

# Force Fields for MD simulations

- Topology/parameter files
- Where do the numbers an MD code uses come from?
- How to make topology files for ligands, cofactors, special amino acids, ...
- How to obtain/develop missing parameters.
  
- QM and QM/MM force fields/potential energy descriptions used for molecular simulations.

# The Potential Energy Function

$$\begin{aligned}
 U(\vec{R}) = & \underbrace{\sum_{\text{bonds}} k_i^{\text{bond}} (r_i - r_0)^2}_{U_{\text{bond}}} + \underbrace{\sum_{\text{angles}} k_i^{\text{angle}} (\theta_i - \theta_0)^2}_{U_{\text{angle}}} + \\
 & \underbrace{\sum_{\text{dihedrals}} k_i^{\text{dihe}} [1 + \cos(n_i \phi_i + \delta_i)]}_{U_{\text{dihedral}}} + \\
 & \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right]}_{U_{\text{nonbond}}} + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}
 \end{aligned}$$

$U_{\text{bond}}$  = oscillations about the equilibrium bond length

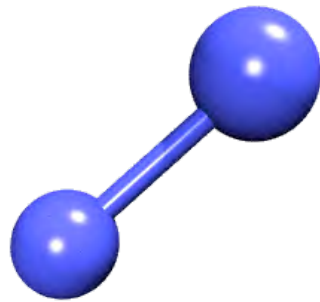
$U_{\text{angle}}$  = oscillations of 3 atoms about an equilibrium bond angle

$U_{\text{dihedral}}$  = torsional rotation of 4 atoms about a central bond

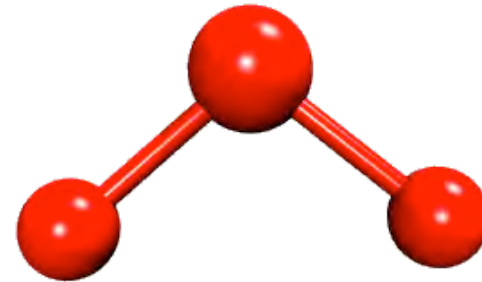
$U_{\text{nonbond}}$  = non-bonded energy terms (electrostatics and Lenard-Jones)

# Energy Terms Described in the CHARMM Force Field

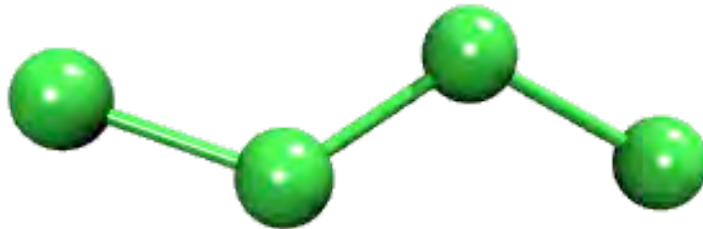
Bond



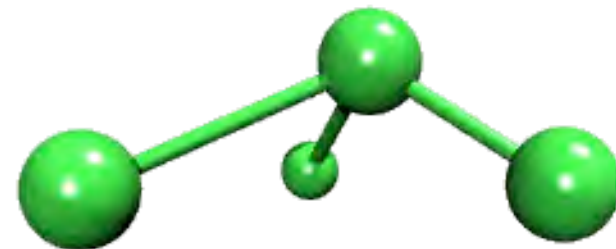
Angle



Dihedral



Improper



# Classical Molecular Dynamics

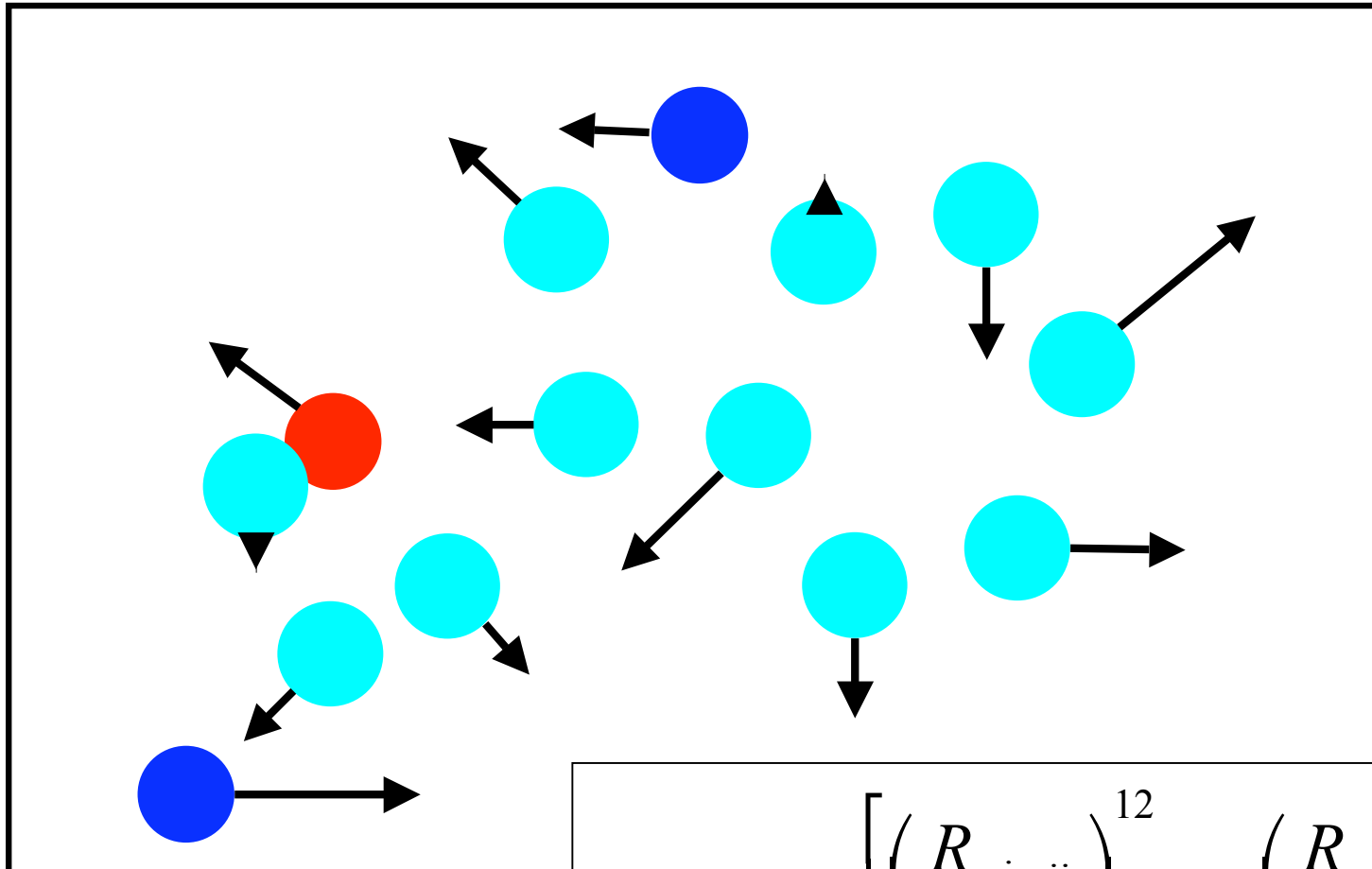
$$\mathbf{r}(t + \delta t) = \mathbf{r}(t) + \mathbf{v}(t)\delta t$$

$$\mathbf{v}(t + \delta t) = \mathbf{v}(t) + \mathbf{a}(t)\delta t$$

$$\mathbf{a}(t) = \mathbf{F}(t) / m$$

$$\mathbf{F} = -\frac{d}{dr}U(\mathbf{r})$$

# Classical Molecular Dynamics



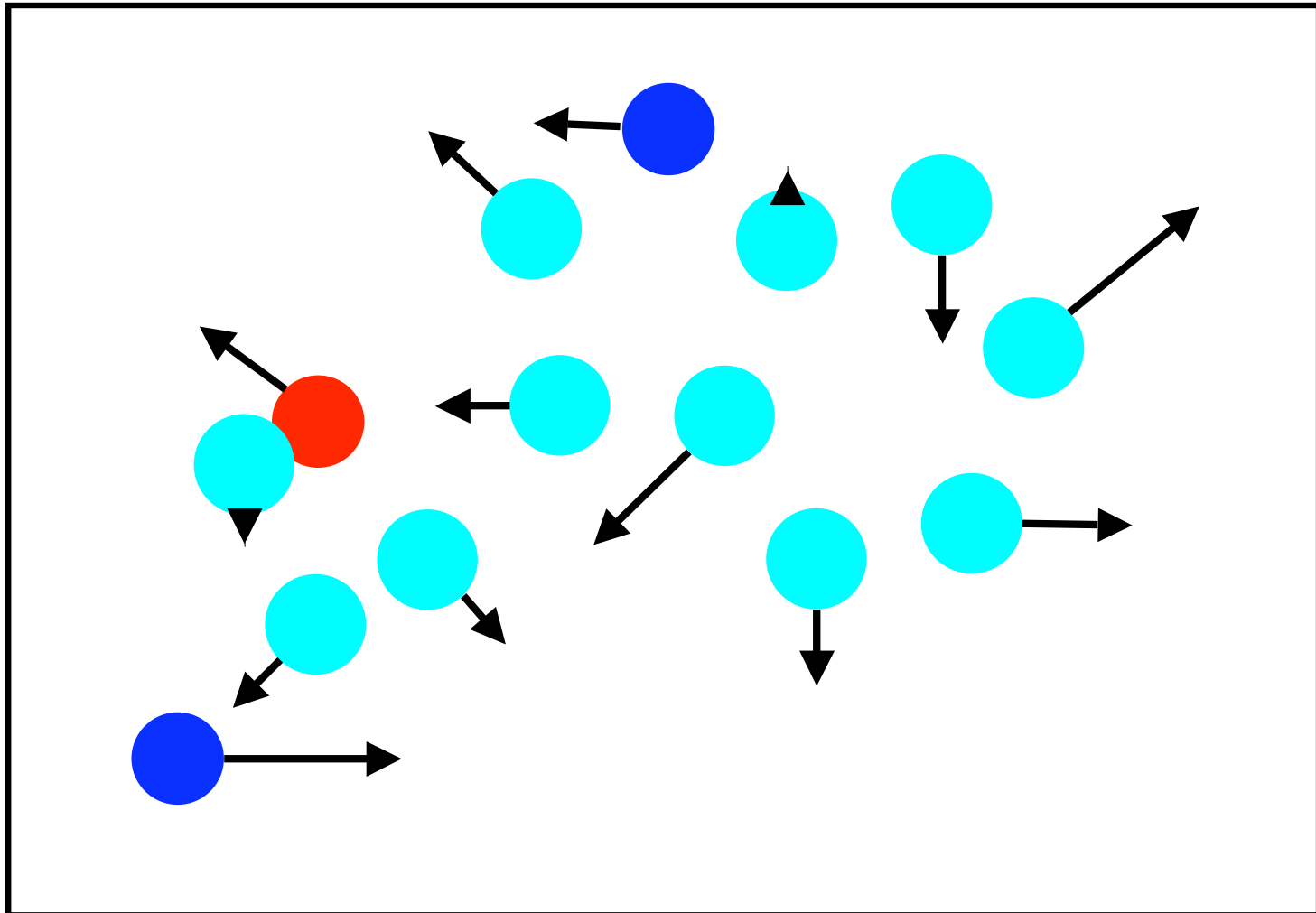
$$U(r) = \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r_{ij}}$$

Coulomb interaction

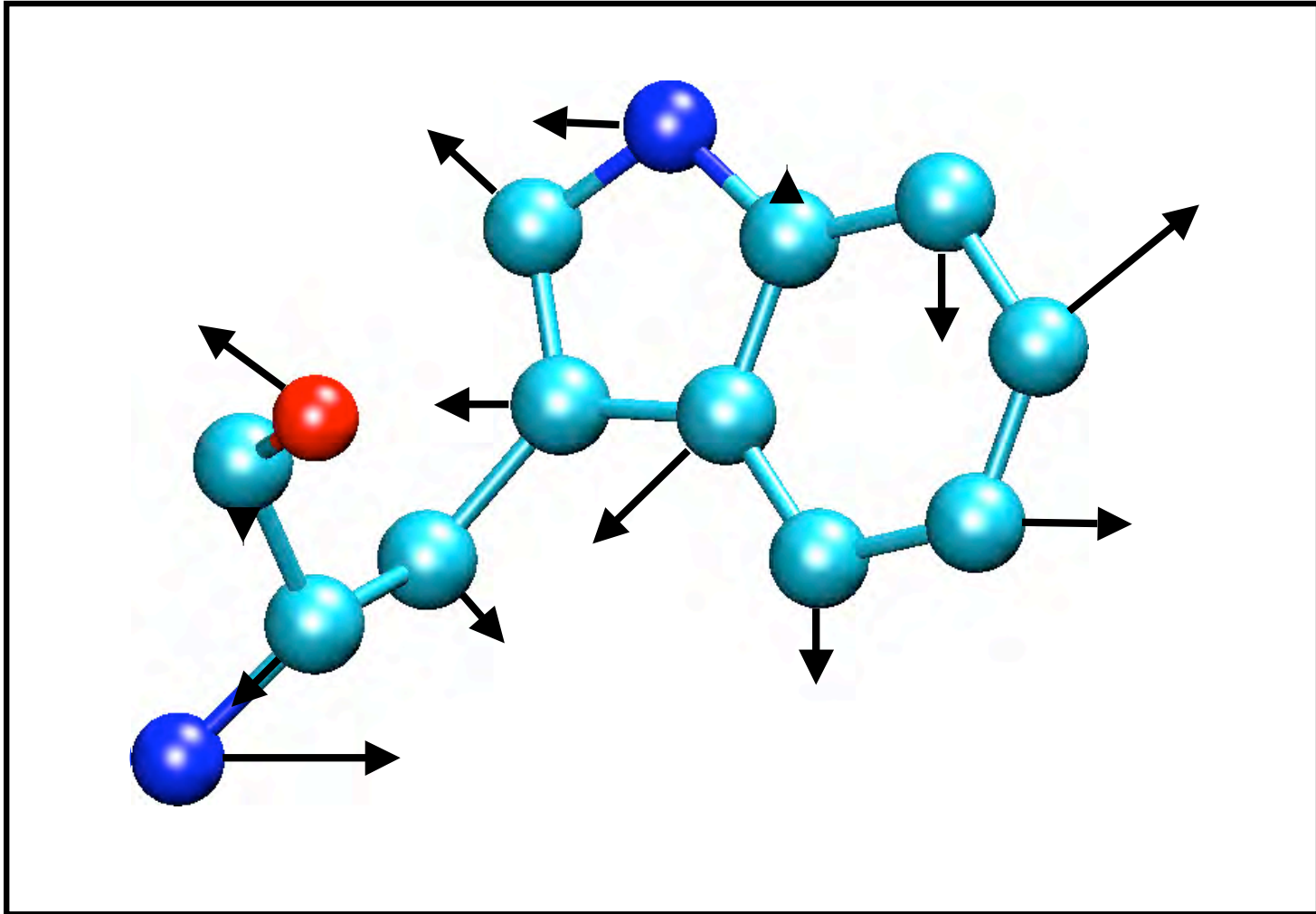
$$U(r) = \epsilon_{ij} \left[ \left( \frac{R_{\min,ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{\min,ij}}{r_{ij}} \right)^6 \right]$$

van der Waals interaction

# Classical Molecular Dynamics



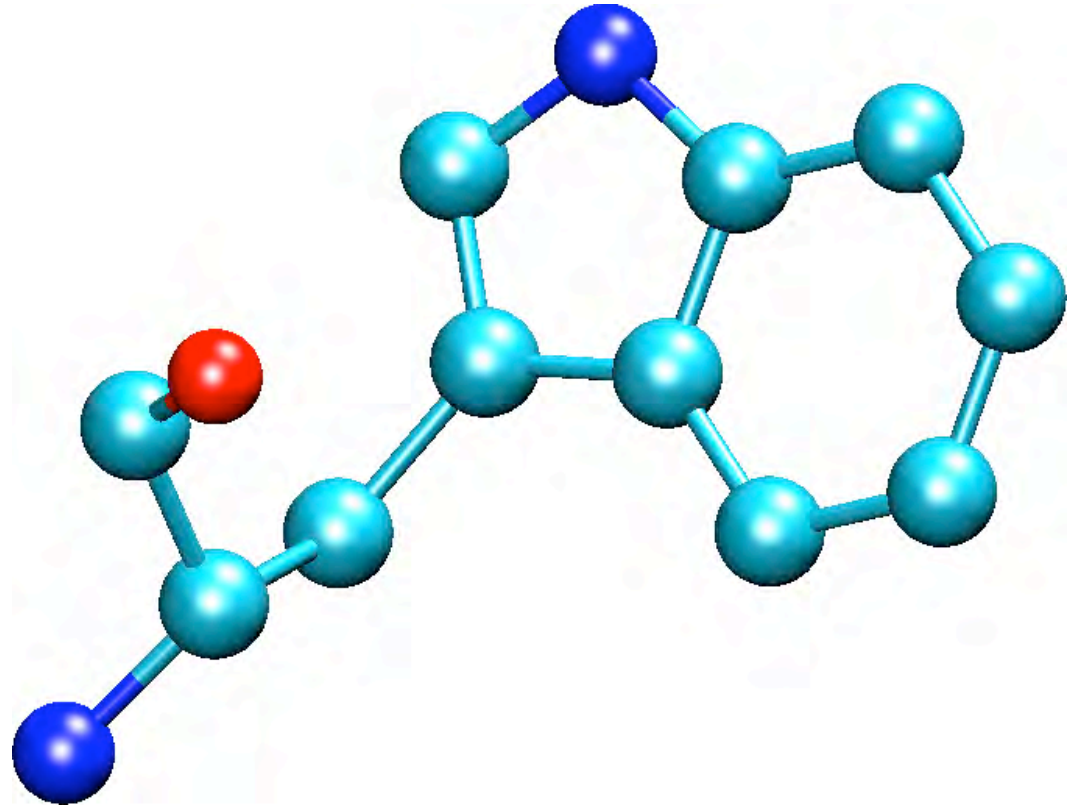
# Classical Molecular Dynamics



Bond definitions, atom types, atom names, parameters, ....

# What is a Force Field?

In molecular dynamics a molecule is described as a series of charged points (atoms) linked by springs (bonds).



To describe the time evolution of bond lengths, bond angles and torsions, also the non-bonding van der Waals and electrostatic interactions between atoms, one uses a **force field**.

The **force field** is a collection of equations and associated constants designed to reproduce molecular geometry and selected properties of tested structures.



# Energy Functions

$$\begin{aligned}
 U(\vec{R}) = & \underbrace{\sum_{\text{bonds}} k_i^{\text{bond}} (r_i - r_0)^2}_{U_{\text{bond}}} + \underbrace{\sum_{\text{angles}} k_i^{\text{angle}} (\theta_i - \theta_0)^2}_{U_{\text{angle}}} + \\
 & \underbrace{\sum_{\text{dihedrals}} k_i^{\text{dihe}} [1 + \cos(n_i \phi_i + \delta_i)]}_{U_{\text{dihedral}}} + \\
 & \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right]}_{U_{\text{nonbond}}} + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}
 \end{aligned}$$

$U_{\text{bond}}$  = oscillations about the equilibrium bond length

$U_{\text{angle}}$  = oscillations of 3 atoms about an equilibrium bond angle

$U_{\text{dihedral}}$  = torsional rotation of 4 atoms about a central bond

$U_{\text{nonbond}}$  = non-bonded energy terms (electrostatics and Lenard-Jones)

# Parameter optimization of the CHARMM Force Field

Based on the protocol established by

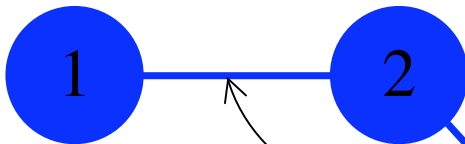
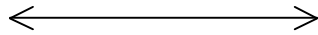
Alexander D. MacKerell, Jr , U. Maryland

See references: [www.pharmacy.umaryland.edu/faculty/amackere/force\\_fields.htm](http://www.pharmacy.umaryland.edu/faculty/amackere/force_fields.htm)

Especially Sanibel Conference 2003, JCC v21, 86,105 (2000)

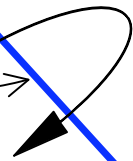
# Interactions between bonded atoms

$$V_{bond} = K_b (b - b_o)^2$$



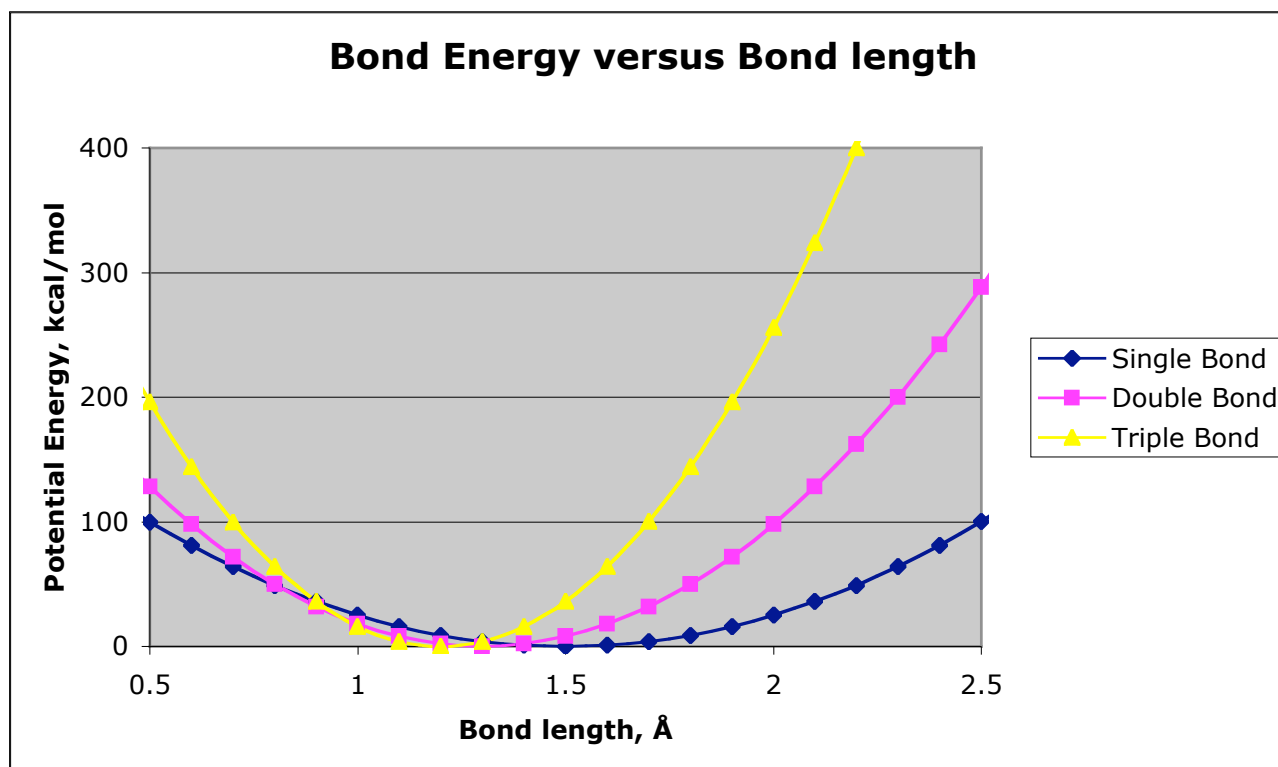
$$V_{dihedral} = K_\phi (1 + \cos(n\phi - \delta))$$

$$V_{angle} = K_\theta (\theta - \theta_o)^2$$



$$V_{bond} = K_b (b - b_o)^2$$

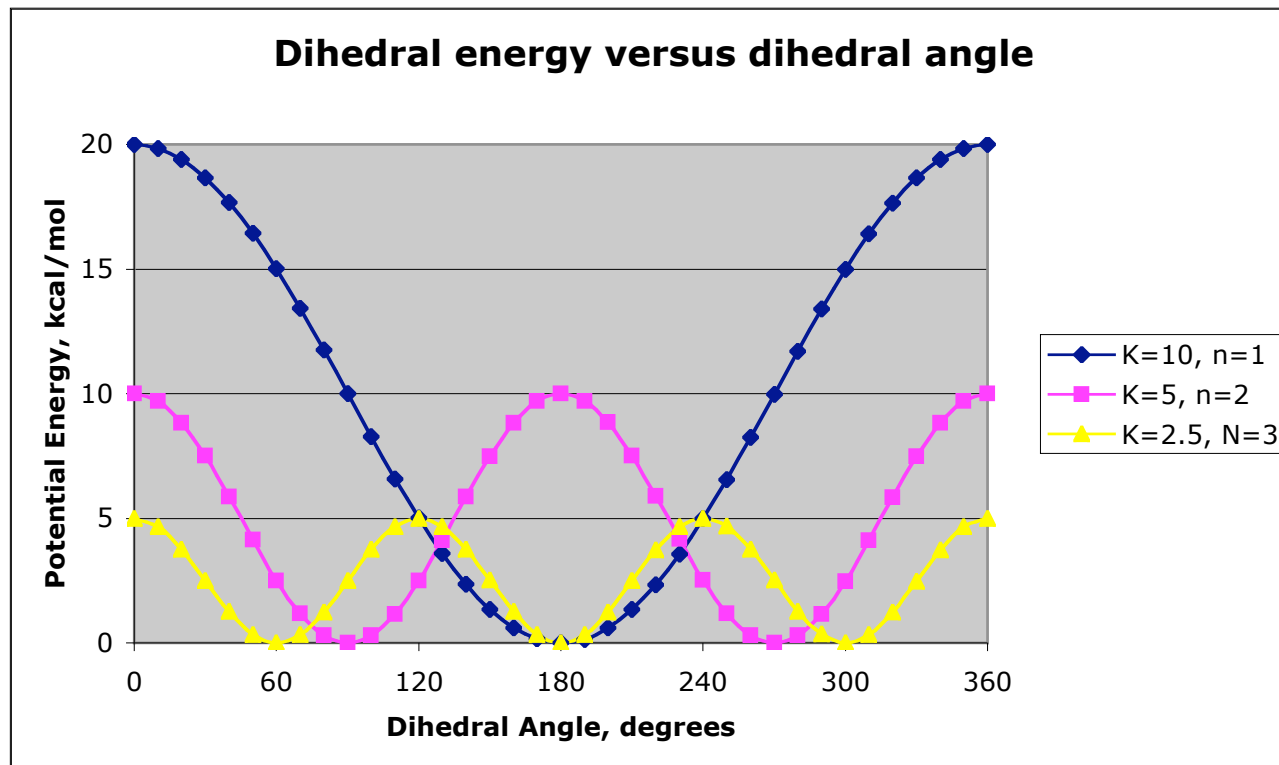
Chemical type	$K_{bond}$	$b_o$
C-C	100 kcal/mole/Å <sup>2</sup>	1.5 Å
C=C	200 kcal/mole/Å <sup>2</sup>	1.3 Å
C≡C	400 kcal/mole/Å <sup>2</sup>	1.2 Å



*Bond angles* and *improper* terms have similar quadratic forms, but with softer spring constants. The force constants can be obtained from vibrational analysis of the molecule (experimentally or theoretically).

# Dihedral Potential

$$V_{dihedral} = K_{\phi} (1 + \cos(n\phi - \delta))$$



$$\delta = 0^\circ$$

# Nonbonded Parameters

$$\sum_{nonbonded} \frac{q_i q_j}{4\pi D r_{ij}} + \epsilon_{ij} \left[ \left( \frac{R_{min,ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{min,ij}}{r_{ij}} \right)^6 \right]$$

$q_i$ : partial atomic charge

$D$ : dielectric constant

$\epsilon$ : Lennard-Jones (LJ, vdW) well-depth

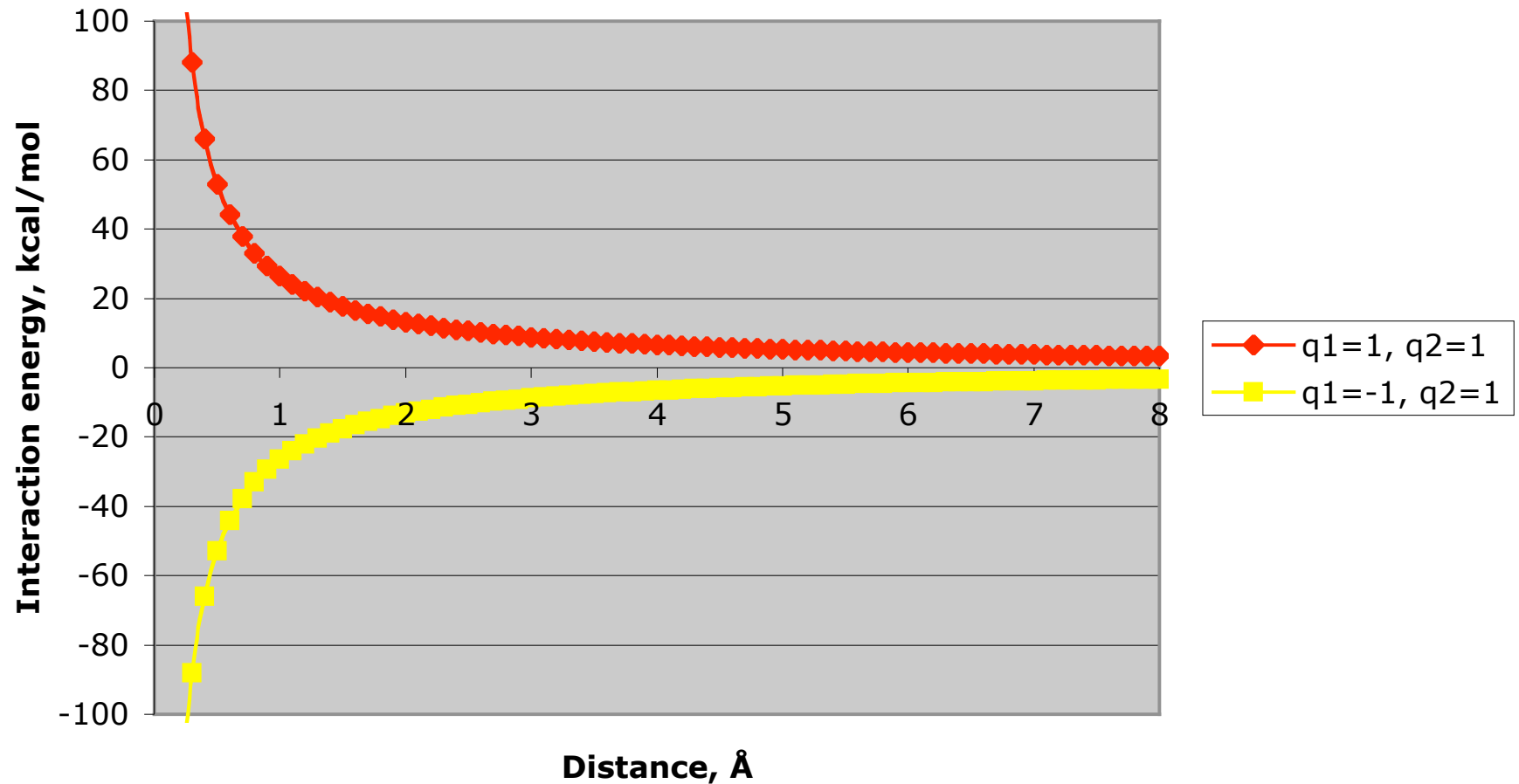
$R_{min}$ : LJ radius ( $R_{min}/2$  in CHARMM)

Combining rules (CHARMM, Amber)

$$R_{min\ i,j} = R_{min\ i} + R_{min\ j}$$

$$\epsilon_{i,j} = \text{SQRT}(\epsilon_i * \epsilon_j)$$

## Electrostatic Energy versus Distance



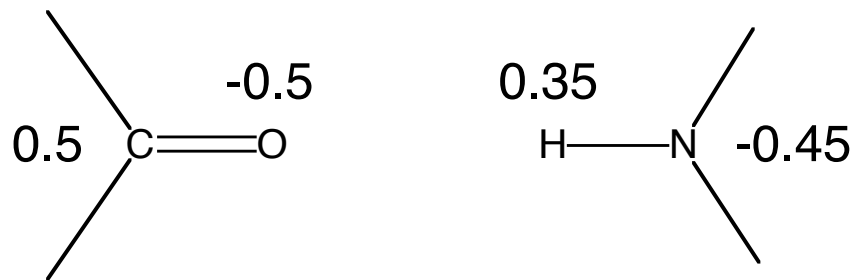
Note that the effect is long range.

# Charge Fitting Strategy

CHARMM- Mulliken\*

AMBER(ESP/RESP)

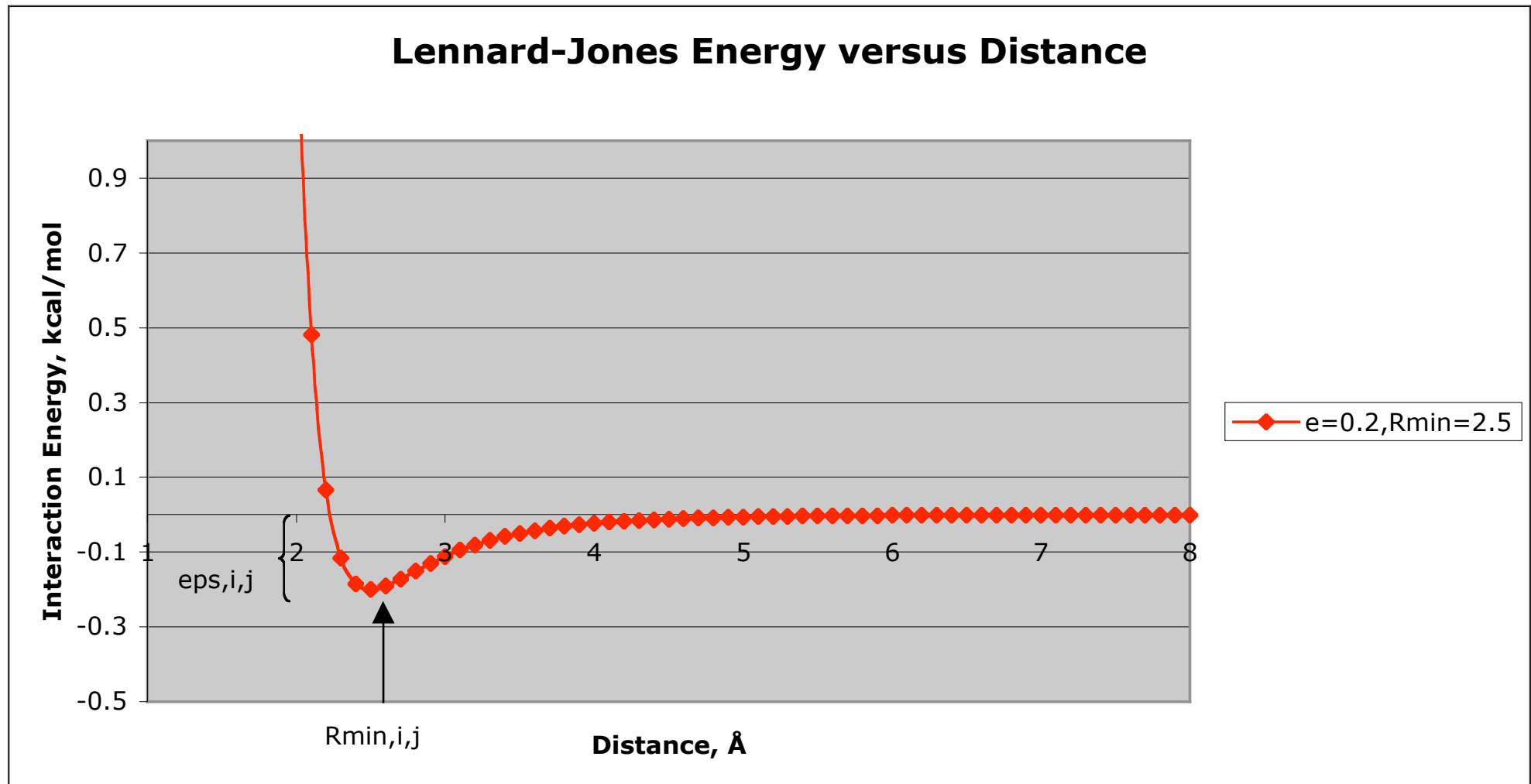
Partial atomic charges



\*Modifications based on interactions with TIP3 water



# van der Waals interaction



$$\epsilon_{ij} \left[ \left( \frac{R_{min,ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{min,ij}}{r_{ij}} \right)^6 \right]$$

Short range

# CHARMM Potential Function

$$\begin{aligned}
 U(\vec{R}) = & \underbrace{\sum_{\text{bonds}} k_i^{\text{bond}} (r_i - r_0)^2}_{U_{\text{bond}}} + \underbrace{\sum_{\text{angles}} k_i^{\text{angle}} (\theta_i - \theta_0)^2}_{U_{\text{angle}}} + \\
 & \underbrace{\sum_{\text{dihedrals}} k_i^{\text{dihe}} [1 + \cos(n_i \phi_i + \delta_i)]}_{U_{\text{dihedral}}} + \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right]}_{U_{\text{nonbond}}} + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}
 \end{aligned}$$

The diagram illustrates the CHARMM Potential Function, showing the contribution of different terms and their associated data sources:

- PDB file** (white box) provides **geometry** (red box), which defines the bond lengths ( $r_i$ ), angles ( $\theta_i$ ), and dihedral angles ( $\phi_i$ ).
- Topology** (white text) and **PSF file** (white box) provide the **parameters** (blue box) for the potential function, including force constants ( $k_i$ ), equilibrium values ( $r_0, \theta_0, \delta_i$ ), and nonbonded parameters ( $\epsilon_{ij}, \sigma_{ij}, q_i, q_j$ ).
- The **Parameter file** (white box) is the source of the **parameters** (blue box).
- The **parameters** (blue box) are used to calculate the nonbonded energy ( $U_{\text{nonbond}}$ ).

# File Format/Structure

- The structure of a pdb file
- The structure of a psf file
- The topology file
- The parameter file
- Connection to potential energy terms



# VMD Atom Selection Commands

The diagram illustrates the fields used in VMD atom selection commands. Arrows point from labels to specific columns in a table of atom data:

- index** points to the first column.
- name** points to the second column.
- resname** points to the third column.
- chain** points to the fourth column.
- resid** points to the fifth column.
- x** points to the sixth column.
- y** points to the seventh column.
- z** points to the eighth column.
- segname** points to the ninth column.

ATOM	22	N	ALA	B	3	-4.073	-7.587	-2.708	1.00	0.00	BH
ATOM	23	HN	ALA	B	3	-3.813	-6.675	-3.125	1.00	0.00	BH

`(name CA CB) and (resid 1 to 4) and (segname BH)`

`protein and resname LYS ARG GLU ASP`

`water and within 5 of (protein and resid 62 and name CA)`

`water and within 3 of (protein and name O and z < 10)`

# Checking file structures

- PDB file
- Topology file
- PSF file
- Parameter file

# Parameter Optimization Strategies

Check if it has been parameterized by somebody else

Literature

Google

## Minimal optimization

By analogy (i.e. direct transfer of known parameters)

Quick, starting point - dihedrals??

## Maximal optimization

Time-consuming

Requires appropriate experimental and target data

## Choice based on goal of the calculations

Minimal

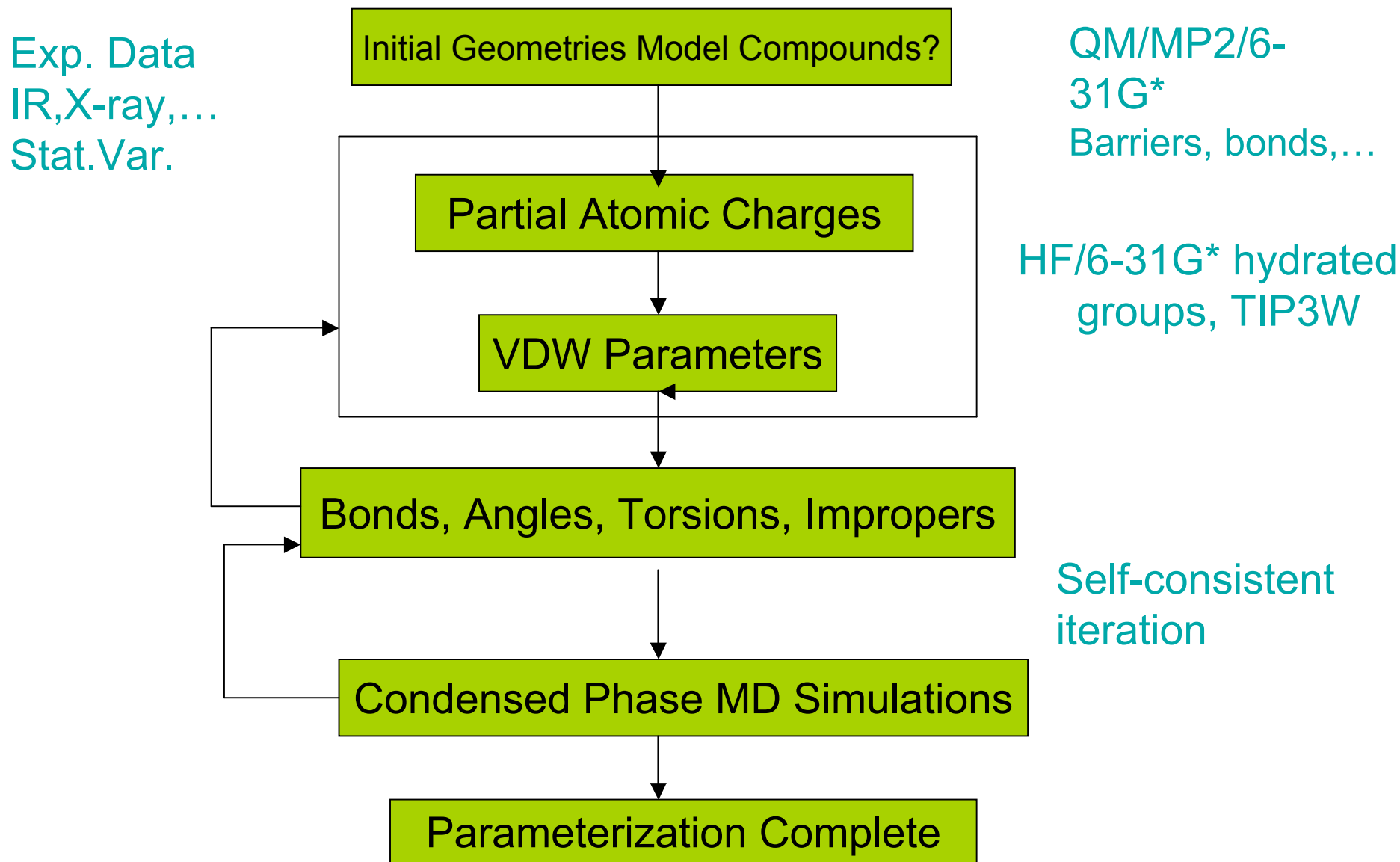
database screening

NMR/X-ray structure determination

Maximal

free energy calculations, mechanistic studies,  
subtle environmental effects

# Roadmap Charmm27 Optimization\*



\*based on MacKerell, JCC v21, 86,105 (2000)



# Getting Started

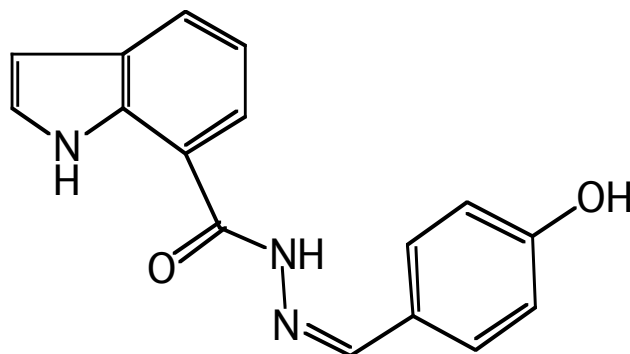
- Identify previously parameterized compounds
- Access topology information – assign atom types, connectivity, and charges – **annotate changes**

## CHARMM topology (parameter files)

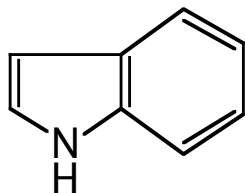
top\_all22\_model.inp (par\_all22\_prot.inp)  
top\_all22\_prot.inp (par\_all22\_prot.inp)  
top\_all22\_sugar.inp (par\_all22\_sugar.inp)  
top\_all27\_lipid.rtf (par\_all27\_lipid.prm)  
top\_all27\_na.rtf (par\_all27\_na.prm)  
top\_all27\_na\_lipid.rtf (par\_all27\_na\_lipid.prm)  
top\_all27\_prot\_lipid.rtf (par\_all27\_prot\_lipid.prm)  
top\_all27\_prot\_na.rtf (par\_all27\_prot\_na.prm)  
toph19.inp (param19.inp)

NA and lipid force fields have new LJ parameters for the alkanes, representing increased optimization of the protein alkane parameters. Tests have shown that these are compatible (e.g. in protein-nucleic acid simulations). For new systems is suggested that the new LJ parameters be used. Note that only the LJ parameters were changed; the internal parameters are identical

# Break Desired Compound into 3 Smaller Ones

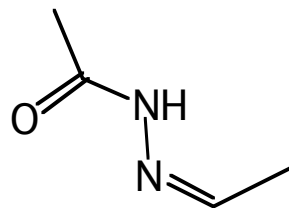


A



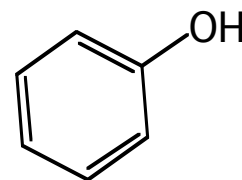
Indole

B



Hydrazine

C



Phenol

When creating a covalent link between model compounds move the charge on the deleted H into the carbon to maintain integer charge (i.e. methyl ( $q_C=-0.27$ ,  $q_H=0.09$ ) to methylene ( $q_C=-0.18$ ,  $q_H=0.09$ ))

## From top\_all22\_model.inp

```
RESI PHEN          0.00  ! phenol, adm jr.
GROUP
ATOM CG   CA      -0.115  !
ATOM HG   HP       0.115  !           HD1  HE1
GROUP                    !           |    |
ATOM CD1  CA      -0.115  !           CD1--CE1
ATOM HD1  HP       0.115  !           //    \\
GROUP                    !       HG--CG           CZ--OH
ATOM CD2  CA      -0.115  !           \           /           \
ATOM HD2  HP       0.115  !           CD2==CE2           HH
GROUP                    !           |    |
ATOM CE1  CA      -0.115  !           HD2  HE2
ATOM HE1  HP       0.115
GROUP
ATOM CE2  CA      -0.115
ATOM HE2  HP       0.115
GROUP
ATOM CZ   CA       0.110
ATOM OH   OH1     -0.540
ATOM HH   H       0.430
BOND CD2 CG CE1 CD1 CZ CE2 CG HG CD1 HD1
BOND CD2 HD2 CE1 HE1 CE2 HE2 CZ OH OH HH
DOUBLE CD1 CG CE2 CD2  CZ CE1
```

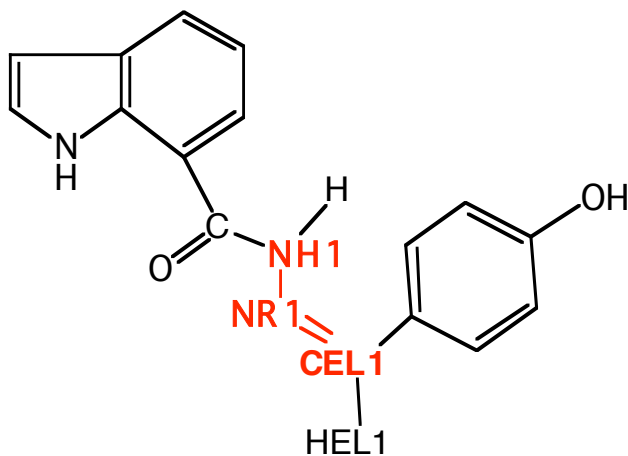
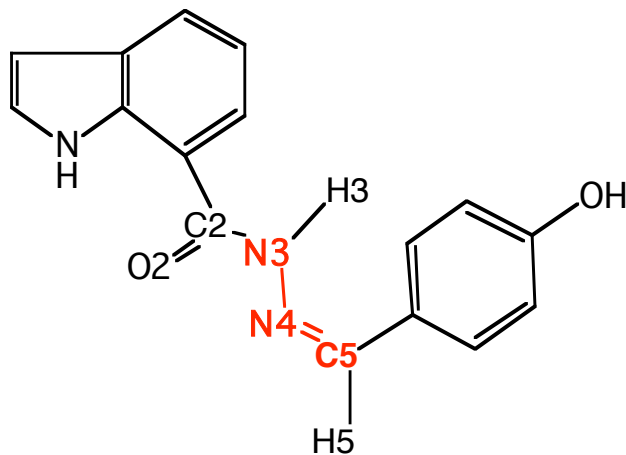
Top\_all22\_model.inp contains all protein model compounds. Lipid, nucleic acid and carbohydrate model compounds are in the full topology files.

HG will ultimately be deleted. Therefore, move HG (hydrogen) charge into CG, such that the CG charge becomes 0.00 in the final compound.

Use remaining charges/atom types without any changes.

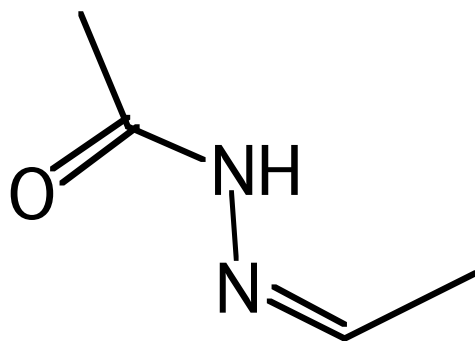
Do the same with indole

# Comparison of atom names (upper) and atom types (lower)



# Creation of topology for central model compound

```
RESI Mod1 ! Model compound 1
Group
ATOM C1 CT3 -0.27
ATOM H11 HA3 0.09
ATOM H12 HA3 0.09
ATOM H13 HA3 0.09
GROUP
ATOM C2 C 0.51
ATOM O2 O -0.51
GROUP
ATOM N3 NH1 -0.47
ATOM H3 H 0.31
ATOM N4 NR1 0.16 !new atom
ATOM C5 CEL1 -0.15
ATOM H51 HEL1 0.15
ATOM C6 CT3 -0.27
ATOM H61 HA 0.09
ATOM H62 HA 0.09
ATOM H63 HA 0.09
BOND C1 H11 C1 H12 C1 H13 C1 C2 C2 O2 C2 N3 N3
H3
BOND N3 N4 C5 H51 C5 C6 C6 H61 C6 H62 C6 H63
DOUBLE N4 C5 (DOUBLE only required for MMFF)
```



Start with alanine dipeptide.  
Note use of new aliphatic LJ parameters and, importantly, atom types.

NR1 from histidine unprotonated ring nitrogen. Charge (very bad) initially set to yield unit charge for the group.

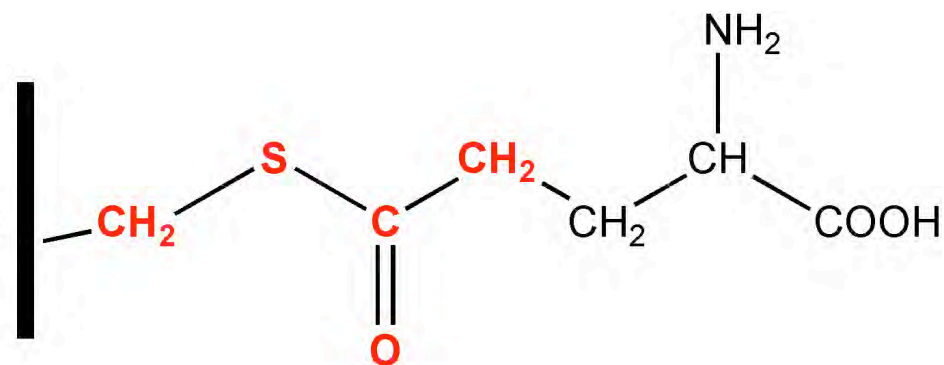
Note use of large group to allow flexibility in charge optimization.

```

RESI CYG 0.00
GROUP
ATOM N NH1 -0.47 ! |
ATOM HN H 0.31 ! HN-N
ATOM CA CT1 0.07 ! | HB1
ATOM HA HB 0.09 ! | |
GROUP ! HA-CA--CB--SG
ATOM CB CT2 -0.11 ! | | |
ATOM HB1 HA 0.09 ! | HB2 |
ATOM HB2 HA 0.09 ! O=C |
ATOM SG S -0.07 ! |
!ATOM HG1 HS 0.16 !
GROUP !
ATOM CDG CC 0.55 !
ATOM OE1 O -0.55 !
GROUP ! HN2G
ATOM CGG CT2 -0.18 ! |
ATOM HG1G HA 0.09 ! HN1G-NG HB1G HG1G\
ATOM HG2G HA 0.09 ! | | |
GROUP ! HAG-CAG--CBG--CGG--CDG=OE1
ATOM CBG CT2 -0.18 ! | | |
ATOM HB1G HA 0.09 ! | HB2G HG2G
ATOM HB2G HA 0.09 ! O1G=CG
GROUP ! |
ATOM CG CD 0.75 ! O2G-HO2G
ATOM O1G OB -0.55
ATOM O2G OH1 -0.61
ATOM HO2G H 0.44
ATOM CAG CT1 -0.12
ATOM HAG HB 0.09
ATOM NG NH3 -0.62
ATOM HN1G HC 0.31
ATOM HN2G HC 0.31
GROUP
ATOM C C 0.51
ATOM O O -0.51

```

Protein-  
backbone



HG1 deleted from CYS and the charge was moved to SG (-0.23 +0.16=0.07) so that the SG charge becomes 0.07 in final compound and the group remains neutral

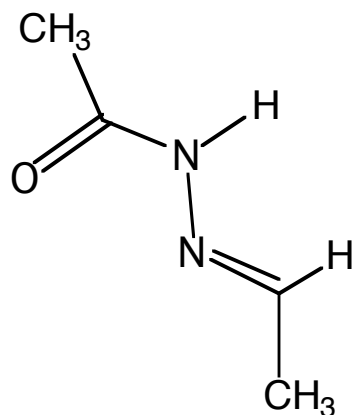
Changes annotated!

# Partial Atomic Charge Determination

## Method Dependent Choices

1. RESP: HF/6-31G overestimates dipole moments (AMBER)
2. Interaction based optimization (CHARMM)

For a particular force field do NOT change the QM level of theory. This is necessary to maintain consistency with the remainder of the force field.



Starting charges??

Mulliken population analysis

Analogy comparison

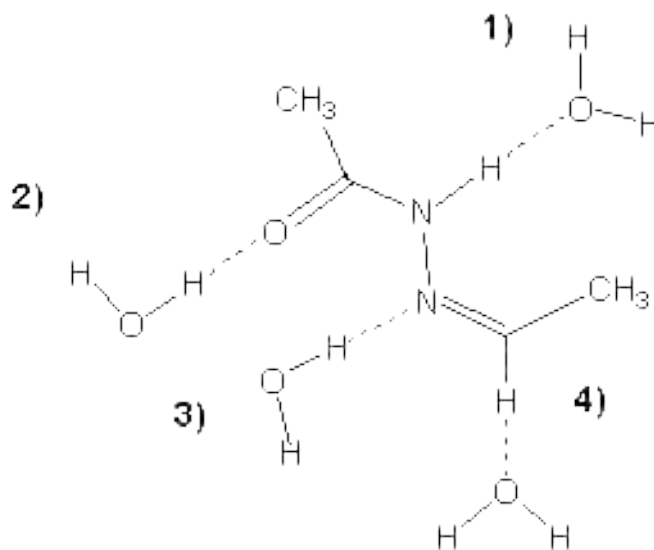
peptide bond

methyl

imidazole (N-N=C)?

Final charges (methyl, vary  $q_C$  to maintain integer charge,  $q_H = 0.09$ )

interactions with water (HF/6-31G\*, monohydrates!)

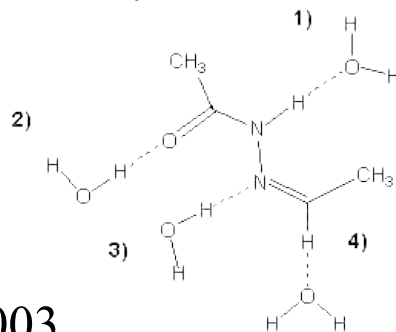




## Model compound 1-water interaction energies/geometries

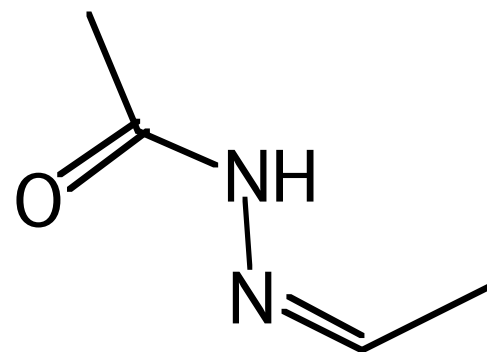
	Interaction Energies (kcal/mole)			Interaction Distances (Å)		
	<i>Ab initio</i>	Analogy	Optimized	<i>Ab initio</i>	Analogy	Optimized
1) O2...HOH	-6.12	-6.56	-6.04	2.06	1.76	1.78
2) N3-H..OHH	-7.27	-7.19	-7.19	2.12	1.91	1.89
3) N4...HOH	-5.22	-1.16	-5.30	2.33	2.30	2.06
4) C5-H..OHH	-3.86	-3.04	-3.69	2.46	2.51	2.44
Energetic statistical analysis						
Ave. Difference		1.13	0.06			
RMS Difference		1.75	0.09			
Dipole Moments (debeye)						
	5.69	4.89	6.00			

*Ab initio* interaction energies scaled by 1.16.



## Comparison of analogy and optimized charges

Name	Type	Analogy	Optimized
C1	CT3	-0.27	-0.27
H11	HA3	0.09	0.09
H12	HA3	0.09	0.09
H13	HA3	0.09	0.09
C2	C	0.51	0.58
O2	O	-0.51	-0.50
N3	NH1	-0.47	-0.32
H3	H	0.31	0.33
N4	NR1	0.16	-0.31
C5	CEL1	-0.15	-0.25
H51	HEL1	0.15	0.29
C6	CT3	-0.27	-0.09
H61	HA	0.09	0.09
H62	HA	0.09	0.09
H63	HA	0.09	0.09



# Summary of Parameterization

1. **LJ (VDW) parameters** – normally direct transfer from available parameters is adequate, but should be tested by comparison to heats of vaporization, density, partial molar volumes, crystal simulations,.... (MacKerell JCC 2002).
2. **Bond, angle, dihedral, UB and improper force constants**

Vibrational spectra- Frequencies  
Conformational Energetics -  
Relative energies  
Potential energy surfaces

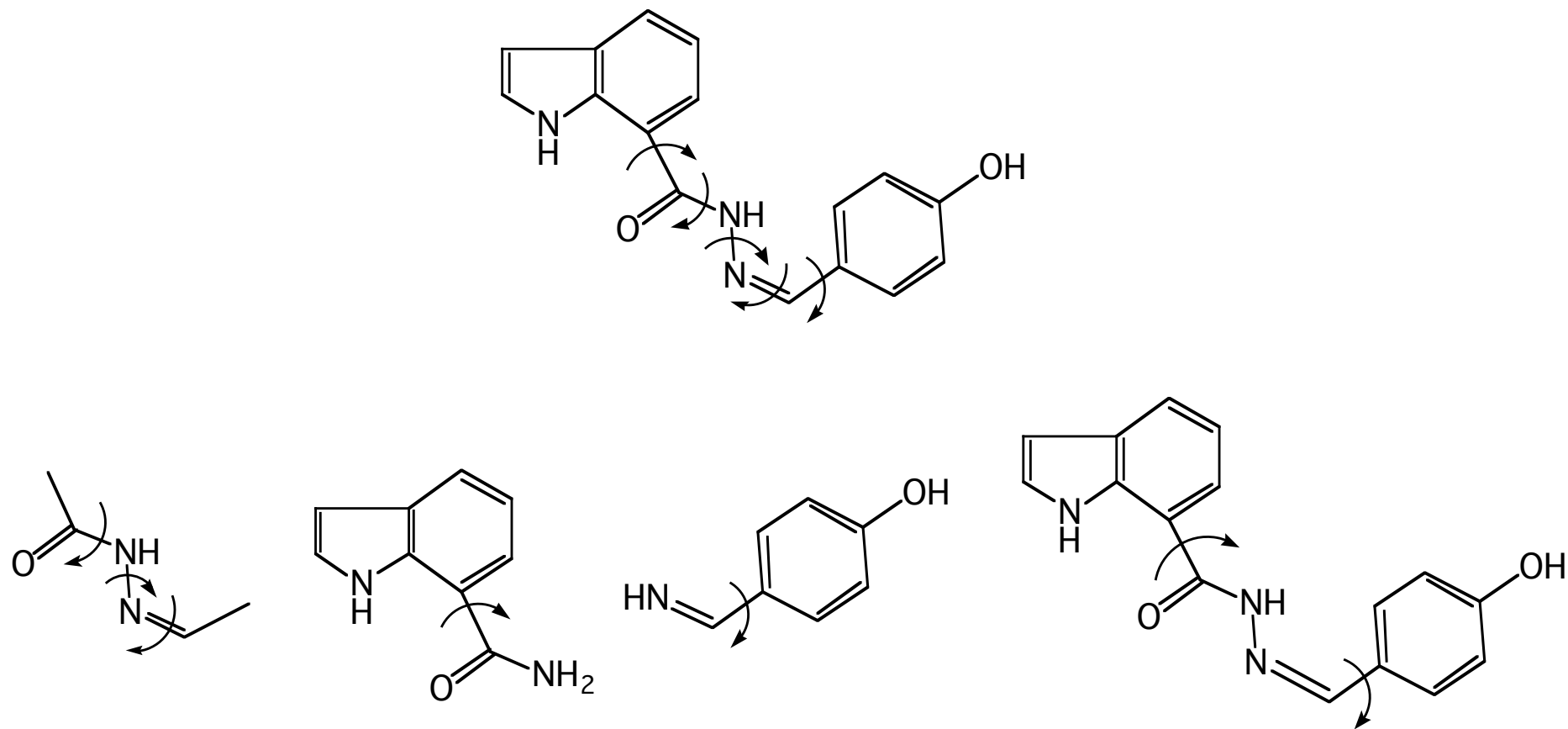
Vibrations are generally used to optimize the bond, angle, UB and improper FCs while conformational energies are used for the dihedral FCs.

## Vibrational Spectra of Model Compound 1 from MP2/6-31G\* QM calculations

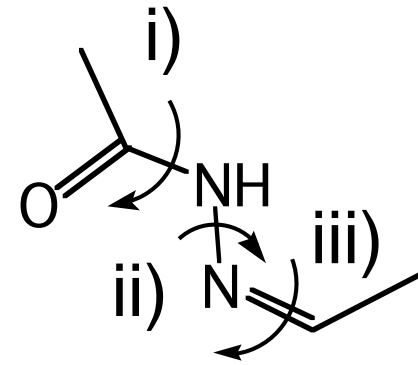
#	Freq	Assign	%	Assign	%	Assign	%	#	Freq	Assign	%	Assign	%
1	62	tC2N	64	tN3N	46			21	1446	rNH	35		
2	133	tC1H3	50	tN3N	18	tC2N	17	22	1447	rC5H	47	sC-N	18
3	148	tC1H3	46	tC6H3	25			23	1527	dCH3	77		
4	154	dC2NN	44	dN3NC	28	dN4CC	16	24	1532	dCH3	88		
5	205	tC6H3	59	tN4C	22	tN3N	21	25	1599	dCH3a'	50	dCH3a	17
6	333	tN4C	73	tC2N	22			26	1610	dCH3a	71	dCH3a'	24
7	361	dC1CN	45	dN4CC	21	dN3NC	16	27	1612	dCH3a'	30		
8	446	rC=O	32	dN4CC	20			28	1613	dCH3a	70	dCH3a'	23
9	568	wNH	77					29	1622	dCH3a'	57	dCH3a	19
10	586	dC1CN	21	dC2NN	20	rC=O	18	30	1782	sN=C	71		
11	618	wC=O	83	wNH	28	tC2N	-26	31	1901	sC=O	78		
12	649	rC=O	27	dN4CC	19			32	3250	sCH3	76	sC5-H	21
13	922	sC1-C	62					33	3258	sC5-H	78	sCH3	21
14	940	wC5H	80					34	3280	sCH3	99		
15	1031	rCH3'	33	sC5-C	31			35	3330	sCH3a	75	sCH3a'	25
16	1114	rCH3	66					36	3372	sCH3a'	100		
17	1139	rCH3'	76	wC=O	20			37	3377	sCH3a'	73	sCH3a	24
18	1157	rCH3	61	wC5H	21			38	3403	sCH3a	99		
19	1234	sC5-C	33	sN-N	32			39	3688	sN-H	100		
20	1269	sN-N	36	rCH3'	18								

Frequencies in  $\text{cm}^{-1}$ . Assignments and % are the modes and their respective percents contributing to each vibration.

Dihedral optimization based on QM potential energy surfaces (HF/6-31G\* or MP2/6-31G\*).



Potential energy surfaces on compounds with multiple rotatable bonds

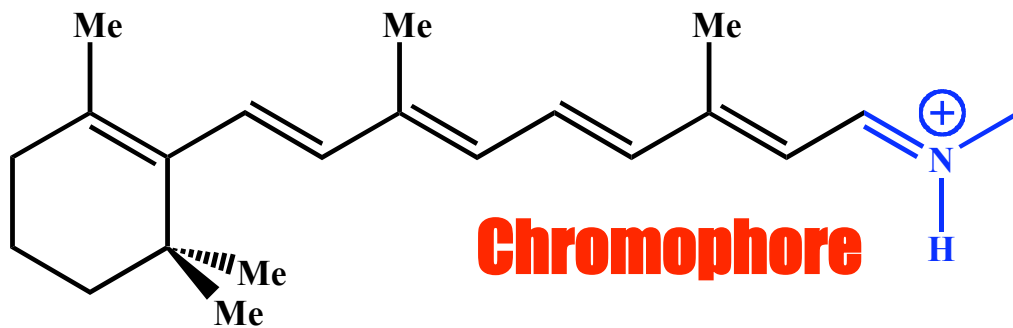
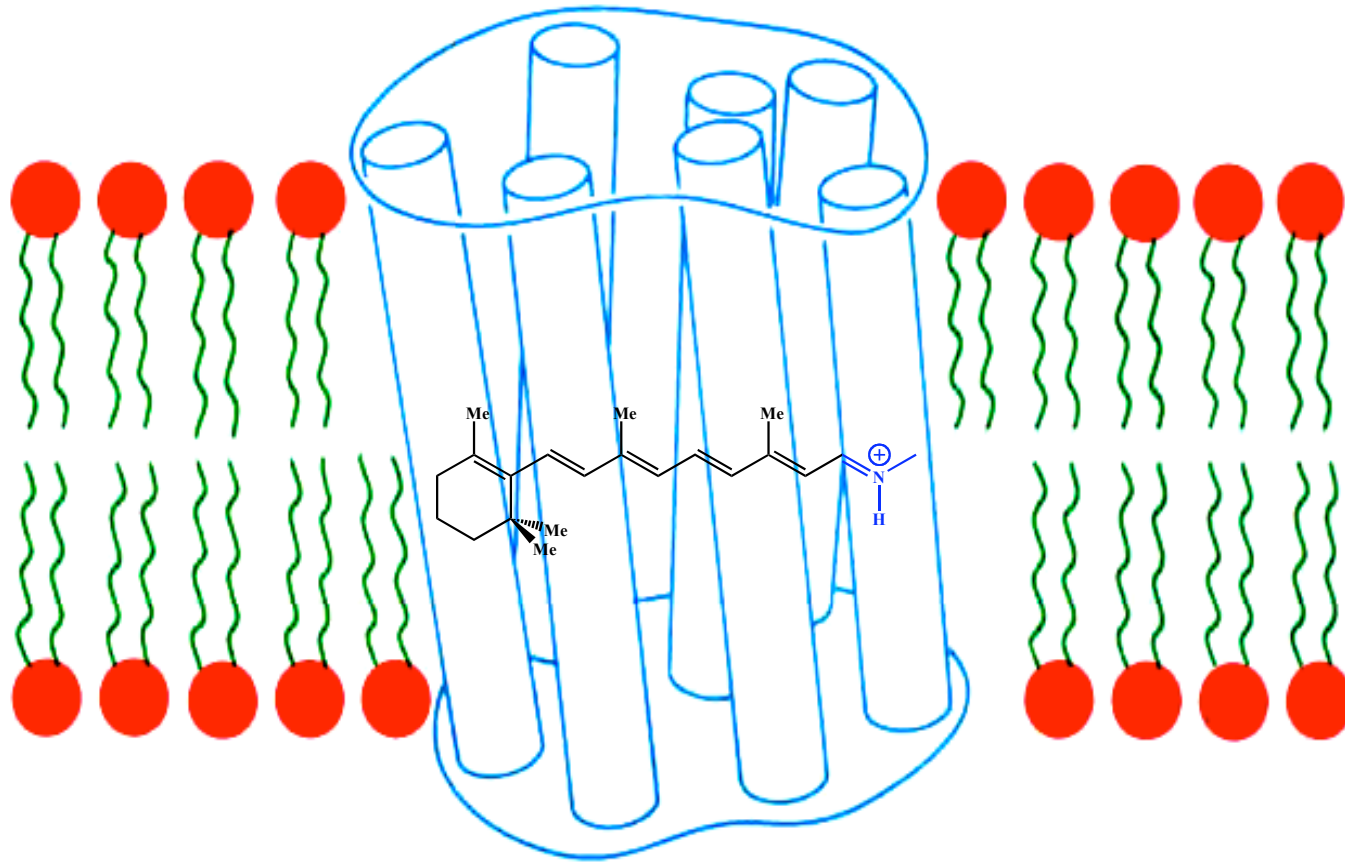


- 1) Full geometry optimization
- 2) Constrain n-1 dihedrals to minimum energy values or trans conformation
- 3) Sample selected dihedral surface
- 4) Repeat for all rotatable bonds dihedrals
- 5) Repeat 2-5 using alternate minima if deemed appropriate

QM development of force field  
parameters for retinal

Used for rhodopsin and  
bacteriorhodopsin simulations

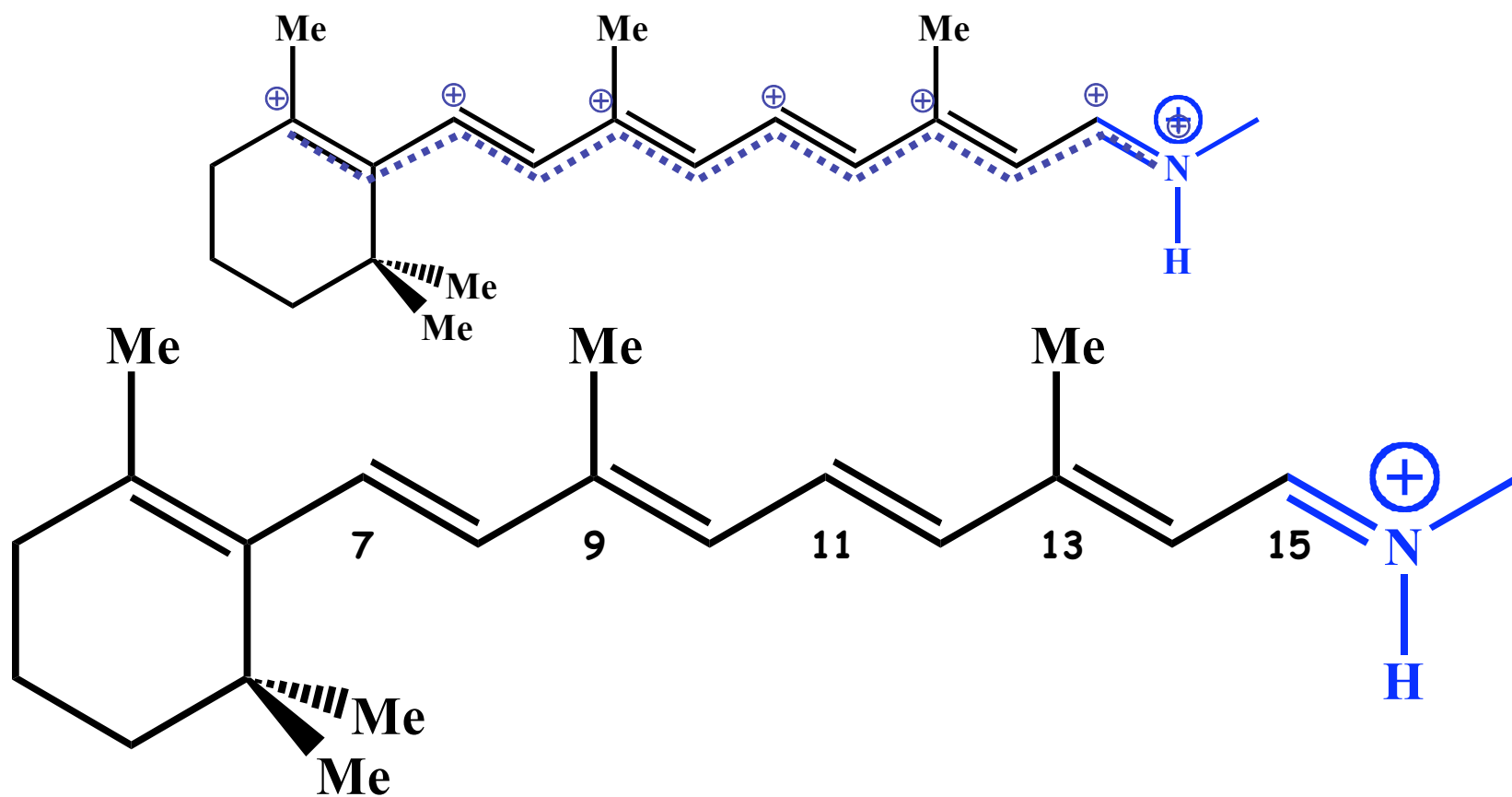
# Retinal Proteins -- Rhodopsins



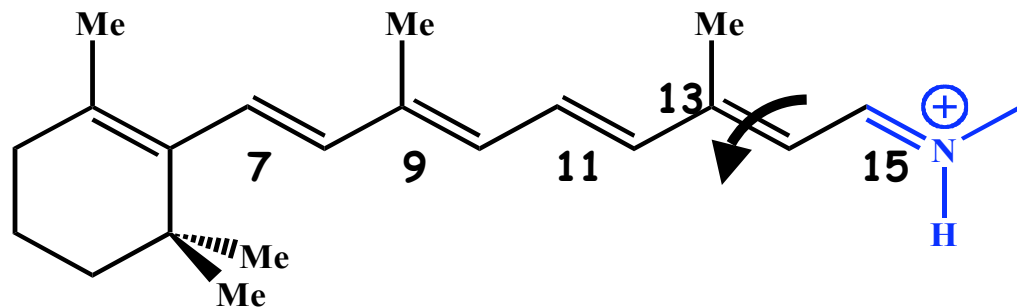
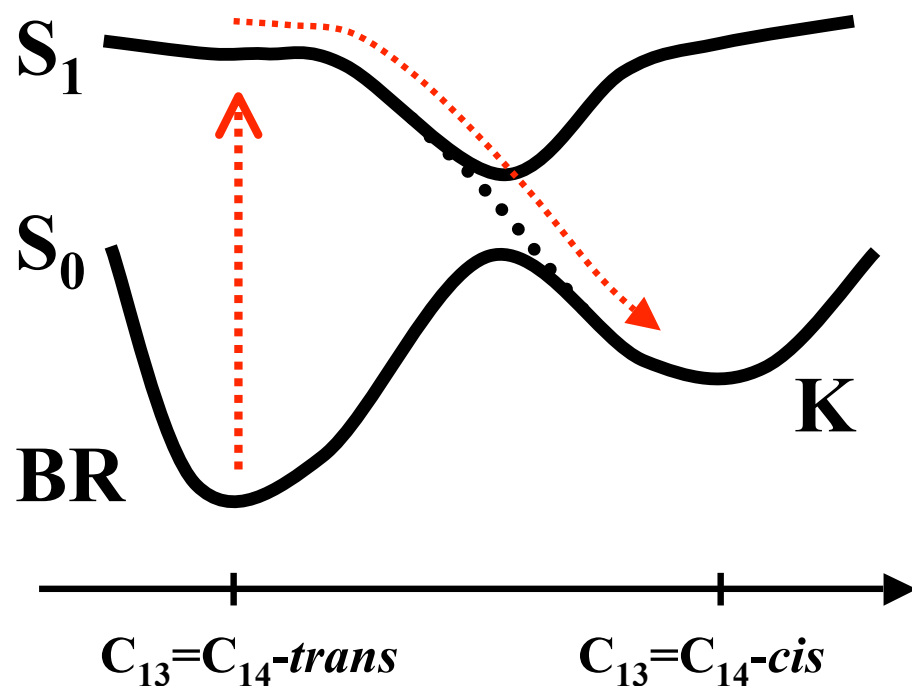
- Covalently linked to a lysine
- Usually protonated **Schiff base**
- all-*trans* and 11-*cis* isomers



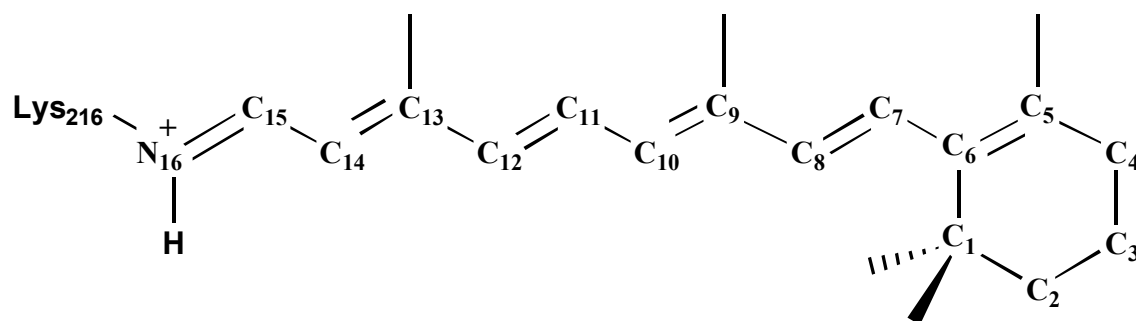
# Unconventional chemistry



# Coupling of electronic excitation and conformational change in bR



# Isomerization Barriers in retinal



DFT/6-31G\*\*

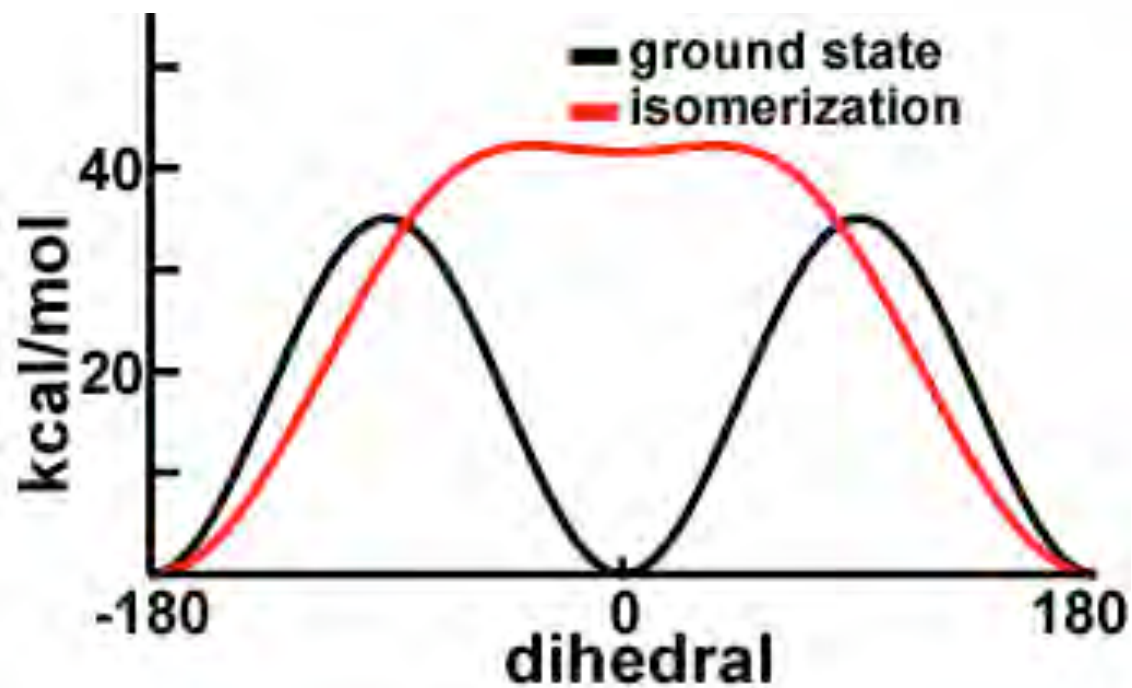
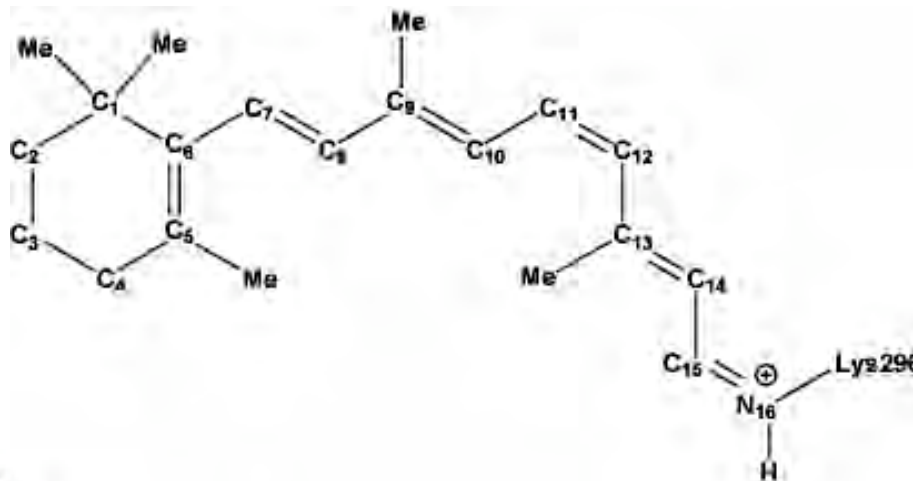
**TABLE 2** The parameter set B used for the torsional potentials of the main polyene chain of the retinal Schiff base

$\phi_i$	$k_i$ (kcal/mol)*	$n_i$	$\delta_i$ (deg)
$C_5=C_6-C_7=C_8$	11.24	2.0	180.00
$C_6-C_7=C_8-C_9$	39.98	2.0	180.00
$C_7=C_8-C_9=C_{10}$	17.03	2.0	180.00
$C_8-C_9=C_{10}-C_{11}$	37.28	2.0	180.00
$C_9=C_{10}-C_{11}=C_{12}$	22.50	2.0	180.00
$C_{10}-C_{11}=C_{12}-C_{13}$	35.08	2.0	180.00
$C_{11}=C_{12}-C_{13}=C_{14}$	28.30	2.0	180.00
$C_{12}-C_{13}=C_{14}-C_{15}$	29.46	2.0	180.00
$C_{13}=C_{14}-C_{15}=N_{16}$	30.43	2.0	180.00
$C_{14}-C_{15}=N_{16}-C_{\epsilon}$	28.76	2.0	180.00

Tajkhorshid et al., 1999.

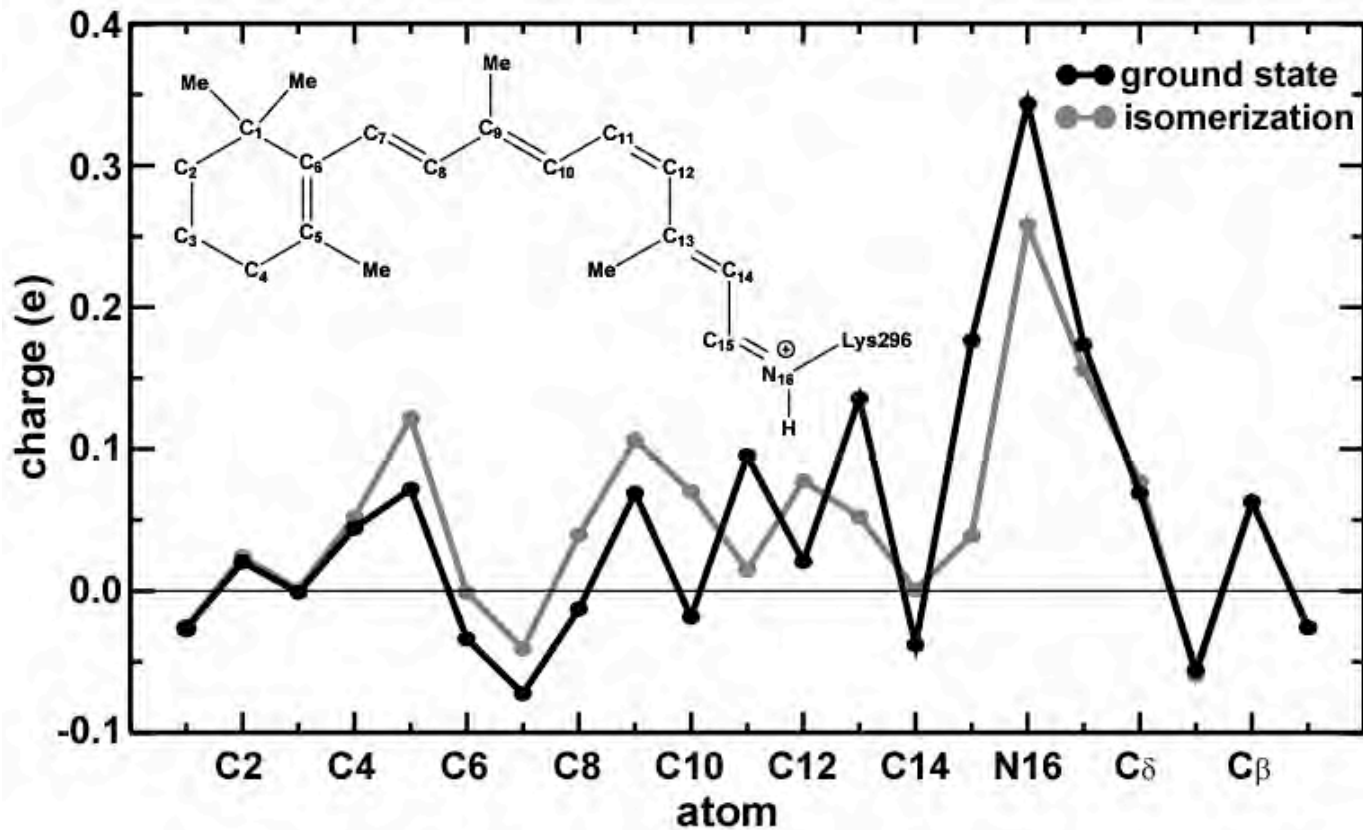
$$*E_i^{\text{dihedral}} = (1/2)k_i[1 + \cos(n_i\phi_i - \delta_i)].$$

# Inducing isomerization



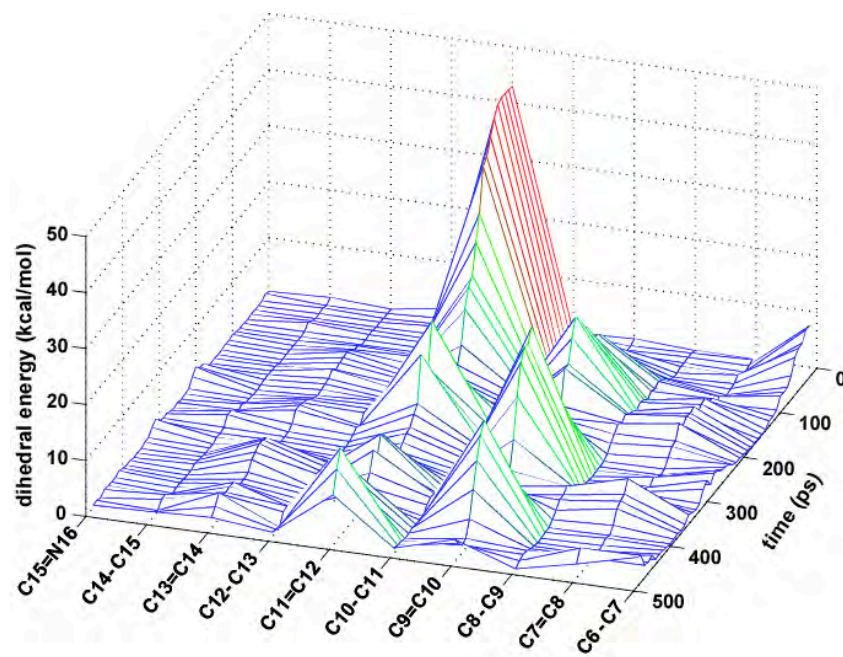
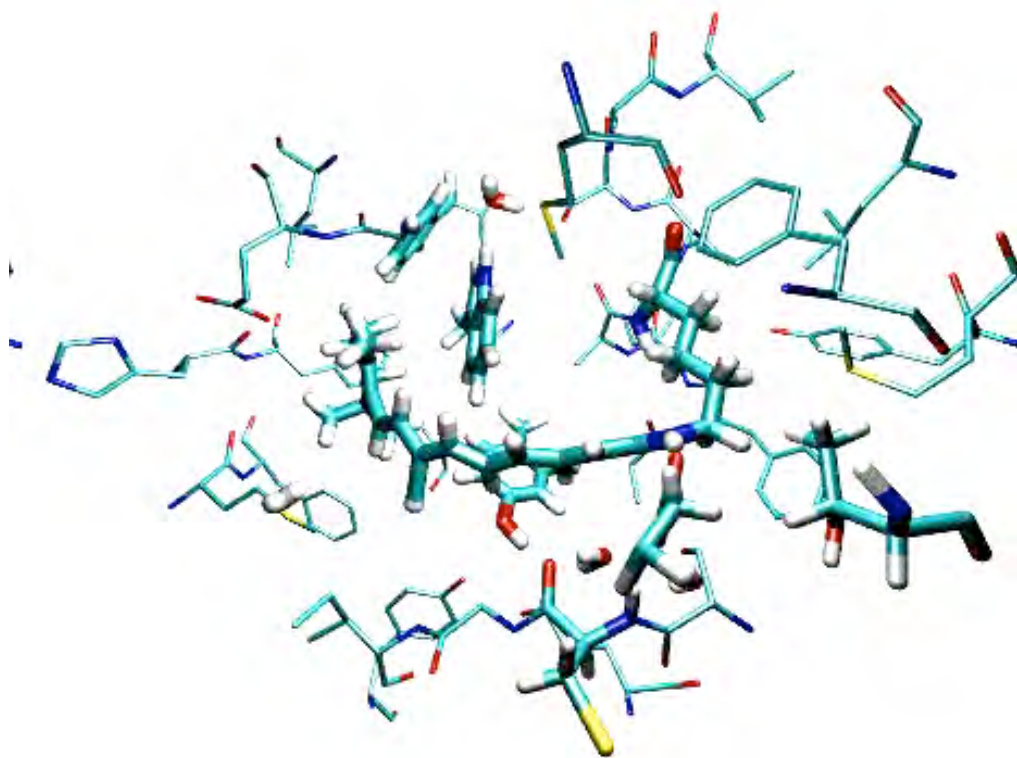
500 nm  
~50 kcal/mole

# Retinal Charge Distribution



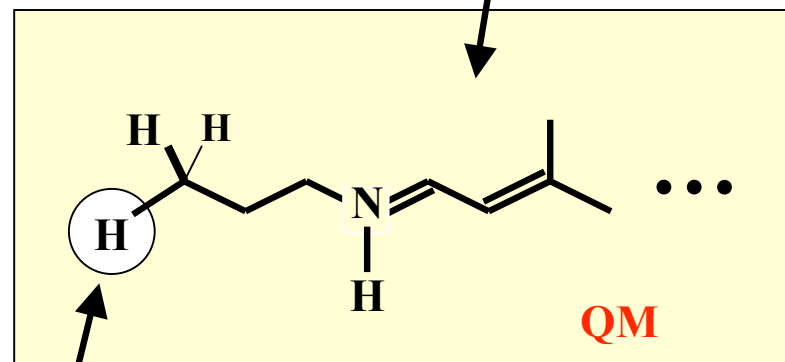
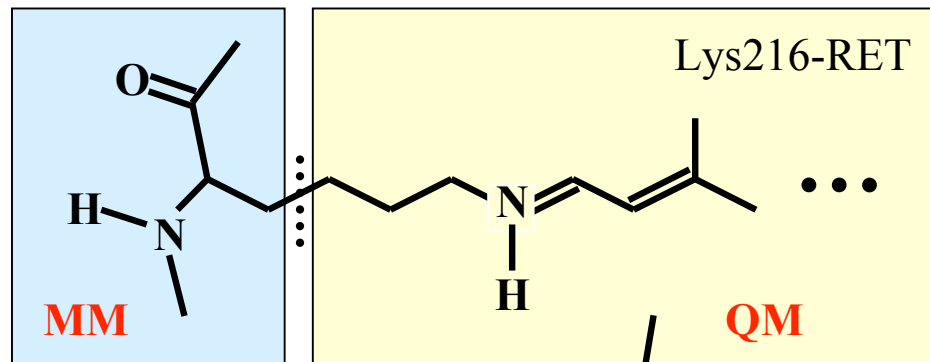
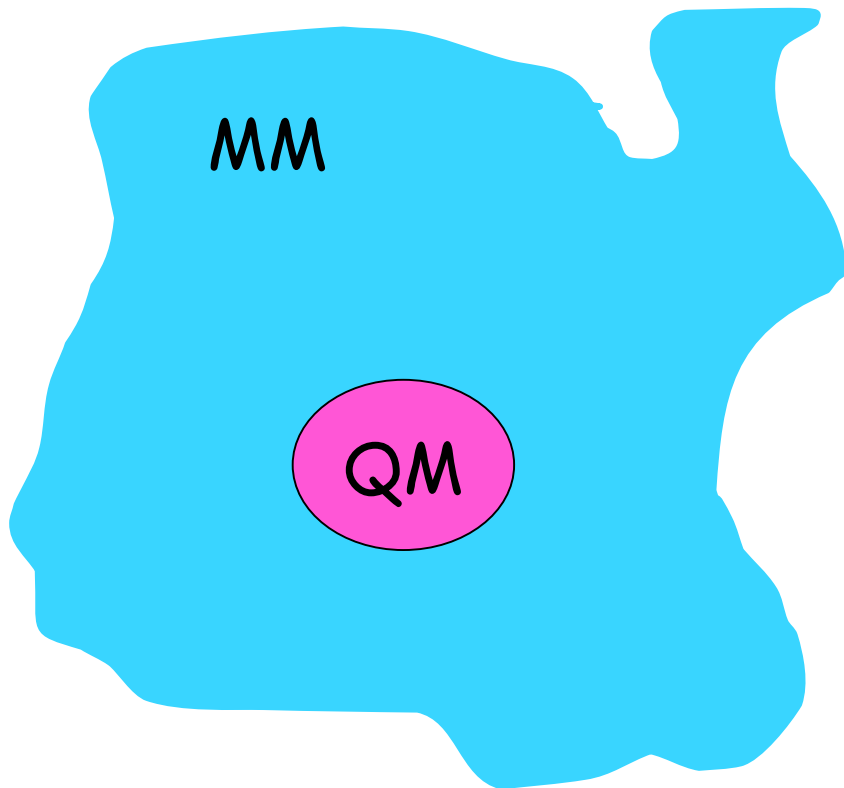
QM/MM derived partial atomic charges

# Classical Retinal Isomerization in Rhodopsin



**Twist Propagation**

# QM/MM calculations

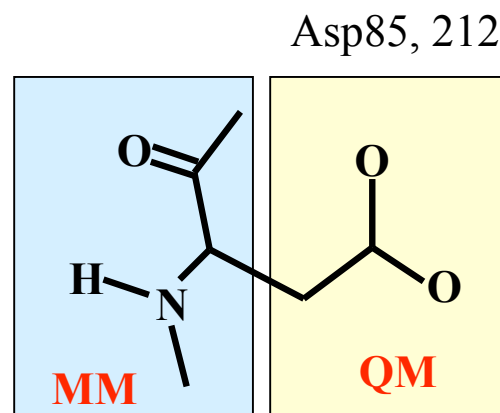


$$\hat{H} = \sum_i \frac{1}{2} p_i^2 + \sum_i \sum_A \frac{Z_A}{r_{iA}} + \sum_{i>j} \frac{1}{r_{ij}} + \sum_{A>B} \frac{Z_A Z_B}{r_{AB}}$$

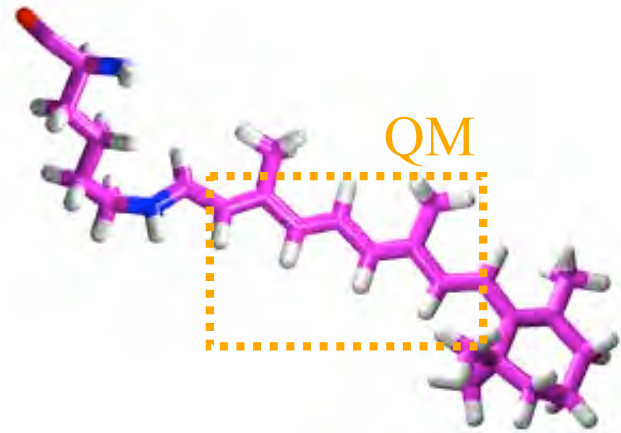
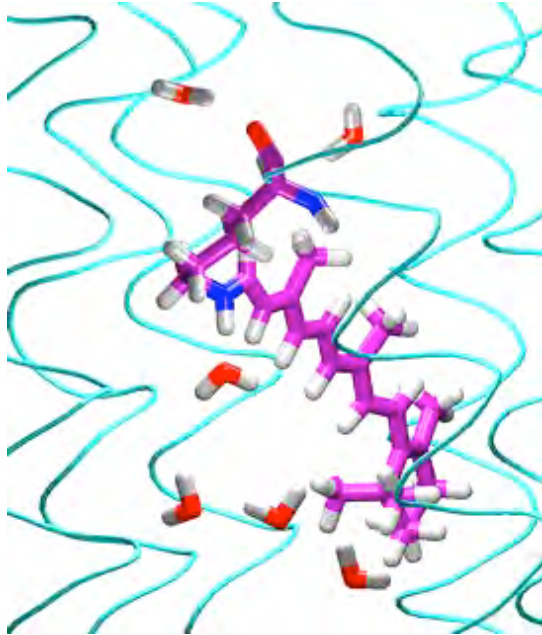
$$+ \sum_i \sum_p \frac{q_p}{r_{ip}} + \sum_A \sum_p \frac{Z_A q_p}{r_{Ap}}$$

$$+ V_{QM-MM}^{MM} + V_{MM}^{MM}$$

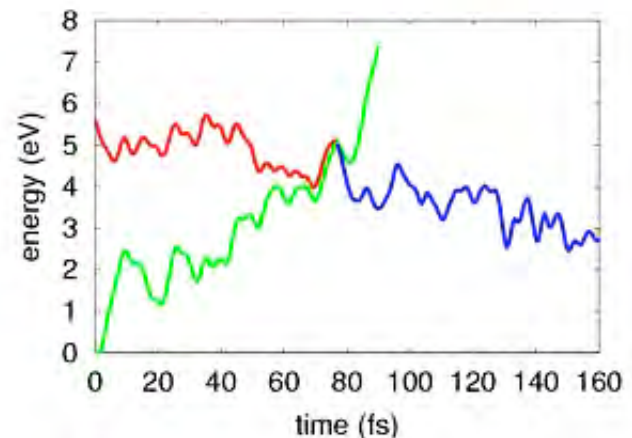
dummy atom



# Ab Initio QM/MM Excited State MD Simulation

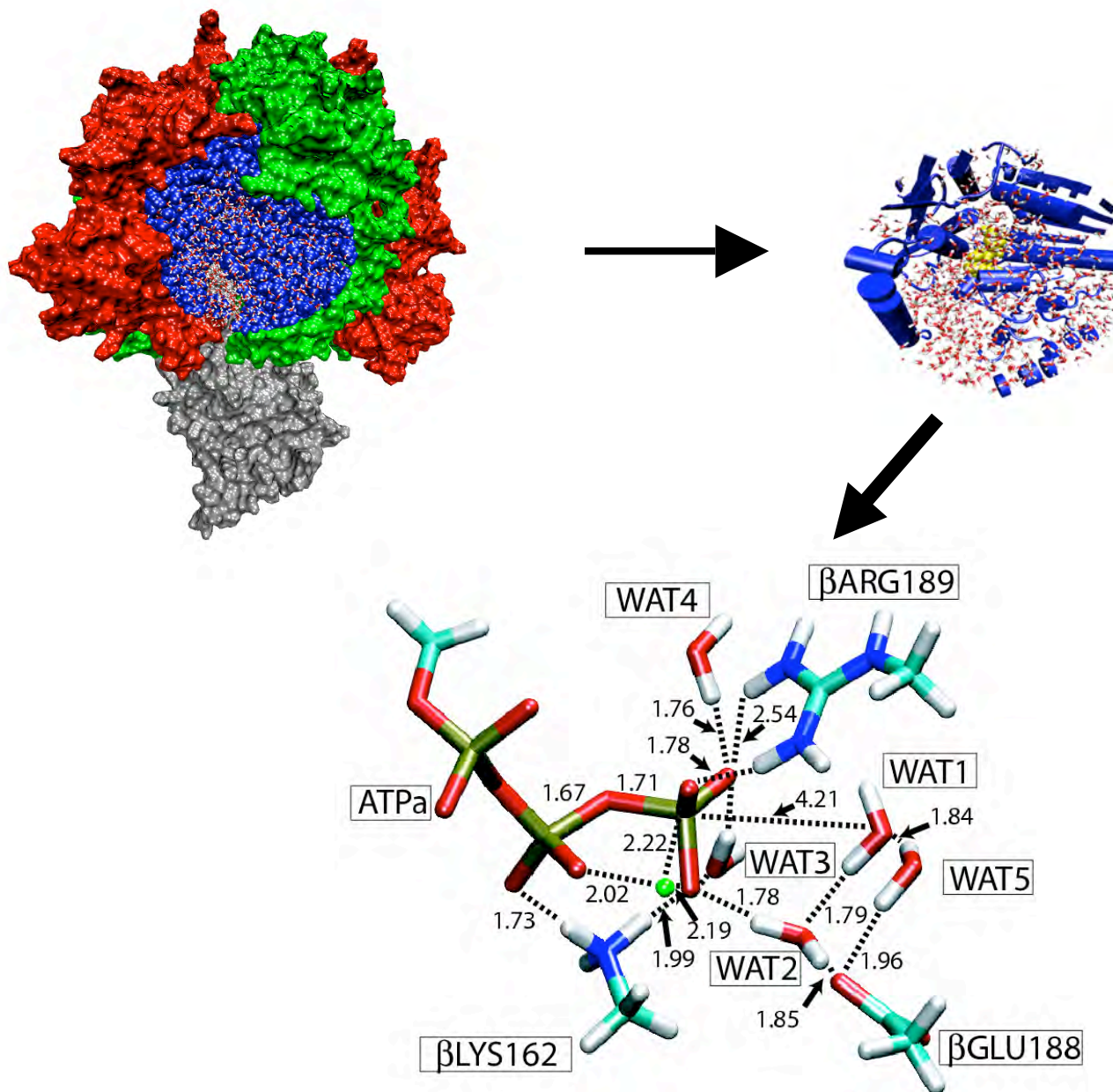


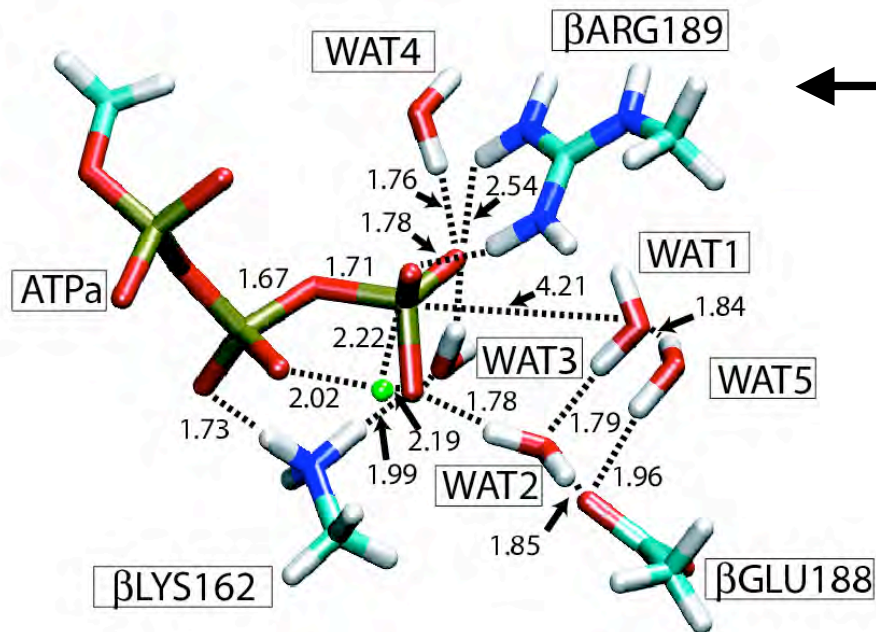
Quantum mechanical (QM)  
treatment of the chromophore,  
and force field (MM) treatment  
of the embedding protein





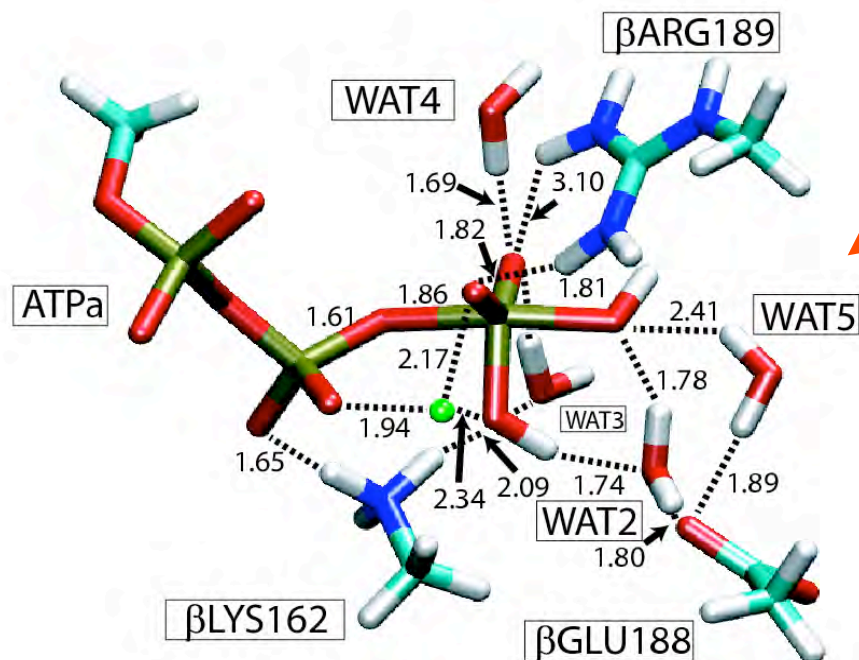
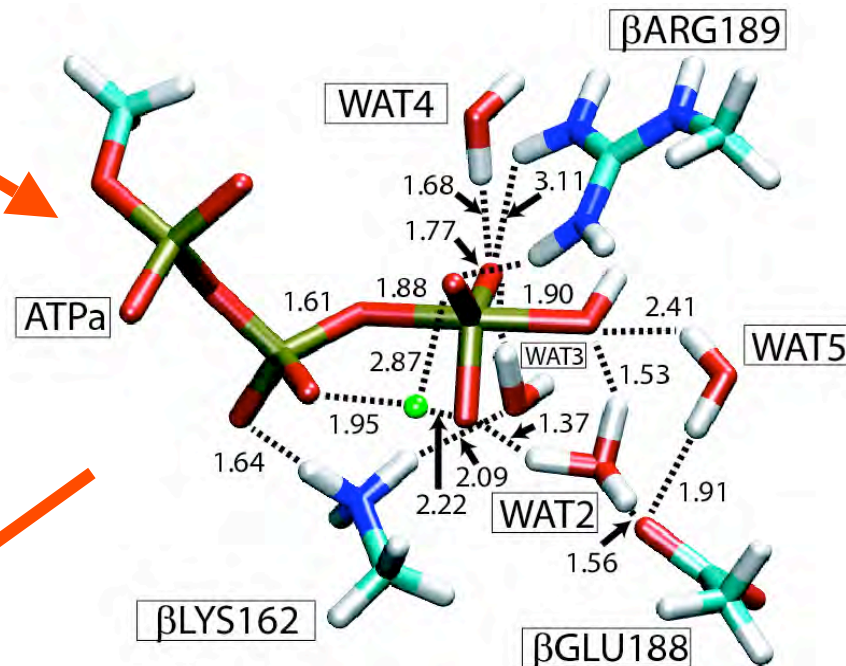
# QM/MM calculation of ATP hydrolysis



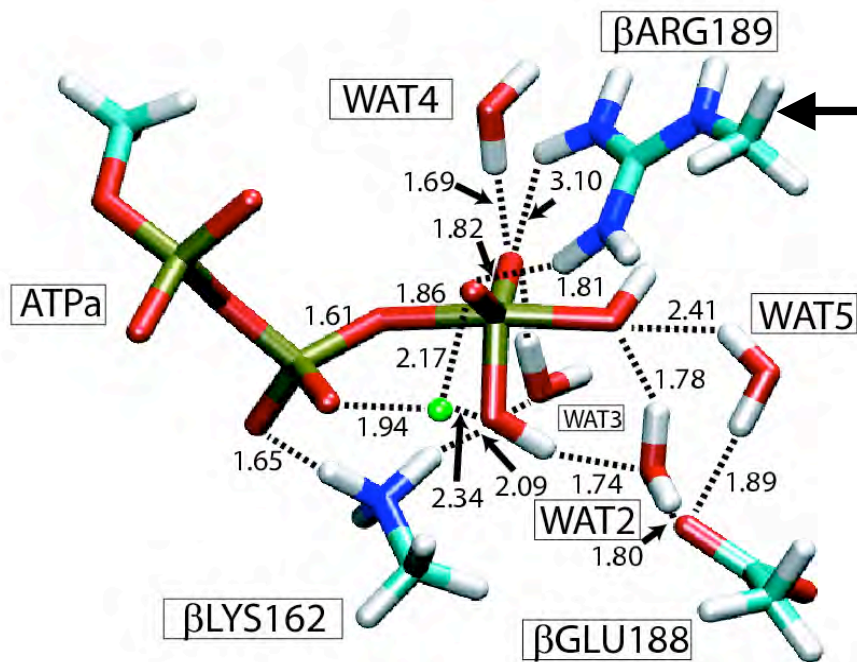


Initial configuration

Transition state

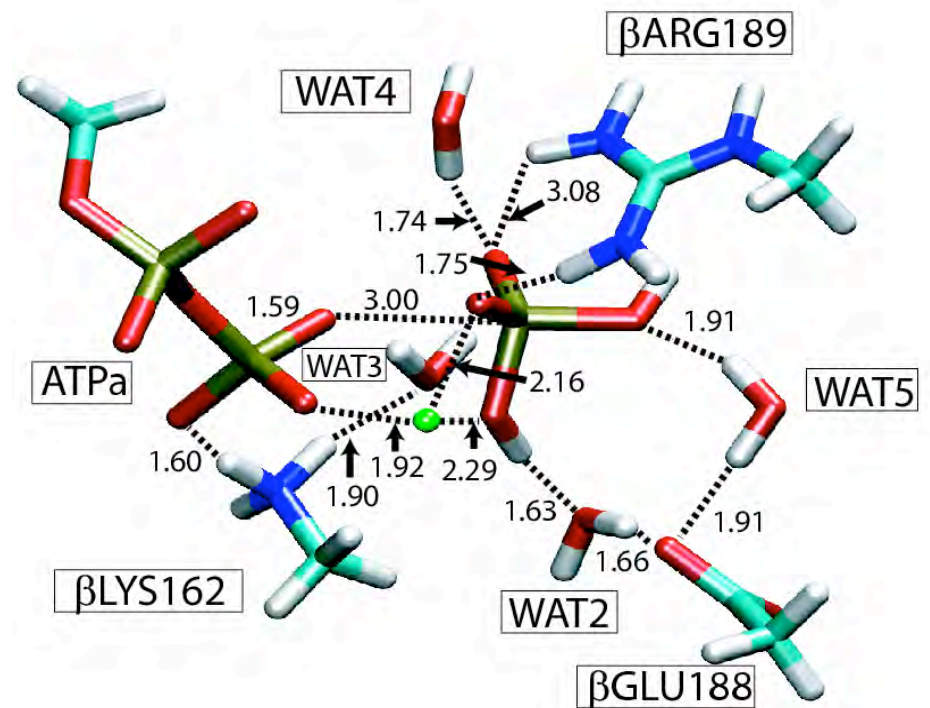


Intermediate structure

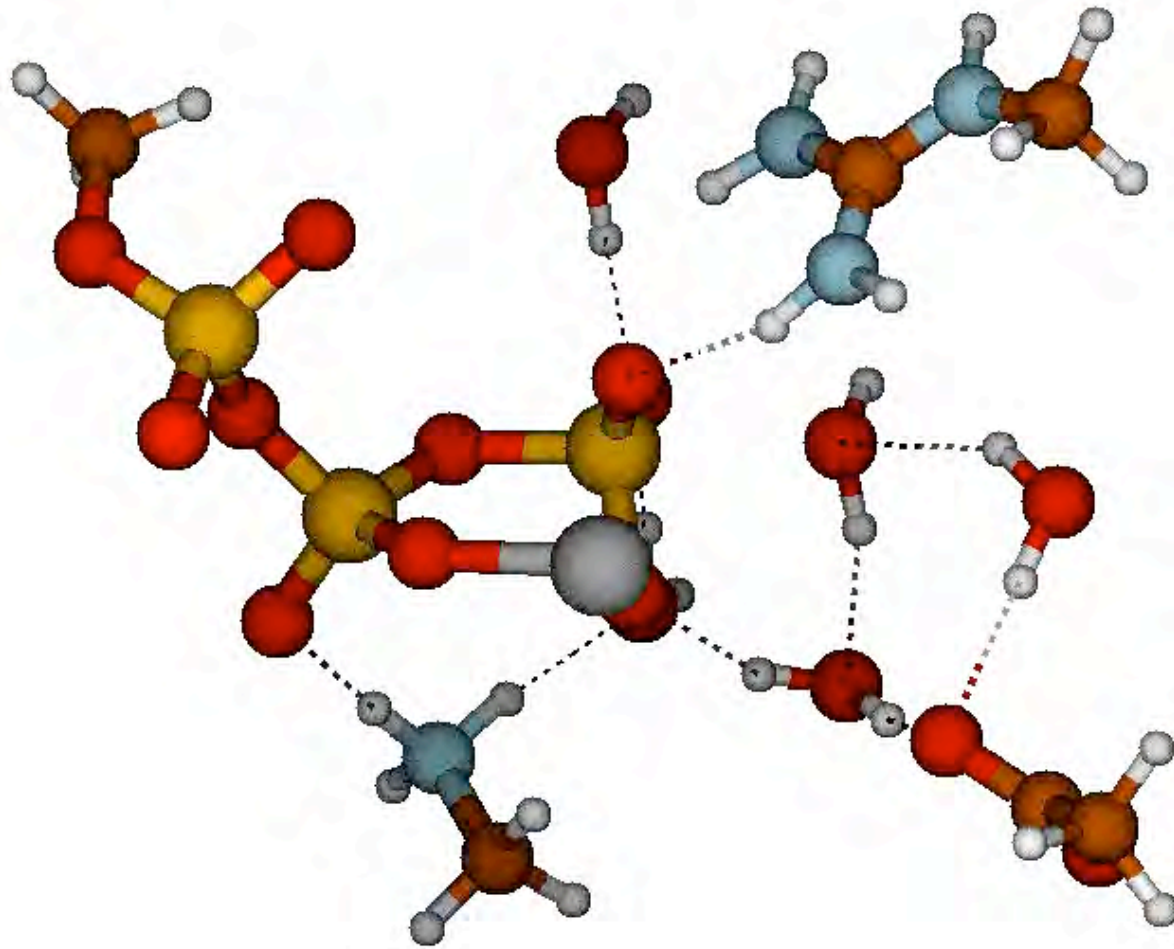


Intermediate structure

Product



# ATP hydrolysis in $\beta_{TP}$



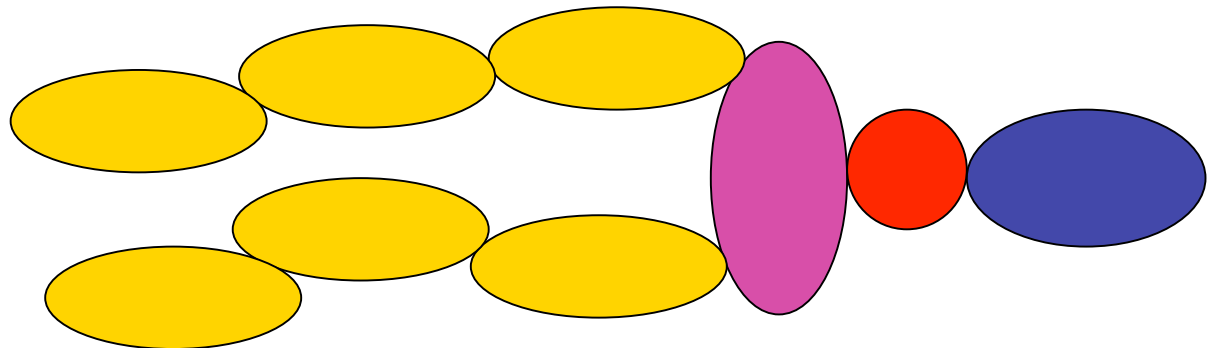
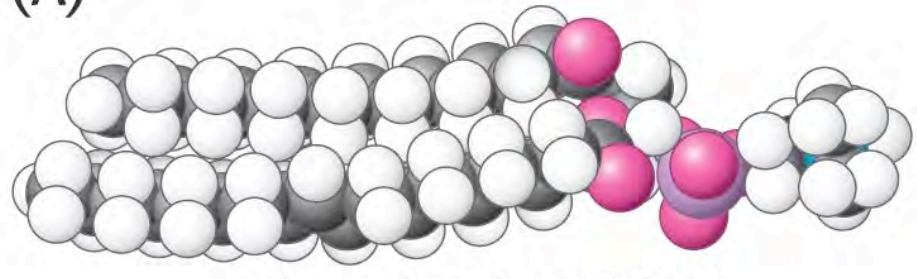
# Coarse grain modeling of lipids

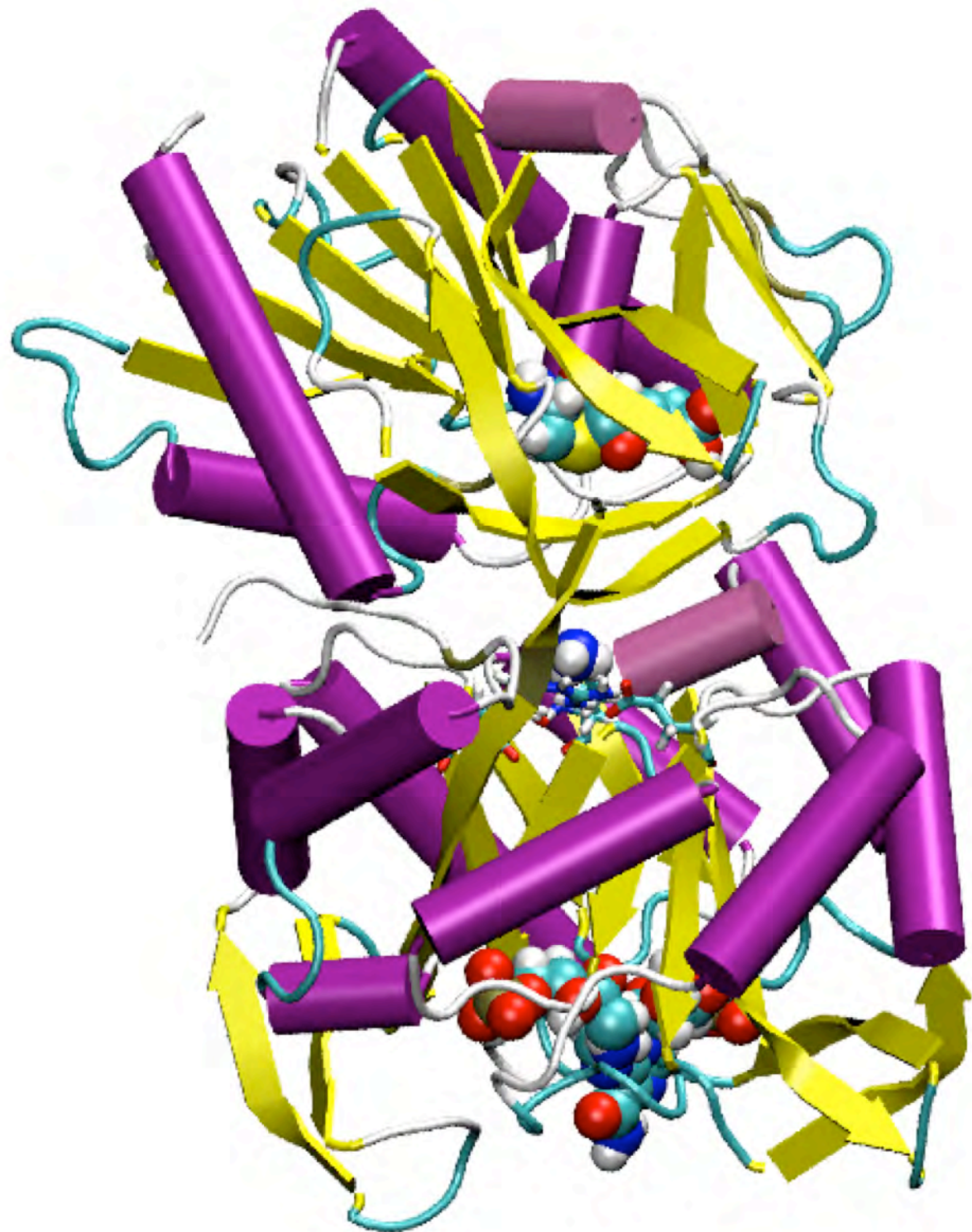
150 particles



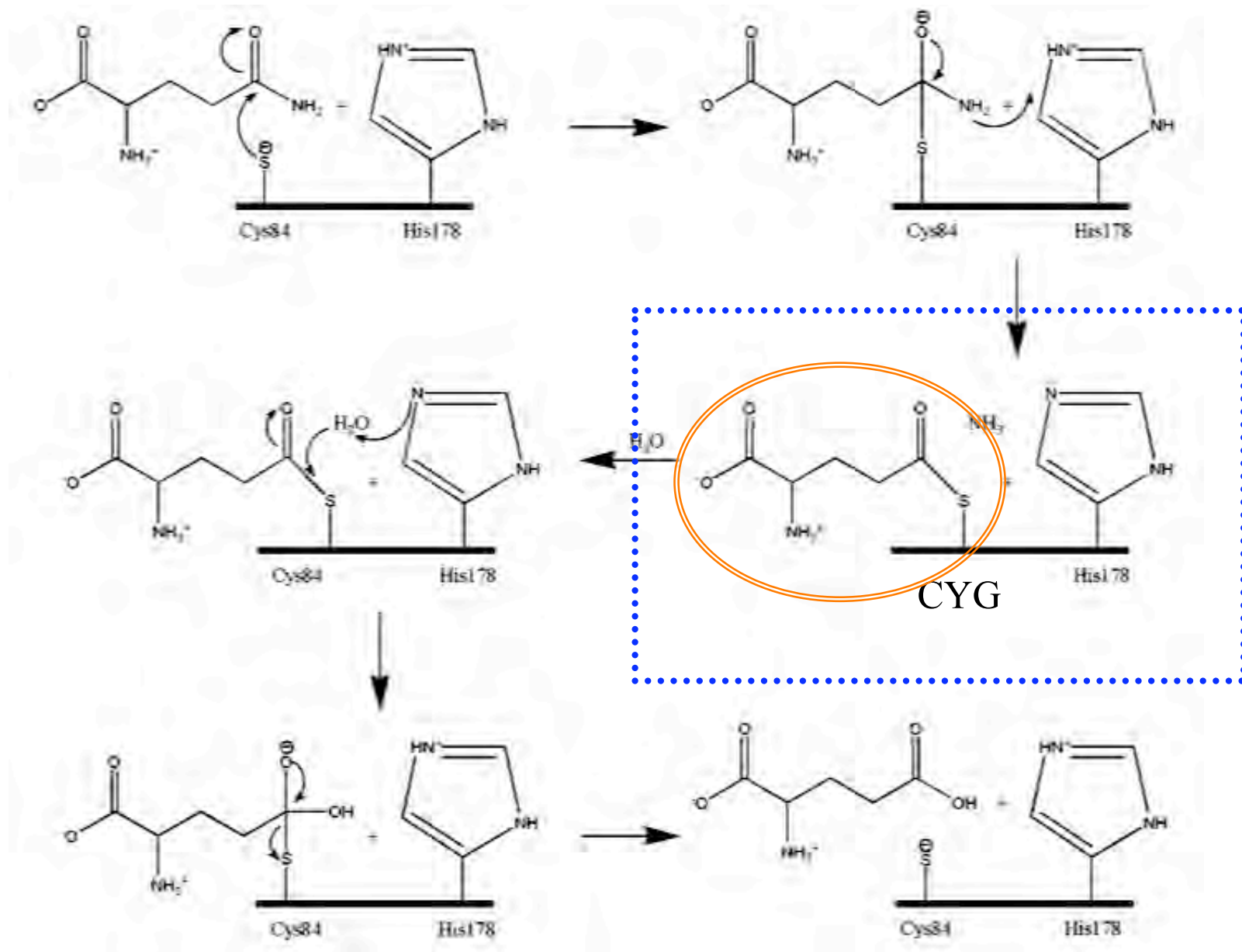
9 particles!

(A)

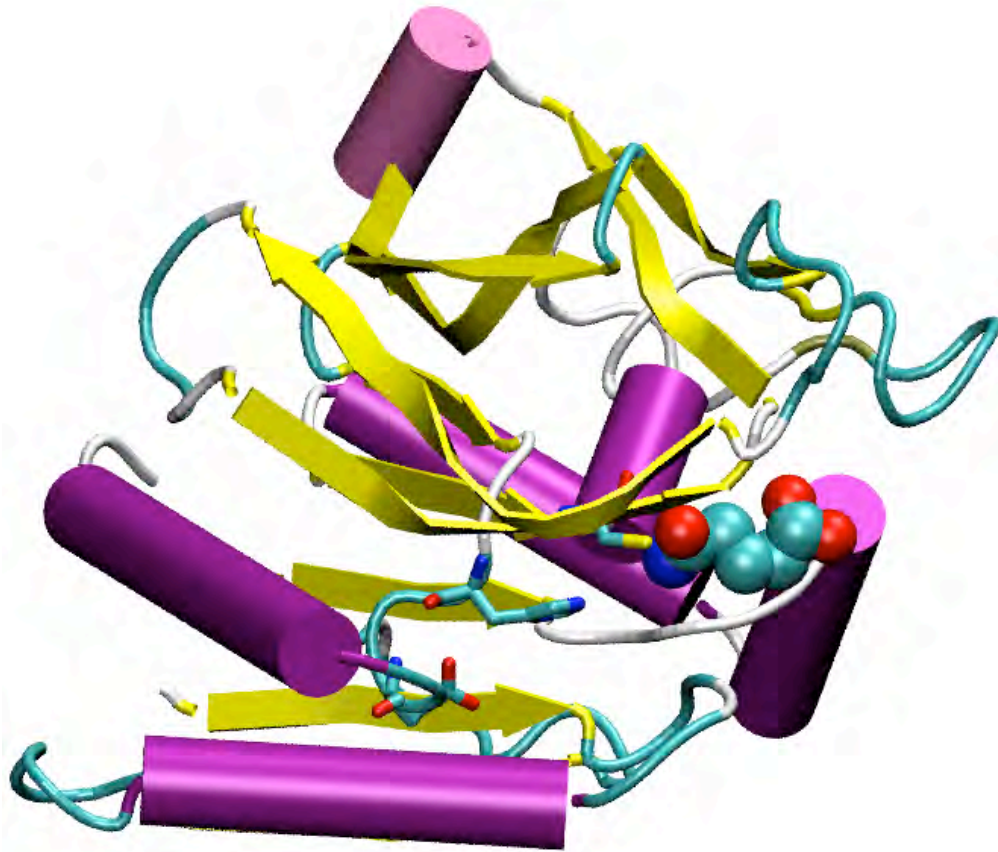




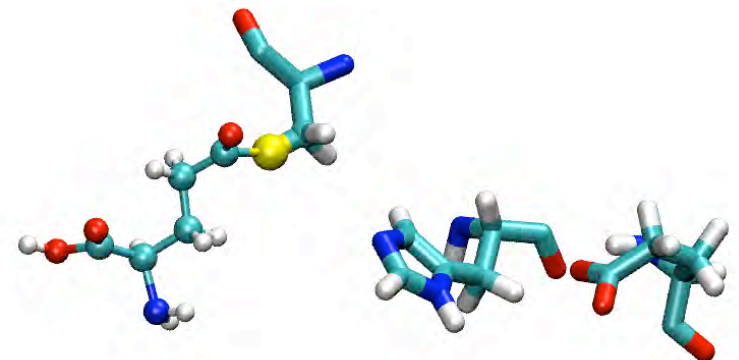
# Modeling the *active-complex*: today's tutorial



# VMD to Attach the substrate GLN to the active site of hisH



CYS & GLN



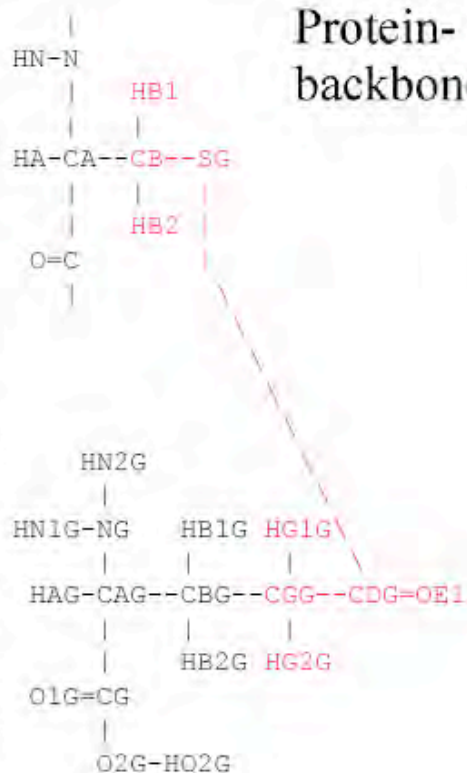
CYG



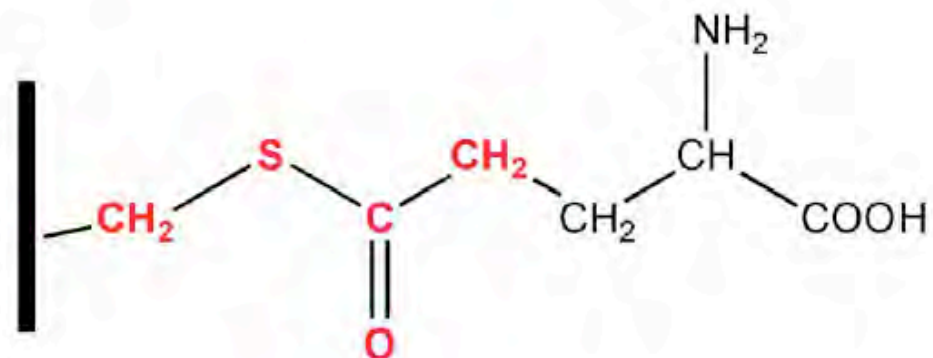
# Creating a new topology file entry

```

RESI CYG 0.00
GROUP
ATOM N NH1 -0.47 !
ATOM HN H 0.31 !
ATOM CA CT1 0.07 !
ATOM HA HB 0.09 !
GROUP
ATOM CB CT2 -0.11 !
ATOM HB1 HA 0.09 !
ATOM HB2 HA 0.09 !
ATOM SG S -0.07 !
!ATOM HG1 HS 0.16 !
GROUP
ATOM CDG CC 0.55 !
ATOM OE1 O -0.55 !
GROUP
ATOM CGG CT2 -0.18 !
ATOM HG1G HA 0.09 !
ATOM HG2G HA 0.09 !
GROUP
ATOM CBG CT2 -0.18 !
ATOM HB1G HA 0.09 !
ATOM HB2G HA 0.09 !
GROUP
ATOM CG CD 0.75 !
ATOM O1G OB -0.55
ATOM O2G OH1 -0.61
ATOM HO2G H 0.44
ATOM CAG CT1 -0.12
ATOM HAG HB 0.09
ATOM NG NH3 -0.62
ATOM HN1G HC 0.31
ATOM HN2G HC 0.31
GROUP
ATOM C C 0.51
ATOM O O -0.51
    
```



Protein-  
backbone



HG1 deleted from CYS and the charge was moved to SG (-0.23 + 0.16 = 0.07) so that the SG charge becomes 0.07 in final compound and the group remains neutral

Changes annotated!

# Creating new parameters

```
BOBDS
|
!V(bond) = Kb(b - b0)**2
|
!Kb: kcal/mole/A**2
!b0: A
|
!atom type Kb      b0
! Modified for CYG residue after 6-31G* geometry optimization
S   CC   240.000    1.7814 ! ALLOW  ALI SUL ION

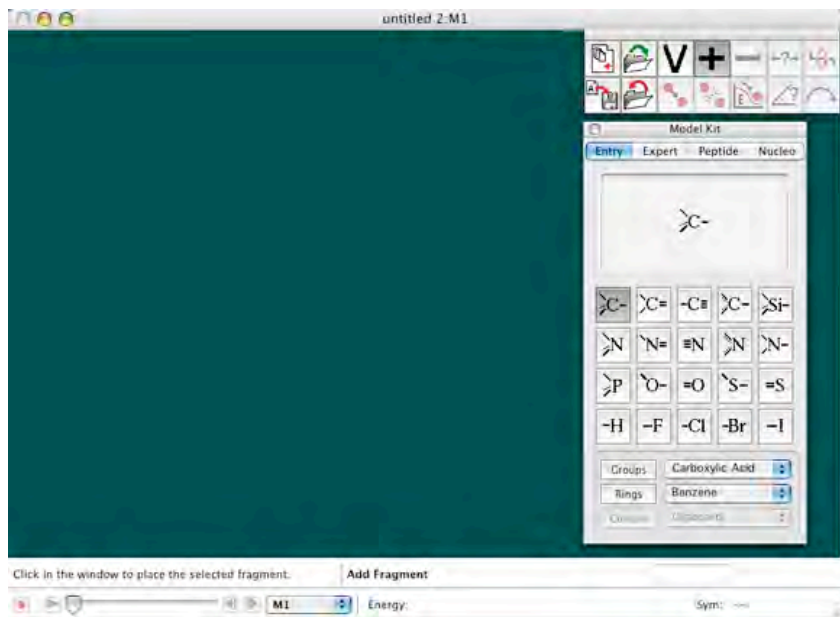
ANGLES
|
!V(angle) = Ktheta(Theta - Theta0)**2
|
!V(Urey-Bradley) = Kub(S - S0)**2
|
!Ktheta: kcal/mole/rad**2
!Theta0: degrees
!Kub: kcal/mole/A**2 (Urey-Bradley)
!S0: A
|
!atom types      Ktheta  Theta0  Kub    S0
|
! Modified for CYG residue after 6-31G* geometry optimization
CT2 S   CC   34.000    100.2000 ! ALLOW  ALI SUL ION

CT2 CC   S   50.000    114.5000 ! ALLOW  ALI SUL ION

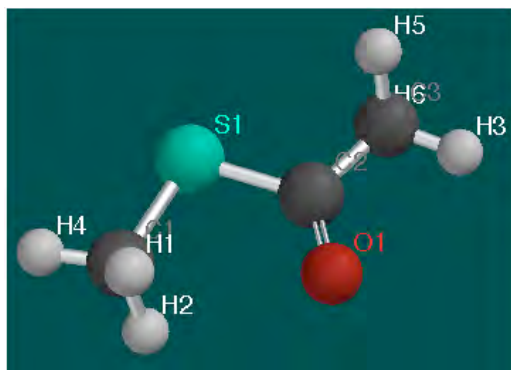
D   CC   S   75.000    122.2000 ! ALLOW  ALI SUL ION
```

```
DIHEDRALS
|
!V(dihedral) = Kchi(1 + cos(n(chi) - delta))
|
!Kchi: kcal/mole
!n: multiplicity
!delta: degrees
|
!atom types      Kchi    n    delta
CC S   CT2 CT1   0.2400  1   180.00
CC S   CT2 CT1   0.3700  3    0.00
HA CT2 S   CC    0.2800  3    0.00
CT2 S   CC CT2   2.05    2   180.00
CT2 S   CC O     2.05    2   180.00
```

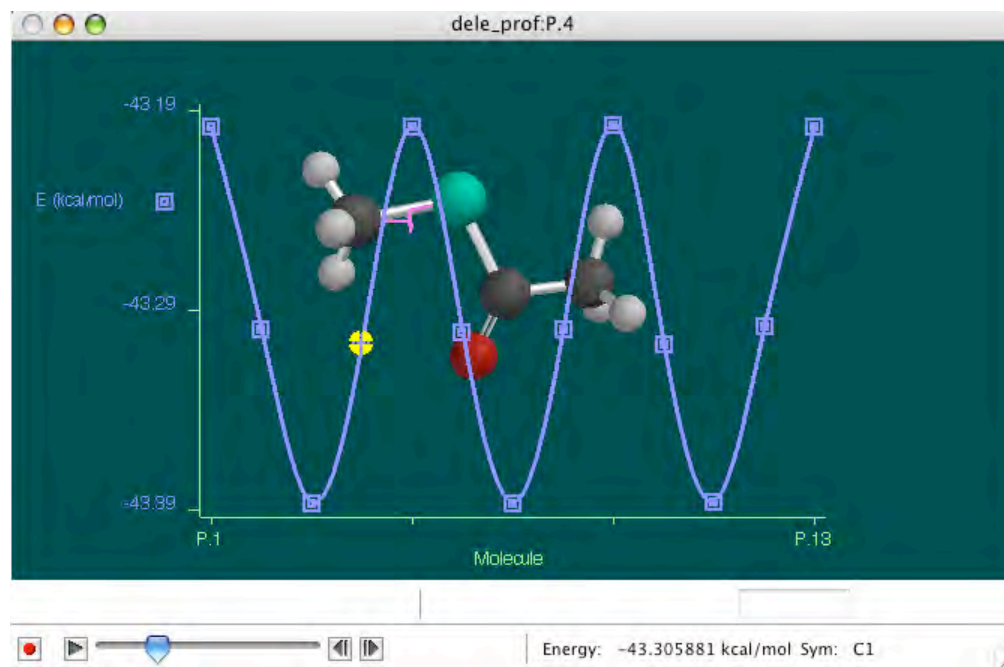
# Semi-empirical Parameter Estimation Using SPARTAN



Main Spartan Window



You build a part of CYG



Be careful with the dihedral drive section!