MOLECULAR MECHANICS TUTORIAL

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UMDNJ Structural Bioinformatics

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Polychlorinated biphenyls (PCBs) are mixtures of synthetic organic chemicals with the same basic chemical structure and similar physical properties ranging from oily liquids to waxy solids. Due to their non-flammability, chemical stability, high boiling point and electrical insulating properties, PCBs were used in hundreds of industrial and commercial applications including electrical, heat transfer, and hydraulic equipment; as plasticizers in paints, plastics and rubber products; in pigments, dyes and carbonless copy paper and many other applications. More than 1.5 billion pounds of PCBs were manufactured in the United States prior to cessation of production in 1977.

Concern over the toxicity and persistence in the environment of Polychlorinated Biphenyls (PCBs) led Congress in 1976 to enact §6(e) of the Toxic Substances Control Act (TSCA) that included among other things, prohibitions on the manufacture, processing, and distribution in commerce of PCBs. Thus, TSCA legislated true "cradle to grave" (i.e., from manufacture to disposal) management of PCBs in the United States.

PCBs have been demonstrated to cause a variety of adverse health effects. PCBs have been shown to cause cancer in animals. PCBs have also been shown to cause a number of serious non-cancer health effects in animals, including effects on the immune system, reproductive system, nervous system, endocrine system and other health effects. Studies in humans provide supportive evidence for potential carcinogenic and non-carcinogenic effects of PCBs. The different health effects of PCBs may be interrelated, as alterations in one system may have significant implications for the other systems of the body. The potential health effects of PCB exposure are discussed here

http://www.epa.gov/opptintr/pcb/effects.html

Today we will take a close look at the basis of these dangerous compounds, explore different molecular mechanics force field trying to choose the best FF for modeling PCBs like chemicals.

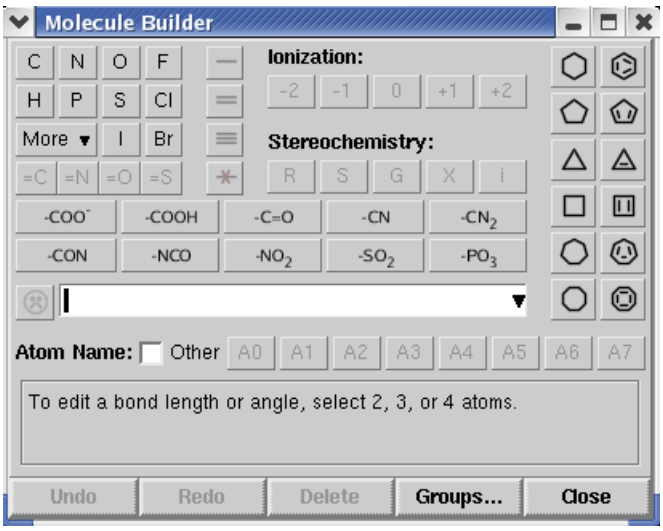
Create directory "**molmech**"

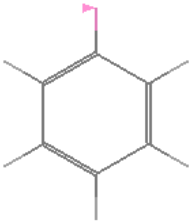
MOE

type **moe**
In the right side menu click on **Builder…**

In **Create Ring** section select benzene ring
You will see a benzene ring in the main window

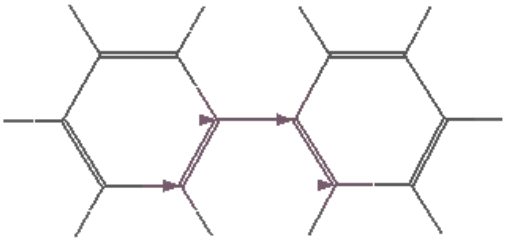
Click on any hydrogen atom of the benzene in the main window.
It should change color to pink with a triangle marker pointed to the atom



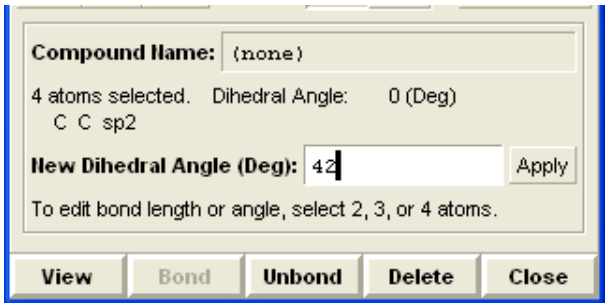


Return to the Builder window and under **Create Ring** section click on **benzene** again.
This time the molecule in the main window grows to biphenyl.
Click on **View** in the side panel of the main window to scale your molecule.

Select four atoms in biphenyl that forms dihedral angle between two rings. For multiple atom selection, keep SHIFT button pressed while you click on atoms.



In the Builder window assign dihedral angle to 42 degree, press **Apply**.



42 is the experimental value for vapor-phase torsion angle in biphenyl.

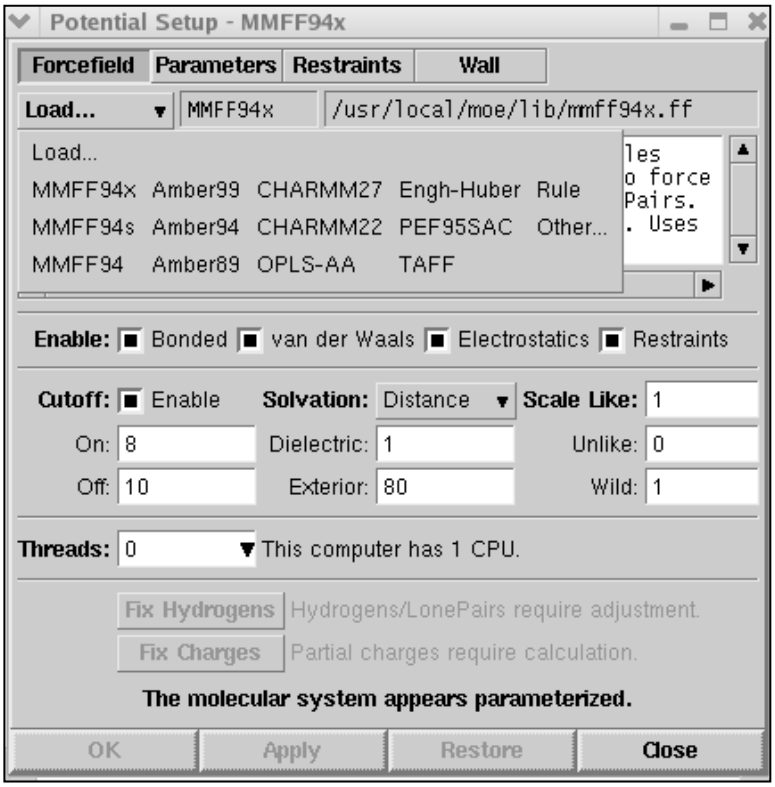
Save molecule in MDLMOL format as “moe_biphen42.mol”.
Make sure to uncheck “Depict as 2D” box

We will use this file as an initial conformation for different force fields later.

Close the **Builder**.

In main window go to Potential Control:
Window->Potential Setup

Click on Load… button



Different force fields, AMBER, CHARM, MMFF, etc can be found in this dialog.
Every time when you click on the button with a field name, you assign parameters of the field to a minimizer.

Chose first FF and press **Minimize** in the right side menu of main window.
Use default parameters in Potential Setup.
Examine a new conformation. To rotate or translate molecule use DIALS at the bottom of main window.

Measure distances between two rings and dihedral angles for different FFs. Use right side menu:
Distances …
Dihedrals…
To clean marks on the screen use **Remove …** button.

Put your results into Table 1.

Molecular mechanics FF methods do not typically calculate charges per se, but each FF has its own assigned parameters for partial charges.

Why do we need to assign partial charges? What type of interactions they are used for?

To see and compare partial charges go to the main window.
Compute->Partial Charges->Force Field Charges
Then click on **Label** in the right side menu and chose **Charges**.
To clear Labels use **Labels->Clear**

Compare charges for different FFs and explain why they differ.

OPTIONAL: Create biphenyl in SPARTAN. Change torsion angle to 42 degree. Run Hartree-Fock single point calculation, with 6-31** basis set. Mark electrostatic and atomic charges.

When calculations finish, Label electrostatic charges and compare them with Molecular Mechanics FFs. *Ab initio* single point calculations take about 15-20 minutes.
You can run also AM1 semi-empirical calculations to get electrostatic charges. AM1 was shown as the best method for biphenyl. (Mulholland J.A. et al. *J.Phys. Chem*, 1993, 97, 6890-6896)

ENERGY CALCULATIONS.

Open the reference molecule "moe_biphen42.mol"
In **Potential Setup** choose FF
In Main window go to **GIZMOE**
Chose **Energy**
Change FF in Potential Control and write down all energies for different FFs into Table 1.

Energy after minimization:
step 1. Open reference molecule "moe_biphen42.mol"
step 2. Choose FF in Potential control
step 3. Minimize molecule by clicking on the **Minimize** button in the right side menu.
step 4. Write down the energy value for new conformer in Table 1.
step 5. Close molecule.

Repeat steps 1-5 for all available FFs.
Note: every time you have to reopen the reference molecule moe_biphen42.mol to avoid a possible trapping into the local minimum obtained from the calculations with the previous force field.

SYBYL: Tripos FF

Due to incompatibility between two major manufacturers of molecular modeling software (Tripos and MDL) we have to draw the biphenyl molecule again.

Open Sybyl

sybyl8.0

Draw molecule:
Edit->Sketch Molecule-> M1:<empty> OK

Group ->Phenyl
You will see phenyl ring in main window

Click again on **Group->Phenyl**

and then on any atom of phenyl ring in main window

Molecule becomes a biphenyl.
Click on **ADDH** to add hydrogen atoms and then on **End Select**.

Modify torsion to 42 degree.
Build/Edit ->Modify-> Torsion
Choose four atoms which form torsion angle and assign the value to 42 degree (see diagram on page 2).

Minimize the structure with Tripos FF.

Compute->Minimize->Molecule

Method : Conj. Grad
Termination: Gradient 0.001 kcal/mol
Max iteration: 1000

Click on **Modify** button…

Force field : Tripos
Charges: Gasteiger-Marsili
OK

select local machine for running job and press **OK**

After completion of the job switch to the terminal window and record the final energy of minimized biphenol. Put it into the table 1.

Measure distance and dihedral angle.
Compute->Measure
Distance

Click on the first atom of one ring and then on the second atom on another ring. Result will be shown in the terminal window. Record it in table 1.
Click End in the measure window.

Now measure the dihedral angle.
Compute->Measure
Torsion
Select the same 4 atoms that you have selected before in MOE and record the result in the terminal window.
Click END in the measure window now.

Table 1. Create and fill up the table for different FFs

FF	Distance C-C between rings	Dihedral between rings	Energy of 42 degree conformer	Energy of minimized conformer
AMBER99				
CHARM22				
MMFF				
MMFFs				
ENGHHub				
OPLS-AA				
PEF95SAC				
TAFF				
RULE				
TRIPOS				

Which FF gives the best results for biphenyl calculations in gas-phase in comparison to experimental data? Explain why this field is better? Is it possible to improve calculation accuracy?

Appendix: Biphenyl structural parameters:

These are some experimental values of biphenyl you could find useful for evaluation of our models with different force fields.

Geometry of the Ground State

In the ground state of biphenyl, the carbon atoms of each benzene-like ring were found to be planar and form the vertices of a regular hexagon. The bond length between the carbons within each ring was calculated to be approximately 1.40 angstroms (+/- 0.008 angstrom), and the carbon- hydrogen bond lengths are each approximately 1.10 angstroms (+/- 0.005 angstrom). The length of the carbon-carbon bond which joins the two rings is 1.46 angstroms. The angle between the carbon atoms within each ring is 120 degrees, and the hydrogen-carbon-carbon angle is also 120 degrees (the hydrogen bonds project radially outward from the center of the ring). The two rings are not coplanar, and the dihedral ("twisting") angle between the rings is 41.21 degrees in the grounds state of the molecule.

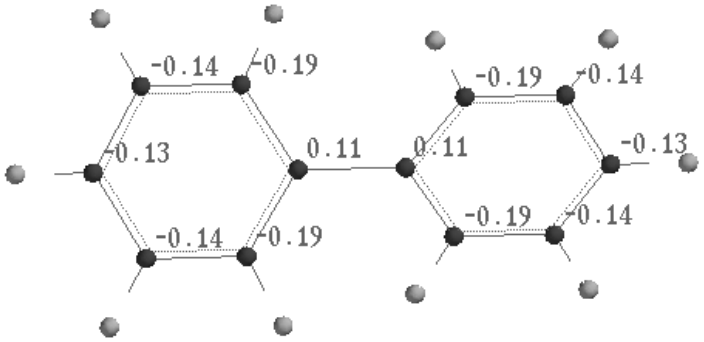
Homework:

From the tutorial choose two best force fields and fill out the following table.

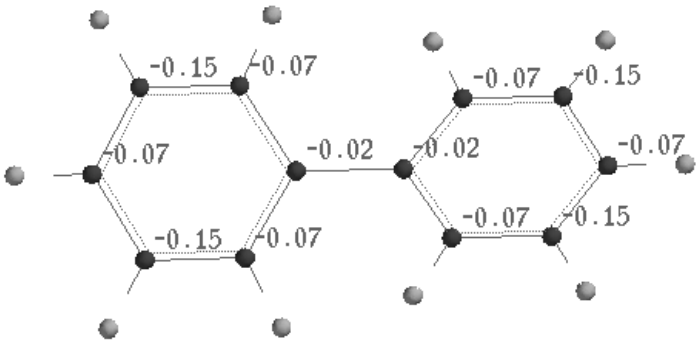
Bond length and molecular mechanics accuracy.

Bond	in	ab initio	expt	best FF #1	best FF #2
C-H	CH_4	1.105	0.094		
O-H	H_2O	0.963	0.957		
C-N	CH_3NH_2	1.486	1.474		
C-O	CH_3OH	1.434	1.425		
N-H	NH_3	1.021	1.012		
C=O	CH_2O	1.228	1.208		
C=C	CH_2CH_2	1.362	1.339		
C≡C	CHCH	1.229	1.203		
C≡N	HCN	1.176	1.154		

Appendix. Not for students!!!



Hartree-Fock 42 degree, electrostatic charges



AM1 42 degree