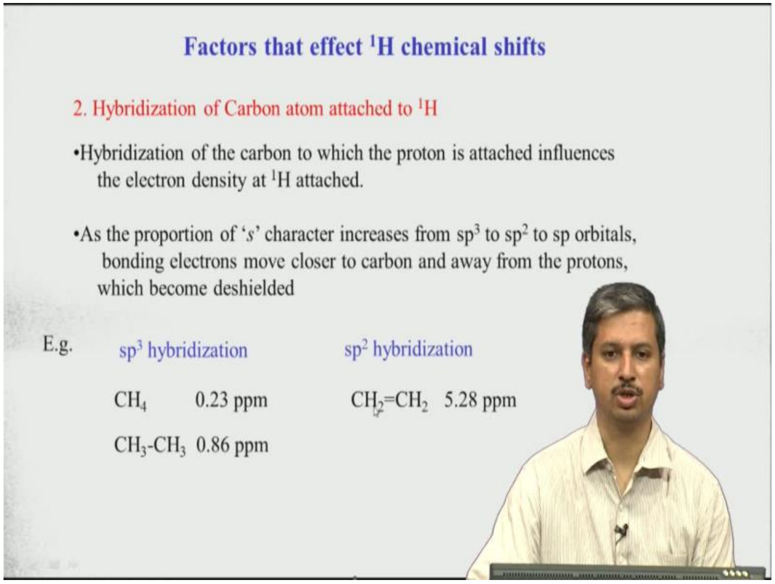

Factors that effect ^1H chemical shifts

2. Hybridization of Carbon atom attached to ^1H

- Hybridization of the carbon to which the proton is attached influences the electron density at ^1H attached.
- As the proportion of '*s*' character increases from sp^3 to sp^2 to sp orbitals, bonding electrons move closer to carbon and away from the protons, which become deshielded

E.g.

sp^3 hybridization		sp^2 hybridization	
CH_4	0.23 ppm	$CH_2=CH_2$	5.28 ppm
CH_3-CH_3	0.86 ppm		

So, we look at the second effect which is very important **in** NMR spectroscopy and that is called the Hybridization. So, all of us in, we have we learnt in the college level or in the postgraduate level what is Hybridization of carbon? So, carbon hybridization basically we talk about the s character in to the s orbital contribution to the bond (())(14:39) to the orbital and the P orbitals. So, these 2 combine to form this sp3 or sp2 or sp kind of orbitals which are involved in the covalent bond.

So, if you look at CH4 in the CH4 system that is sp3 hybridization and that is what we saw it is 0.23 ppm but now if I have a double bond similarly if you look at ethane also is in sp3 system and its value somewhere around 0.86 but if I go to sp2 hybridization what happens is now I have basically attached now have pi orbital. I have an sp orbital and to which the proton is attached and what happens is that has more less spherical. So you can see that it has s character is the least in this case but here as we go to sp2 hybridization the p character increases and therefore, the electron moves closer towards a carbon and it moves away from the hydrogen.

So, in sp2 hybridization system the electron moves away from hydrogen which is similar to the effect we saw that there is electronegative atom attached to this. in a similar manner here the Ielectron density is pulled away from hydrogen and so much so that this hydrogen become really down field shifted and de-shielded and the de-shielded value is around 5.23 to 8 ppm. So, this is a typical effect of hybridization. Similarly, if you go to sp hybridize system it will be even more dramatic.

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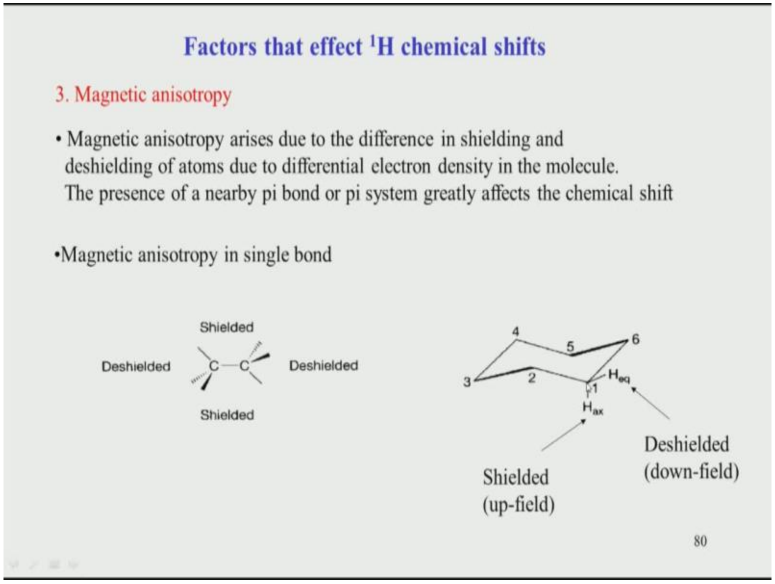

Factors that effect ^{1}H chemical shifts

3. Magnetic anisotropy

- Magnetic anisotropy arises due to the difference in shielding and deshielding of atoms due to differential electron density in the molecule. The presence of a nearby pi bond or pi system greatly affects the chemical shift

- Magnetic anisotropy in single bond

Deshielded (down-field)

Shielded (up-field)

Second, you another important concept the third factor which influences a chemical shift is basically what is called as Magnetic Anisotropy? So, what is an magnetic Anisotropy? The word Anisotropy means it is not in spherical in all direction or it is not uniform in all directions which mean it lacks isotropy. So, isotope is opposite of isotropy is anisotropy. So, what does anisotropy means? It means that suppose if you take a molecule like this with his carbon-carbon single bond the electron density around this system is not uniform, it is not spherical.

There are this side you have more electron density on this and this compared to this side of the bond.So whenever you have more electron density on the top of this bond and bottom of this bond that region becomes shielded because remember shielding is directly related to electron density. The more electron density you pack around a hydrogen you get up field shifted means lower chemical shift value and the more you remove that electron density from hydrogen the more the de-shielded it is.

So, essentially de-shielding and de-shielding are the directly coming from the electron density in a molecule. So, therefore the presence of a pi bond .So, this is what is written here the presence of a pi bond or pi system generally affects the chemical shift.So, if you look at this particular system thus this particular region is more shielded and more electron density here compared to less in there. So, shielding and de-shielding is something which we can very easily calculate nowadays using computer computational methods. There are lot of softwares where if you do the structure of the molecule it can calculate the electron density and based on the electron density it can also calculate the shielding factor or the de-shielding factor.

So, this is how computationally nowadays is done. So, idea is that depends on where the molecule is which side of the bond the molecule is located, the hydrogen atom will either appear downfield shifted if it is here that is de-shield up field shifted. So, this is this is a shown here in this example the cycloaxene, you can see that this equatorial hydrogen atom is now coming in the de-shielded region. It is it comes, you can see it is one of these three shown here comes in the de-shielded region of this bond this particular carbon-carbon bond but this axial hydrogen comes somewhere in **this** region. If you look at this this particular carbon-carbon single bond and because of that it now appears up field shifted.

So, that means the same the two hydrogen there is attached to the same carbon atom do not have the same chemical shift value one where chemical shift there is equatorial is de-shielded whereas axial is shielded up field shifted.

So, this is how the magnetical anisotropy affects the chemical shift values of hydrogen atom.

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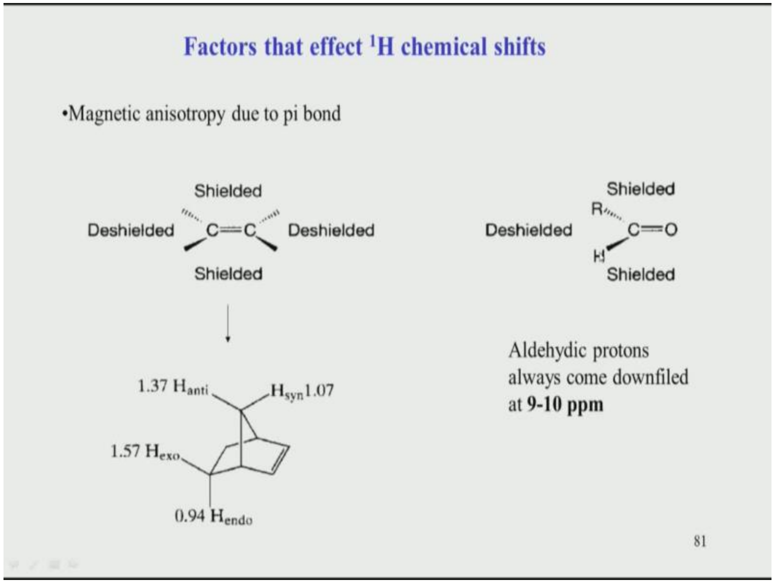

Factors that effect ^{1}H chemical shifts

•Magnetic anisotropy due to pi bond

Aldehydic protons always come downfiled at **9-10 ppm**

So, this is some more examples of a anisotropy effect. See again if you look at this particular molecule there is a pi bond here. So, this particular region is in the shielded region that is more electron density here compared to this region of the carbon. So if any hydrogen which is located in this side will be de-shielded means it will come at a lower ppm value or higher ppm value compared to a hydrogen atom which is located on above this C double bond C.

So, that is what is shown here in this particular molecule. So, we see there is a pi bond here. So, this hydrogen atom, this hydrogen atom comes right on top of this pi bond and it comes therefore in the shielded zone and when it comes there its chemical shift value is 1.07 which is relatively up field shifted compared to hydrogen here which is down field shifted because it comes away from this. Now, the same like in the previous slide we saw that equatorial and axial, here also we can see if I go to this side that is equatorial it is basically a down field shifted compared to the endohydrogen which is axial position that is up field shifted.

So, we can this is how we can figure out that why a particular hydrogen atom is up field or down field depending on the structure of the molecules. So you see the structure plays a very important role here to determine the chemical shift value. A very important another moiety a functional group in a chemistry is carbonyl groups, Aldehyde groups and ketone groups. So, we can see in those kind of systems again carbonyl is a very anisotropic moiety carbonyl C double bond O and this region if you have any hydrogen coming in this side is de-shielded. Sorry, shielded region whereas this side is de-shielded de-shielded.

So, this hydrogen lies in a de-shielded region and therefore, it comes very down field at around 9 to 10 ppm which we saw in one of the slides where, we looked at the chemical shift values of different functional groups. The Aldehyde protons come at very down field shifted because of the fact that in the carbonyl functional group they lie at the de-shielded portion of the molecule if a something comes in this side it becomes very highly shielded.

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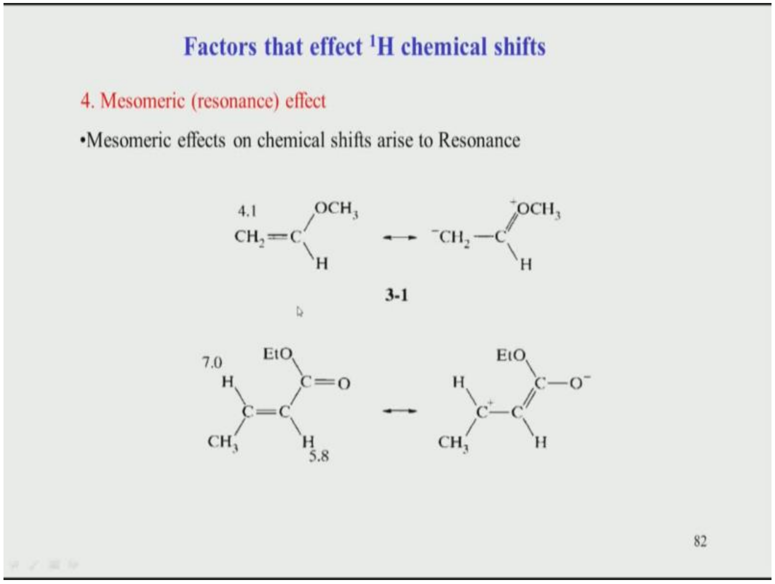

Factors that effect ^{1}H chemical shifts

4. Mesomeric (resonance) effect

- Mesomeric effects on chemical shifts arise to Resonance

So, we look at the next effect which is known as the mesomeric effect and mesomeric effect is basically coming because of resonance conditions. So, this is a very simple example here we can see that in this particular molecule what happens is that it resonates between two different configurations two different structures. So, we can see here there is a negative charge here and that comes to positive. So, when you say negative charge what it means is that basically it has accumulated a negative charge.

So, whenever it accumulates a negative charge it will undergo a of up shielding because whenever you have a negative charge on a carbon it has accumulated electron density and that influences the electron density around this hydrogen. So, this hydrogen will now become down field shifted and similarly, if you look at this particular case this hydrogen will become up field shifted because it has now acquired more of positive charge.

Sorry, this is up field a this is up field shift down up field shifted because of the negative charge accumulated on the carbon whereas this becomes up field shifted. Similarly, if you look at this picture here again there is a resonance effect and what happens is because it accumulates a positive charge because of resonance you can see that this carbon now has become positively charged what it means it means that it has lost electron density. So, it has a propensity to lose electron density towards carbonyl . Its alpha-beta unsaturated system.

So, because of the losing the electron density it also in turn affects this hydrogen because the electron density around this is also reduced because everyone say because of reduction in electron density around this hydrogen it appears at a very down field shifted value of a 7 ppm compared to what you get in a normal if there was no resonance.

So, this is basically how we look at the different mesomeric effects then if there is positive versus negative charge accumulated on this particular carbon and how that carbon influences the hydrogen attached to that previous case.

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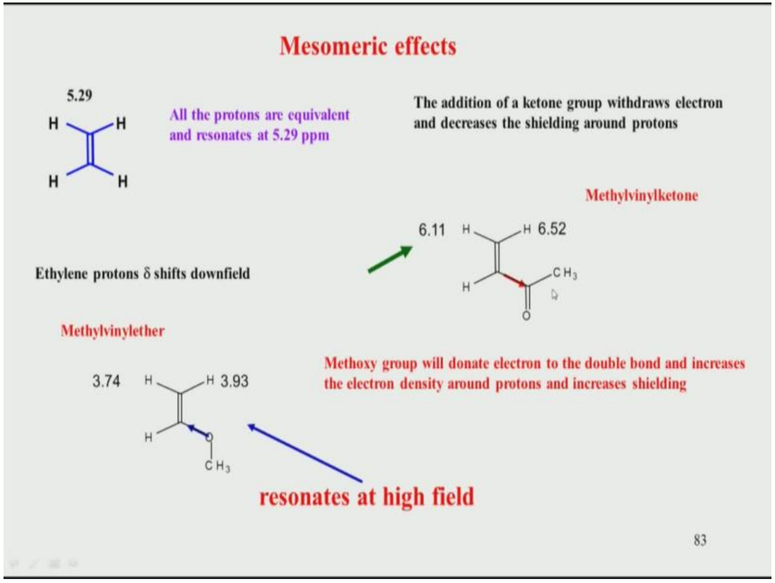

Mesomeric effects

All the protons are equivalent and resonates at 5.29 ppm

The addition of a ketone group withdraws electron and decreases the shielding around protons

Methylvinylketone

Ethylene protons δ shifts downfield

Methylvinylether

Methoxy group will donate electron to the double bond and increases the electron density around protons and increases shielding

resonates at high field

So, we will now look at some more examples of mesomeric effects. So, this is in the case of ethylene molecule where all hydrogens are equivalent. Now, what is the chemical equivalence? We will discuss that in in the next few slides or next class but what is important to understand here is the mesomeric effect, how does it influence?

So, let us say we add a ketone group. So, let us say we add a ketone group to this molecule so this is this original molecule. So, the values of hydrogens they are all same, they come at around 5.3 ppm but when I attached ketone which is electron withdrawing group that electron is withdrawn toward this and because of that **this hydrogens**, get actually there is a positive charge accumulated here.

This is similar to what we saw in the previous slide it is a resonance effect and because of the positive charge here these two hydrogens now lose electron density because all the electron density is being withdrawn toward this oxygen.So, because of this loss of electron density they will start going down field shifted means higher ppm value and that is basically what is how it can be explained. so, we can see here if you look at another system. We let us say you have a Methoxy group a methoxy group is opposite of carbonyl group. It actually donates electrons. So, this is what is shown here. So, if you look at this particular methyl vinyl ether here that the CH2 this actually donates electron.

So, these electron all the way increases in density toward this side.So, we can see that that this carbon now accumulates more electron density around itself compared to this particular ketone here. Here, it was a withdrawing effect and here, it is a electron donating effect. Because of electron donation the electron cloud density around this increases which in turn effects the electron density around this because they are also pushed towards higher electron density and that remember again higher electron density means shielding, lower electron density means de-shielding.

So, because of the higher electron density around this hydrogen they have become up field value compared to this original 5.3 ppm. So, between these two systems now we can explain why these two hydrogens comes up field because of this electron donating nature of the methoxy group or in this case, it is now down field shifted compared to this. So when 6.11 is higher ppm value. So, it is down field shifted and that is primarily because of the electron withdrawing effect of this ketone group.

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So, this can be further extended to aromatic systems where we can see the aniline case, in an aniline case there is a electron donating group. So, the electron donating group increases the electron density. So, if you look at this particular structure the resonance structures of aniline what happens is you can draw a resonance structures of aniline and that we can show that are actually it donates electron to the ring and which in turn donates the electron towards this hydrogen atom and because of that this particular molecule this particular hydrogen atom becomes up field shifted.

So, we will look at more of this aromatic systems and more the different effects of the chemical shifts in the next class where we will see that how the other effect such as ring current, hydrogen bond and so are influence the chemical shifts and that all is based on the structure of the molecule. Thank you.