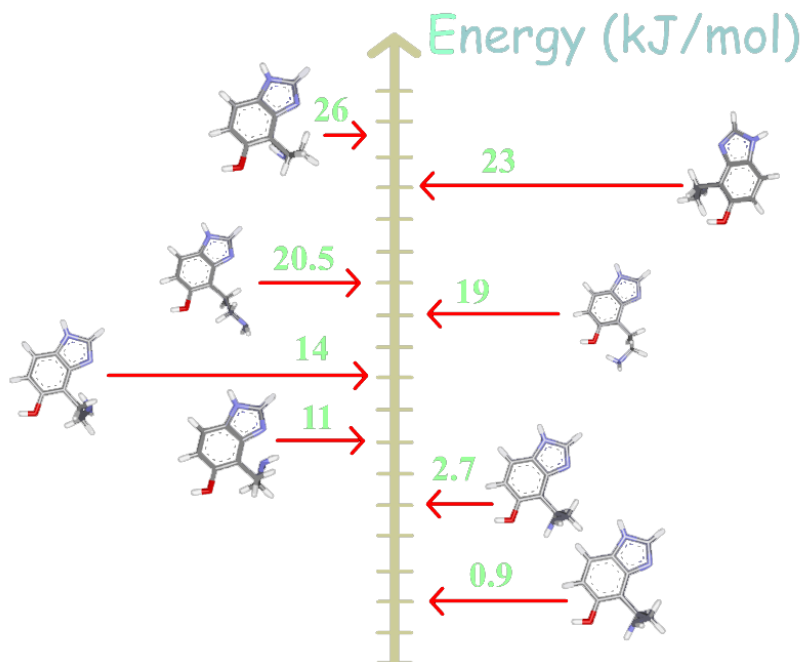


Molecular Energies

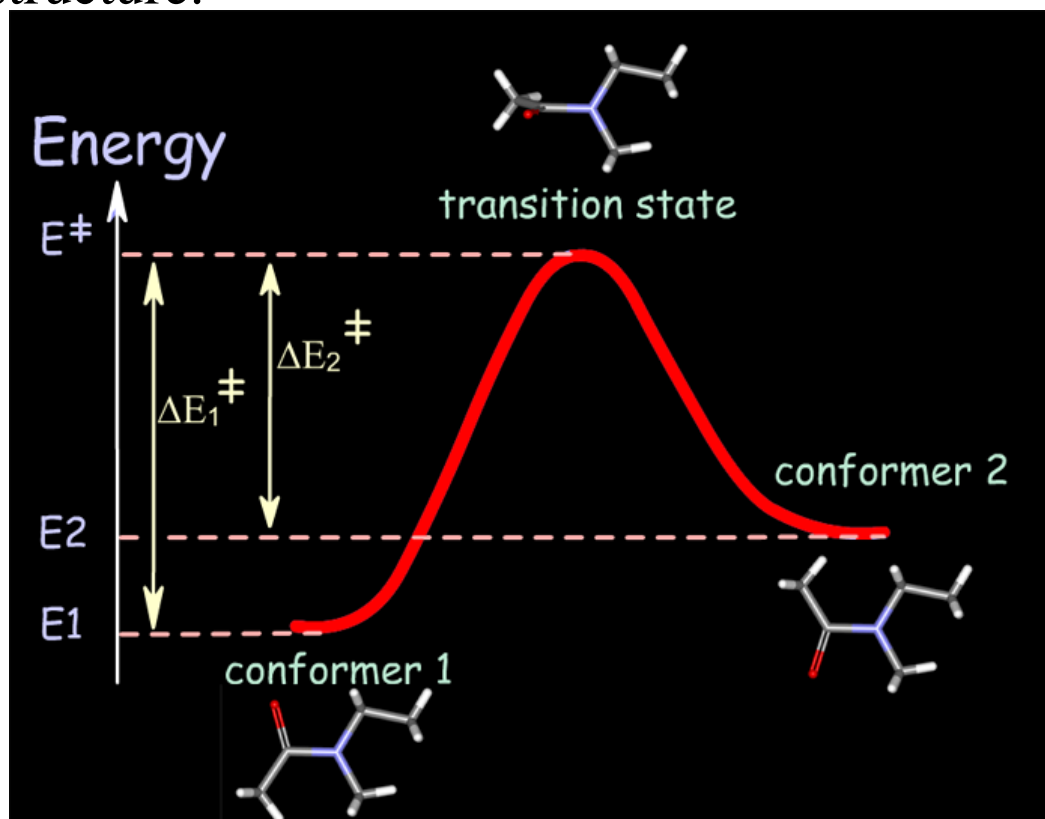
Internal Energy of a Molecule

All chemical systems contain a certain amount of internal energy consisting of potential and kinetic energies. The potential energy is directly related to chemical bonding and non-bonding interactions whereas the kinetic energy is related to random molecular motions. Each conformation of a molecule has its specific internal energy, that is due to different non-bonding interactions.



Internal Energy of a Molecule

The conversion of a conformer of a molecule into another one involves a high energy geometry, also known as the transition state. This higher energy operates as a barrier that the molecule has to cross in order to change its 3D structure.

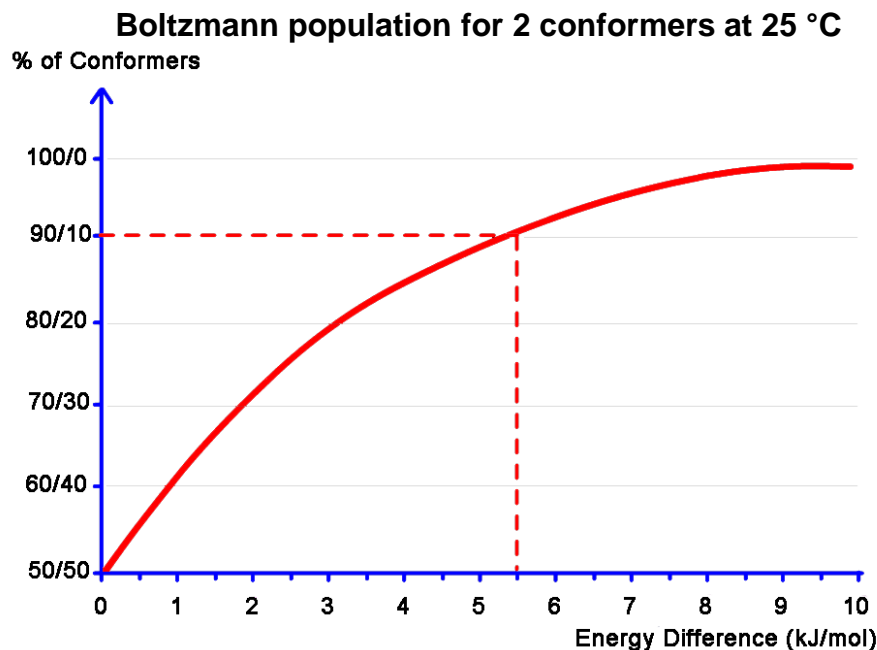


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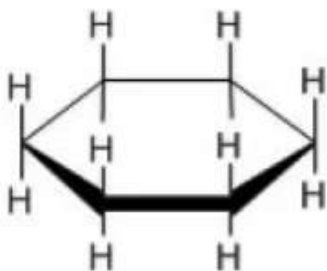
Thermodynamics: Boltzmann Equation

The lower the energy of a specific conformation of a given molecule, the higher the population of such conformation at the equilibrium. Consider the general situation of a molecule in equilibrium in multiple conformational states. The population of each conformer is directly related to the difference of energy between them. The Boltzmann population equations allow the calculation of the proportion of each conformer.

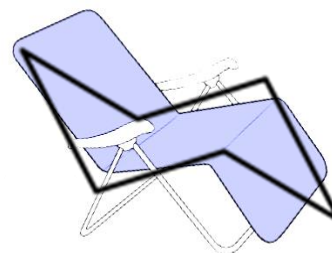


Thermodynamics: Boltzmann Equation

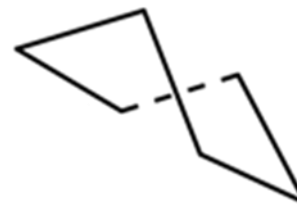
An exhaustive exploration of all the possible conformations of cyclohexane reveals two minimum energy conformations: the chair and the twist-boat.



Planar representation
Explicit hydrogens



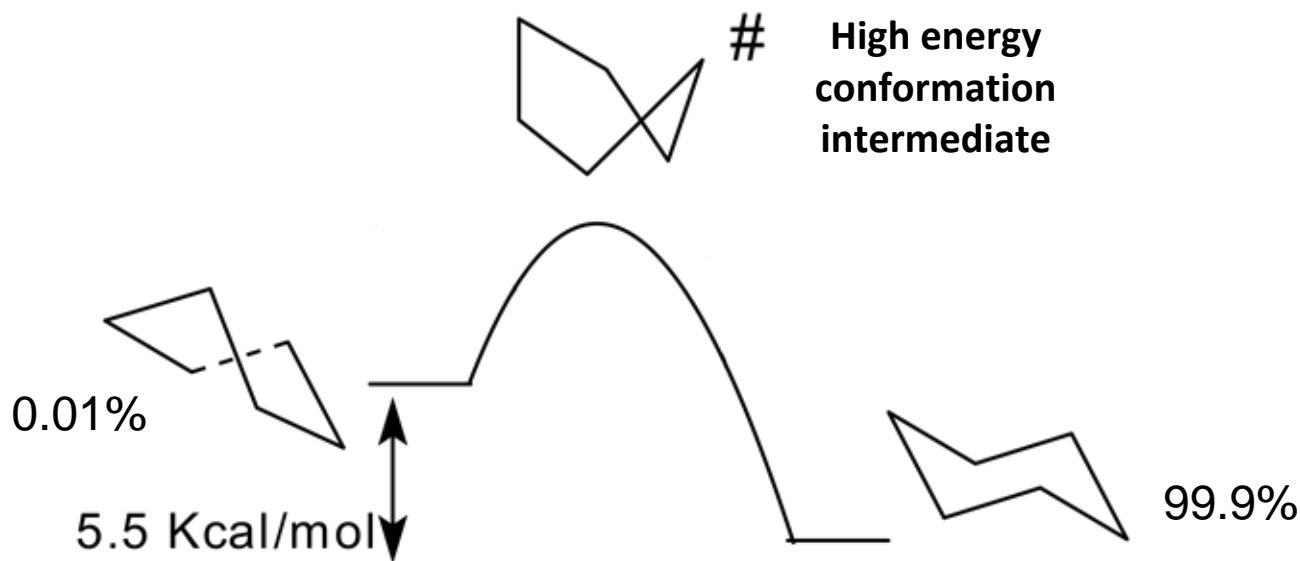
Chair conformation
Implicit hydrogens



Twist-boat conformation
Implicit hydrogens

Thermodynamics: Boltzmann Equation

There is a difference of energy of about 22.5 kJ/mol (5.5 kcal/mol) in favour of the chair conformation, whose population corresponds to 99.9%.



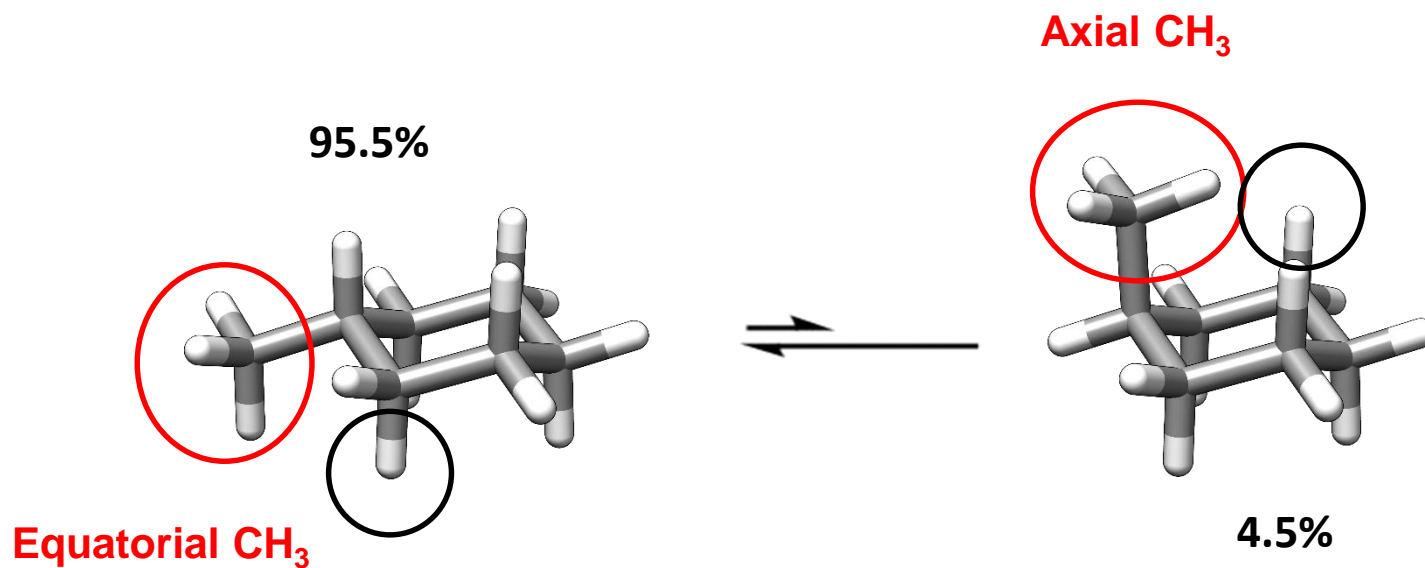
Thermodynamics: Boltzmann Equation

Methylcyclohexane has 5 different conformations. Two chair forms and three twist-boat forms. By taking the lower energy conformer at zero energy, the energy differences and the populations of the different forms are as follows:

Conformer	Methyl position	Energy difference (kJ/mol)	Population (%)
chair	equatorial	0	95.4787
chair	axial	7.5	4.5085
boat	bowsprit	22.7	0.0085
boat	plane	24.6	0.0038
boat	flagpole	30.0	0.0004

Thermodynamics: Boltzmann Equation

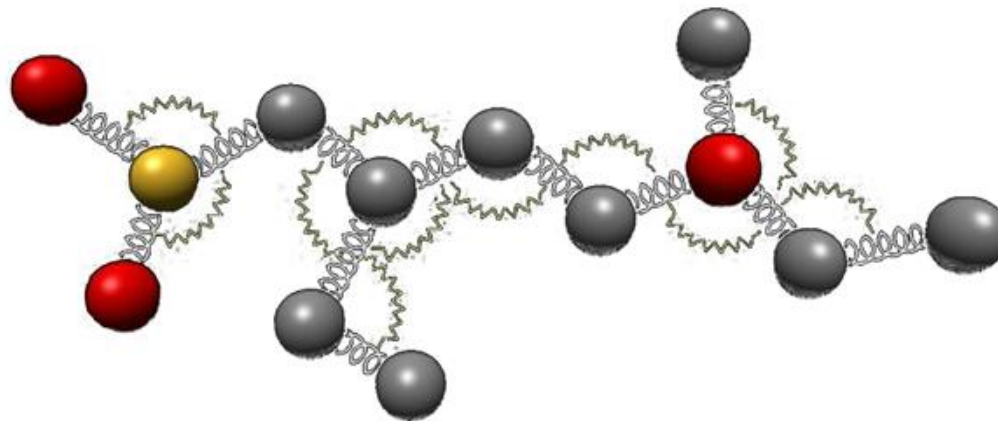
Here are shown the two chair conformations of methylcyclohexane, accounting for a 99.9% cumulative population:



Molecular Mechanics

Molecular Mechanics

Molecular mechanics considers molecules as a collection of atomic masses held together by “sticky” forces. A simple conception is to consider the atoms as balls connected by springs. An empirical set of energy functions called force field (FF) allows simulation of such forces. A typical FF consists of bond stretching, angle bending, torsional rotation, van der Waals interaction, electrostatic interaction, and hydrogen bonding energy functions (more elaborate force fields may also include other contributions). The energy of a conformer is the total sum of all these contributions (also termed Steric Energy of the molecule).



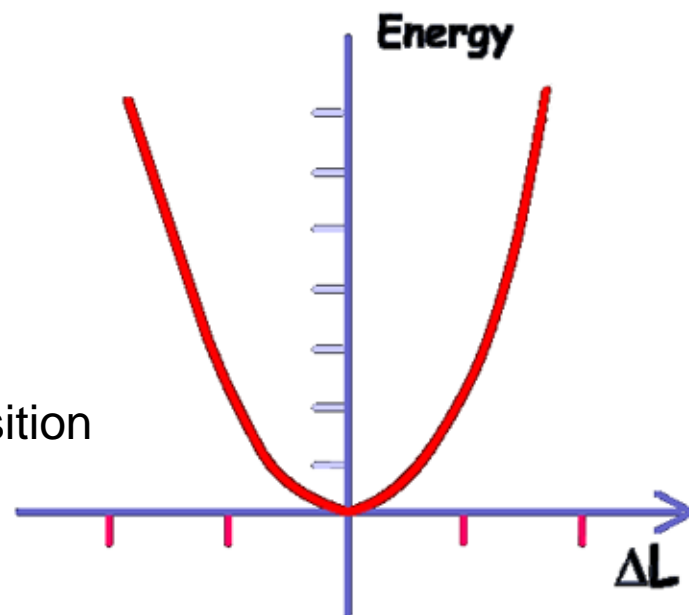
FF components: Bond Stretching

A chemical bond between two atoms has a “natural” equilibrium position. The bond is considered as a spring and an energy penalty is associated with any change of the bond length. The stretching energies can be approximated by using the Hook's law.

$$E_{(L)} = \sum k_{(L)} (L - L_0)^2$$

Stretching Force Constant

Equilibrium Position



The stretching force constants are usually determined experimentally from vibration spectroscopy. The Hook's law description is fairly good at geometries just near the equilibrium bond length.

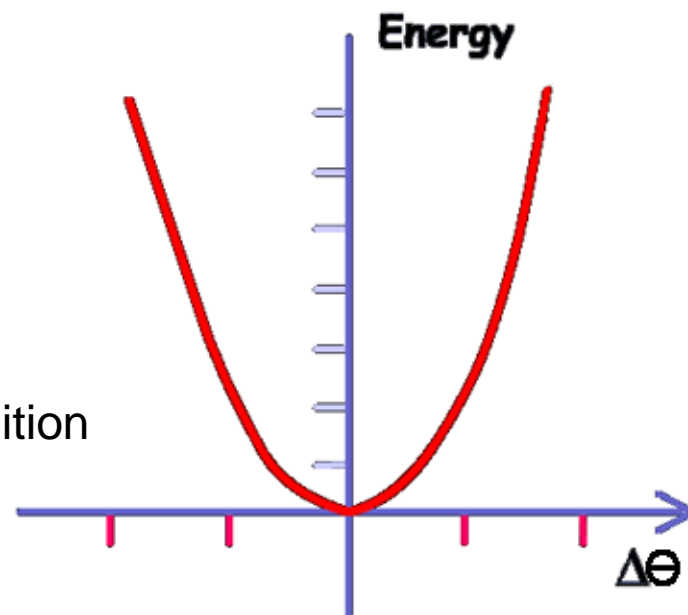
FF components: Angle Bending

A valency angle between three atoms has a “natural” equilibrium position. An energy penalty is associated with any change of the bond angle from its equilibrium value. The bending energies are expressed by a Hookean law formulat.

$$E_{(\theta)} = \sum k_{(\theta)} (\theta - \theta_0)^2$$

Bending Force Constant

Equilibrium Position

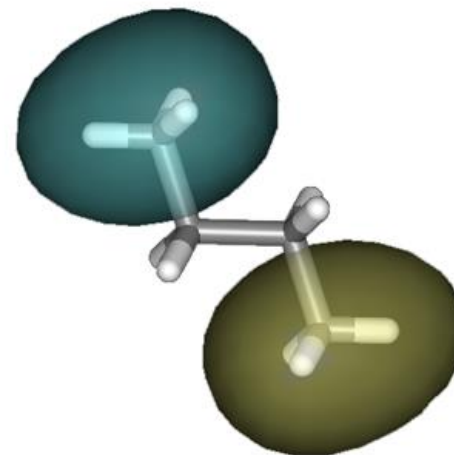
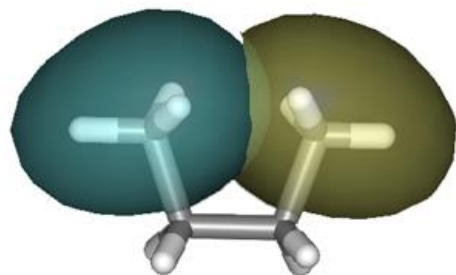


The bending force constants are usually determined experimentally from vibration spectroscopy. The Hook's law description is fairly good at geometries just near the equilibrium bond length.

FF components: Torsional Contributions

An energy is associated with each torsion angle. The origin of this energy comes from through-space steric and electronic interactions between non-bonded atoms. The minimum amount of energy needed to get a molecule undergo one complete rotation around a certain bond can be referred to as the rotational barrier for that bond.

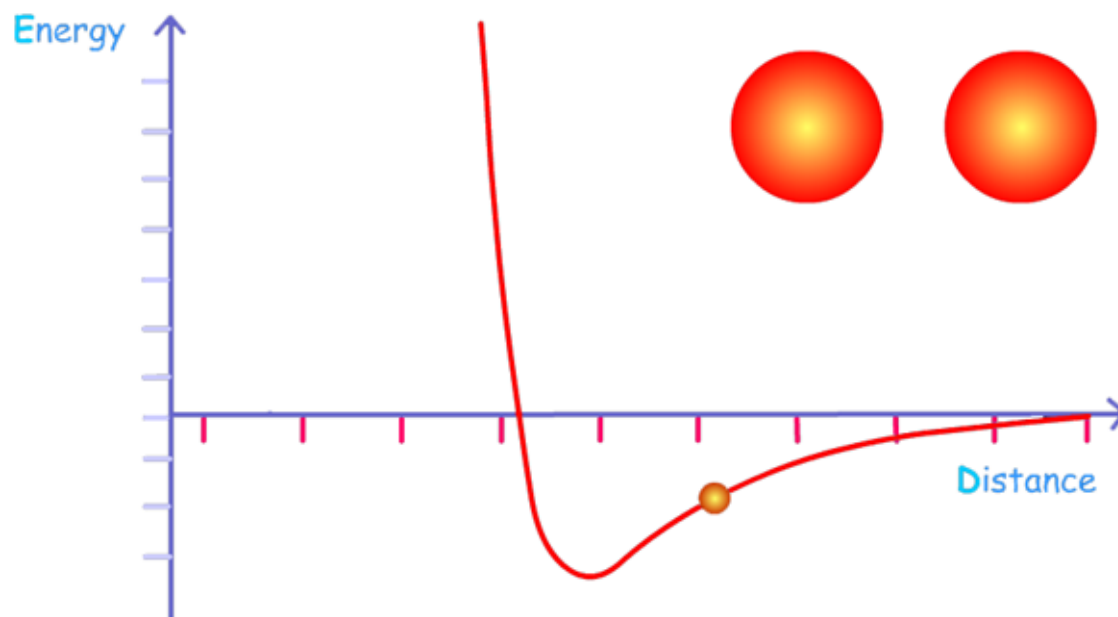
$$E_{\Theta} = \sum V_i [1 + \cos^n(|\Theta| + t)]$$



Generally, three different V terms are considered. The rotational barrier, or barrier to rotation, is the activation energy required to interconvert rotamers (conformational isomers).

FF components: Van der Waals interactions

Interactions exist between non-bonded atoms and are called “van der Waals” interactions. At a short distance, there is repulsion between the two atoms (due to the interpenetration of their electronic clouds), and at a long distance, there is a small attraction (dispersion forces).



Lennard-Jones Potential

$$V_{LJ} = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$

ϵ and σ are the specific Lennard-Jones parameters, different for different interacting particles.

FF components: Electrostatic Dipolar Contributions

Interaction between polar atoms or bonds may result in attractions or repulsions. At the lowest approximation, it may be modelled by assigning charges to each atom or using a bond dipole description. The two descriptions give similar, but not identical results.

$$E_{\text{el}}(R^{\text{AB}}) = Q^{\text{A}}Q^{\text{B}}/\epsilon R^{\text{AB}}$$

Interaction between point charges
(given by Coulomb potential)

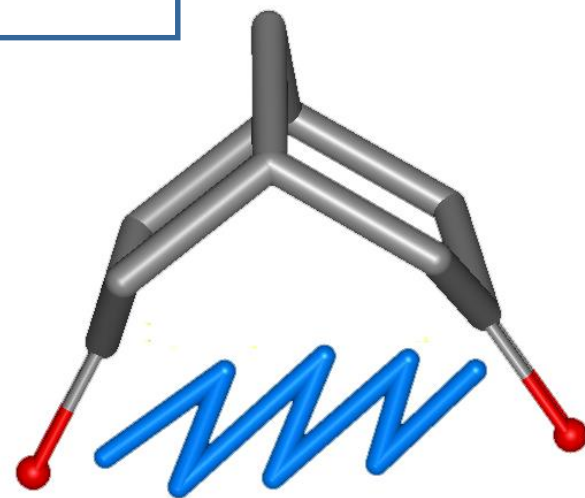
$$E_{\text{el}}(R^{\text{AB}}) = (\mu^{\text{A}}\mu^{\text{B}}/\epsilon(R^{\text{AB}})^3) * (\cos\chi - 3\cos\alpha_{\text{A}}\cos\alpha_{\text{B}})$$

Interaction between bond dipoles

Q is the atomic charge

R is the distance between the two atoms

ϵ is a dielectric constant,



FF components: Hydrogen Bond Energy contributions

A hydrogen bond is an attractive interaction between a hydrogen atom that is covalently bonded to an electronegative element and a second electronegative element. The energy of a strong H-bond is between 12-21 kJ/mol, while the energy of a covalent bond is about 418 kJ/mol.

The hydrogen bond contributions can be calculated with the following formula:

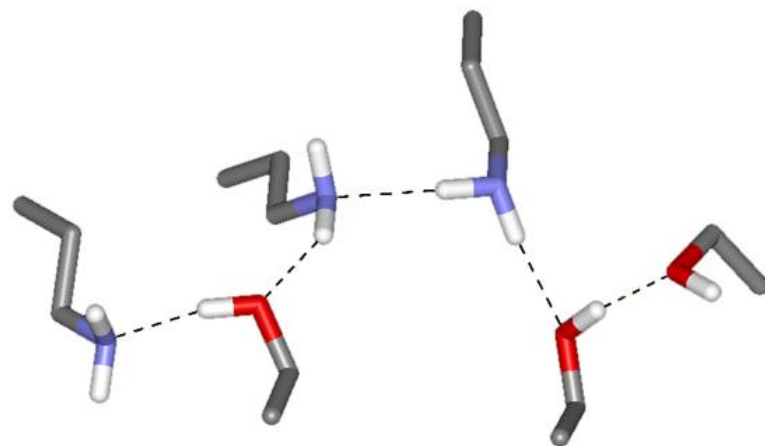
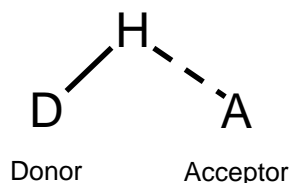
$$E_{HB} = 332/\epsilon \sum ((q_D q_A / d_{DA}) + (AK/d_{HA}^{12}) - (BK/d_{HA}^{10}))$$

ϵ = dielectric constant

q = atomic charge

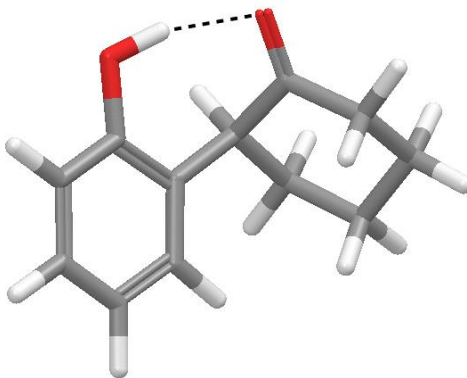
d = distance

AK, BK = parameters



Force Field Calculation

Force Field calculations are based on 3D coordinates and calculate the energy of the corresponding conformation. Here is shown an example (MM2 Force Field):



Stretch:	10.8872	kJ/mol (2.6021	kcal/mol)
Bend:	30.4519	kJ/mol (7.2782	kcal/mol)
Proper torsion:	22.5726	kJ/mol (5.3950	kcal/mol)
Out-of-plane:	1.6357	kJ/mol (0.3909	kcal/mol)
Stretch-bend:	0.2316	kJ/mol (0.0554	kcal/mol)
Van der Waals:	35.1290	kJ/mol (8.3960	kcal/mol)
Electrostatic:	7.7632	kJ/mol (1.8554	kcal/mol)
Hydrogen bonding:	2.4187	kJ/mol (0.5781	kcal/mol)
Total Energy =	111.090	kJ/mol		

Force Field parameters

- Atom Types
- Force Constants
- Equilibrium values
- Van der Waals and H-bond parameters
- Partial atomic charges

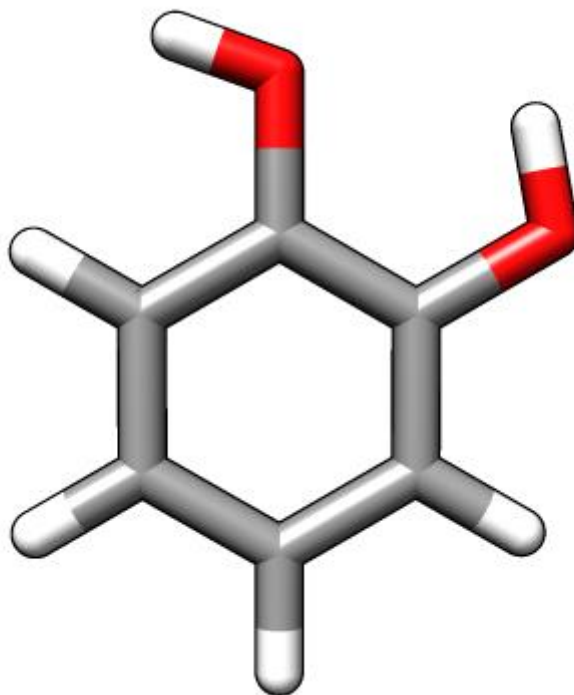
Force Field parameters: Atom Types

The “atom types” concept can be considered one of the most important in the field of the molecular mechanics. The atom types are fundamental for the evaluation of the interactions. They can be defined based on a) hybridization, b) atomic charge and c) bound atoms. As an example, the Amber FF has 5 different atom types for the oxygen:

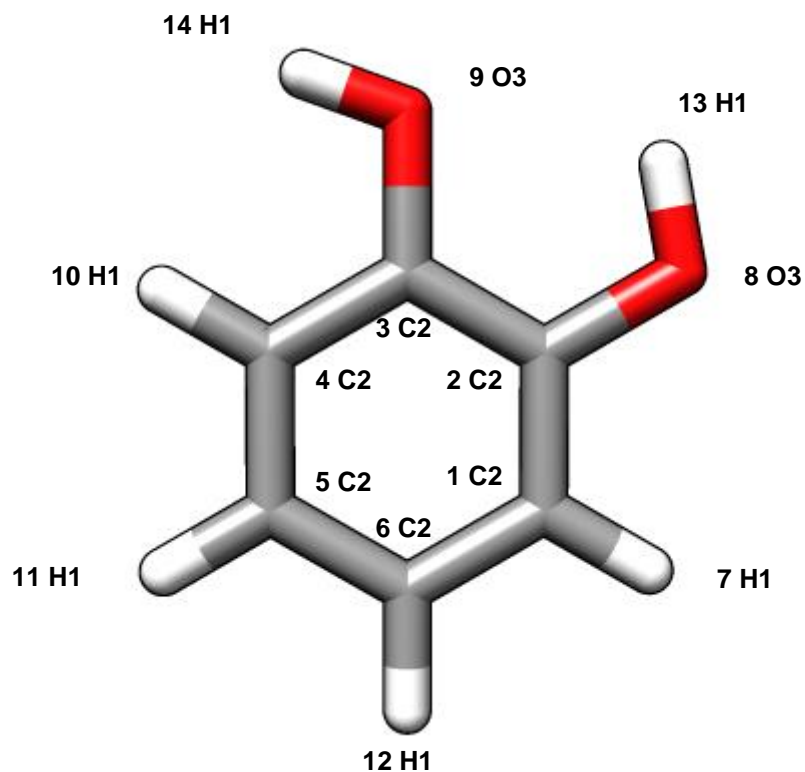
O	carbonyl group oxygen
OW	oxygen in water
OH	oxygen in hydroxyl groups
OS	ether and ester oxygen
O2	carboxyl and phosphate group oxygens

The interactions are calculated on the bases of the atom types and **NOT** of the element types.

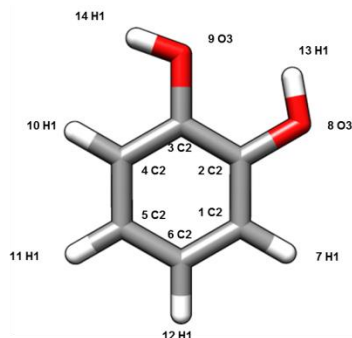
Example



Atom Type



Stretching



14 H1

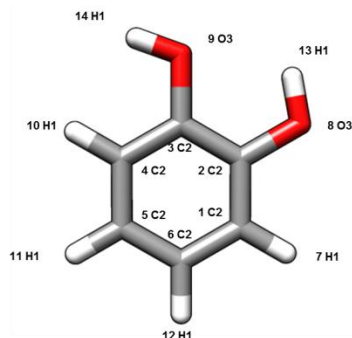
BOND LENGTHS AND STRETCH ENERGIES

14 Stretch interactions present

Comments	Atom Numbers		Force Const	Length (Angstroms)		Energy kJ/mol	Select Alts	
				Ideal	Actual FF Line			
	1	2	5.5730	1.3740	1.4046	1.477	O1	0
	1	6	5.5730	1.3740	1.4045	1.472	O1	0
	1	7	5.3060	1.0840	1.1034	0.578	O1	0
	2	3	5.5730	1.3740	1.4045	1.469	O1	0
	2	8	5.6140	1.3760	1.3640	0.249	O1	0
	3	4	5.5730	1.3740	1.4045	1.472	O1	0
	3	9	5.6140	1.3760	1.3640	0.249	O1	0
	4	5	5.5730	1.3740	1.4045	1.472	O1	0
	4	10	5.3060	1.0840	1.1034	0.578	O1	0
	5	6	5.5730	1.3740	1.4046	1.479	O1	0
	5	11	5.3060	1.0840	1.1033	0.575	O1	0
	6	12	5.3060	1.0840	1.1034	0.580	O1	0
	8	13	7.8390	0.9730	0.9600	0.409	O1	0
	9	14	7.8390	0.9730	0.9600	0.409	O1	0

12 H1

Bending



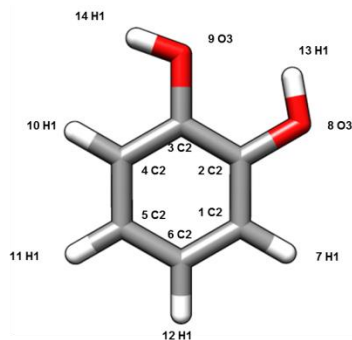
14 H1

ANGLES, BEND AND STRETCH BEND ENERGIES

20 Bend interactions present

Comments	Atom Numbers			Force Consts		Angle		Energy (kJ/mol)			
				KBnd1	KSBnd	Ideal	Actual	EBnd	ESBnd	Select	Alts
	2	1	6	0.669	-0.411	119.977	120.003	0.000	-0.007	01	0
	2	1	7	0.563	0.250	120.571	120.000	0.017	-0.078	01	0
	6	1	7	0.563	0.250	120.571	119.997	0.017	-0.079	01	0
	1	2	3	0.669	-0.411	119.977	120.000	0.000	-0.006	01	0
	1	2	8	0.968	0.339	116.495	119.996	1.062	0.015	01	0
	3	2	8	0.968	0.339	116.495	120.004	1.066	0.014	01	0
	2	3	4	0.669	-0.411	119.977	119.997	0.000	-0.005	01	0
	2	3	9	0.968	0.339	116.495	119.999	1.064	0.014	01	0
	4	3	9	0.968	0.339	116.495	120.004	1.066	0.014	01	0
	3	4	5	0.669	-0.411	119.977	120.006	0.000	-0.008	01	0
	3	4	10	0.563	0.250	120.571	119.997	0.017	-0.079	01	0
	5	4	10	0.563	0.250	120.571	119.997	0.017	-0.079	01	0
	4	5	6	0.669	-0.411	119.977	119.997	0.000	-0.005	01	0
	4	5	11	0.563	0.250	120.571	120.001	0.017	-0.078	01	0
	6	5	11	0.563	0.250	120.571	120.002	0.017	-0.078	01	0
	1	6	5	0.669	-0.411	119.977	119.997	0.000	-0.005	01	0
	1	6	12	0.563	0.250	120.571	120.004	0.017	-0.078	01	0
	5	6	12	0.563	0.250	120.571	119.999	0.017	-0.079	01	0
	2	8	13	0.726	0.241	105.409	109.500	1.083	-0.197	01	0
	3	9	14	0.726	0.241	105.409	120.000	12.733	-0.703	01	0

Torsional



DIHEDRAL ANGLES AND TORSIONAL ENERGIES

28 Proper Torsion interactions

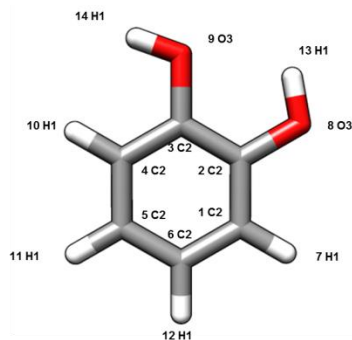
present

Atom Numbers				Force Consts			Angle	Energy	Select Alts	
Comments				V1	V2	V3	FF Line	kJ/mol		
1	2	3	4	0.000	7.000	0.000	0.0	0.000	O1	0
1	2	3	9	0.000	7.000	0.000	180.0	0.000	O1	0
1	2	8	13	0.000	2.801	0.000	180.0	0.000	O1	0
1	6	5	4	0.000	7.000	0.000	0.0	0.000	O1	0
1	6	5	11	0.000	7.000	0.000	180.0	0.000	O1	0
2	1	6	5	0.000	7.000	0.000	0.0	0.000	O1	0
2	1	6	12	0.000	7.000	0.000	180.0	0.000	O1	0
2	3	4	5	0.000	7.000	0.000	0.0	0.000	O1	0
2	3	4	10	0.000	7.000	0.000	180.0	0.000	O1	0
2	3	9	14	0.000	2.801	0.000	180.0	0.000	O1	0
3	2	1	6	0.000	7.000	0.000	0.0	0.000	O1	0
3	2	1	7	0.000	7.000	0.000	180.0	0.000	O1	0
3	2	8	13	0.000	2.801	0.000	0.0	0.000	O1	0
3	4	5	6	0.000	7.000	0.000	0.0	0.000	O1	0
3	4	5	11	0.000	7.000	0.000	180.0	0.000	O1	0
4	3	2	8	0.000	7.000	0.000	180.0	0.000	O1	0
4	3	9	14	0.000	2.801	0.000	0.0	0.000	O1	0
4	5	6	12	0.000	7.000	0.000	180.0	0.000	O1	0
5	4	3	9	0.000	7.000	0.000	180.0	0.000	O1	0
5	6	1	7	0.000	7.000	0.000	180.0	0.000	O1	0
6	1	2	8	0.000	7.000	0.000	180.0	0.000	O1	0
6	5	4	10	0.000	7.000	0.000	180.0	0.000	O1	0
7	1	2	8	0.000	7.000	0.000	0.0	0.000	O1	0
7	1	6	12	0.000	7.000	0.000	0.0	0.000	O1	0
8	2	3	9	0.000	7.000	0.000	0.0	0.000	O3	0
9	3	4	10	0.000	7.000	0.000	0.0	0.000	O1	0
10	4	5	11	0.000	7.000	0.000	0.0	0.000	O1	0
11	5	6	12	0.000	7.000	0.000	0.0	0.000	O1	0

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Nonbonded Energies



NONBONDED DISTANCES AND ENERGIES

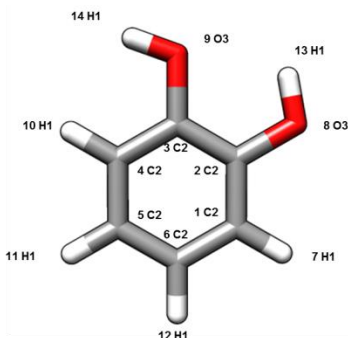
57 Nonbonded interactions present

ATOM NUMBERS		CONST 1	CONST 2	CHARGE*	DISTANCE	ENERGY (kJ/mol)	
						EVDW	ECHARGE
1	4	.6780E-01	4.193	0.0169	2.809	15.769	8.201
1	9	.6270E-01	3.936	0.0599	3.678	-0.201	22.328
1	10	.2457E-01	3.793	-0.0225	3.912	-0.099	-7.889
1	11	.2457E-01	3.793	-0.0169	3.433	-0.037	-6.732
1	13	.3129E-01	3.403	-0.0506	3.193	-0.104	-21.688
1	14	.3129E-01	3.403	-0.0675	4.450	-0.041	-20.841
2	5	.6780E-01	4.193	-0.0093	2.809	15.762	-4.510
2	10	.2457E-01	3.793	0.0093	3.433	-0.037	3.703
2	11	.2457E-01	3.793	0.0124	3.912	-0.099	4.339
2	12	.2457E-01	3.793	0.0093	3.433	-0.037	3.702
2	14	.3129E-01	3.403	0.0278	3.267	-0.122	11.661
3	6	.6780E-01	4.193	-0.0093	2.809	15.760	-4.510
3	7	.2457E-01	3.793	0.0093	3.433	-0.037	3.702
3	11	.2457E-01	3.793	0.0093	3.433	-0.037	3.702
3	12	.2457E-01	3.793	0.0124	3.913	-0.099	4.339
3	13	.3129E-01	3.403	0.0278	2.407	4.137	15.745
4	7	.2457E-01	3.793	-0.0225	3.912	-0.099	-7.889
4	8	.6270E-01	3.936	0.0599	3.678	-0.201	22.328
4	12	.2457E-01	3.793	-0.0169	3.433	-0.037	-6.732
4	13	.3129E-01	3.403	-0.0675	3.804	-0.095	-24.334
4	14	.3129E-01	3.403	-0.0506	2.575	1.812	-26.792
5	7	.2457E-01	3.793	-0.0169	3.433	-0.037	-6.732
5	8	.6270E-01	3.936	0.0799	4.173	-0.234	26.279
5	9	.6270E-01	3.936	0.0599	3.678	-0.201	22.327
5	13	.3129E-01	3.403	-0.0675	4.584	-0.034	-20.239
5	14	.3129E-01	3.403	-0.0675	3.970	-0.078	-23.332
6	8	.6270E-01	3.936	0.0599	3.678	-0.201	22.328
6	9	.6270E-01	3.936	0.0799	4.173	-0.234	26.278
6	10	.2457E-01	3.793	-0.0169	3.433	-0.037	-6.732
6	13	.3129E-01	3.403	-0.0675	4.344	-0.047	-21.341
6	14	.3129E-01	3.403	-0.0675	4.727	-0.028	-19.633
7	8	.3531E-01	3.325	-0.0599	2.648	0.948	-30.852
7	9	.3531E-01	3.325	-0.0799	4.571	-0.034	-24.014
7	10	.2157E-01	2.970	0.0225	5.016	-0.005	6.171
7	11	.2157E-01	2.970	0.0225	4.344	-0.014	7.115
7	12	.2157E-01	2.970	0.0169	2.508	0.170	9.166
7	13	.2114E-01	2.792	0.0675	3.583	-0.031	25.818
7	14	.2114E-01	2.792	0.0675	5.412	-0.002	17.169
8	9	.7625E-01	3.558	0.2127	2.769	2.966	104.833
8	10	.3531E-01	3.325	-0.0799	4.571	-0.034	-24.014
8	11	.3531E-01	3.325	-0.0799	5.276	-0.014	-20.835
8	12	.3531E-01	3.325	-0.0799	4.571	-0.034	-24.013
8	14	.1887E-01	2.469	-0.2396	3.729	-0.010	-88.111
9	10	.3531E-01	3.325	-0.0599	2.648	0.948	-30.851
9	11	.3531E-01	3.325	-0.0799	4.571	-0.034	-24.014
9	12	.3531E-01	3.325	-0.0799	5.277	-0.014	-20.835
9	13	.1887E-01	2.469	-0.2396	2.266	-0.045	-143.757
10	11	.2157E-01	2.970	0.0169	2.508	0.170	9.166
10	12	.2157E-01	2.970	0.0225	4.344	-0.014	7.115
10	13	.2114E-01	2.792	0.0675	4.524	-0.007	20.503
10	14	.2114E-01	2.792	0.0675	2.403	0.090	38.228
11	12	.2157E-01	2.970	0.0169	2.508	0.170	9.166
11	13	.2114E-01	2.792	0.0675	5.670	-0.002	16.397
11	14	.2114E-01	2.792	0.0675	4.698	-0.006	19.753
12	13	.2114E-01	2.792	0.0675	5.323	-0.002	17.456
12	14	.2114E-01	2.792	0.0675	5.816	-0.001	15.987
13	14	.2157E-01	2.614	0.2025	3.190	-0.042	86.842

Department of Pharmacy

Molecular Modeling & Virtual Screening Laboratory

Total Energy



14 H1



9 O3

13 H1

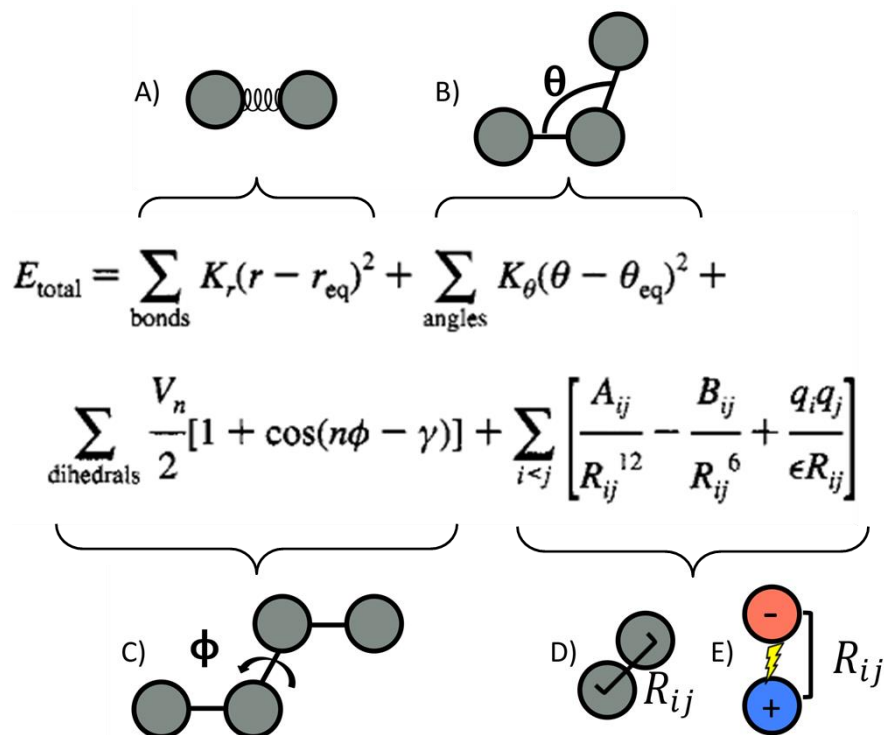


Total energy:	37.1539 kJ/mol (8.8800 kcal/mol)
Stretch:	12.4709 kJ/mol (2.9806 kcal/mol)
Bend:	18.2089 kJ/mol (4.3520 kcal/mol)
Proper torsion:	0.0000 kJ/mol (0.0000 kcal/mol)
Van der Waals:	55.8473 kJ/mol (13.3478 kcal/mol)
Electrostatic:	-49.3732 kJ/mol (-11.8005 kcal/mol)

Maximum van der Waals distance = 7.0 Angstroms
 Maximum electrostatic distance = 12.0 Angstroms
 Maximum hydrogen bond distance = 4.0 Angstroms
 Dipole moment of total system = 3.501 Debyes
 Molecular dielectric constant = 1.00

Amber ff94 force field

Here is the functional form of ff94 FF. Bonds and angles are represented by a diagonal harmonic expression, the VDW interaction represented by a 6-12 potential, EE interactions modeled by a Coulombic interaction of atom-centered point charges, and dihedral energies represented with a simple set of parameters, often only specified by the two central atoms, fit to relative QM energies of alternate rotamers of small molecules.



Amber ff94 force field

In Amber ff94 a function for representing hydrogen bonds is not necessary, due to the improved performance of charge model, van der Waals parameters derived from liquid simulations and hydrogen parameters considering the effects of any geminal electronegative atoms.

New atom types are defined for hydrogen atoms bonded to carbons that are themselves bonded to one or more electronegative atoms, in line with the electronegativity-based bond length correction used in MM2 and MM3 force fields.

Amber ff94 force field

List of atom types for C atoms in Amber ff94

CT	any sp ³ carbon
C	any carbonyl sp ² carbon
CA	any aromatic sp ² carbon and (in Arg)
CM	any sp ² carbon, double bonded
CC	sp ² aromatic in 5-membered ring with one substituent + next to nitrogen (e.g. His)
CV	sp ² aromatic in 5-membered ring next to carbon and lone pair nitrogen (e.g. His)
CW	sp ² aromatic in 5-membered ring next to carbon and NH (e.g. His and Trp)
CR	sp ² aromatic in 5-membered ring next to two nitrogens (in His)
CB	sp ² aromatic at junction of 5- and 6-membered rings (in Trp, Ade and Gua)
c*	sp ² aromatic in 5-membered ring next to two carbons (e.g. in Trp)
CN	sp ² junction between 5- and 6-membered rings and bonded to CH and NH (in Trp)
CK	sp ² carbon in 5-membered aromatic between N and N-R (in purines)
CQ	sp ² carbon in 6-membered ring between lone pair nitrogens (e.g. in purines)

Amber ff94 force field

List of atom types for N, O, S and P atoms in Amber ff94

N	sp2 nitrogen in amides
NA	sp2 nitrogen in aromatic rings with hydrogen attached (e.g. Hip, Gua, Trp)
NB	sp2 nitrogen in 5-membered ring with lone pair (e.g. in purines)
NC	sp2 nitrogen in 6-membered ring with lone pair (e.g. in purines)
N*	sp2 nitrogen in 5-membered ring with carbon substituent (in purine nucleosides)
N2	sp2 nitrogen of aromatic amines and guanidinium ions
N3	sp3 nitrogen
OW	sp3 oxygen in 3 water
OH	sp3 oxygen in alcohols, tyrosine, and protonated carboxylic acids
OS	sp3 oxygen in ethers
O	sp2 oxygen in amides
O2	sp2 oxygen in anionic acids
S	sulfur in methionine and cysteine
SH	sulfur in cysteine
P	phosphorus in phosphates

Amber ff94 force field

List of atom types for H atoms in Amber ff94

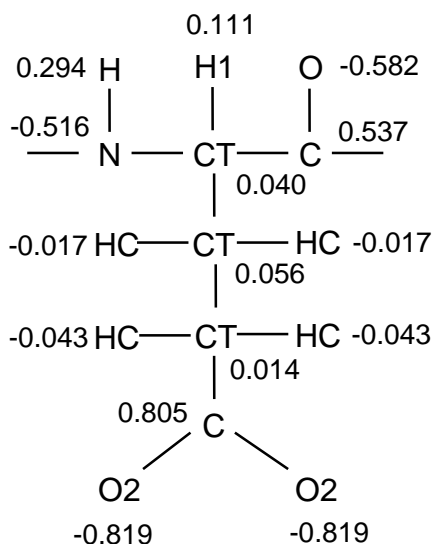
H	H attached to N
HW	H in 3 water
HO	H in alcohols and acids
HS	H attached to sulfur
HA	H attached to aromatic carbon
HC	H attached to aliphatic carbon with no electron-withdrawing substituents
HI	H attached to aliphatic carbon with one electron-withdrawing substituent
H2	H attached to aliphatic carbon with two electron-withdrawing substituents
H3	H attached to aliphatic carbon with three electron-withdrawing substituents
HP	H attached to carbon directly bonded to formally positive atoms (e.g. C next to NH ₃ ⁺ of lysine)
H4	H attached to aromatic carbon with one electronegative neighbor (e.g. hydrogen on C5 of Trp, C6 of Thy)
H5	H attached to aromatic carbon with two electronegative neighbors (e.g. H8 of Ade)

Amber ff94 force field

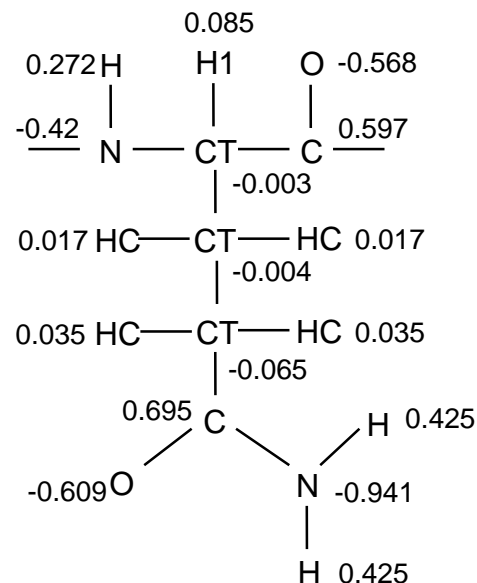
List of residue types in Amber ff94:

ALA, ASN, ASP, ARG, CYS-CYX, GLN, GLU, GLY, HID-HIE-HIP (HIS), ILE, LEU, LYS, MET, PHE, PRO, SER, THR, TRP, TYR, VAL.

Atom type and partial charges scheme for GLU and GLN:



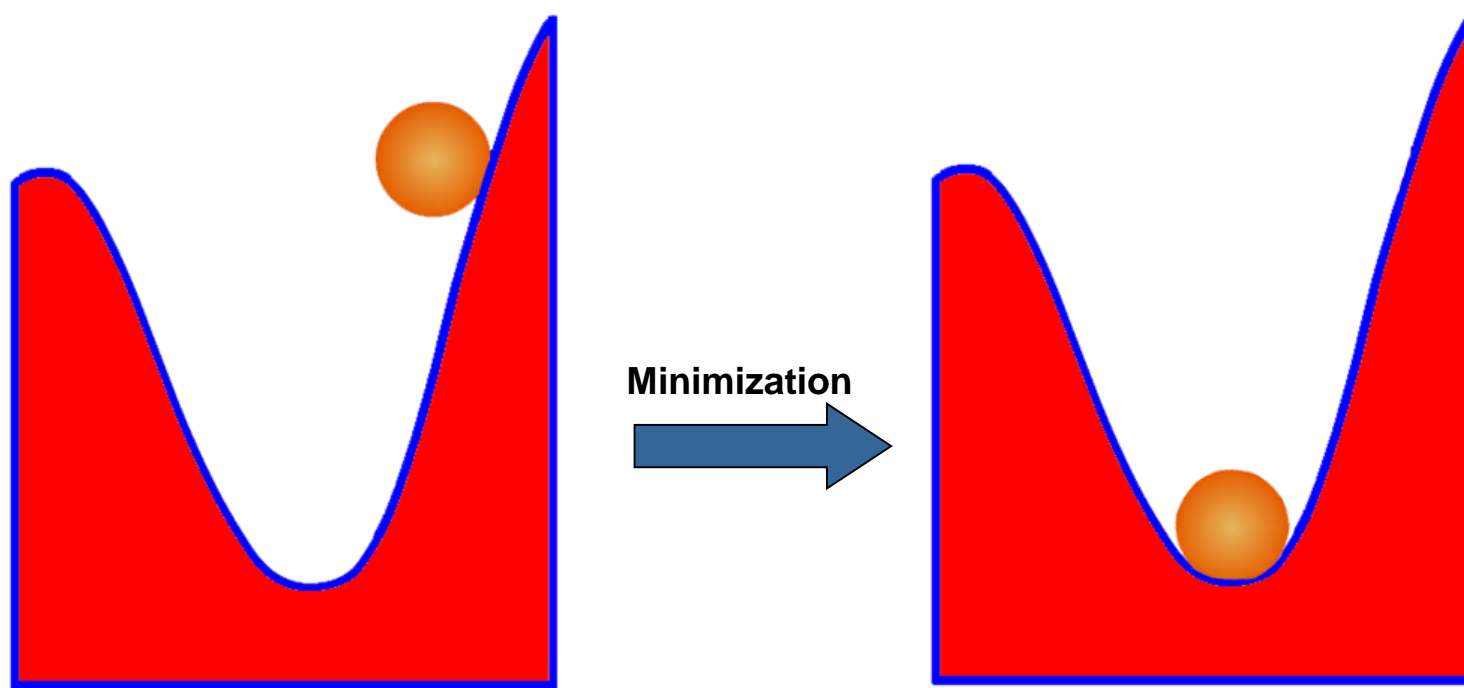
GLU



GLN

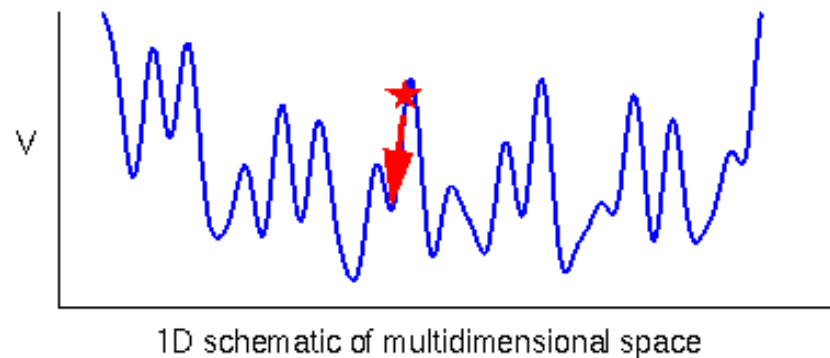
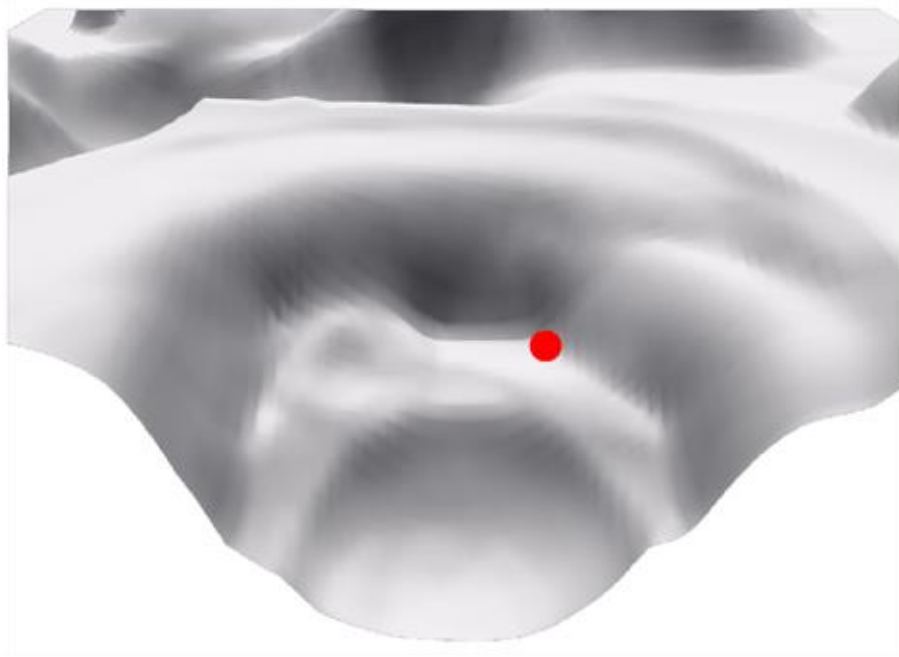
Energy Minimization: Definition

Minimization treatment consists of successive alterations of the geometry of the molecule until an energetically minimum is found. The minimization is terminated when it is not possible to find a conformer of lower energy in the current well considered.



Energy Minimization: Definition

The energy landscape of a molecule possesses different minima. Nonetheless, the goal of energy minimization is simply to find the local energy minimum, i.e., the bottom of the energy well occupied by the initial conformation. The energy at this local minimum may be much higher than the energy of the global minimum.



1D schematic of multidimensional space

The minimization Treatment

In energy minimization an initial conformation is submitted to full geometry optimization, where all parameters defining the geometry of the system are modified by small increments, until the total energy of the system reaches a minimum. Small modifications of the molecular geometry are considered, if the resulting geometry has lower energy than the original, then another step is made in the same direction. Otherwise a smaller step in a different direction is carried out. The process is continued until the energy cannot decrease.



Minimization Methods

There are three main different algorithms for conducting a minimization.

- **Steepest descent (SD):** This is a robust but slowly converging treatment, it is suitable for initial refinement of highly strained structures.
- **Conjugate gradients (CG):** This method is a variation of the SD, is more efficient and makes more intelligent choices of search direction. It is suitable for large systems.
- **Newton-Raphson (NR):** This minimizer calculates both the slope of the energy change with conformation and its rate of change. It is not efficient for large system. However, it can be used for getting extreme convergence on already refined systems.

Minimization Criteria

How do you determine when the molecule is minimized?

The Number of Minimization Steps (Iteration Limit) can be used to stop the calculation. This option is dangerous; you need to realize that if the minimization stops for this reason, the molecule is not necessarily minimized and you may need to continue to submit the molecule to minimization until the energy no longer changes on successive steps.

A better option is to set the number of minimizations steps to a very large number and then use an energy-based criterion for stopping the calculation.

Minimization Criteria

•**Energy gradient tolerance.** The gradient is the derivative of the energy, the energy gradient approaches zero at the energy minimum. The criterion is to stop the minimization if the gradient is less than a selected value (Figure 1).

•**Energy comparison.** An alternate method to stop the minimization is to compare the change in energy between the current step and the previous step. If the change in energy is below the set tolerance, then the minimization is halted (Figure 2).

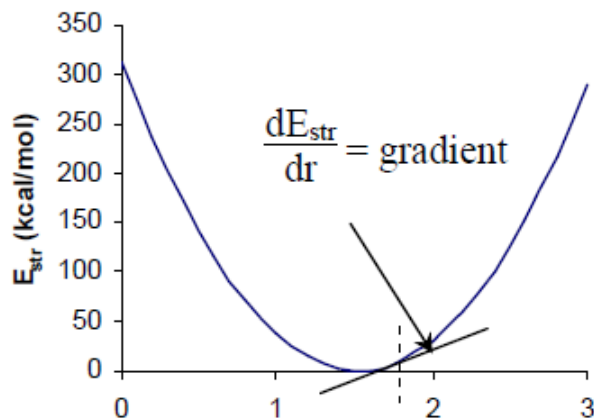


Figure 1

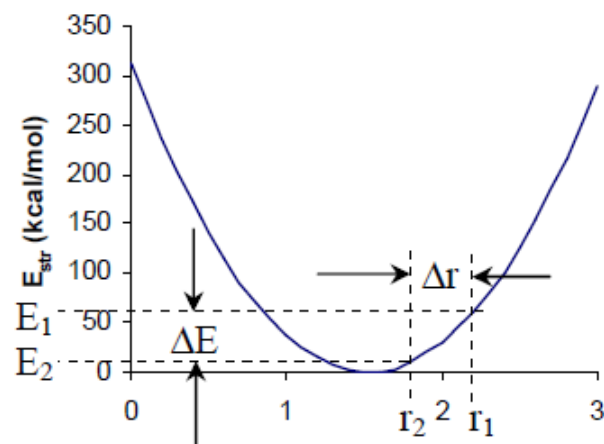


Figure 2