May 21, 2012
Molecular Modeling and Simulation

Potential Energy

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Schedule

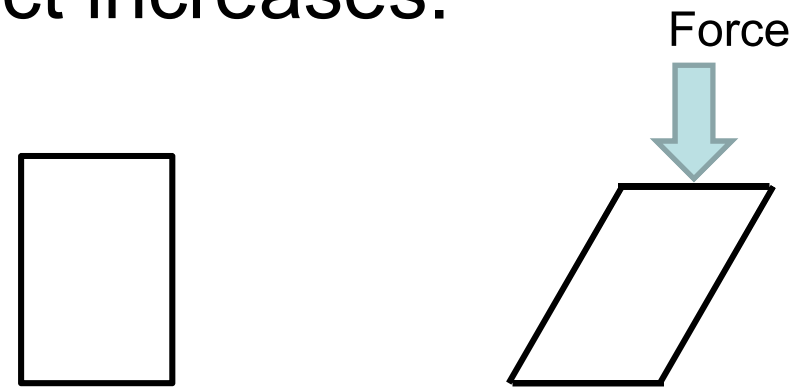
1. May 21	Potential Energy
2. May 28	Molecular Dynamics and Monte Carlo Methods
3. June 4	Applications of Molecular Dynamics Methods
4. June 11	Docking Simulations

Contents

- Practice of molecular orbital (MO) method
  - Exercise 1
- Molecular mechanics
- Energy minimization
- Practice of molecular mechanics
  - Exercise 2

Conformational energy

- When you exert a force on a object, the object deforms and the potential energy of the object increases.



- Similarly, when a molecule changes its conformation, the potential energy of the object changes.

Potential energy of a molecule

- Potential energy of a molecule can be calculated by solving the Schrödinger equation approximately with molecular orbital (MO) method.

$$\hat{H}_{\mathrm{elec}} = -\sum_{i=1}^{N} \frac{1}{2}\nabla_i^2 - \sum_{i=1}^{N}\sum_{A=1}^{M} \frac{Z_A}{r_{iA}} + \sum_{i=1}^{N}\sum_{j>i}^{N} \frac{1}{r_{ij}}$$

$$\hat{H}_{\mathrm{elec}}\Phi = E_{\mathrm{elec}}\Phi$$

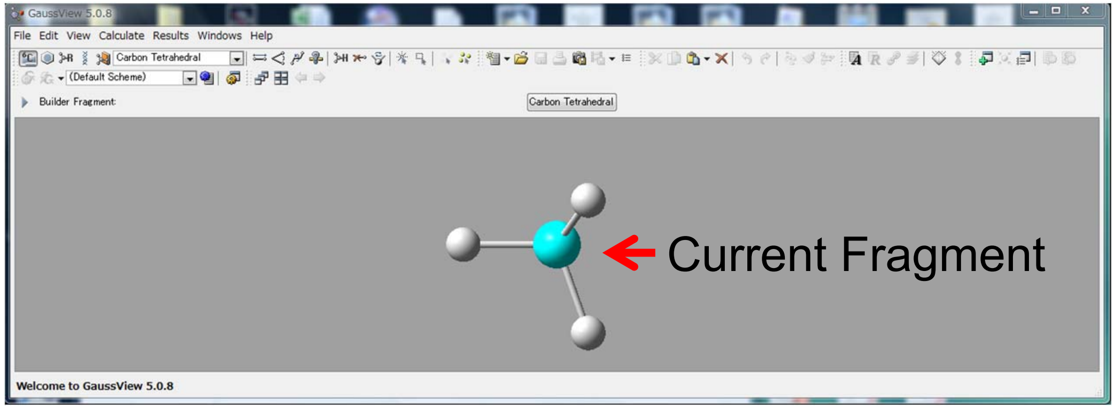
$$\boxed{E = E_{\mathrm{elec}} + \sum_{A=1}^{M}\sum_{B>A}^{M} \frac{Z_A Z_B}{R_{AB}}}$$

Potential energy of the molecule

N: Number of electrons
M: Number of atoms
Z_A: Atomic number of atom *A*
Φ: Wave function

Practice of MO method (1)

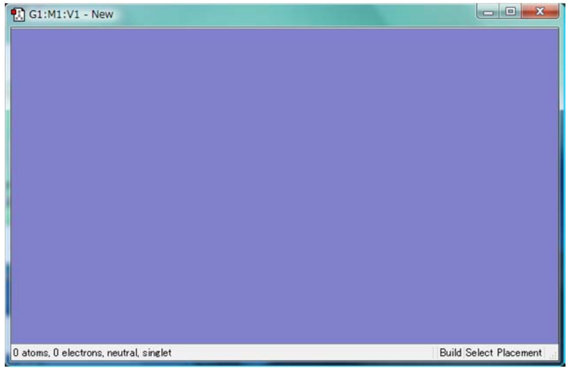
- Here, we use quantum chemical calculation software, Gaussian 09W.
- Double-click the icon to start the graphic user interface (GUI) of this software, GaussView 5.0.



Current Fragment

Welcome to GaussView 5.0.8

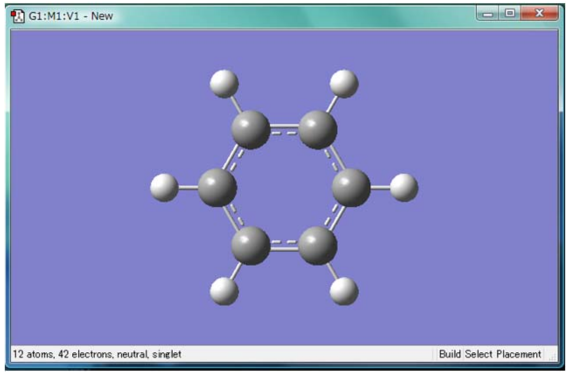
Control Panel



0 atoms, 0 electrons, neutral, singlet

Molecule View Window

Practice of MO method (2)



12 atoms, 42 electrons, neutral, singlet

1. Click Ring Fragment button in the Control Panel, select benzene, and click inside of Molecule View Window
2. Choose “Calculate” → “Gaussian Calculation Setup…” from the menu of the Control Panel
3. Set “Energy” to Job type, Set “6-31G(d)” to Basis set in the Method tab, and click “Submit.”
4. Save the input file as ”benzene.gjf” on Desktop.
5. Click “OK” when Run Gaussian Window appears.

Practice of MO method (3)

6. When the calculation finishes, click “Yes” to close Gaussian window.
7. Select “benzene.log” in the Gaussian Job Completed window and click “OK.”
8. Choose “Results” → “Summary” from the menu of the Control Panel. Potential energy is shown as E(RHF)*.

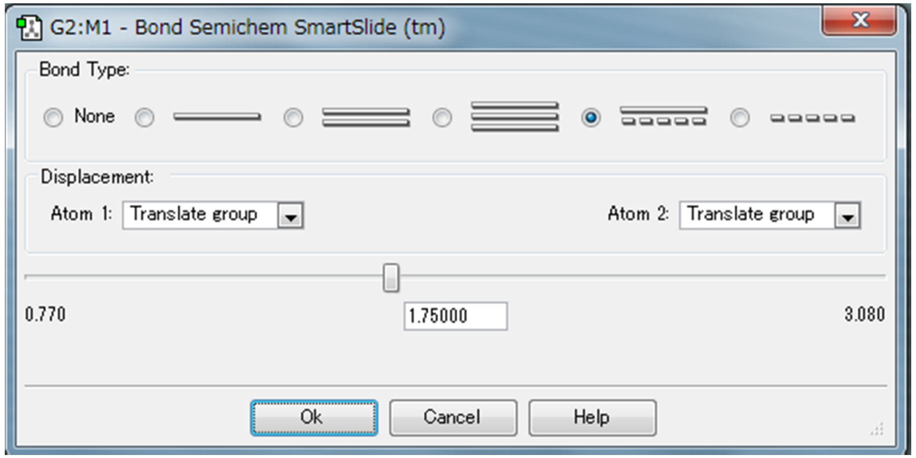
*1 a.u. = 627.509 391 kcal/mol

Technical terms

- Method:
  - Hartree-Fock: the most basic *ab initio* method
  - Semi-empirical: applicable to a large system, but less accurate
  - DFT: more accurate and computationally not expensive. Electron correlation effect is partly considered.
- Basis Set:
  - STO-3G, 3-21G, 6-31G, 6-311G, etc, in order of complexity. The more complex basis set can express the molecular orbital the more accurately.
  - Diffuse (+, ++) and/or polarization [(d), (d,p), etc] functions are added as required.

Deform molecule

- After clicking Modify Bond button in the Control Panel, click two neighboring carbon atoms of the benzene molecule.
- Change the bond length.



G2:M1 - Bond Semichem SmartSlide (tm)

Bond Type:

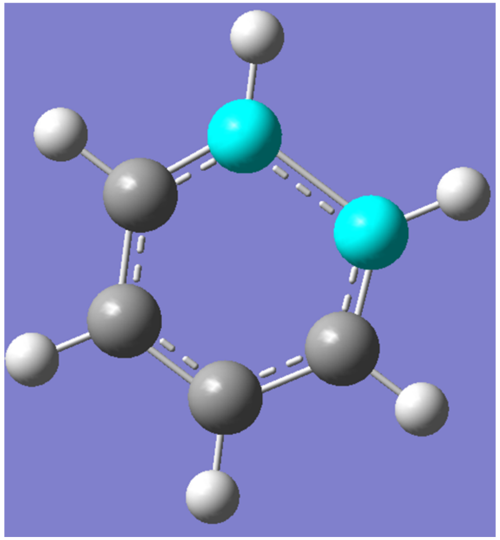
○ None ○ ○ ○ ● ○

Displacement:

Atom 1: Translate group

Atom 2: Translate group

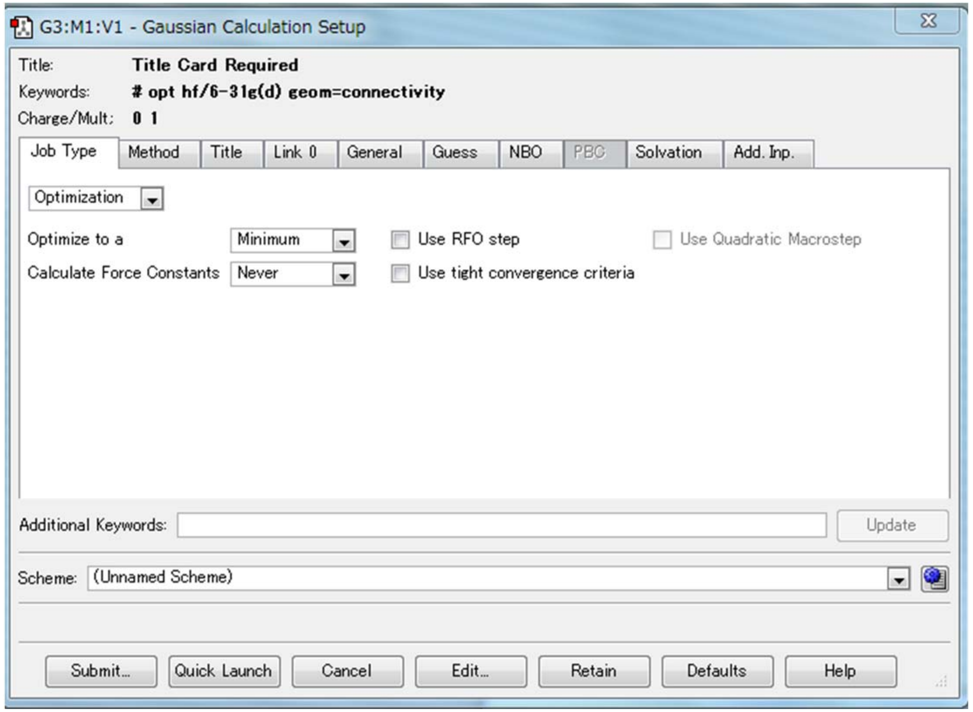
0.770 1.75000 3.080



- Calculate the potential energy.
(Save the input file as benzene2.gjf on Desktop.)

Energy minimization

- Deformation of the molecular structure increases its potential energy.
- Recover the original structure by energy minimization.
- Set "Optimization" to Job Type, and click "Submit." (Save input file as benzene3.gjf.)



G3:M1:V1 - Gaussian Calculation Setup

Title: **Title Card Required**

Keywords: **# opt hf/6-31g(d) geom=connectivity**

Charge/Mult: **0 1**

Optimization

Optimize to a: Minimum

Calculate Force Constants: Never

☐ Use RFO step

☐ Use tight convergence criteria

☐ Use Quadratic Macrostep

Additional Keywords:

Scheme: (Unnamed Scheme)

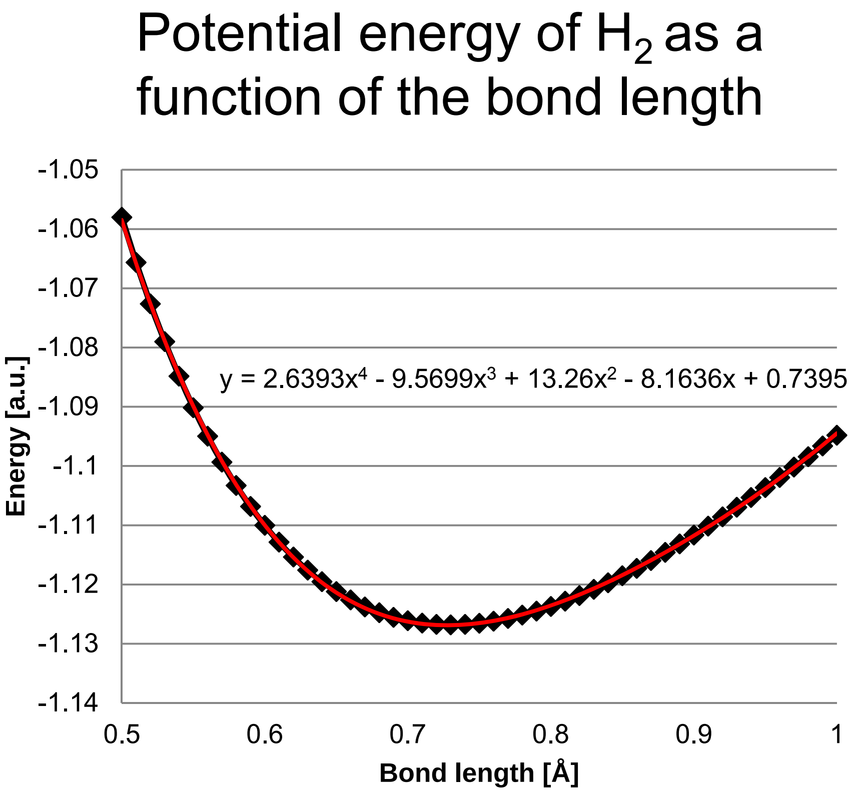
Diatomic molecule (1)

1. Download H2.gjf from this lecture’s web page.
2. Choose “すべてのプログラム” → “Gaussian 09W” → “Gaussian 09W” from Start menu to start Gaussian 09W.
3. Choose “File” → “Open” from the menu to open H2.gjf.
4. Choose “File” → “Exit & Run” from the menu to start the calculation.
5. Save the output file as H2.out on Desktop.

Diatomic molecule (2)

6. When the calculation has finished, choose “File” → “Exit” from the menu.
7. Start GaussView 5.0. Choose “File” → “Open” from the menu of the Control Panel to open H2.out. (Set ”Gaussian Output Files (*.out *.log)” to ファイルの種類.)
8. Choose “Results” → “Scan” from the menu of the Control Panel.
9. Right-click within the Scan plot window, choose “Save Data” from the menu, and save the data as H2_scan.txt on Desktop.

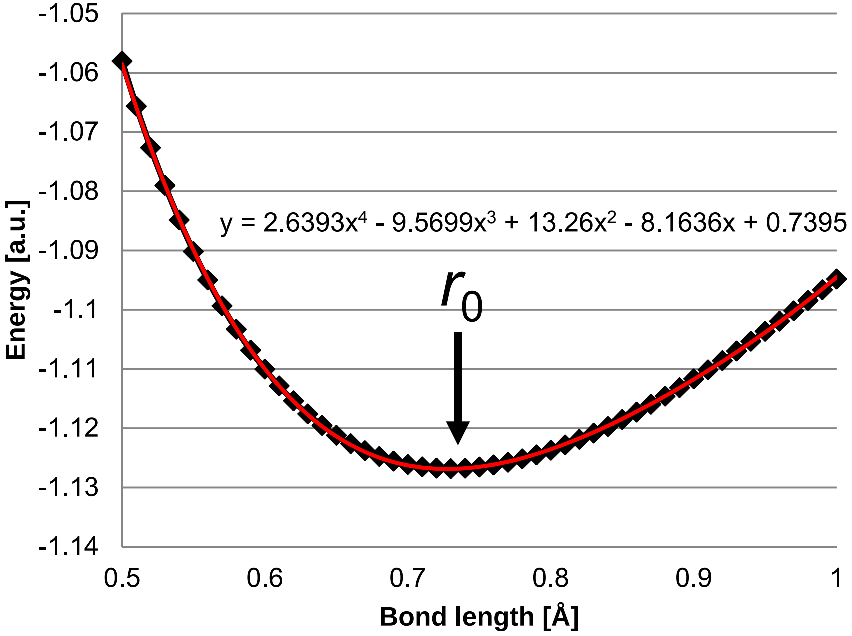
Diatomic molecule (3)



- Open H2_scan.txt with Excel and plot the potential energy against the bond length.
- You find the plot is well approximated with a fourth-order polynomial.
- Potential energy can be calculated at low computational cost with this polynomial function.

Potential energy function

Potential energy of H_2 as a function of the bond length



- The bond length thermally fluctuates about the length at the energy minimum.
- In biomolecular simulations, the temperature is about 300 K. →kT = 0.6 kcal mol^{-1} = 10^{-3} a.u.
- The width of the fluctuation is about 0.04 Å.

$$E(r_0+\Delta r) = E(r_0) + \left.\frac{\partial E(r)}{\partial r}\right|_{r_0} \Delta r + \frac{1}{2}\left.\frac{\partial^2 E(r)}{\partial r^2}\right|_{r_0} \Delta r^2 + O(\Delta r^3)$$

$$E(r_0+\Delta r) - E(r_0) \approx k(r-r_0)^2$$

Taylor series

Taylor series of $f(x)$ in the neighborhood of p.
$\Delta x = x - p$.

$$f(p+\Delta x) = f(p) + \left.\frac{df(x)}{dx}\right|_{x=p} \Delta x + \frac{1}{2!}\left.\frac{d^2 f(x)}{dx^2}\right|_{x=p} \Delta x^2 +$$

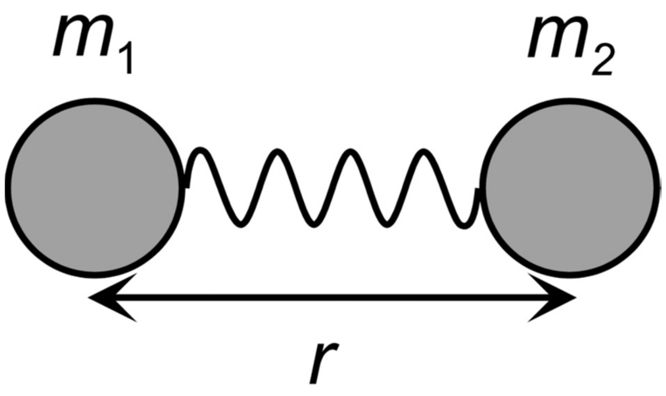
$$+\cdots+\frac{1}{k!}\left.\frac{d^k f(x)}{dx^k}\right|_{x=p} \Delta x^k + \cdots$$

$$= f(p) + \left.\frac{df(x)}{dx}\right|_{x=p} \Delta x + \frac{1}{2!}\left.\frac{d^2 f(x)}{dx^2}\right|_{x=p} \Delta x^2 + O\left(\Delta x^3\right)$$

Truncated at the second order

Error
(order of Δx^3)

Comparison of dynamics



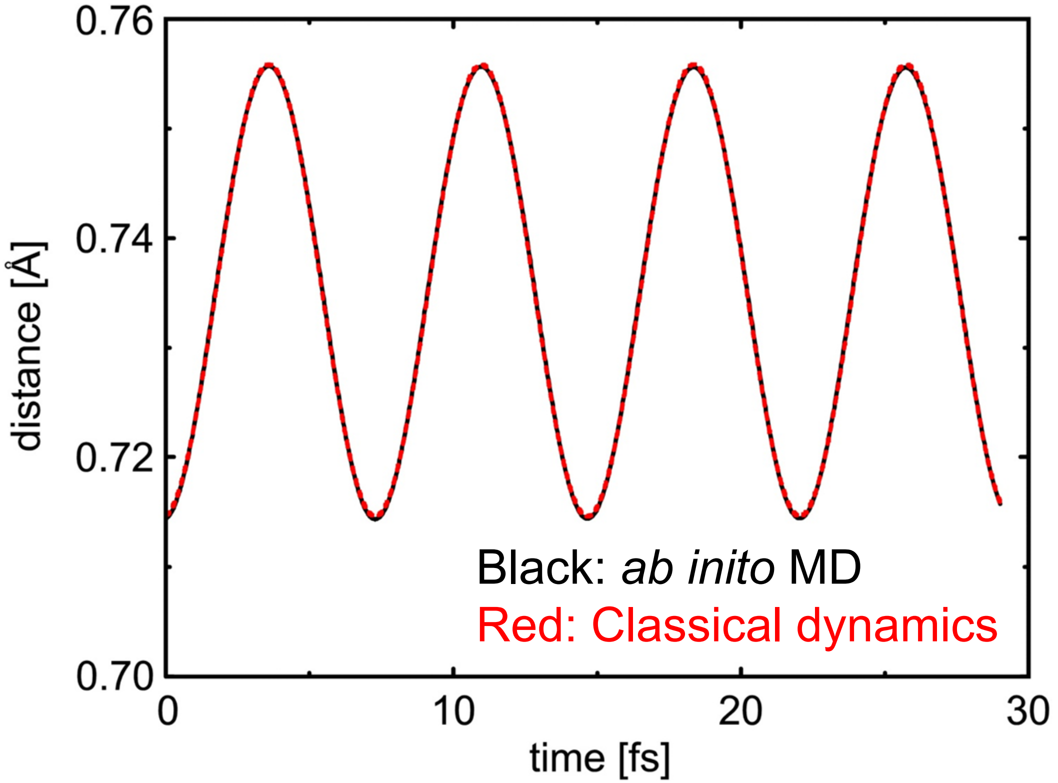
$$E(r) = k(r - r_0)^2$$

$$F(r) = -\frac{\partial E(r)}{\partial r} = -2k(r - r_0)$$

$$\mu \ddot{r} = -2k(r - r_0)$$

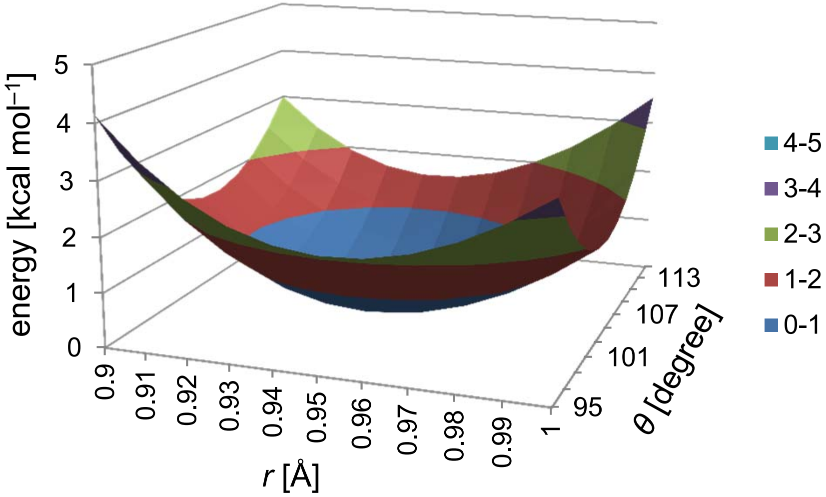
$$\omega = \sqrt{\frac{2k}{\mu}}, \quad \mu = \frac{m_1 m_2}{m_1 + m_2}$$

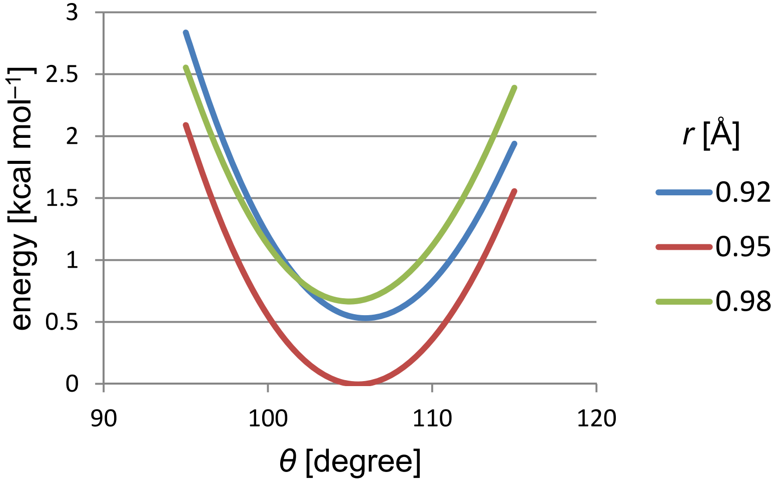
$$r(t) = A\cos(\omega t + \delta) + r_0$$



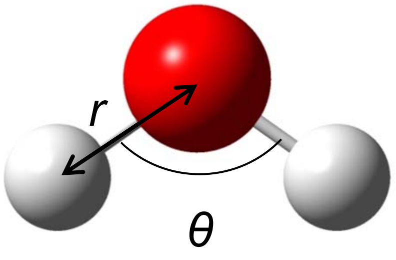
The trajectory of classical dynamics based on the potential energy function is almost the same as that of *ab inito* MD.

Energy of three-atom molecule





Model: water

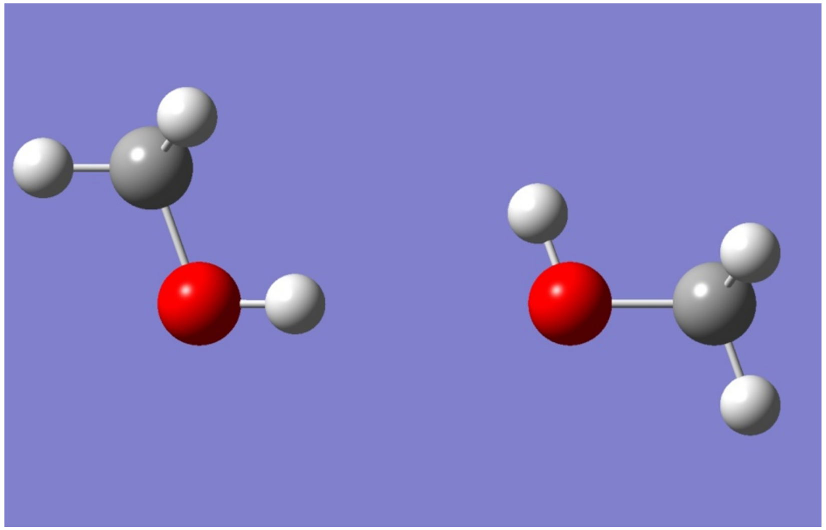


- The energy function is approximated as the sum of *r*-dependent and *θ*-dependent terms.

$$E(r,\theta) \approx k_b(r - r_0)^2 + k_a(\theta - \theta_0)^2$$

Intermolecular interaction (1)

1. Start GaussView 5.0. Click the icon of Element Fragment in the Control Panel, and select “O” to show “Oxygen Tetravalent” in Current Fragment window.
2. Click on two different points within Molecule View window.
3. Select “C” from the Element Fragments to show “Carbon Tetrahedral” in the Current Fragment window. Click on one of hydrogen atoms of H_2O to replace it with CH_3.
4. Similarly, replace one hydrogen atom of another H_2O with CH_3



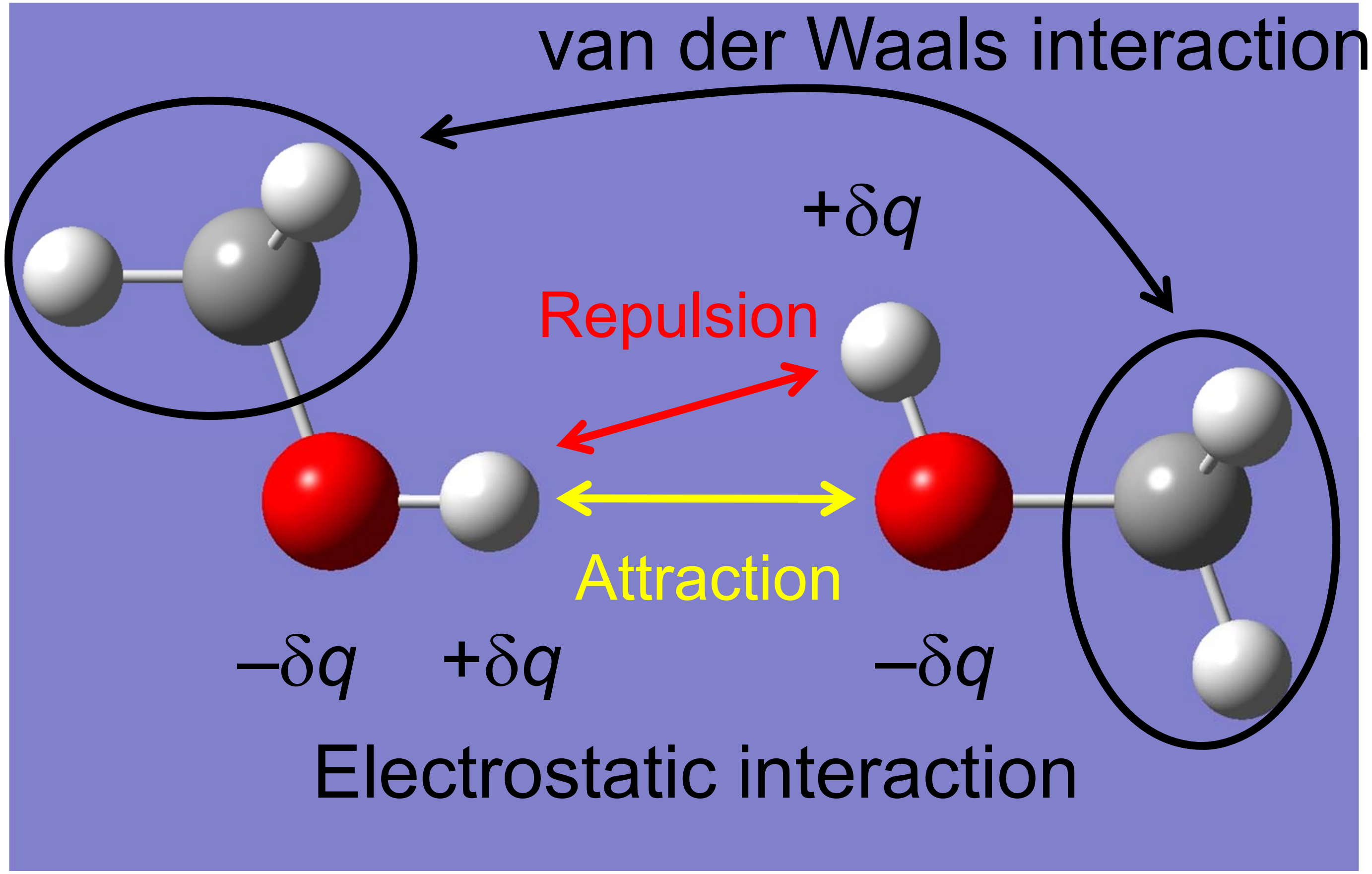
Intermolecular interaction (2)

5. Choose “Calculate” →“Gaussian Calculation Setup…” from the menu of Control Panel. Set Job type to “Energy”, set Basis set of the Method tabt to “6-31G(d)”, and click “Submit.” Save the input file as “methanol2.gjf” on Desktop.
6. Similarly, calculate energy for a single molecule. Save the input file as “methanol1.gjf” on Desktop.
7. Calculate interaction energy as:

$$\Delta E = E_{\mathrm{AB}} - \left(E_{\mathrm{A}} + E_{\mathrm{B}}\right)$$

$$\begin{aligned}\Delta E &= -230.0688122 - [2 \times (-115.0334869)] \\ &= -0.0018384 \text{ a.u.} = -1.15 \text{ kcal mol}^{-1}\end{aligned}$$

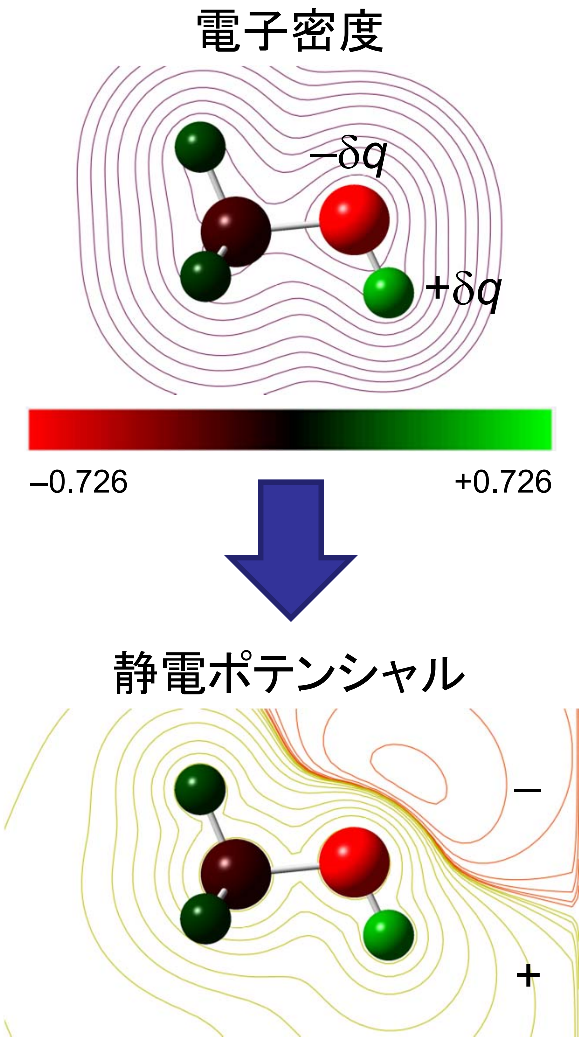
Component of interactions



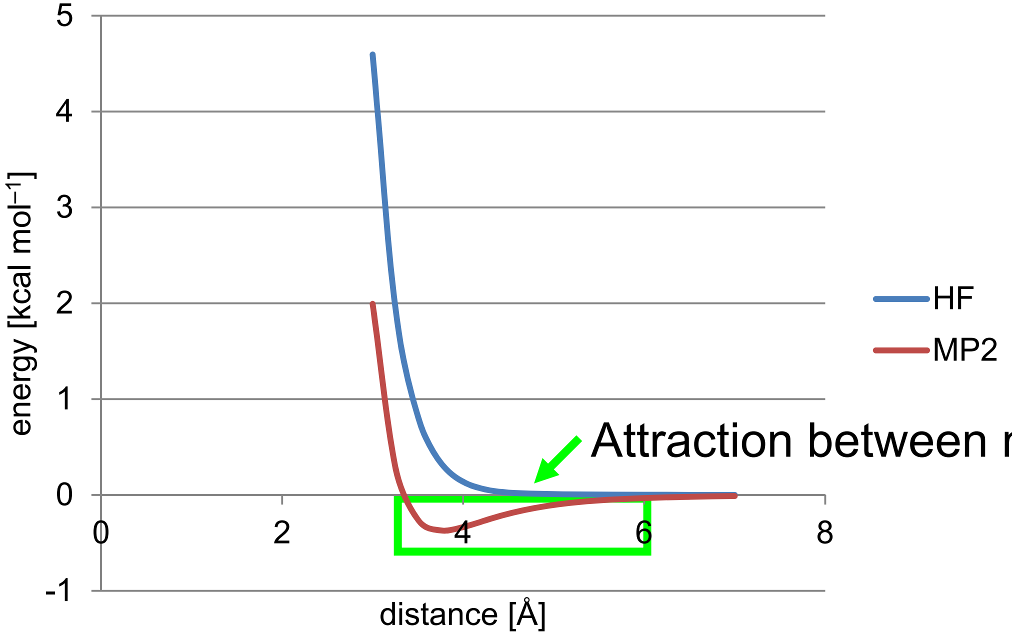
Electrostatic energy function

- Electron density $\rho(\mathbf{r})$ is obtained from the QM calculation.
- Electrostatic potential $\varphi(\mathbf{r})$ is calculated from $\rho(\mathbf{r})$.
- Point charges placed at the center of atoms are determined to reproduce the electrostatic potential.
- Electrostatic energy is calculated as the sum of the Coulombic interactions between point charges.

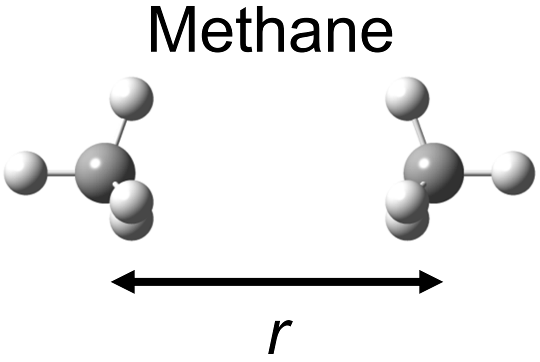
$$E_{ij} = \frac{q_i q_j}{\left|\mathbf{R}_i - \mathbf{R}_j\right|}$$



Van der Waals interactions



Attraction between methane molecules



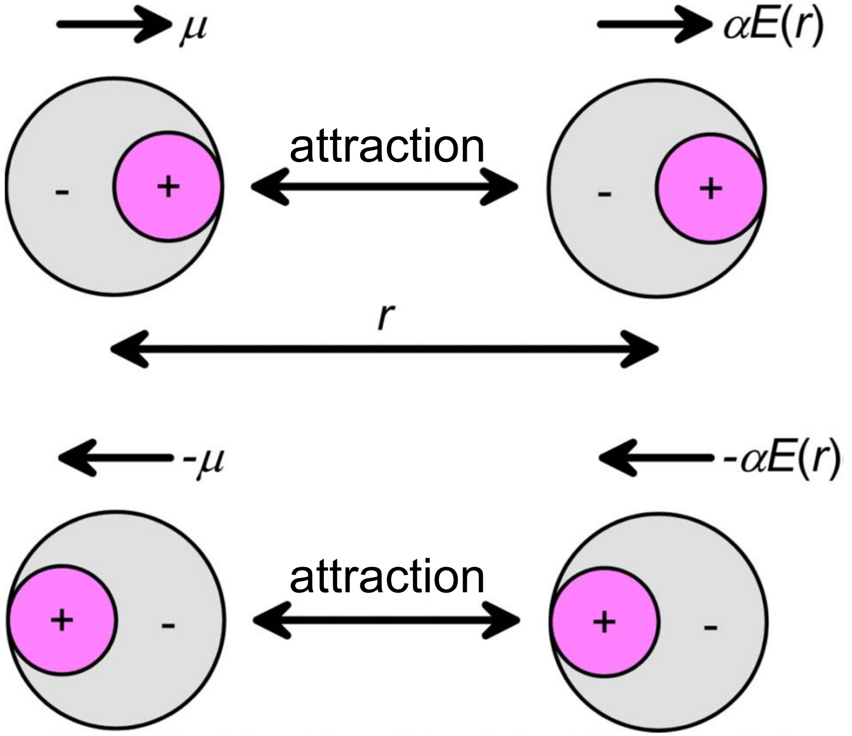
The use of the method that considers the electronic correlation effect is necessary to calculate the attraction between nonpolar molecules.

Origin of the attraction

Fluctuation of the electron cloud produce an instantaneous electric dipole moment even on a nonpolar molecule, which induces an electric dipole on nearby molecules.

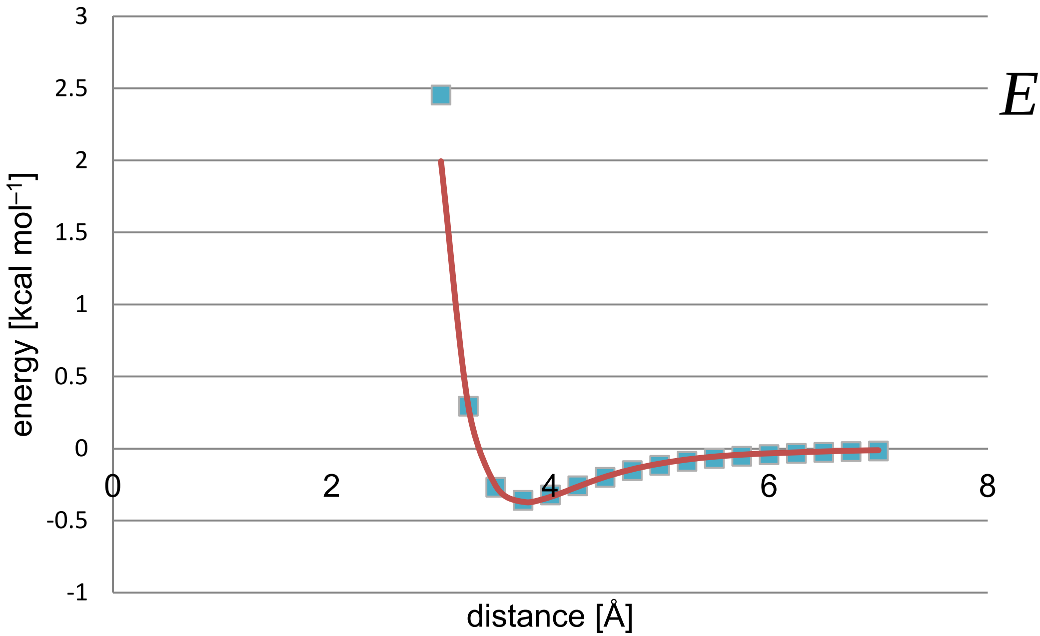
⬇

The interaction between the dipole and the induced dipole is always attractive.



$<\mu>=0$ $<E(r)>=0$

Van der Waals energy function



$$E_{\mathrm{vdW}}(r) = 4\varepsilon\left[\underbrace{\left(\frac{\sigma}{r}\right)^{12}}_{\text{Repulsion}} - \underbrace{\left(\frac{\sigma}{r}\right)^{6}}_{\text{Attraction}}\right]$$

At $r = \sigma$, $E_{\mathrm{vdW}} = 0$

At $r = 2^{1/6}\sigma$, $E_{\mathrm{vdW}} = -\varepsilon$

(Minimum)

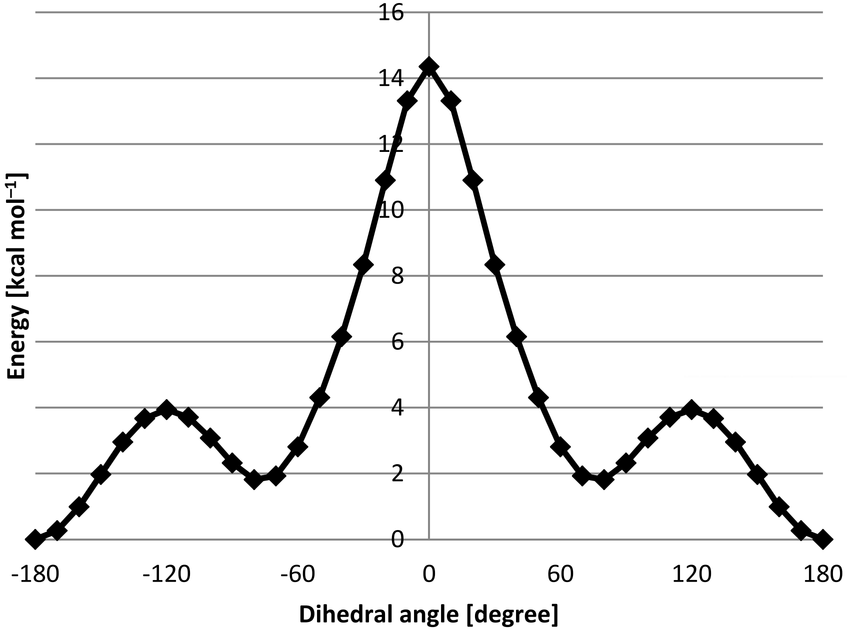
$\sigma = 3.34$ Å

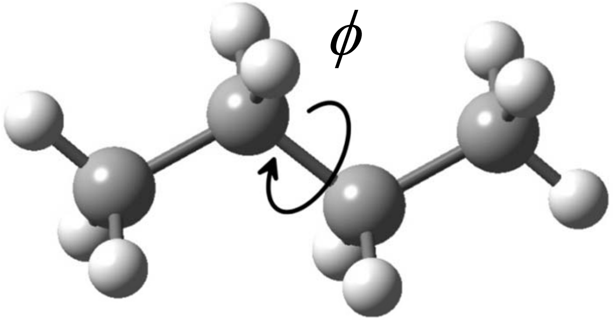
$\varepsilon = 0.36$ kcal mol^{-1}

Dihedral angle energy

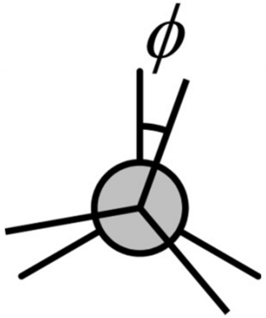
Model: butane

Energy of butane as a function of dihedral angle





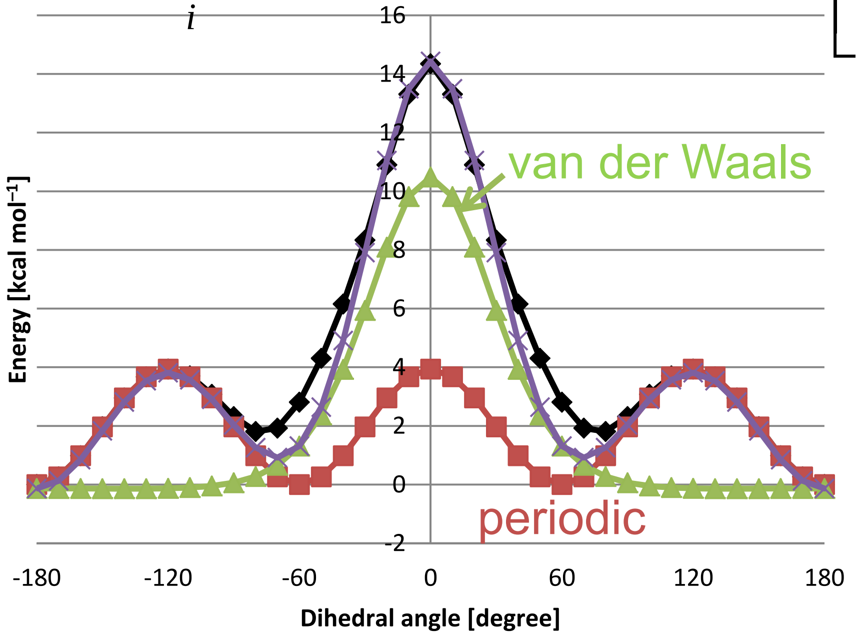
Gaussian job file: butane.gjf

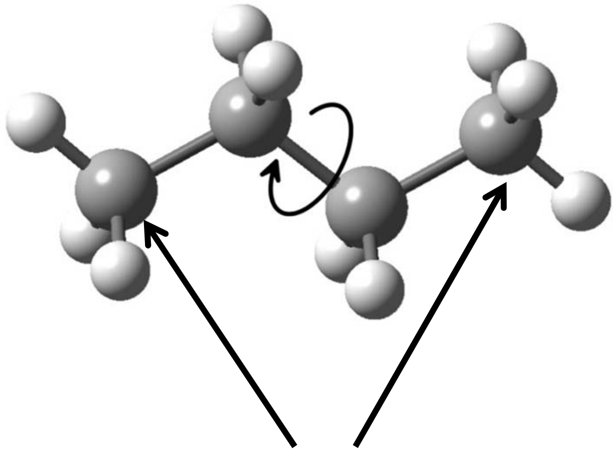


Dihedral angle energy function

- Energy function of butane is expressed as the sum of a periodic function and van der Waals energy function.

$$E(\phi) = \sum_i k_i\left[1 + \cos\left(n_i\phi - \delta_i^0\right)\right] + 4\varepsilon\left[\left(\frac{\sigma}{r_{14}}\right)^{12} - \left(\frac{\sigma}{r_{14}}\right)^{6}\right]$$





Only the van der Waals interaction between the first and fourth methyl groups are considered.

Exercise 1

- Determine n, δ, ε, and σ of the potential energy function of butane.
  - Download “butane_scan.xlsx” from this lecture’s web page.
  - Choose “Plot”→“Plot Molecular Property” from the menu of Scan Plot window and select “Bond” from the pull-down menu and set atom indices to “1” and “4” to obtain the list of the distances between the first and fourth carbon atoms.

Molecular mechanics

- QM calculation demands large computational cost.

- The computational cost can be reduced by using potential energy function that reproduces QM energy values.

$$E(\mathbf{r}) = \overset{\text{①Bond}}{\boxed{\sum_b k_b\left(r_b - r_b^0\right)^2}} + \overset{\text{②Angle}}{\boxed{\sum_a k_a\left(\theta_a - \theta_a^0\right)^2}} + \overset{\text{③Dihedral}}{\boxed{\sum_d k_d\left[1 + \cos\left(n_d\phi_d - \delta_d^0\right)\right]}}$$

$$+ \underset{\text{④Non-bonded}}{\boxed{\sum_{ij}\left\{4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \frac{q_i q_j}{r_{ij}}\right\}}}$$

Force field parameters

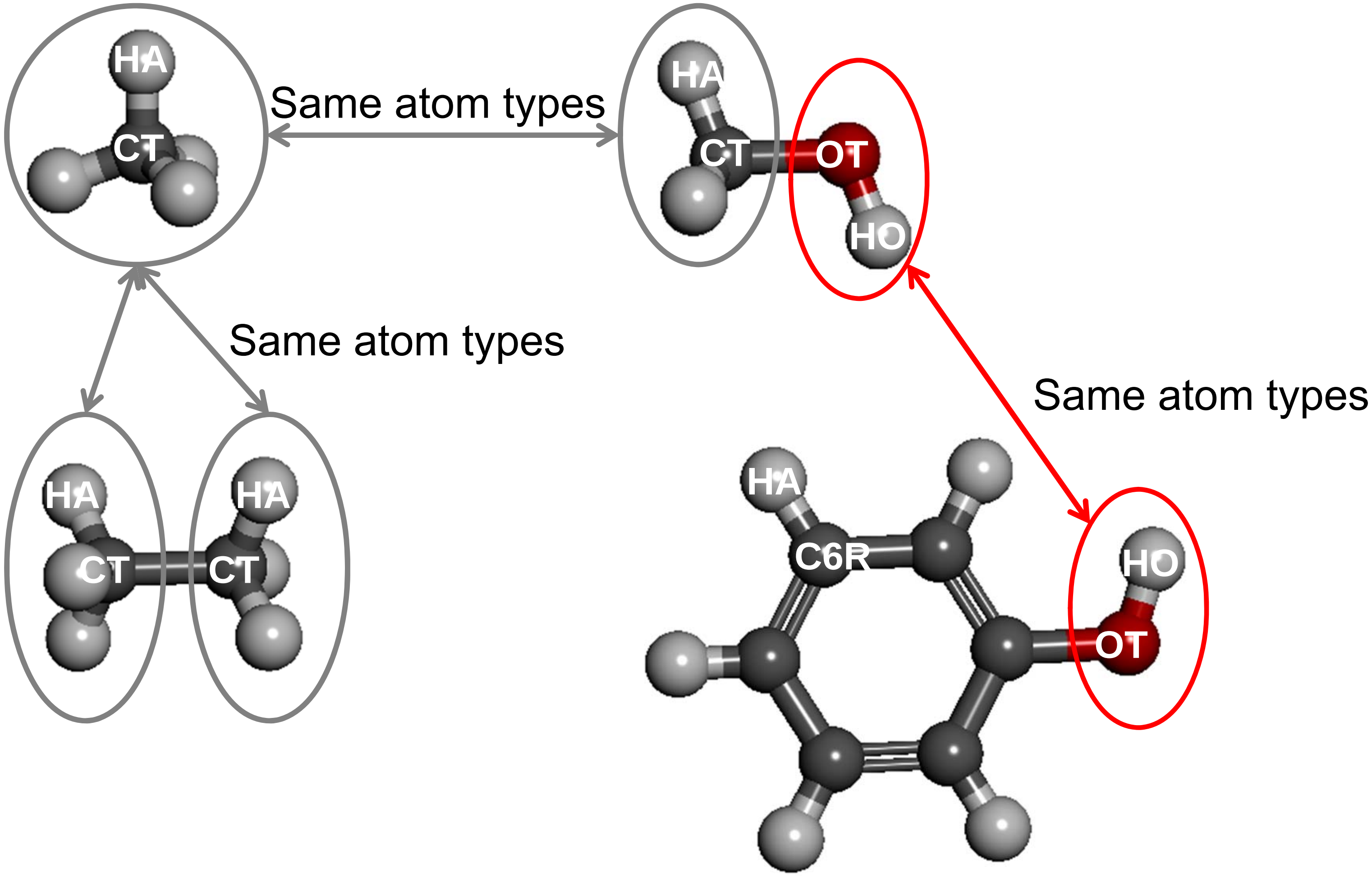
- Force field parameters
  - Parameters used in the potential energy function. (equilibrium bond length, force constant, partial charge, etc.)
- Ab initio force field parameters
  - Derived using QM results.
- Empirical force field parameters
  - Determined so as to reproduce the structure and thermodynamic quantities.

Problems and solutions (1)

- A biomacromolecule is composed of a large number of atoms.
  - It is difficult to apply the QM calculation to the whole molecule.

- Atoms are classified into atom types according to their chemical properties (type of hybridization or substituents). The same parameters are assigned to the atoms of the same atom type.
- Parameters are determined for model compound.

Atom types in CHARMm



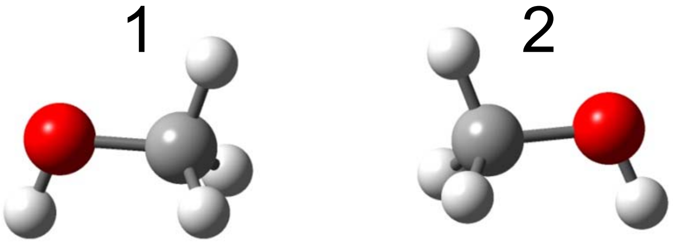
Same atom types

Same atom types

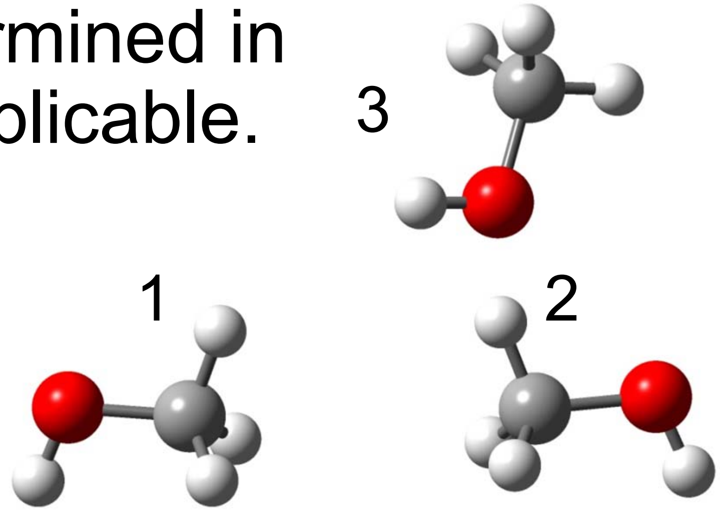
Same atom types

Problems and solutions (2)

- In condensed (liquid) phase, molecules are close to each other. The interaction between two molecules is affected by a third molecule near the molecules.
  - The parameters determined in gas phase are not applicable.



Gas phase



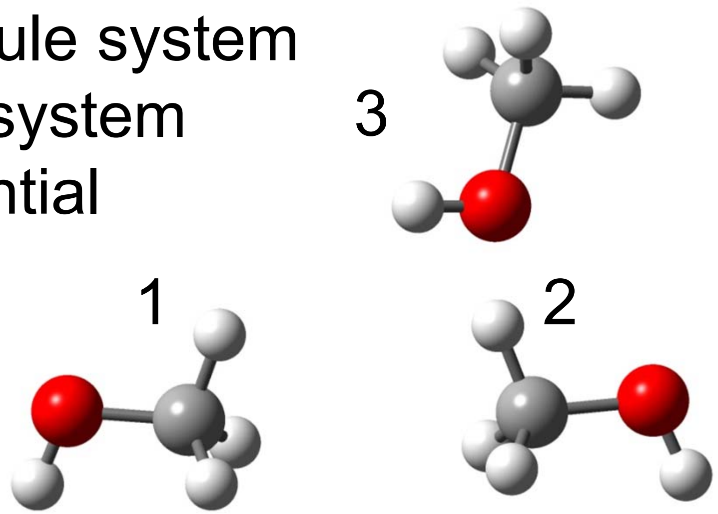
Condensed phase

Effective potential energy

$$
\begin{aligned}
E(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_3) &= E(\mathbf{r}_1,\mathbf{r}_2)+E(\mathbf{r}_1,\mathbf{r}_3)+E(\mathbf{r}_2,\mathbf{r}_3)+\Delta E(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_3)\\
&= E^{\mathrm{eff}}(\mathbf{r}_1,\mathbf{r}_2)+E^{\mathrm{eff}}(\mathbf{r}_1,\mathbf{r}_3)+E^{\mathrm{eff}}(\mathbf{r}_2,\mathbf{r}_3)
\end{aligned}
$$

$E(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_3)$: energy of three-molecule system
$E(\mathbf{r}_1,\mathbf{r}_2)$: energy of two-molecule system
$E^{\mathrm{eff}}(\mathbf{r}_1,\mathbf{r}_2)$: effective pairwise potential

Effect of the rigorous many-body interaction is incorporated in the effective pairwise potential.

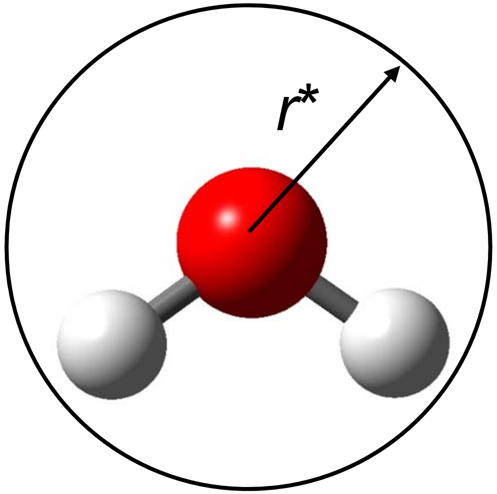


Condensed phase

Parameters are determined to reproduce experiments.

Water models (1)

	SPC	TIP3P
r(OH)	1.0	0.9572
$\angle$HOH	109.47	104.52
r^*	1.7766	1.7683
ε	0.1554	0.1520
q_H	0.41	0.417



Van der Waals interaction is calculated only between oxygen atoms.

r(OH) [Å], $\angle$HOH [degree]

r^* [$Å^{12}$ kcal mol^{-1}], $2r^* = \sqrt[6]{2}\sigma$

ε [$Å^6$ kcal mol^{-1}]

$q_O = -2q_H$

Jorgensen *et al. J. Chem. Phys.* **79**, 926 (1983)

Water models (2)

	SPC	TIP3P	Expt.
d	0.971	0.982	0.997
ΔH_{vap}	10.77	10.45	10.51
C_p	23.4	16.8	17.99
α	58	41	25.7
κ	27	18	45.8

d: density [g cm^{-3}], ΔH_{vap}: heat of vaporization [kcal mol^{-1}]
C_p: molar isobaric specific heat [cal mol^{-1} K]
α: coefficient of thermal expansion [10^{-5} K^{-1}]
κ: compressibility [10^{-6} atm^{-1}]
All values are at 25 ˚C, 1 atm.

Jorgensen *et al. J. Chem. Phys.* **79**, 926 (1983)

Force field parameter sets

- Force field parameter sets are distributed along with molecular simulation software.
- AMBER
  - http://www.ambermd.org/
- CHARMM
  - http://www.charmm.org/
- GROMOS, GROMACS
  - http://www.igc.ethz.ch/gromos/
  - http://www.gromacs.org/

Energy minimization (1)

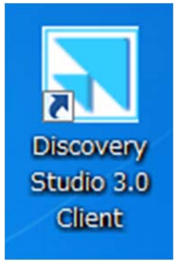
- Changes the conformation to the one having lower potential energy.
- Also called “structure optimization.”
- Must be done in advance of the molecular dynamics simulation to avoid atomic overlaps.

Energy minimization (2)

- First-order algorithm
  - Steepest descent method
    Simple, but many steps are required until convergence.
  - Conjugate gradient method
    When the energy function is a quadratic form of *n* variables, the minimum is reached in *n* steps.
- Second-order algorithm
  - Newton-Raphson法
    Quick to converge, but calculation of Hessian ($\nabla^2 E$) requires a high computational cost.

Discovery Studio 3.0 Client

- Double-click the icon of Discovery Studio 3.0 Client



- Choose “View”→“Explores”→“Tools” from the menu to show the Tools tab.
- Choose “View”→“Toolbars”→“Sketching” to show the Sketching tool bar.

Sketching a molecule (1)

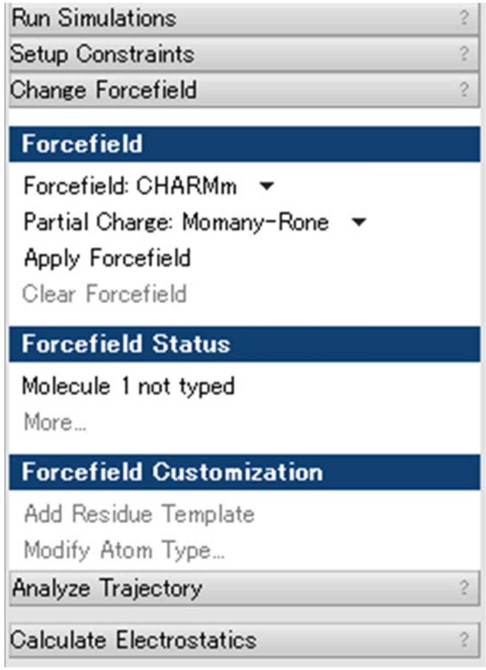
1. Select “File”→“New”→“Molecule Window” to create new window.
2. Chick the Ring icon of the Sketching tool bar and Click within the Molecule Window
3. Chick the Rotate icon to leave the Sketching mode.
4. Choose “View”→“Hierarchy” from the menu to show Hierarchy Window.
5. Click on one carbon atom to select the atom. →Selected atom is colored yellow.
6. Expand the tree in the Hierarchy Window. Confirm that the atom corresponding to the selected atom is marked.

Sketching a molecule (2)

7. Right-click within the Molecule Window to show a menu. Choose “Attributes of C5…” from the menu.
   (Atom name depends on your selection.)
   →Confirm that the Hybridization is Sp3.
8. Remove the selection by clicking background of the Molecule Window.
9. Select all the atoms by “Ctrl+A.”
10. Choose “Chemistry”→“Bond”→“Aromatic” from the menu.
    →Confirm that the Hybridization is now Sp2.

Sketching a molecule (3)

11. Click the “Simulation” button.
12. Click “Change Forcefield” in the Tools tab to show its contents.
13. Set Forcefield to “CHARMm”, Partial Charges “Momany-Rone”, and click “Apply Forcefield.”
14. Confirm that hydrogen atoms are added to the molecule and Forcefield Status is “Molecule 1 typed with CHARMm.”
15. Check the Attributes to confirm that partial charges and force-field types are assigned to the atoms.



Forcefield: CHARMm

Partial Charge: Momany-Rone

Molecule 1 not typed

Manipulating Molecule Window (1)

- Click inside Molecule Window in advance of the manipulation.
- Rotate
  - Click ⟳ to enter the rotation mode.
- Translate
  - Click ✥ to enter the translation mode.
- Zoom
  - Click ⇕ to enter the zoom mode.
- Drag the mouse inside the Molecule Window.

Manipulating Molecule Window (2)

- Select
  - Click on an atom to select the atom. Double-click on an atom to select the residue that includes the atom. →Selected atoms are marked with yellow squares.
  - Click on an item in Hierarchy Window to select an atom or a set of the atoms within a chain, residue, or group.
  - Click on the empty region to unselect atoms.
  - Click on an atom in Molecule Window while holding the Shift key to add the atom to the selection.
  - Click on an item in Hierarchy Window while holding the Ctrl key to add the item to the selection.
- Attribute
  - After selecting an atom, right-click to show a pull-down menu and choose “Attribute.”

Manipulating Molecule Window (3)

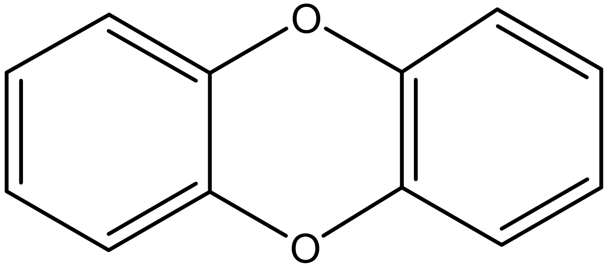
- Home
  - Return the structure to the initial orientation.
- Fit to Screen
  - Scales and translates the selected atoms to center and fit them inside the Molecule Window.
- Center Structure
  - Same as “Fit to Screen” except that it does not change the scale.

Force fields

- CHARMM is integrated into Discovery Studio
- Select an appropriate force field according to the target of the simulation.
  - CHARMm：General-purpose Momany and Rone all-atom forcefield that also provides automatic parameter estimation
  - charmm22：Academic all-atom forcefield used for simulating protein systems
  - charmm27：Academic all-atom forcefield used for simulating DNA and protein systems

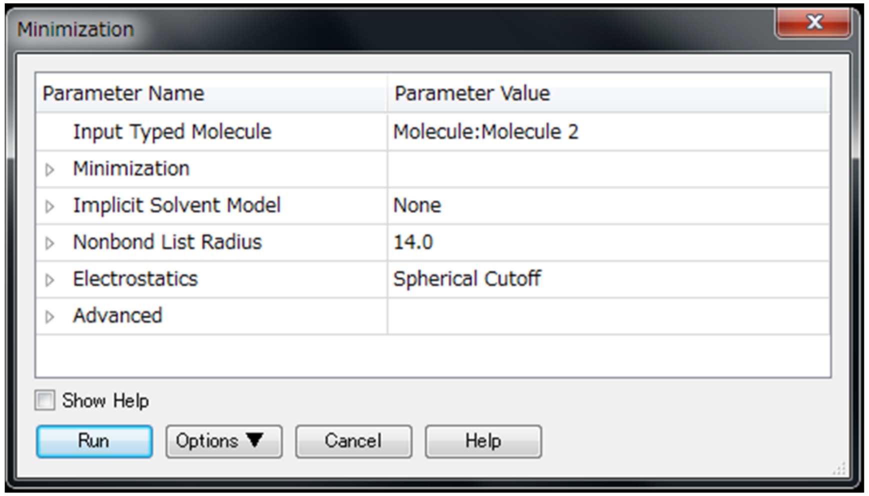
Energy minimization (1)

1. Choose “Window”→“Close All” from the menu to close all the windows. (You do not have to save the data.)
2. Choose “File”→“New”→“Molecule Window” to create a new window.
3. Generate dibenzo-*p*-dioxin by using Sketching tool. (Use “Chemistry”→“Element” to change element.)



Energy minimization (2)

4. Use “CHARMm” for Forcefield.
5. Click “Run Simulation” of the Tools tab to show its contents and click “Minimization.”
6. Set as shown below and click “Run.” (If calculation fails, try “Clear Forcefield”and “Apply Forcefield.”)
7. Choose “View” →“Data Table” to show energy values.



Minimization

Parameter Name	Parameter Value
Input Typed Molecule	Molecule:Molecule 2
▷ Minimization	
▷ Implicit Solvent Model	None
▷ Nonbond List Radius	14.0
▷ Electrostatics	Spherical Cutoff
▷ Advanced	

☐ Show Help

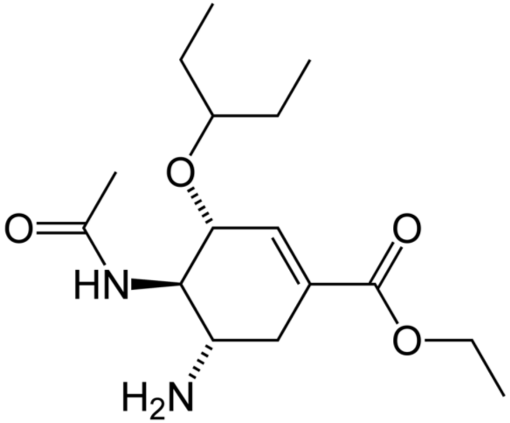
SMILES

- SMILES is a representation of the molecular structure.
- Open a new Molecule Window, and choose “File”→“Insert From”→“SMILES.”
- Enter a Smiles string.
  - benzene: c1ccccc1
    (Lower cases are used for aromatic atoms)
  - dibenzo-*p*-dioxin: c13ccccc1Oc2ccccc2O3
  - alanine: [N+][C@@H](C)C(=O)[O-]

http://www.daylight.com/dayhtml/doc/theory/theory.smiles.html

Exercise 2

- Generate this molecule and do energy minimization.



Oseltamivir: an antiviral drug
(trade name: Tamiflu)

- Use CHARMm for the Forcefield.
- Save the image of the energy-minimized structure in the PNG format.

How to send your report

- Send the Excel file of Exercise 1 and the image file of Exercise 2 as attachments to tterada@iu.a.u-tokyo.ac.jp.
- Write the energy values before and after energy minimization in the body of the e-mail.
- Subject of the e-mail should be “Molecular Modeling” and write your name and ID card number in the body of the e-mail.