Introductory Organic Chemistry
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Lecture - 21
Acids and Bases Part-3

We have now looked at how to predict the acidity of a particular molecule and we have said that in case if it produces a stable conjugate base then that is really a very good acid. So, the conjugate bases of really strong acids are highly stable, right and we also looked at some of the phenomena's that render this acidity to different molecules.

So, for example, we looked at how the molecule that bears the negative charge; if it is more electronegative then the corresponding conjugate base is much more stable and the acid is a much stronger acid; or if the molecule or the atom that bears the negative charge is much larger then also it can make the acid really stronger.

We also looked at some of the other effects like resonance effect and inductive effect. Now, we are gonna continue looking at these effects and the next effect we want to look at is the stabilization due to hybridization. So, if you look in your pKa chart you will see a trend. So, if we really draw the pKa chart.

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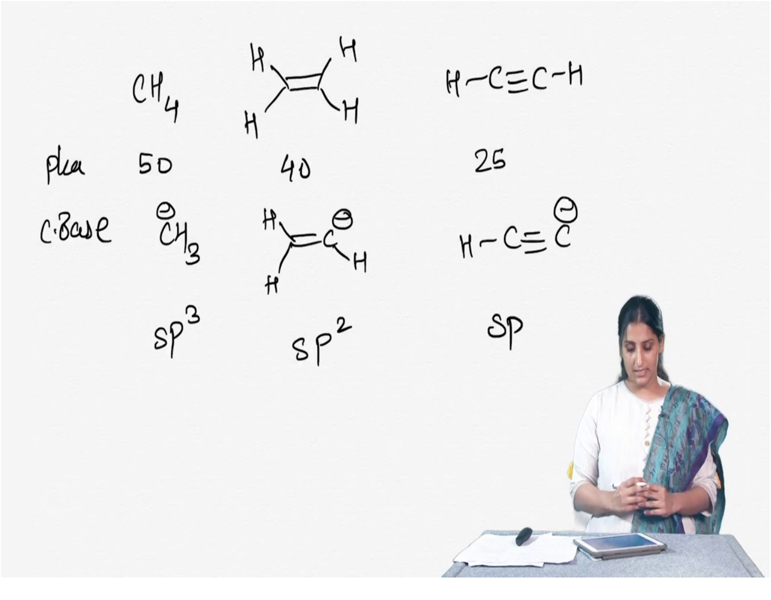

And if we look at the following molecules; methane, ethene and acetylene; what is the trend do we see? We see that the pKa of methane is around 50, the alkene or ethene is around 40 and this one is around 25, right. So, which one is a stronger acid? We know that strong acids have lower pKa's. So, acetylene is definitely a much stronger acid than methane but why is the case?

Now, let us look at their conjugate bases. So, if I remove a proton from methane it becomes CH_3^- in this case; we have this and we have an acetylene, right. If you look at all of these three conjugate bases what you will observe is that the acetylene has a Carbon atom bearing a negative charge; same is the case of the other two conjugate bases as well. So, what really makes a difference here? The difference here is the hybridization of that particular Carbon atom. If you really see the hybridization in methane it is sp^3 hybridized, here it is sp^2 hybridized and here it is sp hybridized.

So, the sp hybridization meaning there is much more s character, almost 50 percent of sp hybridization is s character. Higher the s character meaning more spherical is the shape; meaning the electrons are held much closer to the nucleus. As a result of which the ability for sp hybridized Carbon to sustain that negative charge is much higher because it can hold the electrons very close to the nucleus and which makes it much more stable; whereas, in the other two cases as we go on reducing the s character, what happens is that the electrons are further away from the nucleus and the nucleus cannot really hold those electrons properly.

So, as a result of which we see a trend based on hybridization as well where in the more the s character, that particular conjugate base, the negatively charged atom is much more stable and thus the corresponding acid is much more acidic, okay. Now, let us look at the next trend and the next trend I want to talk to you is something called as stabilization due to aromaticity, okay.

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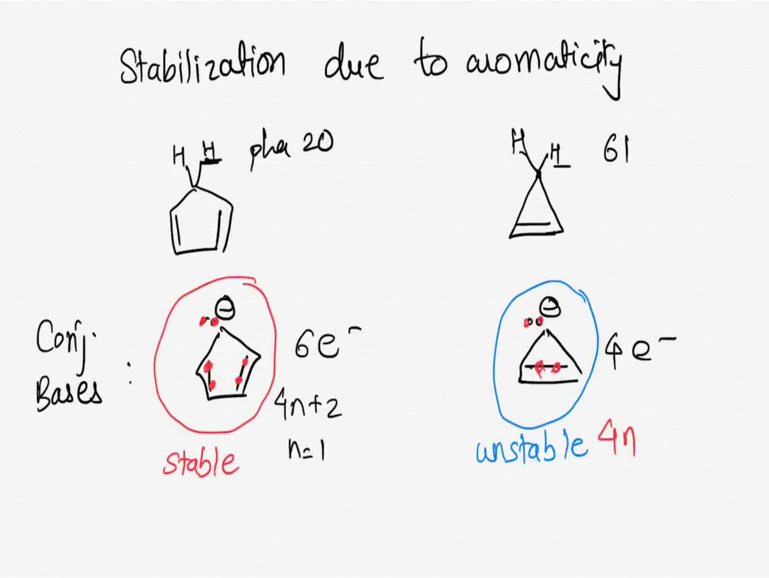

So, we have not really discussed aromaticity but you might have read about it in your earliest science textbooks. Aromaticity is a property of molecule that gives it much more stability as compared to other molecules and there are a few rules which are required to be called a molecule as aromatic molecule. One of the rules is that the molecule needs to be a cyclic structure, it needs to have conjugation and the other, Huckel's Rule is that you need to have (4n + 2) pi electrons in the molecule for it to be aromatic.

When you have (4n + 2) pi electrons; the molecule becomes much-much more stable. So, for example, benzene and its derivatives are much more stable than the corresponding non aromatic compounds whereas, if you take antiaromatic compounds, now antiaromatic compounds have 4n pi electrons in conjugation. So, antiaromaticity is exactly opposite to aromaticity. So, aromaticity makes a molecule much more stable, antiaromaticity on the other hand will make it much more unstable; right.

So, now we are going to look at these two properties and how they affect the acidity of a particular molecule. What I have here is a cyclopentadiene molecule. If you look the pKa of one of these protons, any one of these protons; the pKa is highly-highly acidic. So, the pKa here is around 20 right as compared to when you have a cyclopropane molecule and the pKa of any one of these goes to close to 61.

So, it's really not acidic; that particular proton you are gonna have a really tough time removing that proton from the, from this position. So, why is that? Now, let us look at their conjugate bases. What do we have? We have a conjugate base that looks like this; in this case we have a conjugate base that correspondingly looks like this. If you calculate the number of electrons that are in the conjugation or conjugated system, remember the conjugated systems are the ones that are, that either have a pi electron or the lone pair electron. Just like when we looked at resonance when we are talking about conjugated systems; we have to look at the electrons that can be moved around. So, in this case we have 6 electrons, in the other case we have 4 electrons; right.

So, in this case for example, we have 2 electrons in this pi bond, 2 in the other pi bond and 2 that are here, right. So, that's how we calculate the (4n + 2) pi electrons for this particular moiety because 6 fits (4n + 2) where n is equal to 1, right; whereas, these 4 electrons here, they are really fitting the 4n electrons, right; and as we said one of the rules for aromaticity to render stability to the molecule is that to have (4n + 2) pi electrons.

So, this particular anion is highly-highly stable; as a result of which the corresponding acid becomes much more acidic whereas the other anion here is highly unstable, right; as a result of which the corresponding acid is not at all acidic, okay. So, aromaticity can also play a role in making the molecule acidic or non acidic. The next effect that I want to talk about is called as electrostatic effect.

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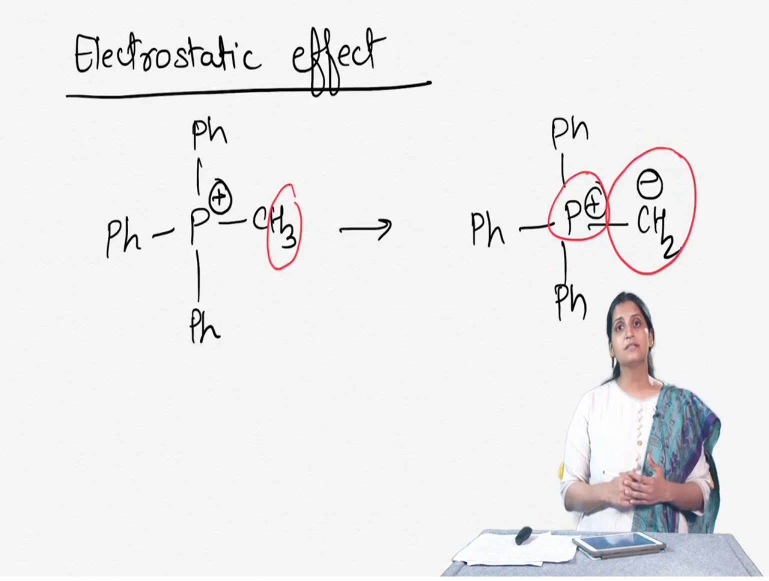

So, what are we going to do here? I am gonna talk about something called as a ylide. This is particularly famous for some reaction called as a Wittig reaction which we are gonna cover later on in the semester but ylides are zwitterionic compounds. So, we are looking at the particular step where we are about to prepare a zwitterionic ylide and in this particular case the proton that we have circled is quite acidic; why is it so?

If we really draw the conjugate base of the corresponding, right; if I draw this particular conjugate base, you can see that a positive charge and a negative charge are right next to each other which really gives it the stability it needs. So, sometimes even electrostatic effect which is the effect due to a positive or negative charges that render the stability to the conjugate base and make the acid much more acidic.

Okay, so now, we have looked at all these criteria's that make an acid a stronger or a weaker acid but what about bases; can we really measure the strength of a base? So, the answer to this question is that the strength of a base you can image is the extent to which the base wants to grab the proton. So, if you really want to think of a hungry-hungry person and how badly it really wants the food that is the question; right.

So, a really good base basically wants to attack that proton and quickly grab that protons. That's a layman version of describing a really strong base but in other words we could really look at how effectively the base wants to hold on to the proton. So, let's say that the once the base has caught the proton, does it really want to hold on to it or is it okay letting it go; right.

A really strong base would not want to let go off the proton because it really needs those, the positive charge to stabilize itself right; whereas a weak enough base does not really care and is stable enough, right, such that it is okay if the proton is later on taken away from it. You can also imagine it in terms of magnets; so a really strong magnet is the one that attracts magnetic objects to itself and does not let them go, it is going to be tough to separate them later; right. So, a really strong base does not let that proton go away.

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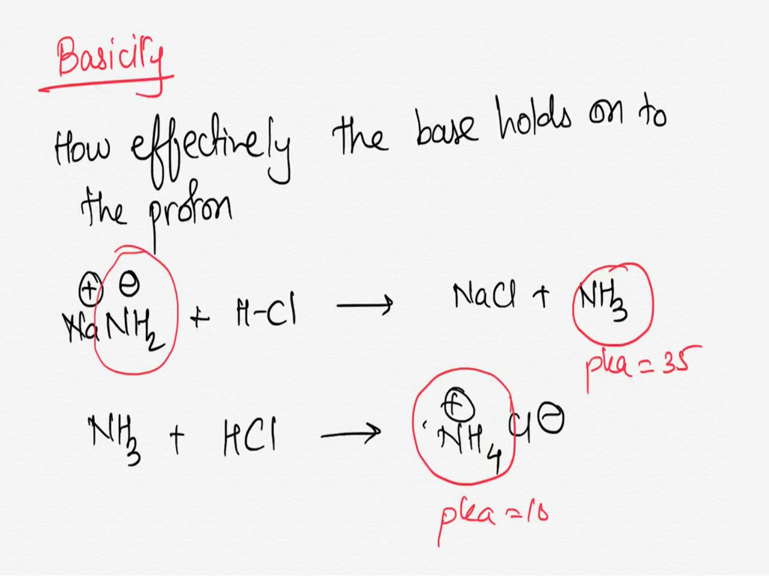

Basicity

How effectively the base holds on to the proton

$$\overset{\oplus}{Na}\overset{\ominus}{NH_2} + H\text{-}Cl \longrightarrow NaCl + NH_3$$

pka = 35

$$NH_3 + HCl \longrightarrow \overset{\oplus}{NH_4}Cl^{\ominus}$$

pka = 10

Just to give you an example of basicity and the property which we are talking about; okay. So, what we are talking about is how effectively the base holds on to the proton; right; that's what we are talking about.

So, now if I take $NaNH_2$ versus ammonia right; so $NaNH_2$ is going to act as a base and it's going to let's say react with HCl to give you,

$$Na^+NH_2^- + HCl \rightarrow NaCl + NH_3$$

pKa =35

Whereas, when NH_3 acts as a base with HCl, what you get is,

$$NH_3 + HCl \rightarrow NH_4^+Cl^-$$

pKa = 35 pKa = 10

So, now, let us look at these two equations. The base is forming a conjugate acid; right.

So, if the reaction were to happen backwards; NH_3 would be my conjugate acid and the pKa of this conjugate acid is around 35; in this case the pKa is about 10, right. So, that tells you a lot of things; pKa 35 meaning that ammonia is not going to ever try to go back to form that NH_2^-, whereas a pKa 10 of $NH_4^+Cl^-$ meaning if a strong enough base appears this particular molecule can really act as an acid and the reaction can go backwards.

So, a really strong base does not let the proton go away once it claims it and that can tell us that NH_2^- is much stronger a base than NH_3. The other way we can think of basicity is that how accessible is the lone pair for that Nitrogen to attack and grab that particular proton. So, let's take an example where in we have a molecule that looks like this.

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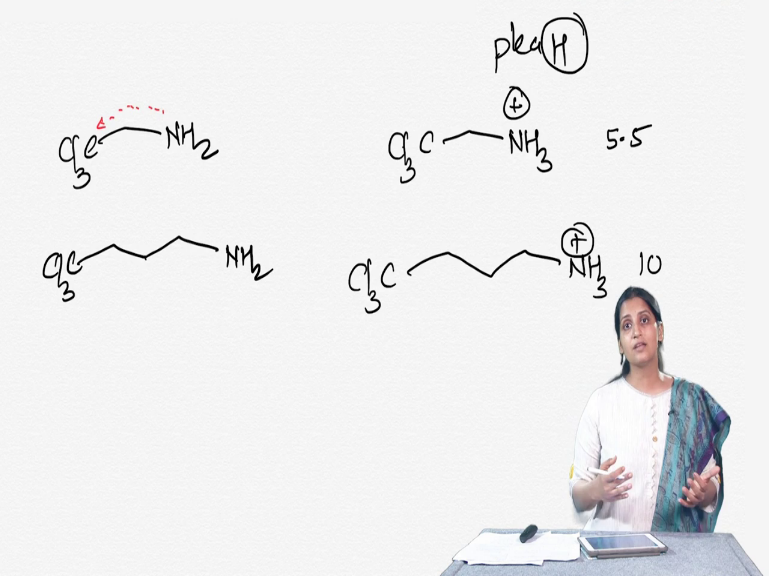

We know that Chlorine is much more electronegative. So, Chlorine what it does is, it does exhibit something called as inductive effect where it pulls electrons through bonds; right. So it is gonna put a through-bond effect and it is gonna pull electrons from that Nitrogen. So, really if you see the Nitrogen's electrons are going to get pulled towards Chlorine. As we go on increasing the distance between Nitrogen and Chlorine, that affect gets lower and lower.

So, for example, in the molecule that is the bottom molecule; it does not really have much inductive effect by the Chlorine. The same thing is seen in the corresponding pKaH values; so pKaH meaning the conjugate acid of the corresponding base; right. So, let's look at the pKaH value of the conjugate acid. Now, the conjugate acid here is this; in the other case; it is this; right.

If you look at the top one; the top one has pKa value of around 5.5; the bottom one has pKa value of around 10 which means that the bottom one is a much stronger base because it does not want to let the proton go; right. In other words, you can explain it such that the Nitrogen is really free to attack a particular proton and grab it because its electrons are not being pulled much more effectively by the Chlorine.

So, it has its share of electrons to do that particular chemistry. The same thing can be seen when we have instead of CCl_3 we can have even Fluorine and it will still do the same thing. So, CF_3 will also pull electrons towards itself.

When we are talking about basicity; one of the key things to really talk about is the basicity of amine functionality because amine groups are present in amino acids right and amino acids are one of the main compounds that are present in our body.

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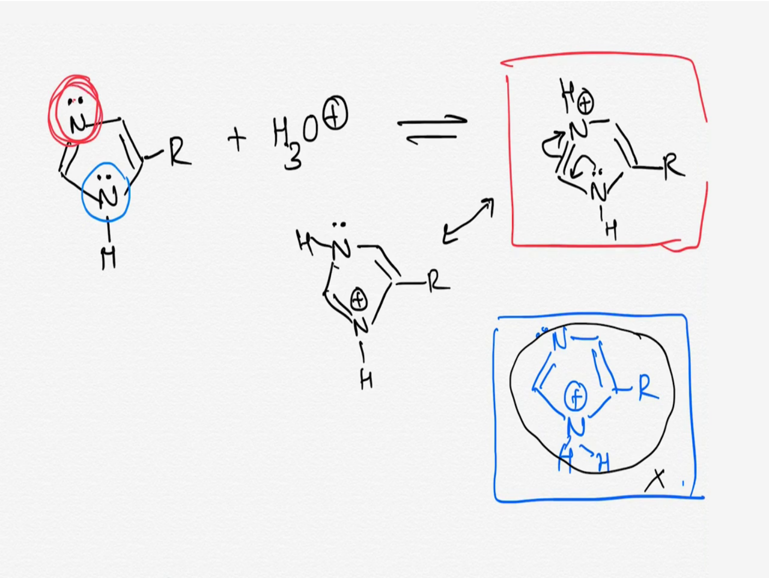

Okay, so, now I want to discuss the case of Imidazole. Now what we have here are two particular molecule, two particular Nitrogen’s. One of them is this Nitrogen which is double bonded and other one is the single bonded Nitrogen, right; or I have denoted them using a red and a blue ink.

Now, the question is if imidazole wants to act as a base which one of these Nitrogen’s will act as a base right. So, whenever you are stuck with the question like this wherein you want to debate which one will really act as a base; the best thing to do is to make it work function like a base and see how stable is the conjugate acid; right.

So, what I am going to do is, I am going to put it in H_3O^+ and in one case, the first case I am going to draw the conjugate acid such that top Nitrogen gets the proton whereas the bottom Nitrogen gets the proton in this particular bottom case; right. Now, we want to question which one among these two is really more stable. Now, you can discuss the stability based on aromaticity but if you don't want to talk about aromaticity here; what you can also talk about is the ability to draw resonance structure.

So, which one of the structures have resonance structures that will make the molecule more stable. If you really look at this; this particular molecule at the bottom does not have any more resonance structure that we can draw. That is because the positive charge really breaks the conjugation that is present in the molecule. If I really take this other case, I can draw resonance structures wherein this particular electron pair goes here and this electron pair goes on top of the top Nitrogen. So, what I have here is this; right. So, I have a resonance structure; I can even further have a resonance structure wherein you can move any of these electrons towards that Nitrogen.

So, there are many more resonance structures possible but the key thing is that because of the presence of these resonance structures the molecule becomes much more stable. Meaning if the top Nitrogen; the red one gets protonated I do not give rise to something unstable and as a result of which the top one, this particular Nitrogen here is the one that acts as a base much more often, okay.

One of the key things about imidazole is that this protonated proton or the protonated structure here has a pKa close to 6 or 7 which is very similar to the physiological pH of around 7, or 7 to 8, right. So, that means, that particular Nitrogen can exist as a protonated form or it can also exist as a deprotonated form. It is very easy for that Nitrogen to shuffle a proton and become protonated or deprotonated when in need.

So, you see that particular Nitrogen playing a role of both acids; when it is protonated and as a base when it is deprotonated in biological enzymes. When we are discussing acids and bases a generally helpful thing would be to know about the pH and pKa's. See we have only talked about pKa's so far, of different acids we have seen what makes, what is the relationship of strong acids and their pKa's and how are the, what is the co relationships of weak acids or weak bases or strong bases; right.

So, we have seen all of this but we never really talked about something called as pH right and if you must remember from your earlier text what you have learnt is something like a pH scale. So, the pH typically ranges from 1 to 14 of the things around us. So, we can say that strong acids have a pH close to 1 and strong bases have a pH close to 14 but how does the relationship between the pH and pKa of a particular acid vary?

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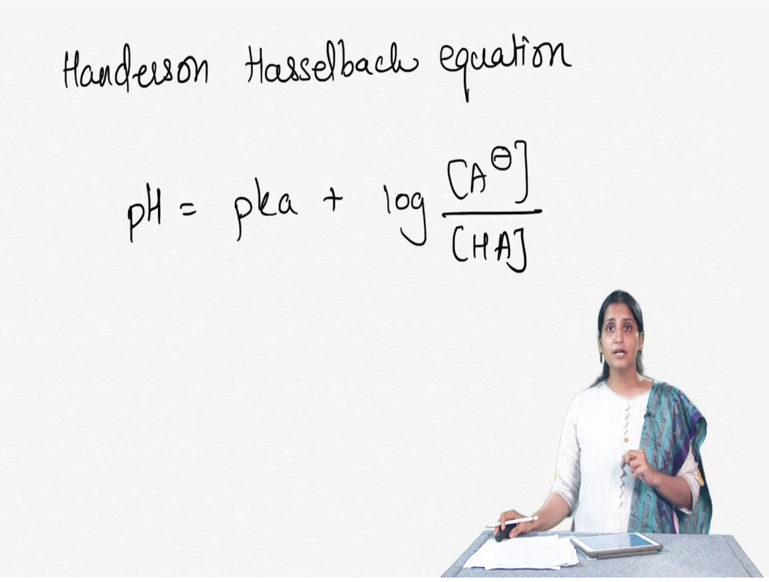

Handerson Hasselbach equation

$$pH = pka + \log \frac{[A^{\ominus}]}{[HA]}$$

So, if I want to get to that; what I have to make use of is called as a Henderson- Hasselbalch equation. So, if we now look at this equation it states that pH is,

$$pH = pK_a + \log [A^-] / [HA]$$

So, what it really tells me is that if I take a particular acid HA; will it exist as A^- or will it exist as HA at a particular pH. Meaning that what would be the dominating form; will it dominate as a protonated species or will it dominate as a deprotonated conjugate base kind of a species. So, if we really think about it when pH is equal to pKa; what does it tell you when pH is equal to pKa; log of A^- over HA will be equal to 0.

So, at pH equal to pKa; your concentration of A^- will be equivalent to the concentration of HA meaning when pH and pKa are equal or if I take an acid of a particular pKa and if I put it in the pH of the same value; what I have; what I will have is the same concentration of the deprotonated form and the same concentration of the protonated form in the mixture.

The pH of living cells is around 7 to 8.5 which is also the physiological pH. So, at this pH several common functional groups are not really what we put them on paper but they exist in their ionized form.

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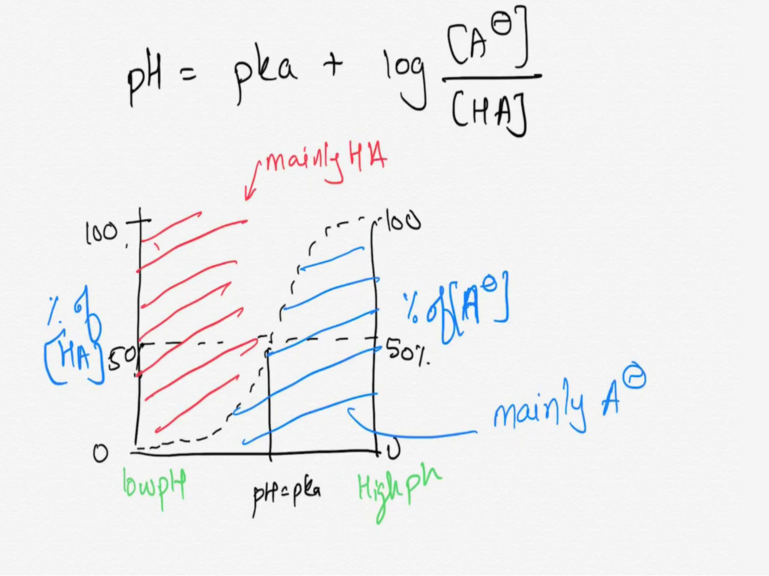

And if we really plot the concentration of free conjugate base as a function of pH; so, if we really plot the concentration of free conjugate base as a function of pH, this is what the graph mainly looks like. So, at around low pH and high pH; this is what the percentage of HA and the percentage of A^- goes on appearing. So, at pH equal to pKa; as I said you can see that it is almost the same concentration of A^-, as well as HA. So, at around 50 percent of each; you will have a break in the graph; right.

Now, if you really look, think about a particular acid and if you look at it at a low pH, the main appearance is going to be like, in the, it's going to be mainly like HA; at low pH when the pH is acidic, the acid is going to be mainly like HA, whereas at high pH; the same acid will be like mainly in the form of the conjugate base like A^-, right.

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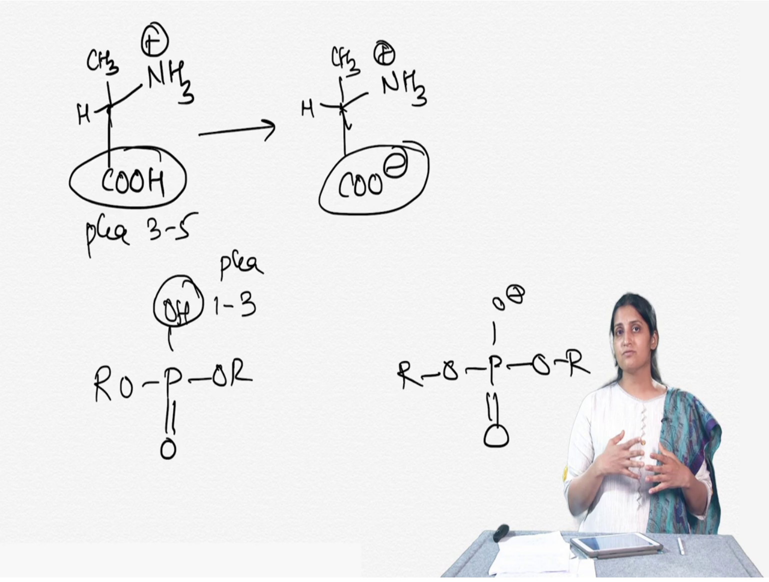

A good rule of thumb is that the acids will be substantially deprotonated if the pKa is two or more units lower than the pH. So, let us take an example of amino acids. Now in the case of amino acids we know that it has an amine group and an acidic functionality and the carboxylic acid functionality of amino acids has a typical pKa of 3 to 5 right. So, at physiological pH, which is the pH of around 7 to 8; what is going to happen? At physiological pH all carboxylic acids are not going to be really in the form of COOH but it would be right or more correct to write them as COO^-; right.

So, this is the right form, way to represent the carboxylic acid at a physiological pH. The same case goes with the phosphodiester functionality. So, let us take the phosphodiester bond and this particular compound looks like this and we know that phosphodiester groups are present in our DNA. Now the pKa of this particular proton is around 1 to 3; meaning at physiological pH, it's not going to exist like that but instead it is going to have a strong negative charge on it because it is going to be a deprotonated form and when we say that our backbone of the DNA, the phosphodiester has a strong negative charge; it is mainly because of this twist, is that although the phosphodiester has that OH; at physiological pH, it exist as a deprotonated molecule.

Now, the rule of thumb for basic functional groups is that the bases will be substantially protonated; if the pKa of its conjugate acid is two or more units higher than the pH; okay. So, the bases will be substantially protonated, okay. So, now what we going to do is; we are going to have a look at one of the amino acids and we are gonna predict what is the form in which this particular amino acid exists, okay. So, we are going to talk about glutamic acid. Okay, so, let me draw the structure here; okay.

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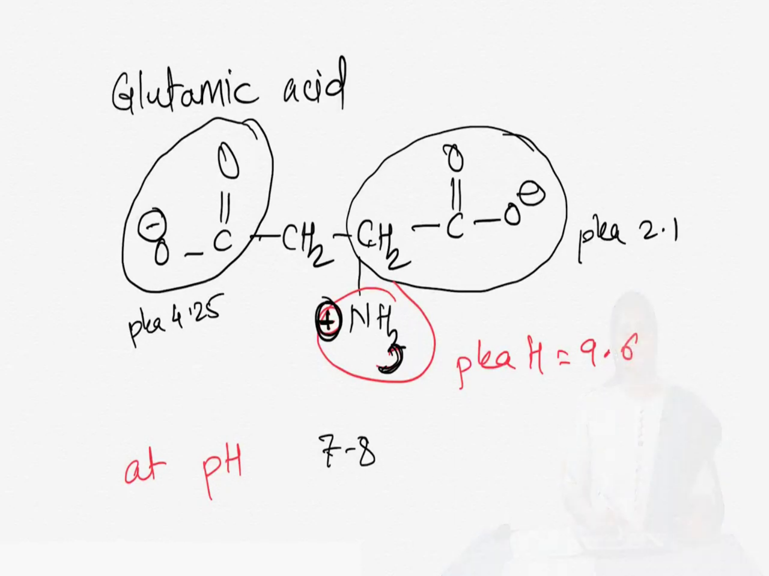

So, that's the structure of glutamic acid and now I want to predict how it's gonna exist at a physiological pH that is around pH 7 right; 7 to 8. Now, I know that the carboxylic acid of any amino acid has a pKa range between 2 to 3; this one is at a pKa of 2.1. This particular carboxylic acid on the other hand has a pKa of 4.25 and if I take the protonated form this amine pKaH that is around 9.6. So, at pH 7 to 8 what is gonna happen?

So, now let us look at the first one; the one that has a pKa of 2.1; that one is definitely going to be deprotonated, right because the difference between the pKa which is 2.1 to the pH is much more than 2 units right. So, this one is going to be not existing as an acid but will rather function as a corresponding conjugate base. Now, let us look at the other one; at pH 7 to 8, again this is more than the 2 units higher; so this one also will be deprotonated; okay.

Now, what about that amine? That amine we said that the; if the difference between the pKa of the pKaH of the base or of the amine and the pH, is more than 2 units, then it will be in the protonated form. So, between 7 and 9.6; the difference is more than 2 units so in fact, this particular amine will be in the form of the corresponding protonated form. Okay, so, that's how the glutamic acid will exist at the physiological pH. So, acids and bases or the corresponding pH and pKa's of acids and bases really helps us to predict the kind of form the molecule takes at a particular pH; whether it is gonna be in the protonated form, whether it is gonna be in the deprotonated form becomes much more important when we have to think about the reactions that this particular compound is going to do; and thus knowing the Henderson-Hasselbalch equation becomes much more important when we have to think about Organic Chemistry reactions at physiological pH's.