Computer Aided Drug Design
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Lecture - 19
Molecular Mechanics/Force Field

Hello everyone, welcome to the course on computer aided design we will continue on the topic of molecular mechanics forcefield so what did we talk about in the past few classes.

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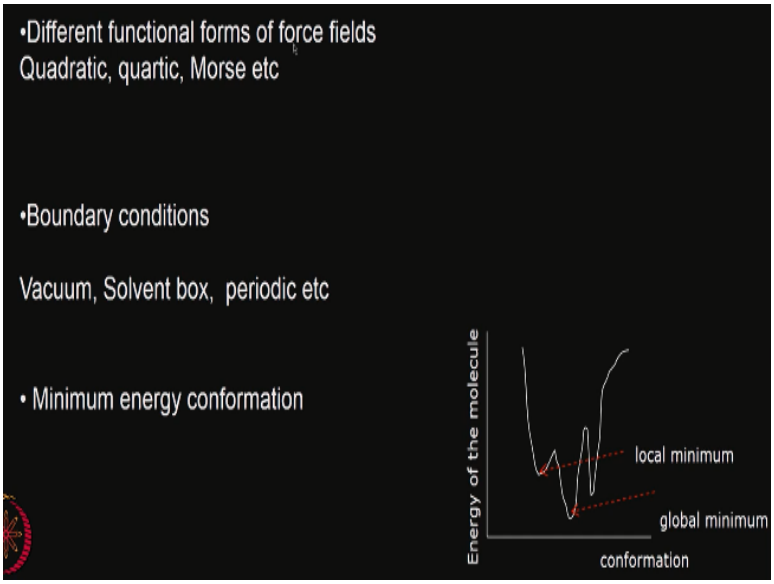

There are different functional forms for forcefield we have terms for stretching of the bond, bending, torsion non-bounded. So, they could be in quadratic form that is like Hookes law r-r0 whole square where r is the new distance r0 is the equilibrium or there could be quartic type that is raised to the power 4 as you can see cubic is not generally preferred or most type e power because when the bond lengths are very large long quadratic form gives a very high energy.

As you know quadratic is a square term. So, the energy goes up in a quadratic fashion, so this approach is also followed boundary conditions should I have the molecule in a vacuum that means that there is no interaction with solvents or any other molecule of that type it is more like a gas phase. So, if I want to simulate gas phase this is the best then comes solvents box I put in a lot of solvents around it.

So, I explicit solvents and that means I put the molecules of solvent and or implicit solar and I can add change the dialethic constant then comes periodic box we have box where you know molecule is inside which is surrounded by lot of water, so you have this type of box and all the 6 faces of the original box it could be a cubic or it could be a rectangular box okay. So, if 1 water or molecule goes out from one side.

Yes, you might of that water molecule entering from the opposite side so that the density is maintained constant and generally period box is one approach which is very liked and most of the simulation studies then them we talked about minimum energy conformation that means as you know molecule reaches the thermodynamic equilibrium where the energy is minimum okay. So, you may have different conformations, but the energies may be higher.

But you need to find a conformation at which the energy is minimum that means most negative. So, if you look at conformation on the x axis and energy of the molecule so minimum energy conformation is this of course you may have local conformations also like I said if you start with some conformation and keep changing the conformation calculate energies you may come here, and you may think this is the minimum energy.

But that is not very true okay that is not very true, or it is a local similarly you may start from somewhere here and as you go down down down down and you think that is the minimum energy conformation but that is also not true but actually you need to reach this this is the global minimum energy conformation of the molecules so there are many approaches to arrive at this starting from different starting conformation and try to avoid the pitfall of local minimum.

We will talk about that later. So, these are the different things which we talked about in the past few classes.

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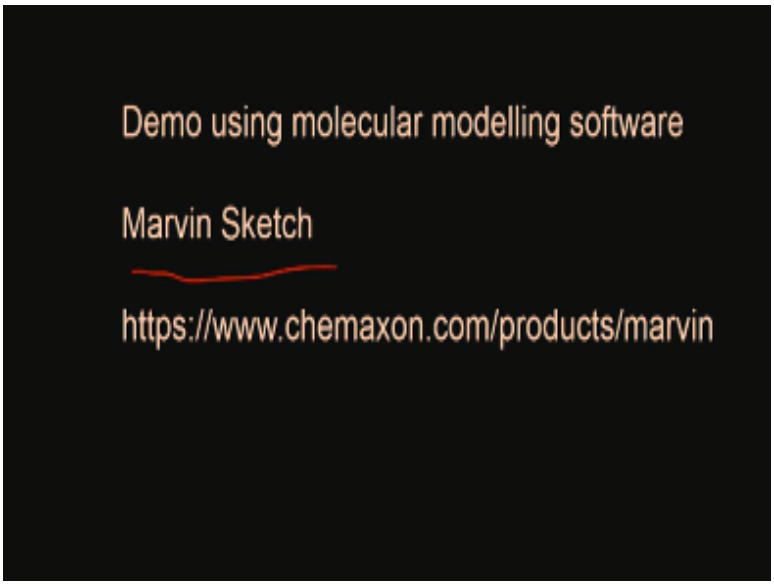

And we also looked at a demo more of molecular modeling software called Marvin sketch okay this is a freeware and it is very good, and it is free for academic for faculty okay, so you do not need commercial software for this we can sketch molecule that means we can draw molecules in 2 dimensional and then we convert it into 3 dimension and then we can calculate the energy. I mean you manage a conformation.

Then we can calculate lot of structural features structural parameters the 3-dimensional structural parameters lot of. So, this is a very good software we demonstrated last week so I suggest that you go and then get that software I think you have to register and so on and then start playing with that we can even text structure from seizing because zinc already has built in structures many of many molecules.

So, we can take it from there and then bring it to Marvin view sketch and then look at the 3d conformations and so on or if it is a new molecule we can draw it in the 2d pad available in this particular software. This is a very good software, so you do not have to think about they are going for a commercial software and so on do not get fooled by commercial software the software are good enough.

Suppose the number of force fields maybe less okay some commercial software may have many force fields and so on but for academic purposes for teaching purposes training purposes I think

this is a very good software you do not have to buy your commercial software.

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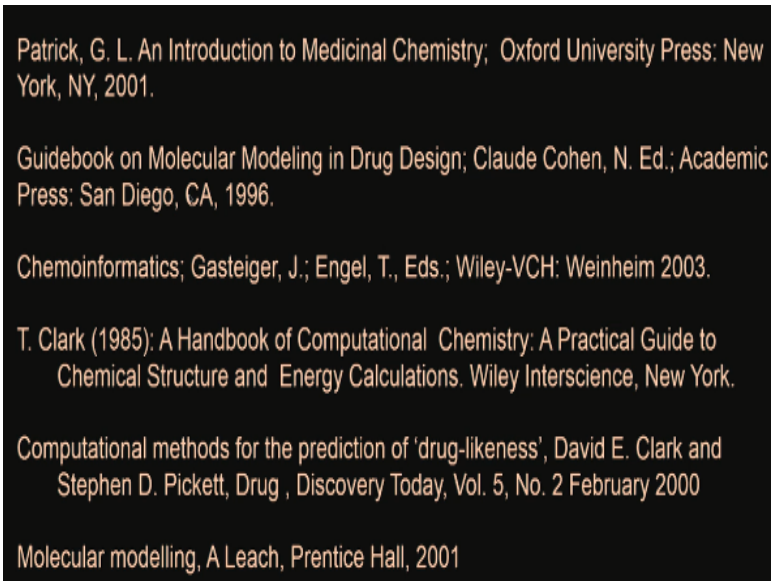

Okay there are many different books I am minded using here I suggest you get some of them for your library and start reading them guide book on molecular modeling in drug design, Cheminformatics, A handbook of computational chemistry, Computational methods for the prediction of drug likeness molecule modeling. So, you can see a lot of books actually this is quite a good book.

So, many different books are there because in this book you may find 1 or 2 chapters on molecular modelling. So, you can read them of course not all the books cover will all the topics and so some books may cover certain topics based on their focus okay let us go for that on this topic.

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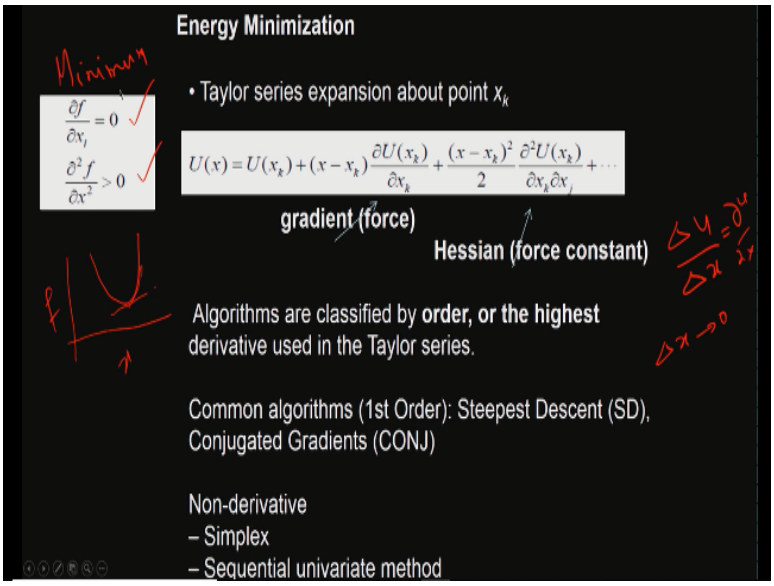

What is this energy minimization okay let us look at these energy minimizations now you have to recall your calculus which you must have studied long time back in your first year ug engineering session. If you look at Taylor series expansion Ux if you want to expand the function Ux at the point xk how do, we write Uxk+x-xkdu/dx and then subsite for xk +x-x square/2 factorial d squareu/dx square or you can put dxk dxj expand it at k and so on.

Actually, okay this is called a gradient and is called a Hessian and okay so that algorithm which make use of only the gradient there are algorithm which make use of this as well as this and of course they do not calculate this analytically, but they calculate numerically. How do they calculate numerically you take the value of find out the value of u at one particular point and then you find a value of u at a very small incremental point delta?

Okay so the difference in the u value is divided by the delta x gives you du/dx okay as you know you must have studied du/dx. It can be approximated to delta u/delta x okay delta u/delta x because delta x tends to 0 this will be=du/sorry =du/dx. Okay so if you want to look at so the algorithms are classified by order are the highest derivative used in Taylor series okay. First order methods are common you have steepest descent method, conjugated gradient method.

And of course, you have non-derivative method, simplex method, sequential method and so on actually. So, if am looking at a minimum okay then it should satisfy df/dx or if you are talking

about u then du/dx should be=0 and df square/dx square should be >0 because as you know if you have a like this okay x and f for example it is a minimum df/dx=0 because as you can see the slope 0 and also when you take the second derivative ratio it should be >0.

Because it is increasing there okay so for a minimum what are the two conditions df/dx=0 because it will be sort of a parallel line that is the minimum and then d square f/dx square should be >0 of course for maximum df/dx=0 df square/dx square will be <0 okay. So, this is for minimum so the criteria for the function f to have a minimum value rest as you keep changing x will be df/dx=0 d square f/dx square is >0.

So, if you have simple small functions you can do it analytically just differentiated with respect to the independent variable equally to 0 and then calculate the parameters and then you cross check by say taking the second derivative and see whether the second derivative is>0 okay that is for the minimum.

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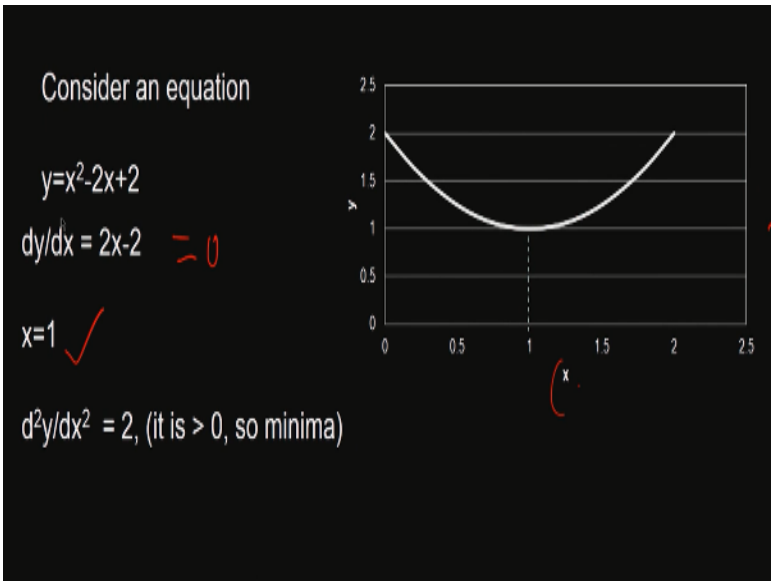

Okay so let us look at some simple thing look at this function y=x square-2x+2 so I want to find out the minimum, so I take y is the dependent variable x is the independent variable it is a very simple problem one independent variable problem. So, dy/dx=2x-2 okay then I equate it to 0 okay so when I equate it to 0 it comes out to be x=1.Now I need to find out whether this is a minimum or a maximum.

So, what is the condition for minimum here I had mentioned right d square y/dx square should be >0 d square y/d x square I differentiate again it comes to 2 because this will become gone this is 0 this is 2 this is greater than 0. So, it is a minimum so if you plot it also on, so you can cross check it and go to excel and plot it y= x square-2x+2 this is y. So, I take different values of x what happens it comes down down down.

And then it goes up because it is a parabolic relation at x=1 here x=1 so if you see 1-2 okay x=1 and I take x=1/dx=2-2=0. So, simple equation we can even plot it in excel and find that x=1 is the minimum value for x okay or how do we do it, we take a dy/dx and then equate it to 0 from there you calculate x to cross check whether it is minima you take a second derivative d x square/d y square here in this case it is true it is greater than 0 so it is a minimum.

So, two conditions like I mentioned we need to look at these two conditions for minimum. Okay let us look at this is a 1 independent variable problem.

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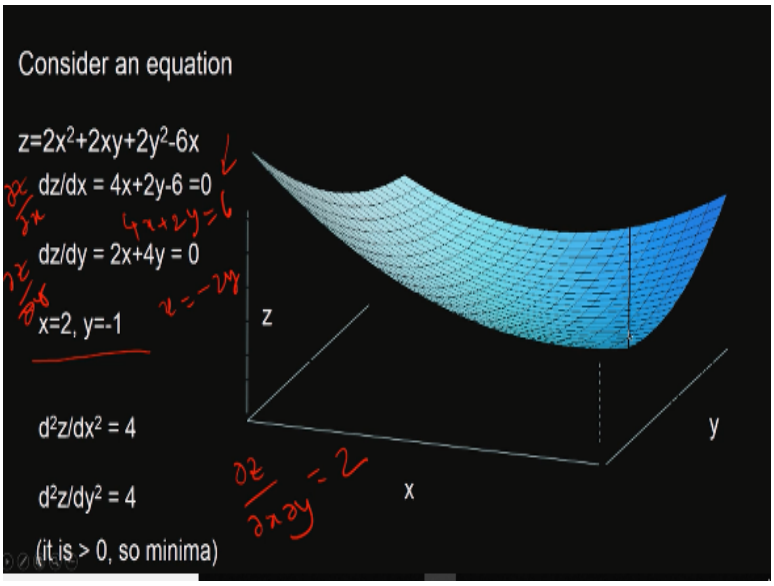

Let us look at 2 independent variable problems x and y and z is your dependent variable. So here how do I find x and y I need to partially differentiate the z function with respect to x and with respect to y and then equate it to 0. So, if you take dz/dx okay partial differential actually I should not put a dz/dx. I should actually put it like dz/dx and here it should be dz/and dy. So, if

you put dz/dx.

I am differentiating only with respect to x so 4x+2y-6=0, so similarly dz/dy and this will not come 2x+4y=0 s and so I have 2x+4y=0 4x+2y=6 okay 4x+2y=6 okay I can solve these two simultaneous equation or or if you take this look at the second equation second equation will be x=-2y and then we can substitute this into this so you end up with x=2 and y=-1 so how do I do it if there are two independent variables.

Okay I differentiate partial differentiate with respect to x and with respect to y and then equate it to 0 .So, I will get a simultaneous equation for x and y I solve them okay this is where minimum happens okay you have to cross check whether it is minimum. So, what do you do you take the second derivative, so we have dz/ dou z/dou x we call it because it is partial so again differentiate with x.

For example, so it comes to 4 take dou z/dou y and differentiate with respect to y again it comes to 4 again they are >0. So, like I mentioned in the in this particular side, so they are >0. So, it is a minimum that is for cross-checking actually it is a minimum. Okay you can also do the same thing for a dou z/dou x dou y. So, if you take this equation and what do you get you are now into for differentiating the dou x differentiate it with dou y, so it comes to 2.

Okay so again this is >0 so we can say this x=2 y=-1is the minimum of this particular function okay if you draw them graphically as you can see the x axis then this is independent variable y axis another independent variable, z is your dependent variable, so it is a parabolic plane, so it goes like this and you get at x=2 and y=-1 okay you get the menu option. So, if the functions are very simple you can do it analytically.

Okay like I just showed you in the previous case one variable problem x is the only independent variable or in the second problem you have two independent available x and y z is your dependent variable, so we can easily do it analytically but if the function is very complicated with lots of terms you cannot do that problem analytically if there are many variables and many independent variables x y z and so many.

Like you in you are a force field you may have r you may have theta you may have phi so many terms maybe there are so many independent variables maybe there so it may be difficult to integrate I am sorry how to differentiate and then solve the sides of simultaneous equation so best approach is to do it numerically that means you get the dou z/ dou x numerically dou z/dou y numerically and then try to calculate the values where the function will be minimum okay.

So, that is how software do actually so that is called the numerical differentiation they call it numerical differentiation. So, we will look at these numerical differentiation numerical integration you must have studied, and you are as I said the first semester or second semester ug engineering courses or even in eleventh and twelfth standards okay, so I am sure you must have studied. Let us not spend much time okay.

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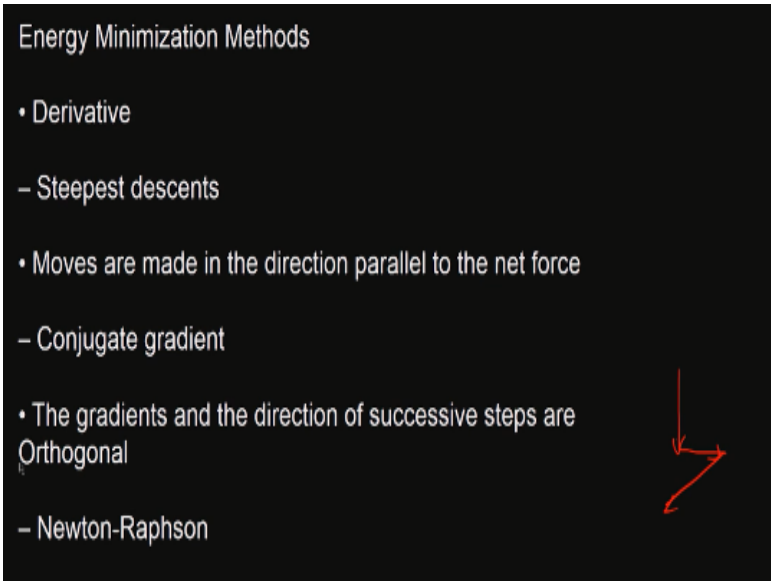

So, there are many energy minimization methods the derivative method where you first calculate the first derivative, or you calculate Hessian we have the steepest descent that means you take the direction in which the slope descends very very steep and follow that so moves are made in the direction parallel to the net force and then we have conjugate gradient. The gradient in the direction of successive steps are orthogonal okay.

So, if you move in one direction next time you are moving the second direction third time you

move in the third direction like that you know each one is orthogonal to another and then you have the newton Raphson, and this is again based on some sort of a gradient method okay gradient method is basically derivative based method you can use Hessian, or you can use first derivative and so on.

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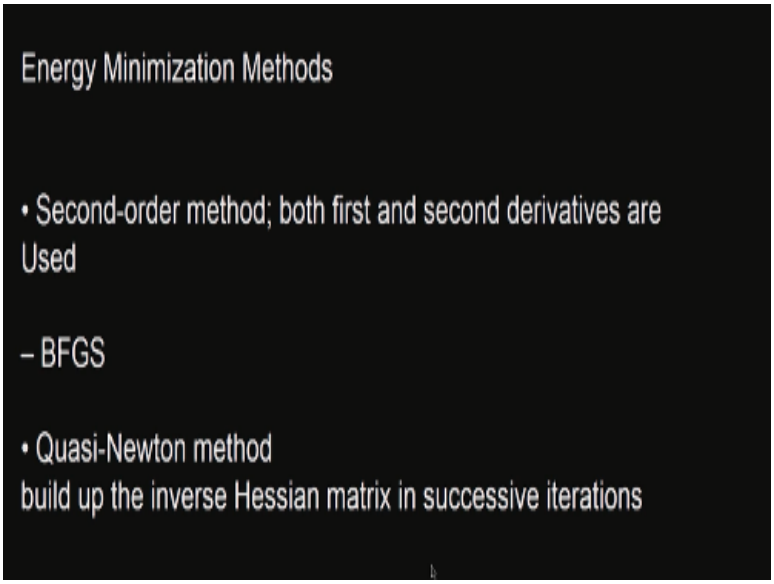

Then Second order method like I said first, and second derivative are used then Quasi newton method build up the inverse Hessian matrix that is d square f and d square f/d x square dx dy like that that is called the Hessian matrix. So, different methods are there some of them are very time consuming because it involves a lot of terms to be calculated so it would require lot of computational effort then minimization of a function is always a challenge okay.

Minimization of a function is a challenge especially when you have a lot of independent variable is okay. So, it is not very straightforward, so lot of methods are used in the software so if you look at the software I think if you use a Marvin they also have different methods for energy minimization. I think I did not show it to you, but you can have a look at it and as you can see there are different methods for energy minimization.

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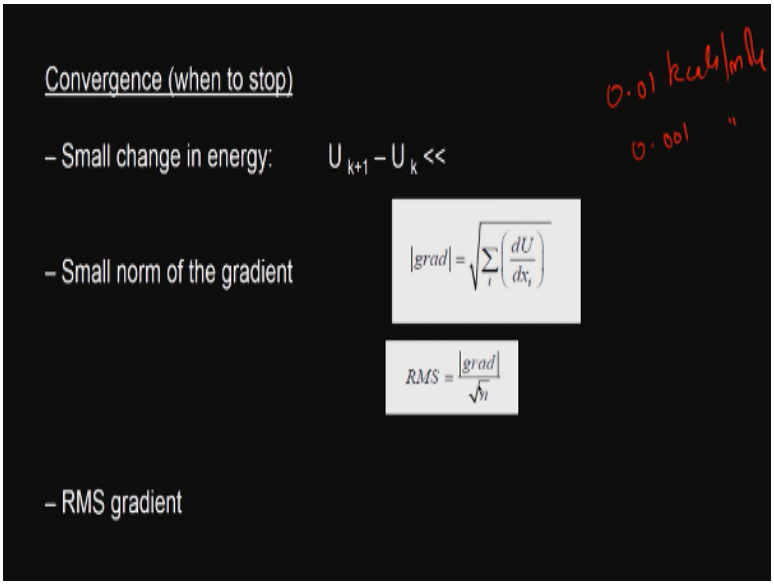

Okay how do you know it is enough to stop okay which you keep trying to change until we get the minimum values how do you know when to stop when there is a very small change in energy that means I change I get a conformation I guess I have some energy when I get another conformation the change is very, very small okay then I would say let me stop so very, very small means I may give a number like if the difference is 0.01 kilo cals per mol.

There is no point you may stop or if I am interested in more accurate I may say .001 cals per mol okay so depending upon number I feel I make. Another approach is small a change in the gradient, so you calculate the gradient all the gradient square root then you say there is not much change very little change in the gradient third approach is a small change in the root mean square gradient ok so gradient whole root square of n.

So, these are the different approaches one is to see the energy change, if the energy change between one conformation of that information is very very small many say enough we have reached our minimum or if you look at the gradient okay take the square root add all the gradient in the square root this value you see you give some number okay it is <.01 or you do the RMS gradient.

That means you take the gradient take the square of n and that is called the RMS gradient and then you say if it is smaller than .01 enough is enough we will stop okay these are the different

approaches maybe you stop being conformational minimum energy conformation.

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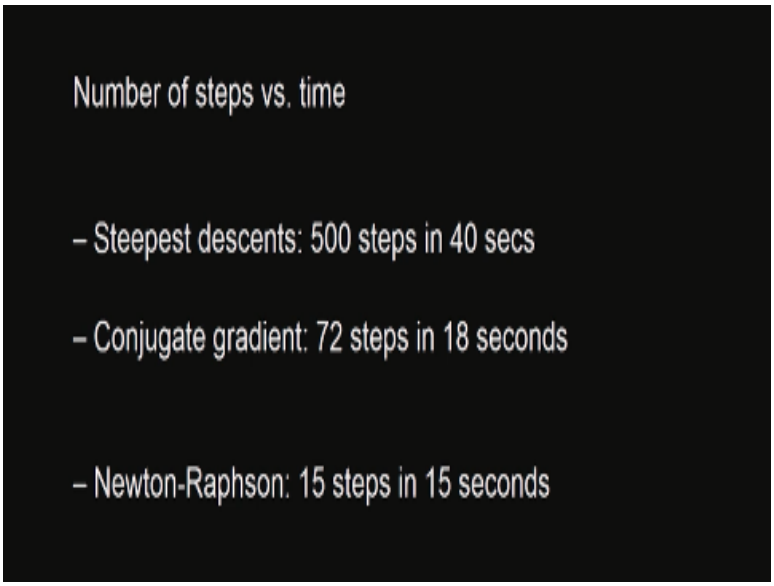

Okay so time steepest descent though generally need at least 500 steps to reach a minimum 40 seconds of the computation time conjugate gradient is much faster or the number of steps required is much less and it also takes less time. Newton Raphson method again it takes less number of steps and less time. SO, these are like I said numerical methods okay you must have studied many of them, so I will not go too much into that.

Because that is not our focus but there are many numerical differentiation integration methods which are used by all these molecular modeling software to arrive at the minimum energy conformation.

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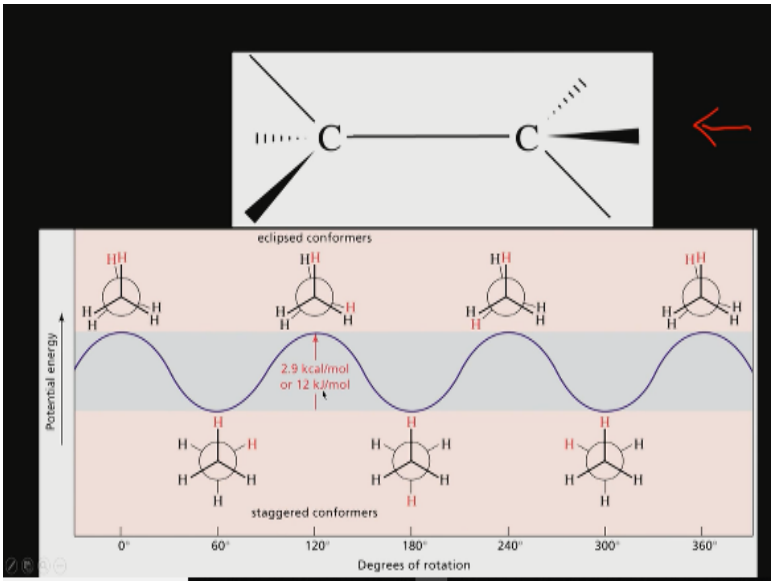

Look at this let us look at the Methane for example 2 cs are there we have hydrogen hydrogen hydrogen one hydrogen could be sticking out one hydrogen may be going back so it can take many, many different conformations the way you look at no suppose you are looking at it like this okay you may have the hydrogen okay the hydrogen hydrogen is almost exactly over lapping looking.

So, that will have higher energy okay almost look at them in the hydrogen hydrogen and all these are almost over lapping up each other whereas when the hydrogens already distributed and not over lapping with each other staggered conformers this is eclipsed conformers because exactly hydrogen is looking at the is this looking at this is this looking at this or that we call it eclipsed conformers we do not want to see all the 6.

Whereas if you have this type of conformation staggered you can see all of them energy is low look okay it can be very quiet large 2.9 kilo cal 2.9 kilo cals which is a big number or 12 kilo joule per mol okay that is a big number that is why you will always see systems holding on to this type of conformation.

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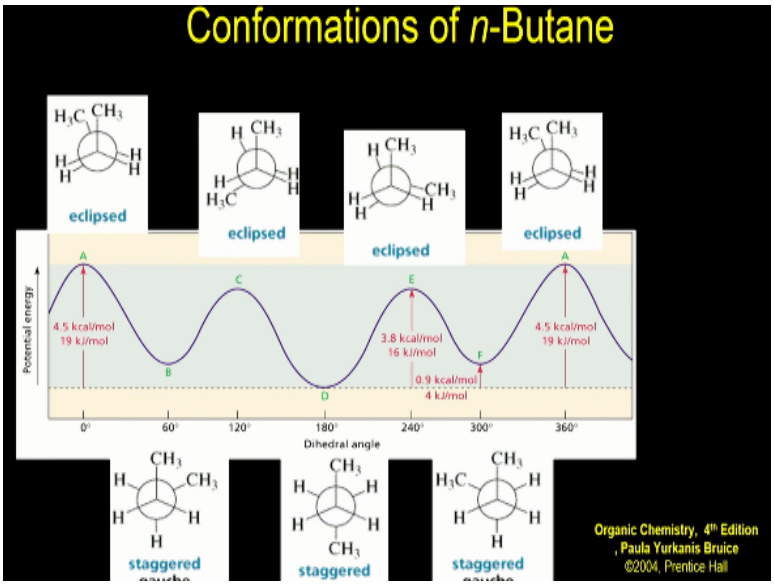

Let us look at n-Butane okay again as you know n Butane has four k I guess as you know, and butane has 4 carbons 1234 and so we have CH3 CH2 CH2 CH3. So, it takes different conformations okay staggered gauche eclipsed okay eclipsed eclipsed and this is staggered gauche you see CH3 is here, okay it is called staggered anti-so different types of conformations this is taken from this particular reference okay organic chemistry fourth edition.

So, each one of them has a different energy values the potential energy as you can see here okay the energies could be of the order of difference it could be of the order of 4.5 kilo cals per mol okay 3.8 kilo cals per mol 19 kilo joules 16 kilo joule and so on actually okay okay so defending upon the conformation did take you are going to have a different energy values and it could be quite high.

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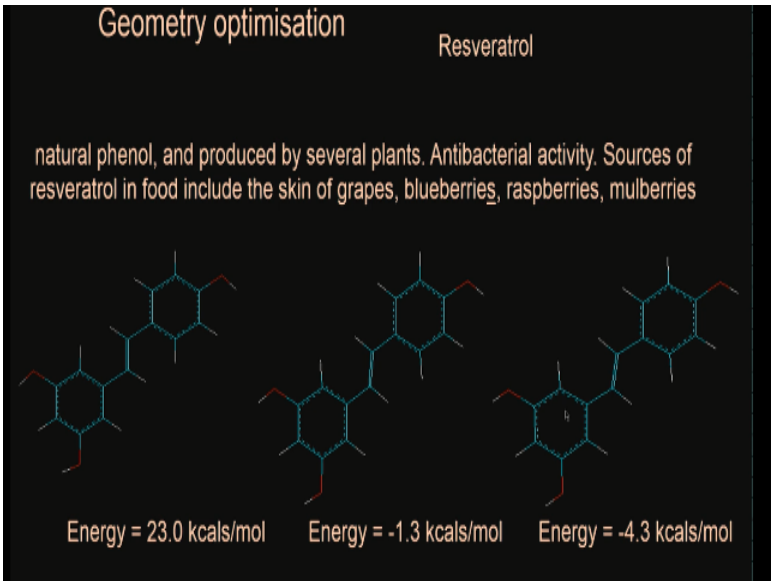

So, look at this Resveratrol, Resveratrol is a natural product and is a phenolic component okay produced by several plants and they exhibit antibacterial activity it is found in food fruits like skins of grapes, blueberries, raspberries, mulberries okay, it has got 2 benzene ring and there is a double bond here this is CH CH 2 Benzene ring there is a OH here and 2 OH so when it occupies this the energy is 23 kilo cals positive.

Look at this it can go to -4.3 kilo cals from 23 to-4.3 depending upon how these orientations of these 2 Phenol rings are okay by from that energies can change dramatically look at this this is going to -1.3 this is got -4.3. Okay so energies can be dramatically different okay a small change the way these two benzene rings orient with respect to these these double bonds.

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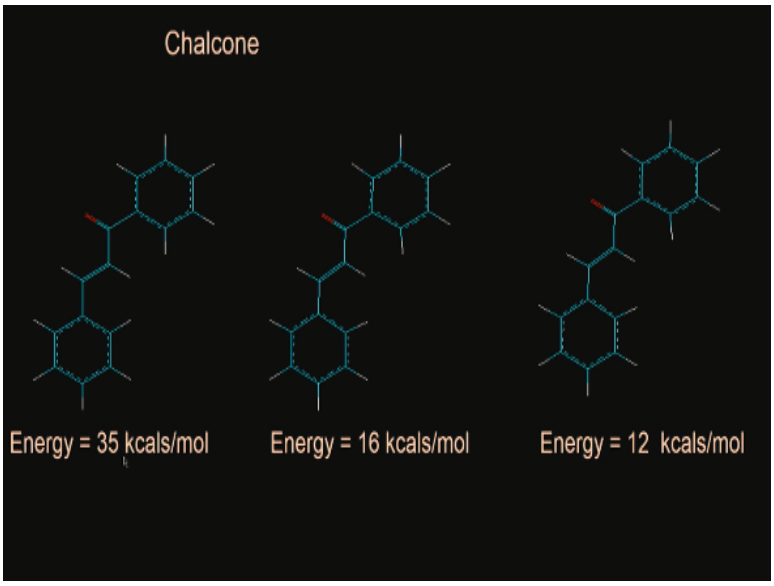

Chalcone Chalcone looks like it was a troll, but it has got a Methane there is alpha, beta there is a double bond here. So again, we have Phenol Benzene rings here so look at this this is a 35 kilo cals goes down to 16 can even goes down to 12 and so these the way they hold themselves here that makes a lot of difference okay. So, depending upon the conformation small changes in the conformation.

You would see a lot of difference in these and energy values okay we will continue more on this topic of conformation and minimum energy. Thanks very much for your time.