Computer Aided Drug Design
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Lecture - 18
Molecular Mechanics/Force Field

Hello everyone, welcome to the course on computer aided drug design we will continue on the topic of molecular mechanics and force fields.

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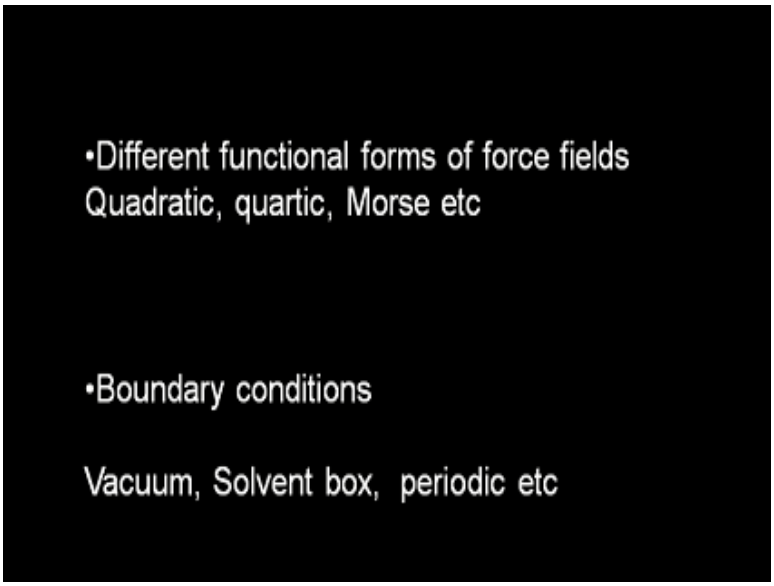

I showed you different types of functional forms of force fields MM2 MM3 and then CVFF CHARM and so on so the sum of the force field terms has a quadratic that means R mean as R0 square or quartic R-R0 to the power of 4 sometimes Morse forms that is exponential form is also used. So, basically force field contains terms related to bond stretching, angle bending, torsion and non-border interactions.

Those include electrostatic forces van der val forces hydrogen bond. So, we looked at different forms of force field and then I also mentioned about boundary conditions okay. We can model the molecule in the form of a vacuum that means there are no solvents nothing around it the molecule is all alone maybe it is in vacuum or it is in a gas phase or we can consider a solvent solvent surrounding 1 layer of solvent,2 layers of solvent and many layers of solvent.

Or even we could even consider a periodic box that means as I mentioned before it is a rectangular box or a square box. The molecule is inside surrounded by lots of water and we assume similar box on all the 6 faces of this rectangular box or the square box and then if a water molecule goes out then another comes in from the opposite direction so that the density is maintained constant that is called periodic box.

And generally periodic box is preferred when you are doing molecular dynamics type of situation and also if you want to look at the protein folding, unfolding and so on. Okay now you have the molecule you have the boundary condition, but you need the molecule to attain certain minimum energy conformation okay.

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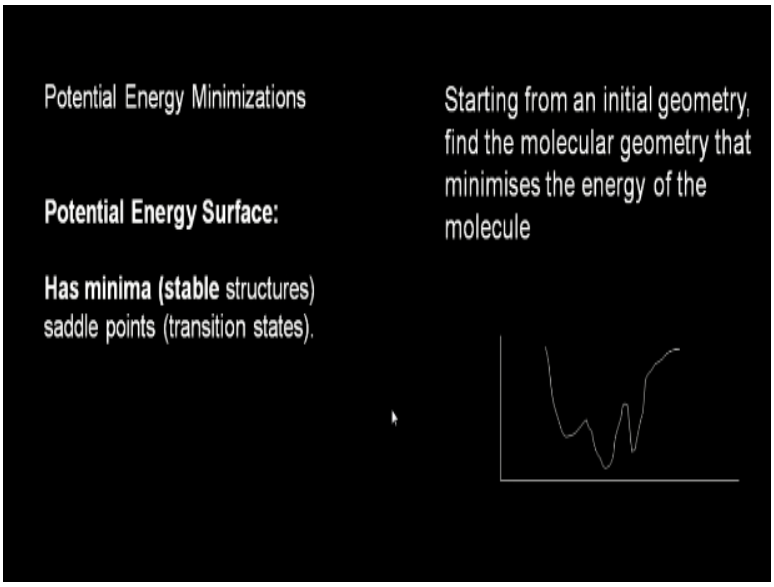

That is called the minimum energy thermodynamically stable conformation because all systems like to attain a minimum energy conformation at that particular set of conditions whether it is density or temperature or pressure and all that and that is called a stable structure okay whereas a transition state the saddle points that means they are not very stable but only the minimum energy conformation may be stable.

For example, look at this graph so if I am changing certain bond distances energy may be coming down down down there could be many minima we call this global minima, we call this local minima. So, you may start with a single conformation of the structure we keep changing the

angles, the lens and so on so that the energy keeps going down and hopefully you want to reach here. You may be starting from here you want to reach here you may be starting from here you want to reach there.

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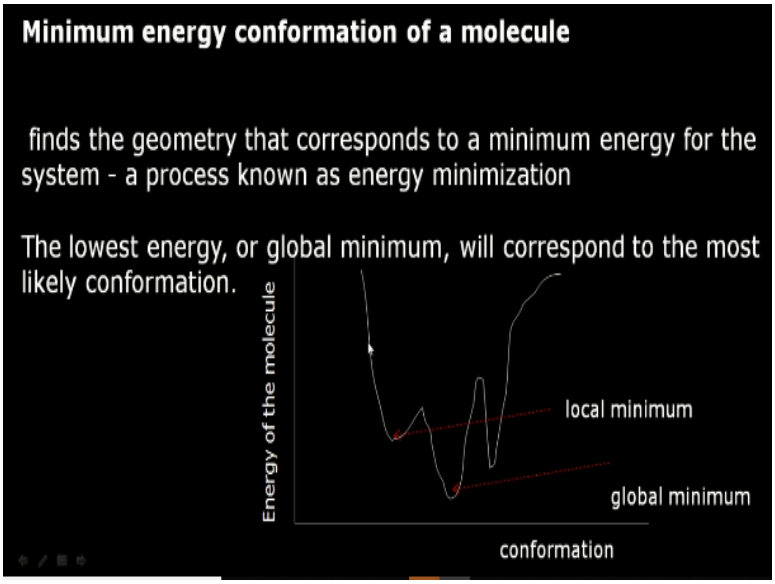

Okay so these are called local minima whereas this is the global minima the main challenge in molecular modeling is to find a global minima that is as you keep changing the conformation and energy will come down and down and down and not stuck in a local minima. Okay so this process is called energy minimization process you may start with one conformation as you change the features bond length, bond angle torsion energy may be coming down.

But you will only end up here because this is a local venue why you want to end up here. So, software starts with different conformations and hopefully try to see whether they are able to reach the global minimum that is the biggest challenge in finding out the minimum energy conformation of molecules okay.

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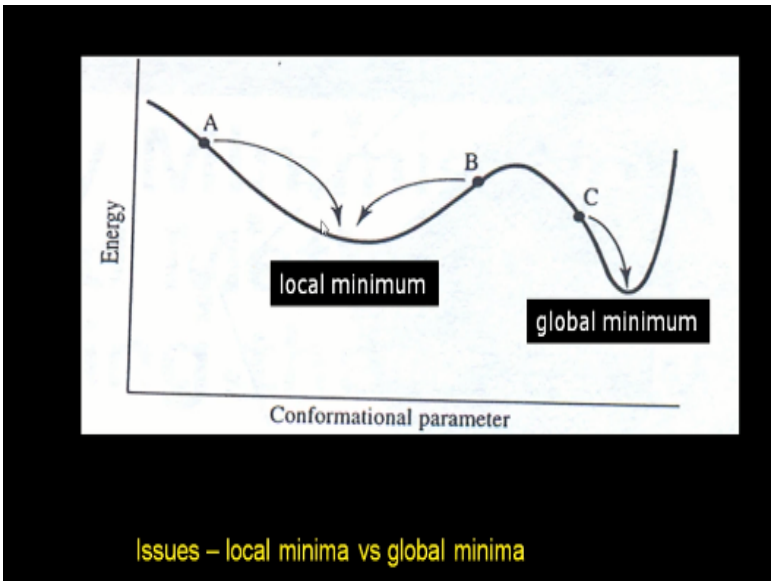

So, again once more this is called the local minima for example if I have a ball I just drop it it will come here whereas if I have a body here it will come here. Whereas if I have a ball here it will come here if you drop it okay. So, the balls since they are dropped very slowly it will invariably end up here unless the energy is high enough for the ball to cross and go the other side.

So, you may start at different starting conformations and see how the minima is reached okay and you will get different minimas and select the minimum of the minimum and we call that global minimum. Generally, for small molecules it is not very difficult to attain global minimum but if you are talking about large molecules like peptides, proteins it is very very difficult to attain a minimum energy conformation okay.

So, we need to have the minimum energy conformation because that gives you the three-dimensional shapes, size the polar surface area, the volume and so on actually there are many software commercial software is available in the market. There are many free software is available in the market you do not need to use a commercial software it is good enough to use a free software one of them I am going to show you that is called MARVIN.

And that is called MARVIN sketch. So, you have to go to the site and then you have to download that software and then maybe you have to register before you start using it. So, you can register

as a student or a faculty it is free okay it is completely free. You do not need to pay anything, but you have to register in that software that is called.

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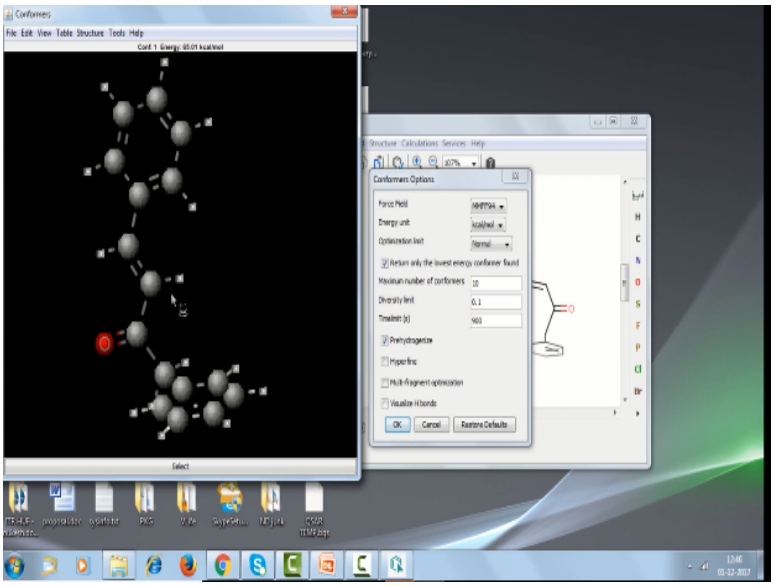

It belongs to this company, but it is a free software, but you have to register as a student or as a faculty in MARVIN sketch where we can draw structures we can sketch the structure okay and then we can use it, or we can take small files of SDF files downloaded from zinc and then we can upload it here and so on. For example, and this is this sketch option you have got a lot of things here.

Okay imagine I am drawing a benzine and then I am connecting it to the different bonds okay I am putting a double bond there. So, I am making a ketone here as you can see then I put again a double bond there and then I am putting a single bond there and then I am adding another benzene here okay. So, we have a benzene here. We have a ketone alpha, beta unsaturated this is called chalcones.

Chalcones are molecules which have good antioxidant property anti-bacterial property and so on okay. So, we can make the structure into put it in a 3-dimensional form, so it becomes in 3-dimensional form as you can see so okay we can rotate it in 3d as you can see here now the molecule is in 3d form. We can shrink it or enlarge it we can move it forward or backward okay, so we can do all those things now we can even get the conformation of this molecule.

How do I get the conformation let us go to calculations then we can get conformation you see confirmers I talked about force field and you remember this MM FF 94 force field or draining force field imagine we will go to mm4 F4 and energy is given in kilo cals per mole optimization we do it normally return only the lowest energy conformer. So, we just say okay okay, so we got the minimum energy conformation of this particular molecule is called chalcone.

As you can see the energy is 65 kilo calories. So, we can rotate this molecule the oxygen is the there is a double bond here okay alpha, beta double bond there is finale group there is another finale group here this is called chalcone, we can do lot of data calculations.

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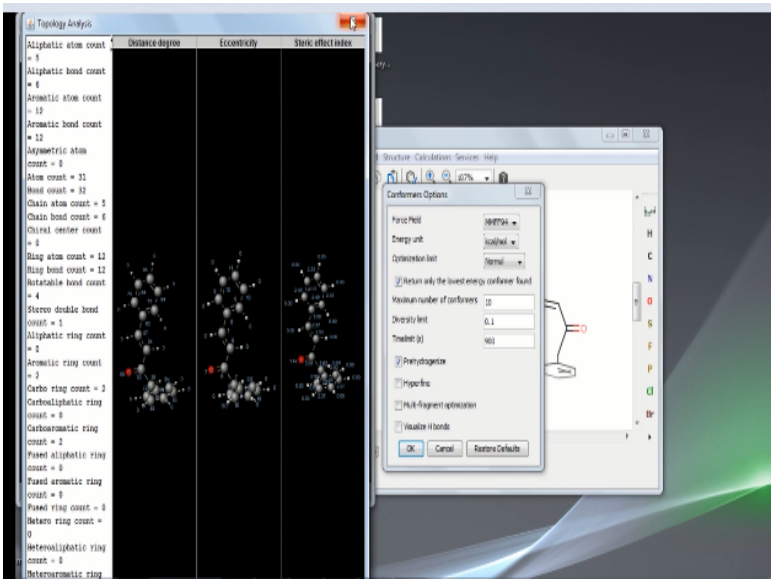

For example, I can calculate log p of this molecule as you know log p is most important okay I can give chem axon type of p gives you okay. Okay so it is given log p it is highly hydrophobic you can see 4.7 and this is called a group contribution method-based log p. So, all these carbons are given certain values okay and the oxygen gets a negative value okay as you can see this is the log p okay.

And you can see the ones which contribute towards okay this is called I can measure the log p. So, this is called a group conformation method. So, when you have ch2 or a aromatic CH they all contribute so they all get added up oxygen gets a negative. So, it is given a negative value so that

is log p. Now similarly we can do other calculations also we can do geometry calculation topology analysis.

So, we can do a lot of these calculations have a look at it okay, so you can see how many aliphatic atoms are there how many aliphatic bond counts you can see right aromatic atoms okay. And then chain atom cones aromatic ring cones fused aromatic. So, this is the distance degree state effect effecting the exits giving it a static effect. As you can see have these steady confect and this gives you the eccentricity part of it this is the degree of distance so a lot of information on this.

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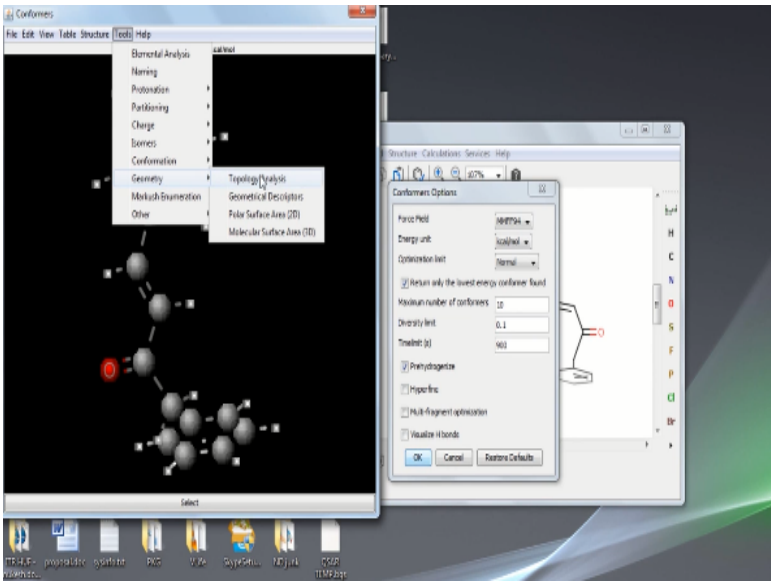

Okay again we can look at pka and thus we can look at pka here for example this gives you the pka of the molecule okay two it gives between ph of 0 13,14 okay. So, it gives you the pka of this it gives you micro species distribution micro species distribution to different ph range. And then we can also calculate polar surface area. So, it gives you the polar surface area it is 17 it is quite low because when oxygen is the polar molecule remaining is a non-polar okay.

Then we can do other molecular surface area, so it gives you the molecular surface area as you can see 320 Armstrong square at the molecular surface area. This conformation can be stored for more in many more calculations. So, we can look at the charge distribution oxygen is the only negative that is going to be contributing okay. So, as you can see oxygen is the only thing

-0.41okay oxygen where many of them be all these are positive.

Here again you get some minus on these carbons because you have a double bond and you see this red color red color that is negative the blue color is more on the positive side. So, we can see the charge distribution on the molecule. Okay so there are some negative regions here because of this the double bond here okay that is contributing to that whereas this is totally positive then we can look at okay we looked at geometry geometrical descriptors okay. I think we looked at that also okay.

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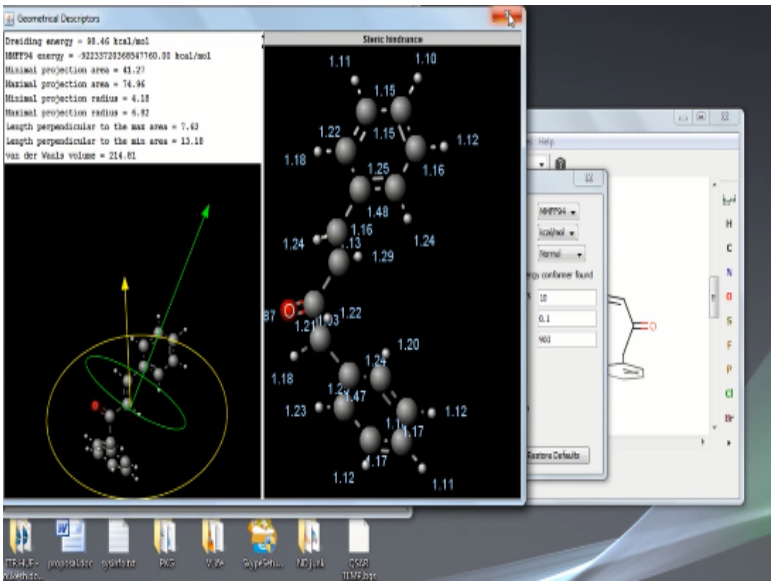

As you can as you can see here it gives you the static hindrance of these molecules okay the lower it gives the energy for F4. This is based on the software minimal projection area maximal projection area. As you project it on a 2-dimensional plane and both the directions as you can see here 2 options.

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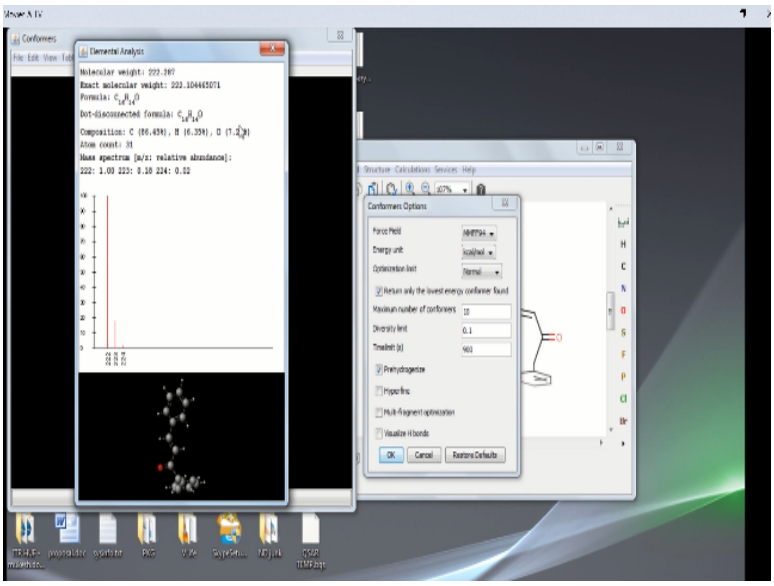

Elemental analysis it gives you the CHN ratios carbon hydrogen oxygen ratios. It also gives you the mass spectrum. This is mass spectrum theoretically calculated. So, if I do a mass spectrum using experimental I can always crosscheck it gives you atom count it gives you formula, molecular weight and also the mass spectrum as you can see molecular weight 222, 223, 224 and so on. It actually it gives you a CHN ratio. So, if do a CHN analysis I can cross check whether I get the same thing but then I can get bond lengths.

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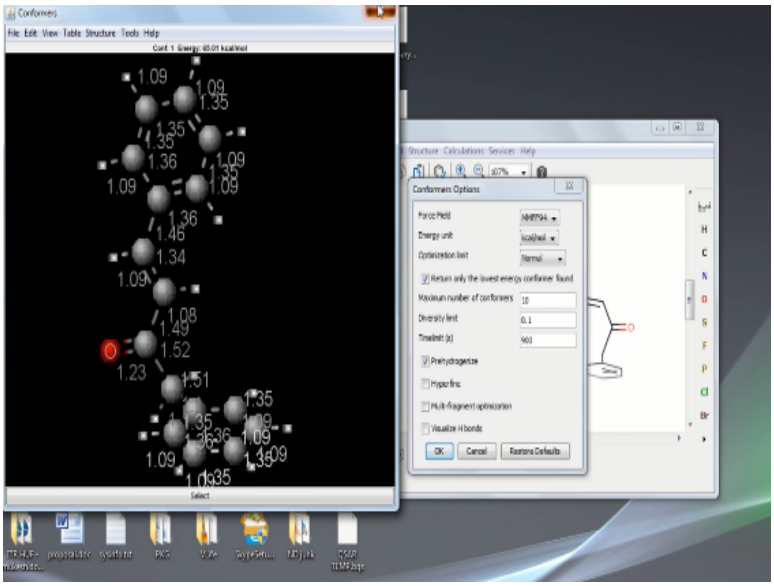

Okay as you can see you get the bond length here quite a quite a long 1.23 this is got short that is the ketonic bond okay of course carbon hydrogen bonds are very small whereas carbon carbon bond you can see 1.46 okay the double bond is 1.34 here carbon carbon double bond okay

aromatic bond 1.36. So, we can get the bond lengths also, so a lot of calculations can be done that is the beauty of it okay we can get the energy is in kilo cal and kilo joule.

Also, this software has only 2 force fields there are software which have many many force fields okay.

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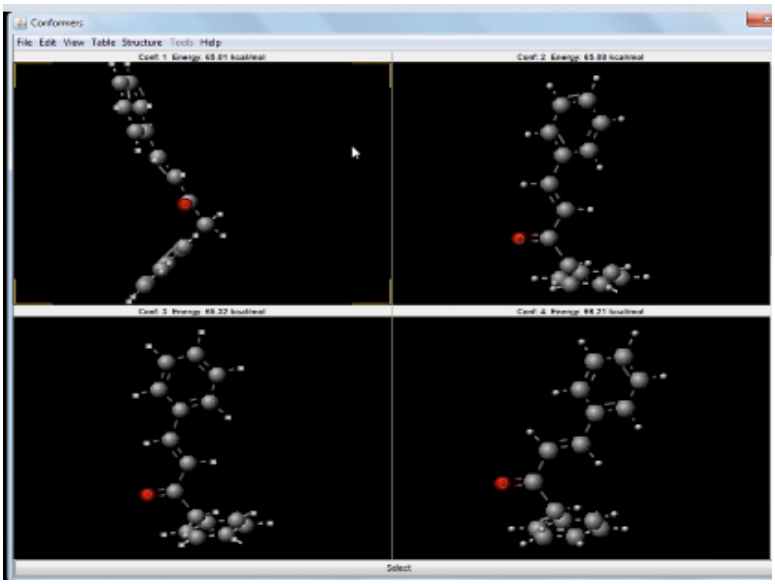

Okay so it gives you 10 different conformations with the different energies as you can see this is 66 kilo calories conformation this is a 65 kilo calories conformation. Okay 65 kilo calories this is 66 kilo calories it gives you the conformation of count1, count2 count 4 then count 5 count 6. There is a 69-kilo calorie conformation as you can see here this is 67. So, if I am looking at the minimum energy I will go for may be some 65.

So, this is the top the best one 65.01. So, if you look at the 10th one you will get 69.53 as you can see here between this and this one there are changes in the bond length or angle or torsion. So, that there is a 4 kilo cal almost a 10% reduction in the minimum energy conformation. So, we can look at large different types of conformations also. Because conformations are important if am looking at the flexibility of the molecule.

And also, how the docks to the active side okay in such situations also it is very very important to understand okay. So, I had explained PKA, log p, charge. We can look at the charge

distribution on the molecule, polarizability. Okay this is the polarizability of the molecule well okay as you can see the polarizability of the molecule. Polarizability is a function of charge as well as the volume of the molecule okay.

So, many many calculations can be done with this particular MARVIN software actually. We can also do 3d alignments if we have many molecules together we can align it. I will show when we do something called a pharmacophore modeling okay that is later on actually. Okay so one approach is by drawing the structures like I showed here.

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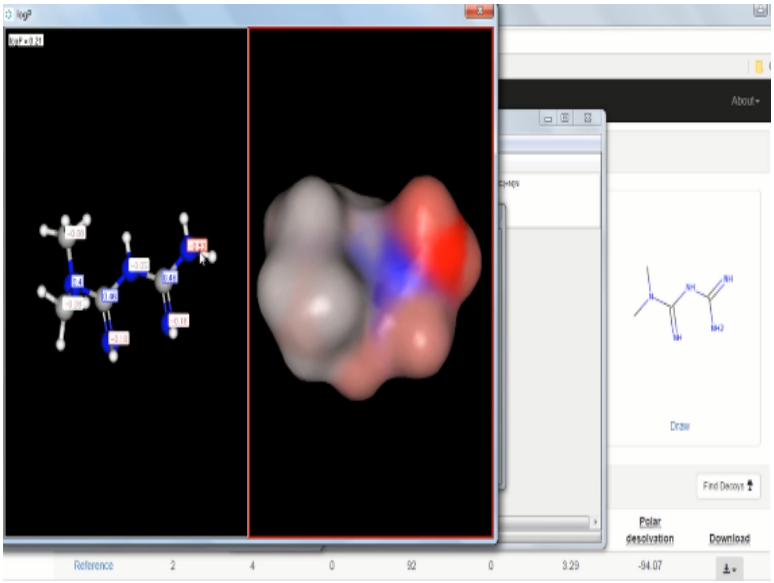

Another approach we can get it through zinc and swiss ADME look at this, so I have this metformin how do I get metformin zinc database as you know we can get metformin okay another approach maybe we can do it through the SDF approach yeah SDF itself we can open it using MARVIN view okay. So, it gives you the metformin as you know metformin has a lot of nitrogen here okay.

And you can look at the log p you will see very negative because it is highly hydrophilic okay log p .21 because a lot of nitrogen here okay so this nitrogen has -.53. So, it is very red and many red colors here – so log p is quite negative and compared to the previous one which I showed you where log p is almost 4.

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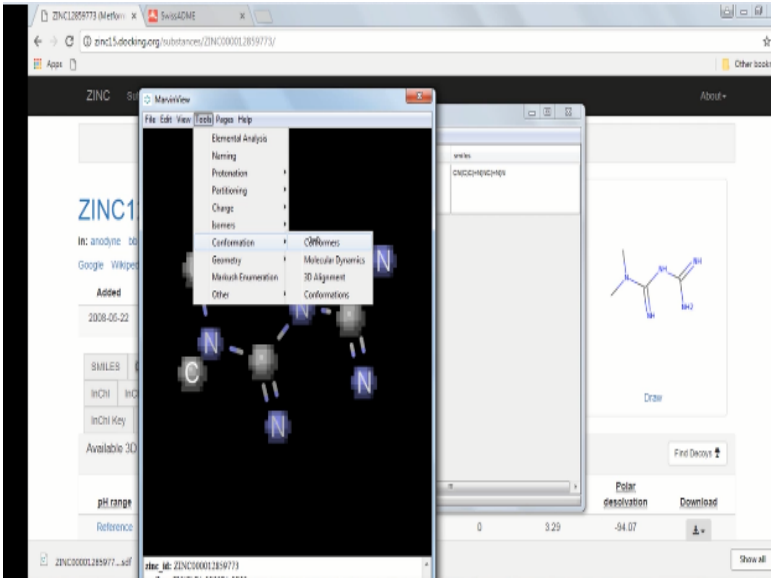

So, again we can look at different aspects of metformin we can go to the tools page. We can look at confirmers okay it gives you the best conformation of this molecule okay, so we got the best conformation of metformin okay and then we can do the same calculations like I mentioned okay. So, in this okay in this technique what would we do here I got the structure from zinc database the SDF.

And then opened it is in MARVIN view so you get this then we can do all these calculations getting log p getting charge distribution. Looking at different conformation topology analysis we can look at hydrogen bond donor acceptors okay, okay so it gives you the hydrogen bond donor acceptors as you can see there acceptors generally they are only acceptors, donor count, donor sites, acceptor count it is 5 okay.

Because as you can see here acceptor, acceptor, acceptor these are donor, donor, donor. So, the nh can be a donor and n can be acceptor okay as you can see here okay. So, all the calculations all the information related to the molecule can be analyzed using this MARVIN. So, one approach is drawing the structures on that approach is to take it from the zinc database as an sdf file and open it with MARVIN and MARVIN does it.

And then we can do a lot of calculations as you can see here we can be a minimum energy conformation of the molecule okay. So, lot of things can be done with it with this tool options we

can look at that this is quite a clean in 3 dimensional. So, you can look at and so on okay so this particular software the MARVIN is extremely useful for getting 3 dimensionally conformation of various structures.

Getting the information about the molecule related to the electrostatic geometric charge related information we can then use these 3 dimensional structure for other calculations suppose later on I want to do pharmacophore studies I can do that and the beauty of it.

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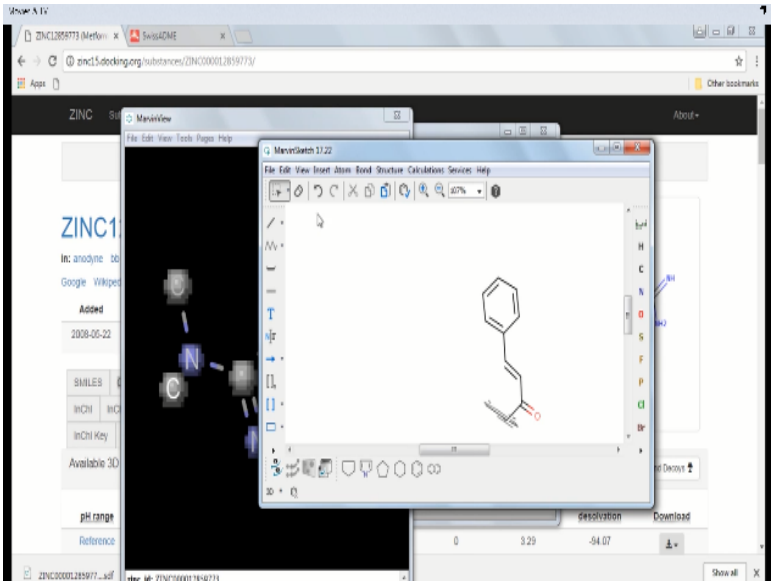

I can draw these structures okay I can draw the structures using this sketch pad and then take it for a 3-dimensional conformation. Okay analysis that is the beauty of this particular software MARVIN and as I showed you, we can do so many different types of data analysis okay that is the main advantage of this particular software and there is many other software free software but this is one of the best ones I would recommend.

And as I said it is a free software we do not need to have any payment on this you just have to register and register as a student or a faculty and so on. So, that is the advantage of this particular software okay so getting the conformations 3 dimensional conformations when you are manage a conformation and it is quite simple using a free wares like I showed you this. So, I would like you to explore on this MARVIN further in your room in your office okay.

And you can get more information using this. So, we can draw a very complex structures also or we can go to zinc database and the structure is available. We can download sdf and then take it to MARVIN view and then do all the calculations and store it in MRV format for further analysis because later on we are going to study pharmacophore analysis where this particular information will be very very essential and okay we will close this okay.

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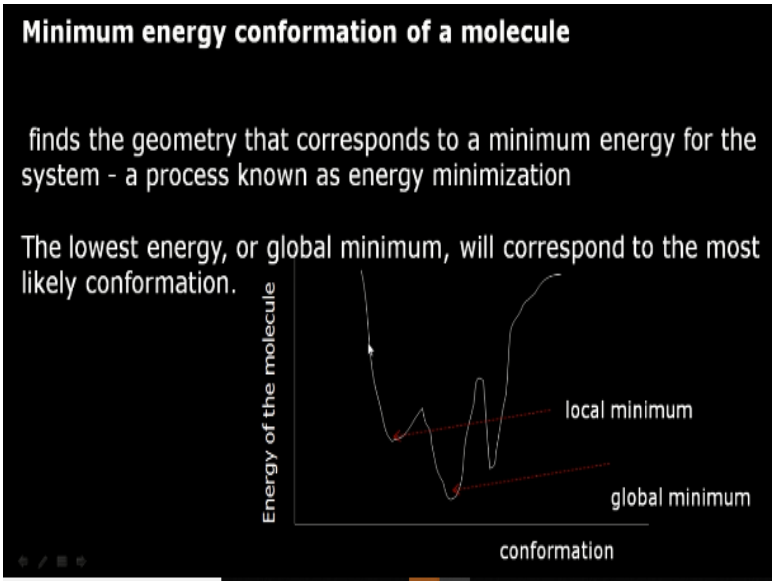

So, as I have been telling that getting the conformation is a big challenge of particular molecule okay you may end up with the local minima. Most of the time rather than global minima so you may have to start with different starting conformations so that you end up with a local minima I mean you skip the local minima and end up in the global minima there are many other approaches which are suggested.

We will talk about it in the forthcoming classes to see how to arrive at the global minima not get stuck in the local minima generally for small molecules. You may be able to reach a global minima but if you have big molecules this type of minimum energy conformation analysis is quite difficult okay because it is going to be very time consuming there could be millions of possible conformations.

And you might not be ending up at the global you may be ending up getting stuck in the local here it is like a car if it comes down the slope so there are many techniques available. We will

talk about it as we go along okay, and those techniques are simple, complicated and time consuming, but it is very essential for us to understand the 3-dimensional conformation of molecules.

Because it is very important to understand the minimum energy conformation of a molecule because the molecule may attain that conformation when it is stable instead and that sometimes when it goes into the active side of the protein it may like to modify its 3-dimensional minimum energy conformation. Also, okay depending upon the interaction it has with the active site. So, we will talk more about the conformation analysis in the next class as well okay. Thank you very much for your time.