Computer Aided Drug Design
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Lecture – 24
Quantum Mechanics

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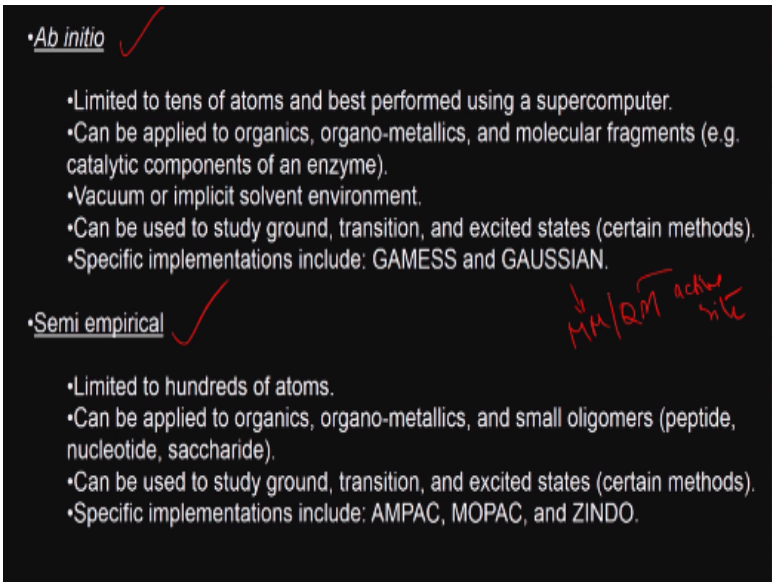

Hello everyone, welcome to the course on computer aided drug design, we will continue on the topic of quantum mechanics. I did introduce 2 different quantum mechanics method; one is called the Ab initio method, other is called the semi empirical method. The Ab initio method is detailed calculations, very accurate, so it is limited to tens of atoms only okay, so we need a very good computational resource.

It can be applied to organics, organometallics, molecular fragments and so on; enzymes and so on, it can be done in vacuum or implicit solvent okay, we can look at ground state, transition state, excited states okay, some of these software's like GAMESS, Gaussian they all work on Ab initio. So, it is not really useful for computer aided drug design, semi empirical methods or that way much more relevant for us.

We can go quite lot hundreds of atoms unlike tens of atoms okay, this can be applied to organics, organometallic, small oligomers, peptides, nucleotide, saccharides, we can look at again ground, transition excited states but a little bit approximate, so there are many methods;

AMPAC, MOPAC, ZINDO and so on. Of course, the other one molecular mechanics, which we spent a lot of time in the previous classes, is good for thousands of atoms.

And generally we use that for docking purposes, so for limited active site maybe you can go into this side of semi empirical methods okay whereas, rest of the protein you use molecular mechanics method, so nowadays a combination of semi empirical methods and QM methods are coming into MMQM, so predominantly we use MM method and only the active site, you use a QM method, so that your computational effort is not too much.

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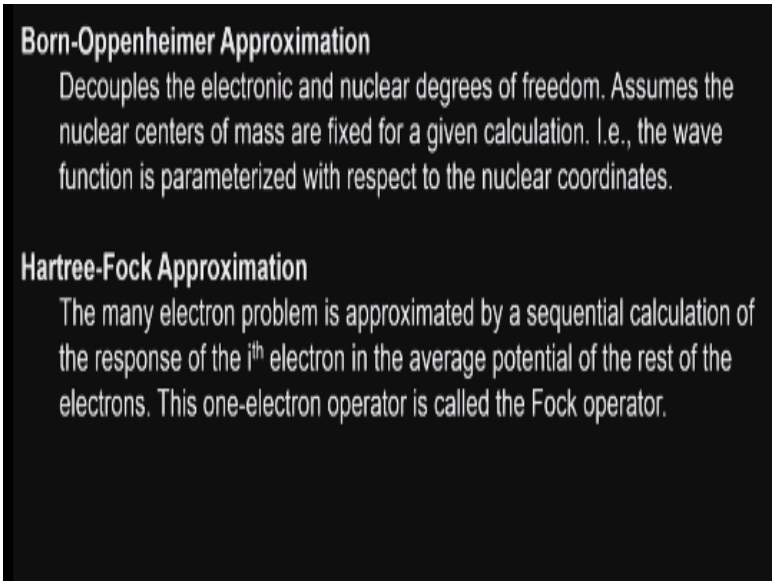

So, we looked at some approximations, one the most important is the Born-Oppenheimer approximation. What it does is it reduces the degrees of freedom between decouples the electron and nuclear degrees of freedom, so they assume; this approximation assumes that the nucleus is fixed, so we have only degrees of freedom for the electrons okay. Then came the Hartree-Fock; this is a very important one as well.

So, the main electron problem is approximated by a sequential calculation, so you take the ith electron and you take the average potential of rest of the electrons and then see the interaction okay, so it becomes one electron operator. Then you take the next electron, then take the average of rest of the electrons and then see the interaction. So, you do not look at all the electrons which maybe; if you look at each electron interacting with the remaining electron, you are going to have huge number of calculations.

Whereas, by doing this you reduce the calculations tremendously but still Ab initio methods take more time, so semi empirical methods take care of many of these calculations using as certain fitted equations and parameters.

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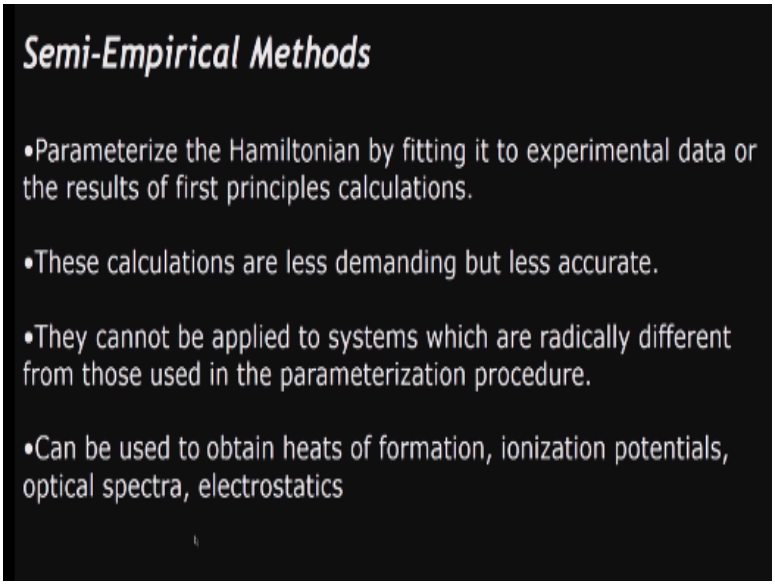

Some of the major methods in Ab initio GAMESS and Gaussian, semi empirical method; so parameterize the Hamiltonian by fitting into experimental data or results from Ab initio, so these calculations in semi empirical are much less demanding unlike Ab initio and they cannot be applied to systems which are radically different from those used in the parameterization. It can be used for heat of formation, looking at ionization potential, optical spectra, electrostatic.

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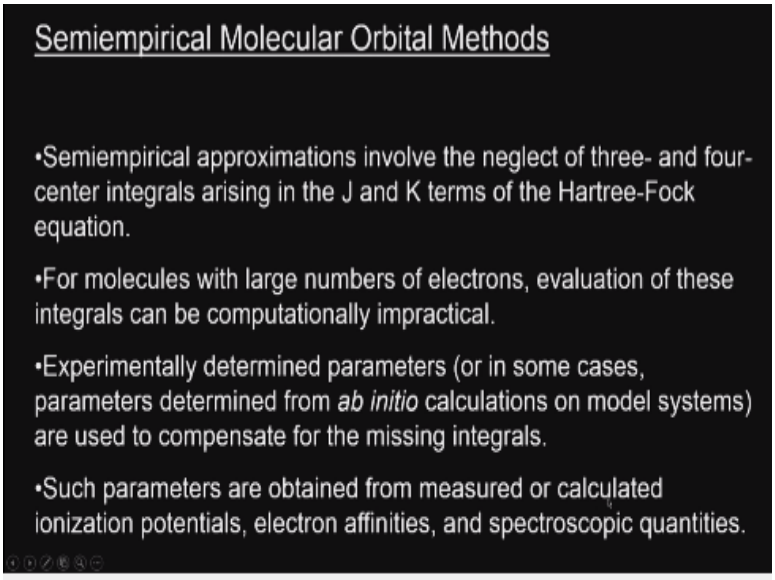

So, we can simulate some of the spectroscopic behaviour of molecules and so on, so the molecular orbital methods, most of the semi empirical methods are based on molecular orbital,

so it approximates neglect of 3 and 4 center integrals in the J, K terms of the Hartree-Fock equation okay, so some methods give certain parameters or certain equations to consider these three and four okay.

So, for molecules large number of electrons evaluating of these integrals can be very computationally challenging, experimentally determine parameters or sometimes from the Ab initio for compensate the missing integrals three and four okay, so it can be obtained from measured or calculated from ionization potentials, electron affinity, spectroscopy and so on.

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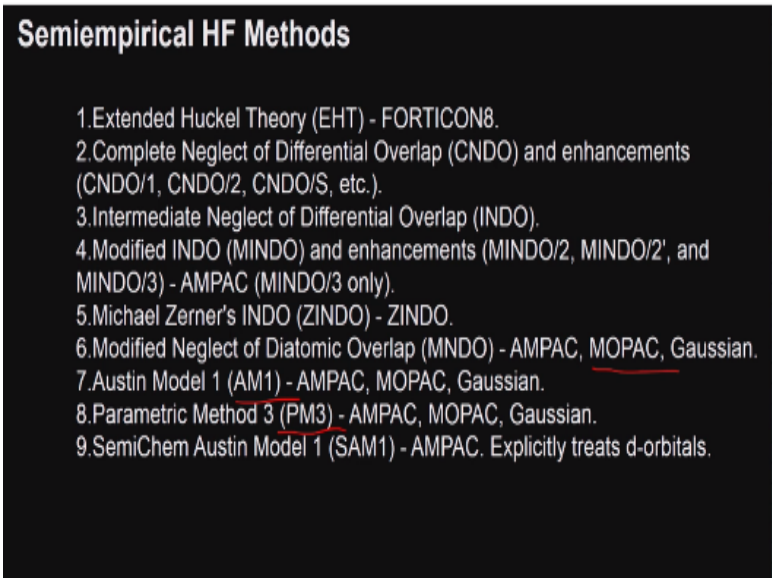

So, some of these methods, large number of methods are there for semi empirical methods okay CNDO, CNDO/1, CNDO/2, CNDOS then intermediate neglect of differential overlap INDO, we looked at the some of those definitions yesterday then MINDO that is modified INDO, then we have the AMPAC, then we have the INDO ZINDO, then modified neglect of diatomic overlap MNDO, MOPAC is there, MOPAC takes care of that.

Then we have AM1, Austin model 1, then parametric model PM3, then SAM1 and PM3 has become even PM6, so large number of semi empirical methods generally, MOPAC is a good program and we can use these methods which are really good for your calculations.

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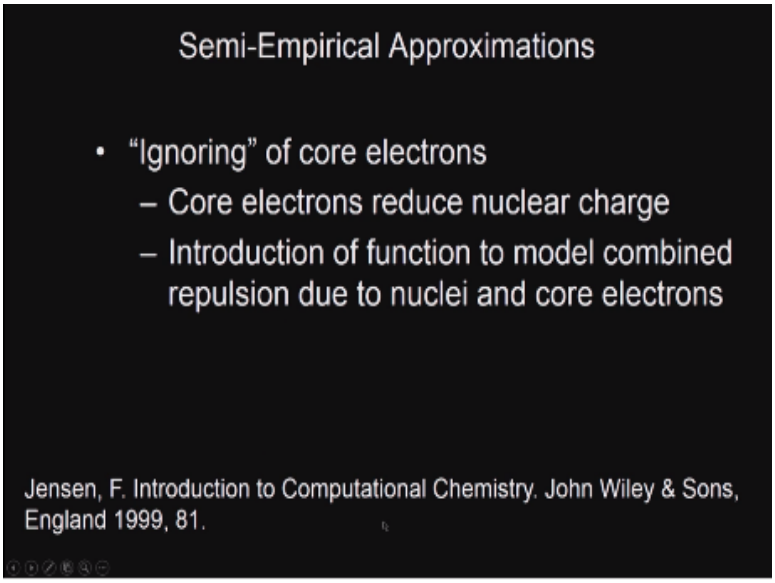

So, what it does is; it ignores core electron; semi empirical method, so it takes only core electrons reduce nuclear charge, introduction of function to model combined repulsion due to nucleus and core electron. So, you have function which take care of that rather than using integrals okay. This is taken from this reference, a minimum basis set of functions to account for valence electrons okay.

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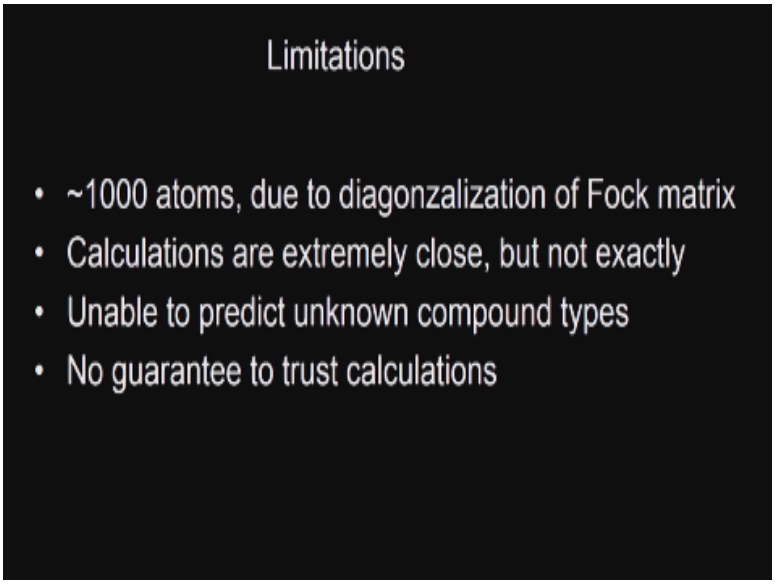

So, we have a basis set, I will be defined what is the minimum basis set, so we take that to model the valence electrons that is electrons in the outermost orbit. So, what are the limitations? We can do thousands of atoms due to diagonalization of Fock matrix, calculations are extremely close but not exact, it cannot predict for unknown compound, so you need to keep that in mind, cannot predict for unknown molecules and unknown compounds.

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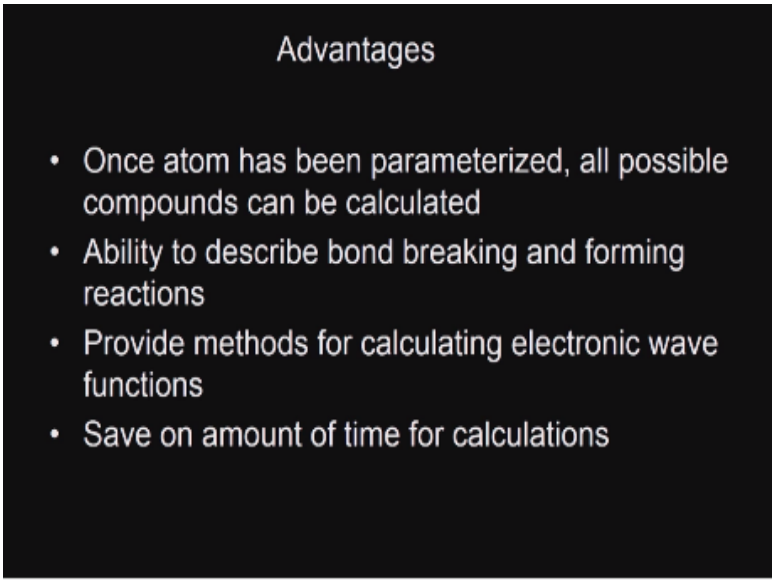

So, sometimes you cannot trust the calculations because there are lot of parameterization and equation fitting. but once the atom has been parameterize to all possible compounds can be calculated, so that is the advantage and for especially for drug discovery, we are talking about carbon, nitrogen, oxygen and sulphur maybe chlorine, so there is no problem at all okay, mostly for drug discovery, semi empirical methods can be used without any problem.

So, it can look at bond breaking and forming reactions that is very important. Suppose I am making a prodrug, as you know prodrugs are not really drug but molecules which go inside the body and they get broken because of action of some enzymes, then the active ingredient comes in, so we can look at bond breaking energies for that bond forming reactions also we can look at.

Whereas molecule mechanics methods cannot be used for that, that is the main advantage of semi empirical quantum mechanics method. We can look at electronic wave functions also okay, that is another advantage of that, so we can look at energies of various orbitals, we can calculate them that is another advantage. So, what is the energy difference if you want to move an electron from one orbital to one unoccupied orbital, so we can do that sort of calculations?

And of course, it saves lot of time for calculations although it is quantum mechanics, it is much faster, so we get lot of information but with less amount of time, so that is the advantage of using semi empirical methods okay.

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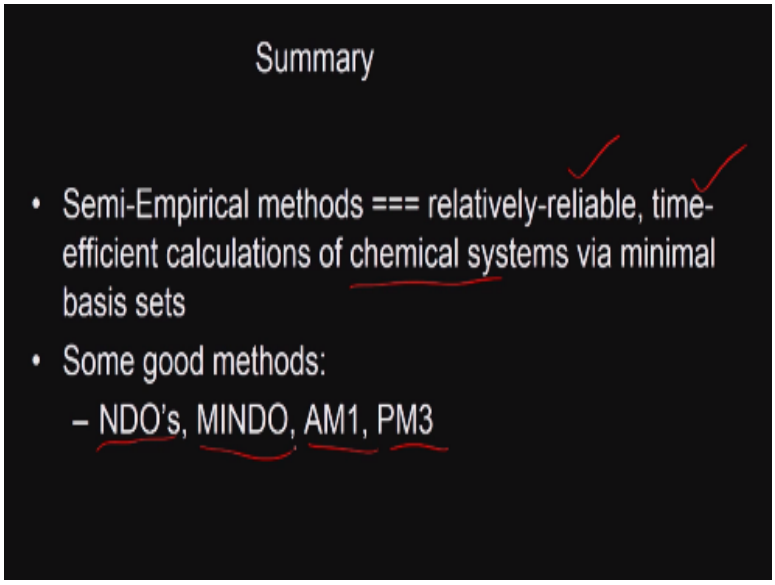

So, semi empirical methods relatively reliable, time efficient calculations of chemical systems by a minimal basis set, so that is the main advantage of a semi empirical method, it is relatively reliable, time efficient calculations chemical system, so we can look at the bond breaking, bond forming, moving activated state, ground state of molecules, so we can look at all these energy values using this electronic energy, nuclear energy.

So, we can calculate all that using semi empirical method, so some good methods like I mentioned; neglect of differential orbitals okay, AM1, PM1, PM3, they are all very good methods actually okay, so these are all really good methods, okay.

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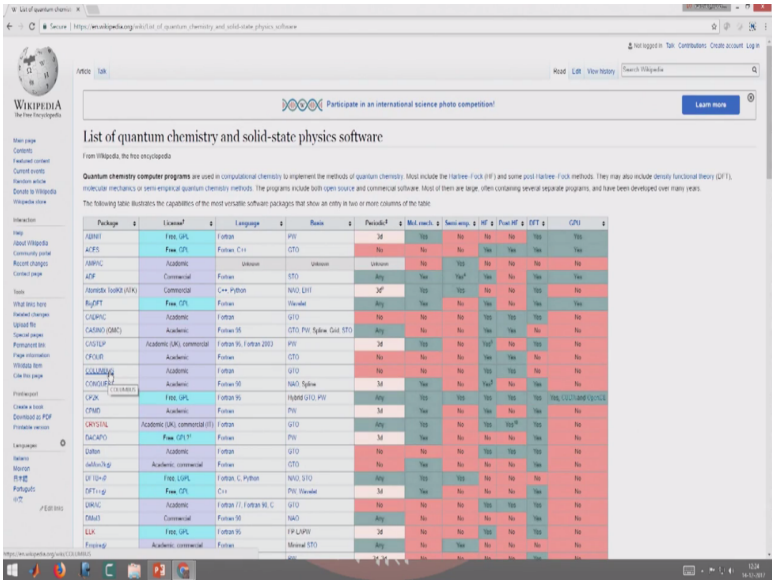

Let us look at one of those website, where there are a lot of methods are given in this website okay, so you see a list of quantum chemistry and solid state physics software's, huge number of

softwares are given, so this is a very nice resource for you guys, so have a look at it, licensed; academic license generally we get it free commercial means, you may have to pay, so these are the various packages.

So, we can look at what these methods are by clicking on that so, you can see so many different MOPAC, commercial is also there, academic is also there, so if you show that your academic they give you a license key okay, so large number of methods you can see this okay, so many different methods, the language they have used Fortran 1995, okay basis set, what is the basis set?

They have used okay molecular mechanics calculation, some of them do molecular mechanics as you can see, SSS some of them cannot do, semi empirical calculations some of them can do, some of them cannot do okay, Hartree-Fock calculation; some of them can do, some of them cannot do, density function method; some of them can do okay and so on, so large number of methods we can use.

As you can see some of them are academic, so it is free, free academic, academic, free, free okay, some of these are downloadable, executable some of them needs to be compiled, so if you need to compile them obviously you may require certain library functions and all those things actually and so if you get a help from some IT person, it is easy for you to compile them, so you can see free, free, free, free academic.

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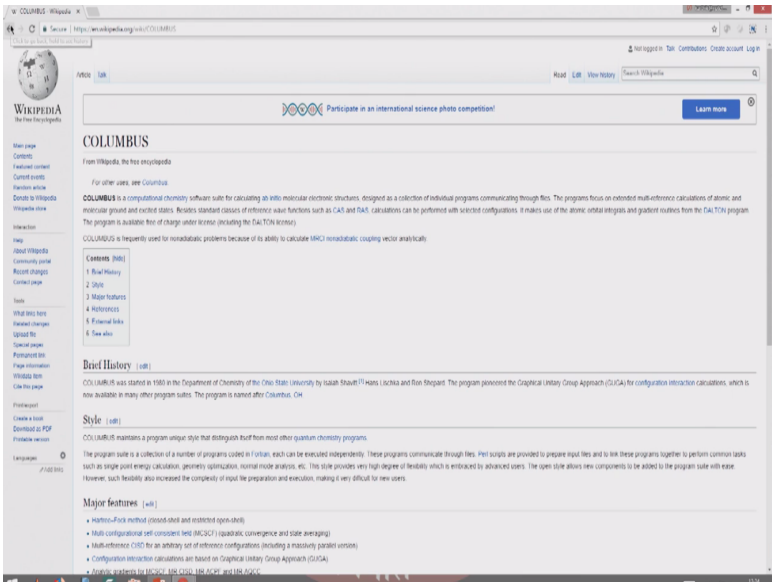

Academic means you get academic license claiming that you are a student or a faculty, free GPL, so we can see free, free of them okay, quite a lot of these methods. So, look at this Columbus, as for example if you click on that Columbus, the computational chemistry software suit for calculating Ab initio molecular electronic structures designed as a collection of individual okay.

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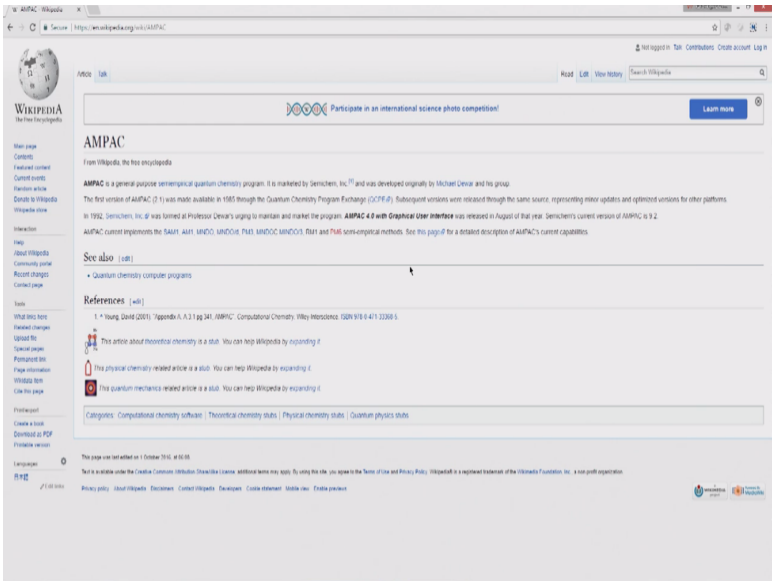

It has got of course; Ab initio, so it has got a Hartree-Fock self-consistent field and so on, so let us look at something which has got semi empirical also. AMPAC is there, there is an academic, so AMPAC is a general purpose semi empirical, marketed by SemiChem was developed originally by Michael Dewar, so in some methods are now a graphical user interface, whereas the older methods will not have graphical user interface okay.

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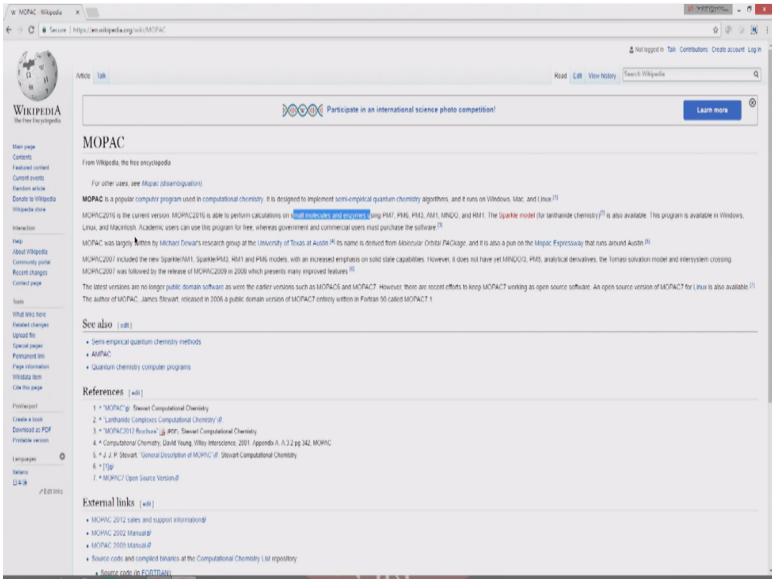

So, look at some other semi empirical method; DFT is there, DIRAC, Dmol3, these are all commercial methods, MOPAC is academic, so that means you have to show that you are in academic and then it also has the semi empirical okay, so we can go to MOPAC okay, so this is a very popular; MOPAC is a very popular computer program using computational chemistry, semi empirical quantum chemistry.

MOPAC has a several thing; PM7, PM6, PM3, AM1, MNDO, RM1, so I would suggest that you should go for MOPAC 2016 okay, so it is for academic, it is free, various methods are there, so many different methods for calculating the molecules is there, it is good for; very good for small molecules and enzymes okay, so MOPAC is available in Windows, Linux, Macintosh, so if you can get completely downloadable MOPAC16 claiming that you are an academic.

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Then you can start using and you can use all these various semi empirical methods; PM6, PM3, PM1, MNDO, RM and so on, so it is really nice to have them okay. For example, let us look at the MOPAC, as I said MOPAC 2016 is available free for academic and non-profit organizations, so I suggest that you all get that and then start using some of the semi empirical methods okay.

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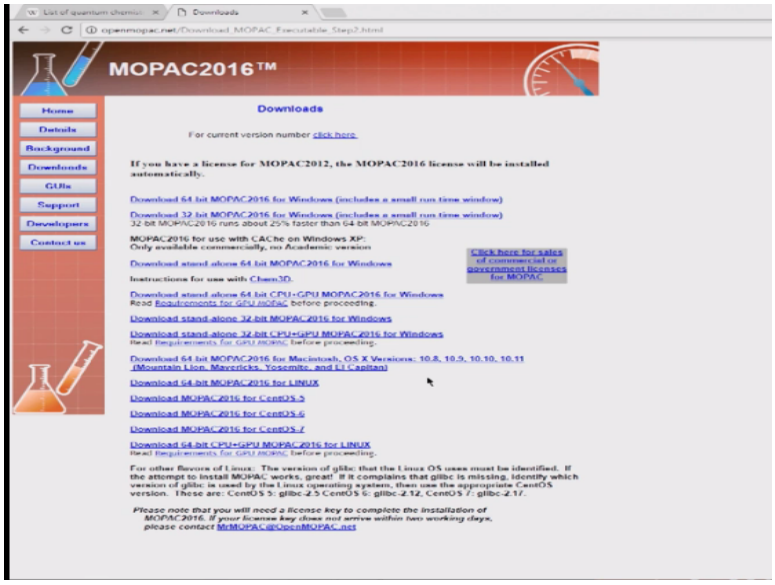

So, you see MOPAC2016, so you can get a license okay, so you have download standalone 32 bit MOPAC2016 for Windows, you can get here license from them, once you get the license you can run the program and insert the license key okay, so as you can see here, it gives you zip okay then we can run and then we can put the license key inside and so on actually, so it is not difficult okay.

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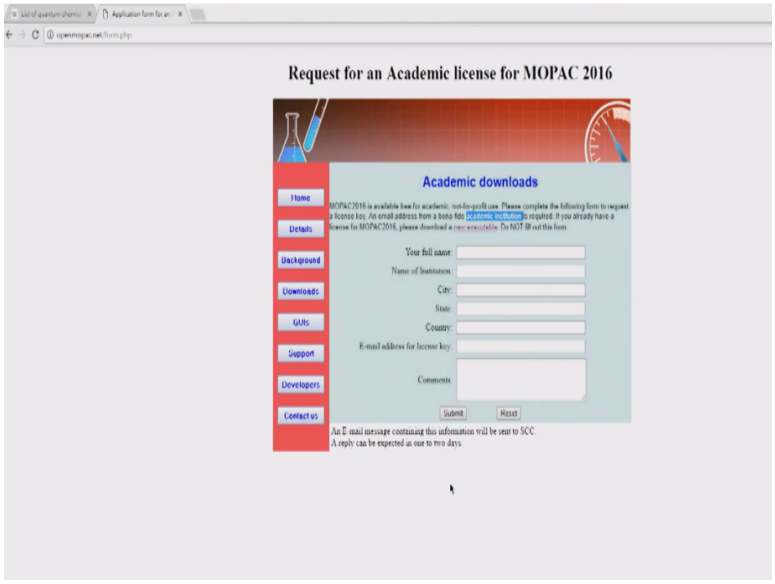

So, but in order to get a license, you need to go okay to get a license okay, so okay, so if you give the name of the institutions; name, city, state, country, email address for a license key, so email address has to match your academic institution okay, so that they will confirm it is a bonafide academic institution okay, from bonafide academic institution is required okay, so you cannot give any email id, which does not reflect your institution.

So, if you do that and you submit to that particular mail, you will get the license key and once you do that we can download like I said we can download and then okay, we can download the 32 bit version and then incorporate the license key, so it is one of the best semi empirical methods I can think of.

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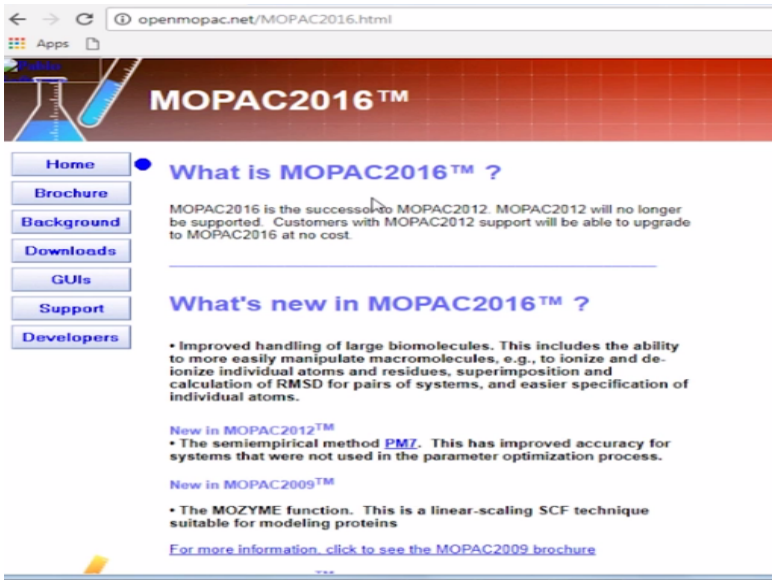

MOPAC is a software which can be used for calculating the semi empirical quantum mechanic features of any molecule, it is a free software downloadable and as I mentioned it can do PM3 type of calculation.

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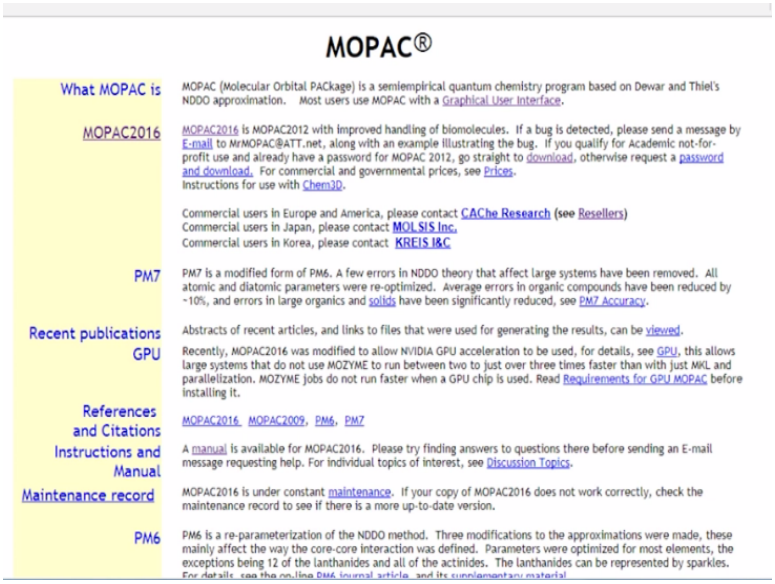

And now currently, it does a PM7 type of calculation, so we can download and then we can install that and then we can get the semi empirical features of molecules.

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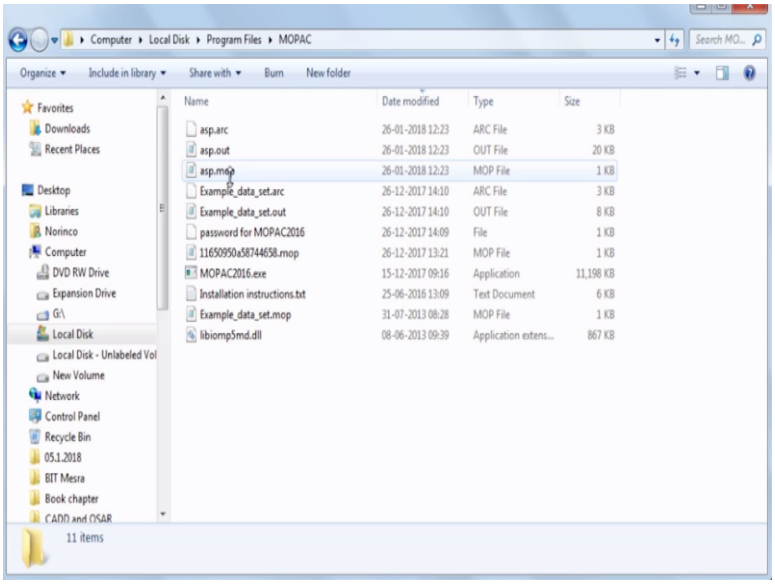

For example, let us take aspirin; aspirin you need it in the dot MOP file, we can use open babel to convert as I said any format any format, so aspirin we can download the mol2 or SDF file from zinged.

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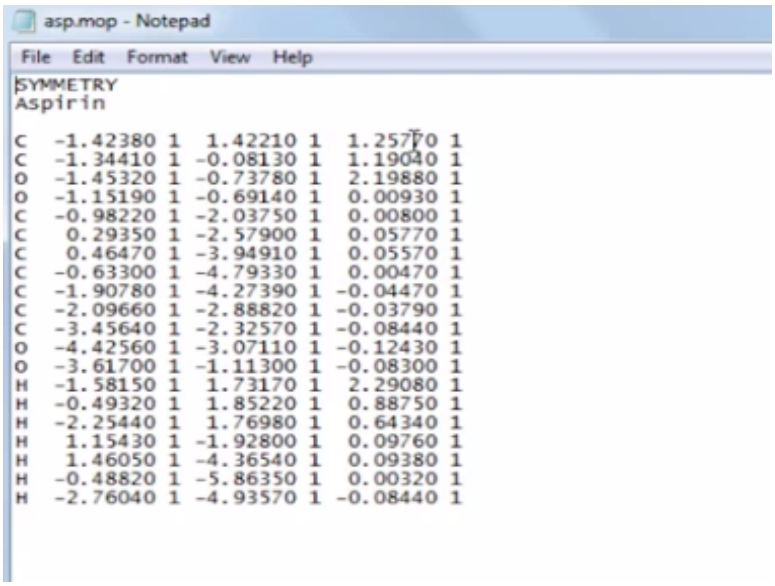

And then we can use open babel to convert, so if you look at the aspirin, this tells you the XYZ coordinates okay, tells you the XYZ coordinates and then okay, so and then it also tells we can optimize the structure, so basically MOPAC can optimize using semi empirical methods, so you have carbon, carbon, oxygen, carbon and what are the various XYZ coordinates of each one of them, so you can see carbon oxygen hydrogen.

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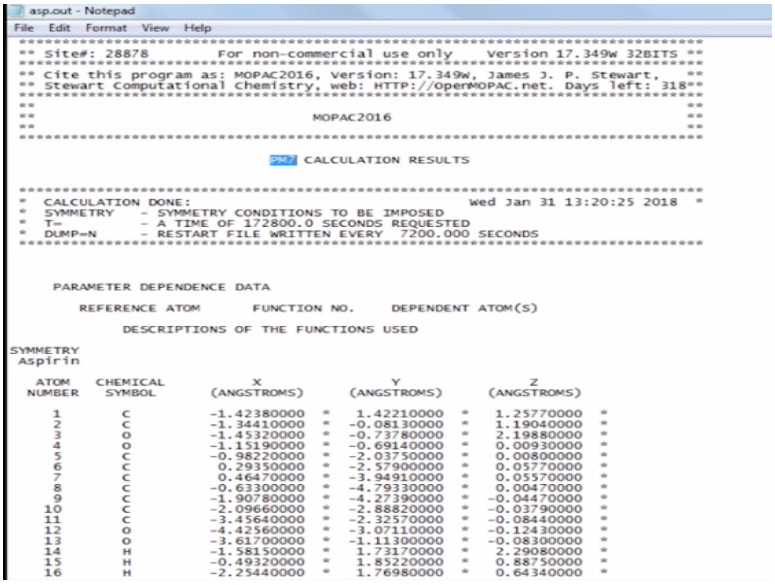

So, everything is there, this is called a dot MOP file, we can give that okay. Now, we can run this using MOPAC and I have it on my desktop in the back, so I just say aspirin MOPAC and then they transit okay, so you get the aspirin out file. The out file gives you all the information; the semi empirical information, so it runs a PM7 calculation okay, it gives you the symbol, the coordinates has given by us okay.

Then, it does; in this particular case, I think 10 different conformation, we can give 100, 200 so that you get the best minimum energy conformation based on electronic semi empirical calculation. So, as you can go, it gives you a lot of electronic features okay electrons and so on okay, then gives you the heat of formation, total energy, electronic energy, core repulsion all the information okay, molecular weight, Lumo, ionization potential.

So, everything that is related to electronic is given using MOPAC okay that is the usefulness of having MOPAC because the force field or molecular mechanics calculations cannot be used for getting these type of electronic information okay, it gives you the heat of formation and gives you electronic energy, core repulsion everything, okay all related to and it uses this particular case PM7 as I mentioned here.

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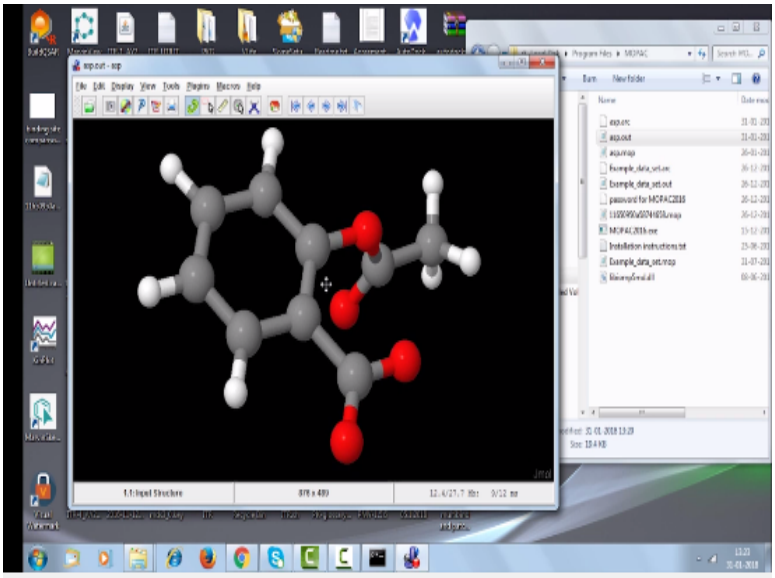

So, we can give different types of semi empirical method also for doing the calculation, we can play around with that and MOPAC is very, very useful for us to run and we can view the structure of this using a software called and jmol which we have okay, this is software called jmol and so we can look at the structure of the output from MOPAC, okay so we can look at the structure as you can see here.

This is the aspirin which I have done okay, we can use in the jmol and as you know jmol has lot of features which it can calculate lot of information, whatever data which we have collected from MOPAC okay, actually we collected from MOPAC that is the advantage of using this particular software, we can do measurements, we can look at distances and we can vibrate, we can do vibration.

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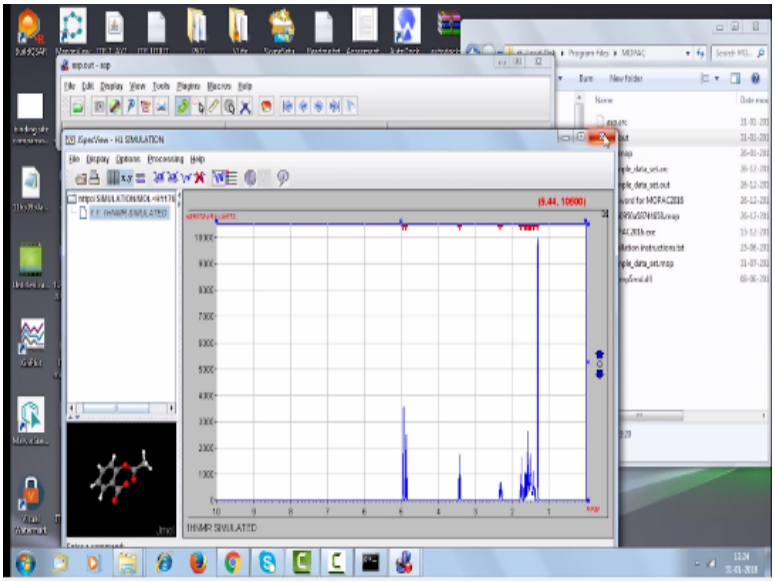

So, many things can be done; surface tools, okay all the spectra as we can simulate spectras okay, so we can simulate by NMR spectras, all these can be done using jmol, that is the beauty of this software and you need this software if you want to look at the output from the MOPAC, surface tools, look at the surfaces and so on okay.

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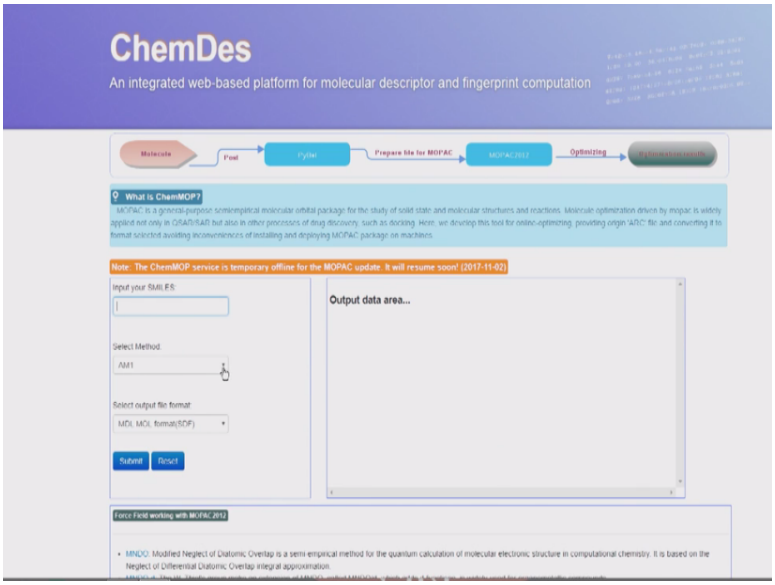

Then, look at this particular resource also, this is also very useful, SE BDD; okay, so what it does is; we can input the smile and then we can select which method, so it will create files; output file format based to that method and then we can go to MOPAC, say 2012 or MOPAC 2016 and run that okay, so basically this particular page helps you to create files, we can input the smile file very simple okay.

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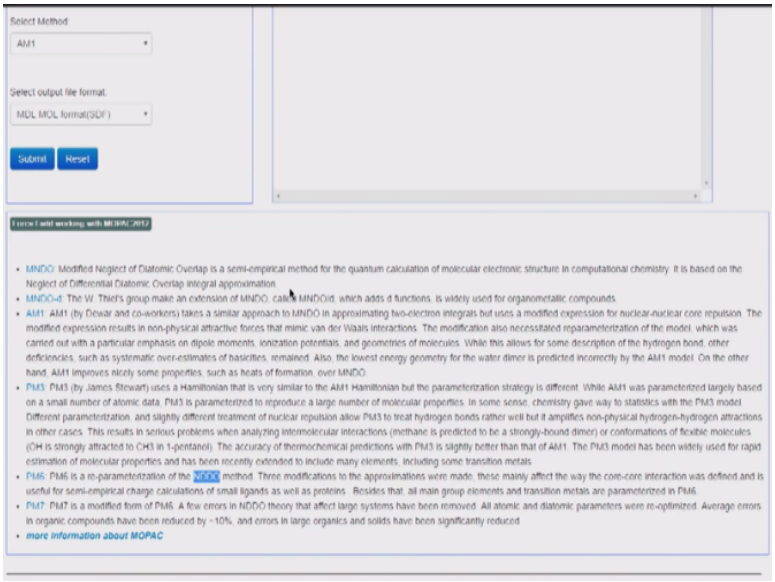

And then we can select which method you want to file for okay and then select the output file and then we submit and then you get the output file in that particular format for that method and then we go to MOPAC and run that particular system. So, it can be done for MNDO, MNDOD, AM1, PM3, I said PM6 is a reparamerization of the NDDO okay, 3 modifications to the approximations made.

Beside that all main group elements are transitional or parameterized in PM6, so you get all the main group elements and transition metals okay. PM7 is a modified version of PM6, a few errors in DDO theory are improved on that. PM3 uses a Hamiltonian that is very similar to M1 okay, Hamiltonian but the parameterization strategy is different, AM1 has parameterization largely based on a small number of data.

PM3 is parameterization which large number of molecular properties okay, so PM3, I would use rather than M1, whereas PM6 is taken re- parameterization of NDDO method, so MOPAC contains all these different methods, as you know MNDO modified NDO; neglect of diatomic overlap for the quantum calculation of molecular electronic structures. It is based on the neglect of differential diatomic overlap integral approximation okay.

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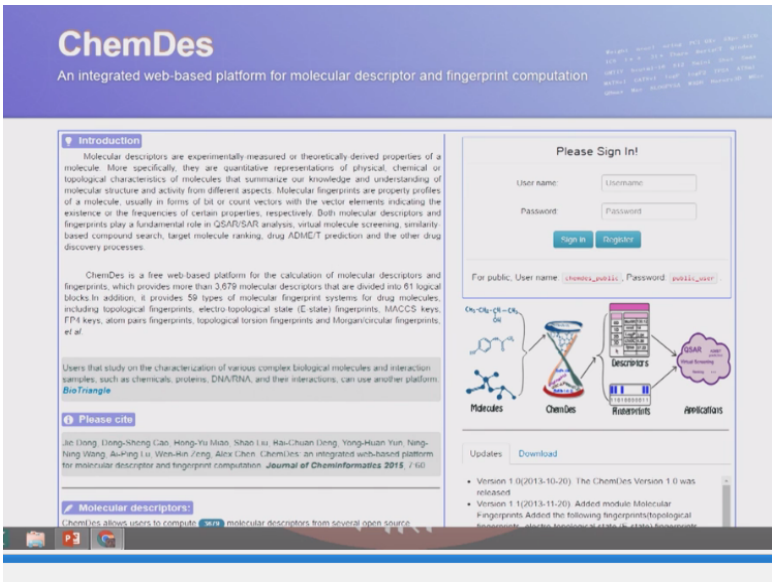

So, this can do all these calculations, this software is web based software is very useful, we will look at it later in the course of our work okay because it calculates many molecular properties, it calculates many molecular properties, large number of properties or it is called descriptors; molecular descriptors, once we give the molecular structure okay, so we can sign in or we can use as a public also and then we can do this type of calculations.

We will come to that when we talk about QSAR, looking at descriptors and so on actually okay, so what does that mean? So, we come to the end of the quantum chemical techniques, so quantum chemical techniques basically deal with the Ab initio and semi empirical Ab initio method is a very detailed type of calculations, so it can be done only for a few atoms but not for large set of atoms.

Even for doing that you need to use certain approximations like Born-Oppenheimer approximations and Hartree-Fock type of approximation okay, so whereas semi empirical method, parameterises many of these calculations, it takes in some equations thereby it simplifies the number of calculations involved but advantage of this is we can still use it to determine electronic energy, we can use it to determine the nuclear energy.

We can use it for finding bond; energy required for bond breaking, bond formation, we can look at energies of transition state, the ground state and so on actually, which cannot be done with molecular mechanic's method. So, molecular mechanics methods have limitations although it is very, very fast, highly parameterised, the force field methods are highly parameterised but it cannot do the chemistry related calculations.

So, you need to go for quantum mechanics methods and basically these are there and in semi empirical method, MOPAC is one of the best packages I would recommend, which is free for academic users and so it can do lot of semi empirical calculations based on say, AM1, PM3, PM6, PM7, okay, neglect of differential, NDO type of methods, so as I said it is free, you can download it get the license and start using them.

And it can give you a lot of information regarding the molecule under study okay, so we will continue further on the computer aided drug design in the next class as well. Thank you very much for your time.