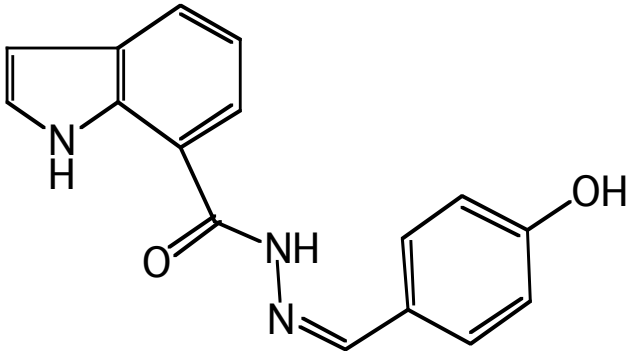
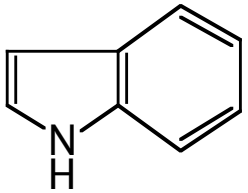
Break Desired Compound into 3 Smaller Ones

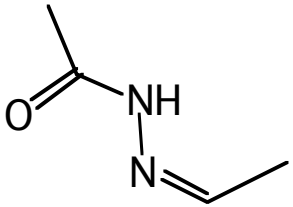


A



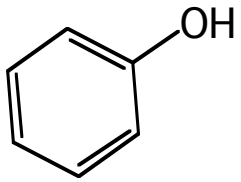
Indole

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 MacKerell

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
```

From MacKerell

Top_all22_model.inp contains all protein model compounds. Lipid, nucleic acid and carbohydate model compounds are in the full topology files.

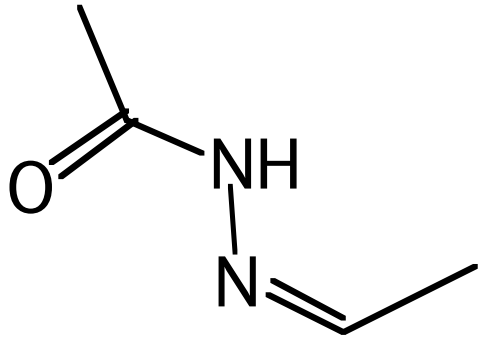
HG will ultimately be deleted. Therefore, move HG (hydrogen) charge into CG, such that the CG charge becomes 0.00 in the final compound.

Use remaining charges/atom types without any changes.

Do the same with indole

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.

From MacKerell

Partial Charge Assignment

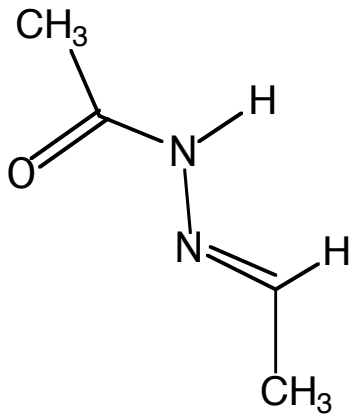
- Most important aspect for ligands

- Different force fields might take different philosophies
  - AMBER: RESP charges at the HF/6-31G level
    - Overestimation of dipole moments
    - Easier to set up
  - CHARMM: Interaction based optimization
    - TIP3P water representing the environment
    - Could be very difficult to set up

- Conformation dependence of partial charges
- Lack of polarization

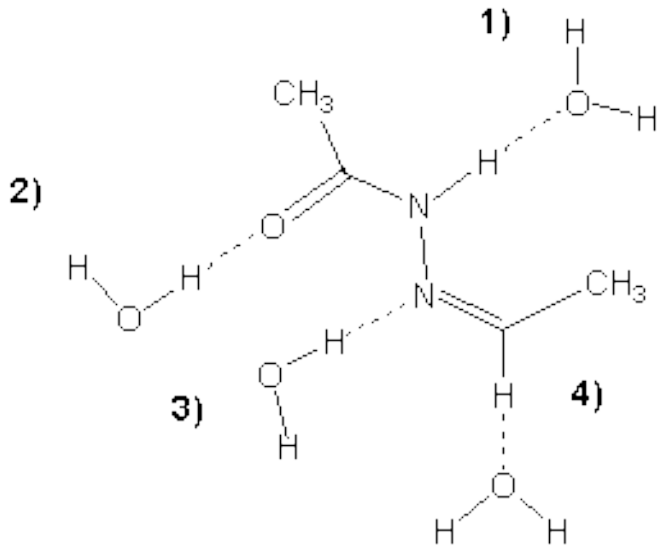
- Try to be consistent within the force field

- pKa calculations for titratable residues



Starting charges??
Mulliken population analysis
Analogy comparison

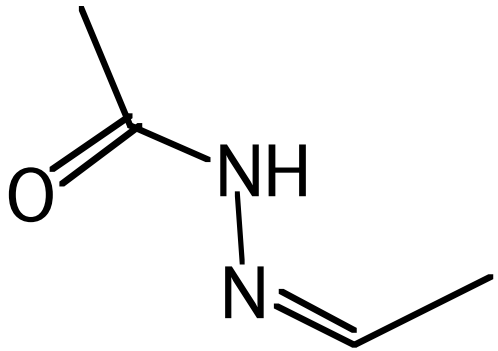
Final charges (methyl, vary q_C to maintain integer charge, $q_H = 0.09$)
interactions with water (HF/6-31G*, monohydrates!)



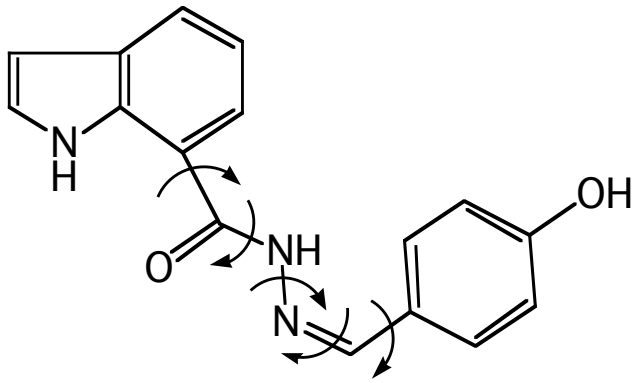
From MacKerell

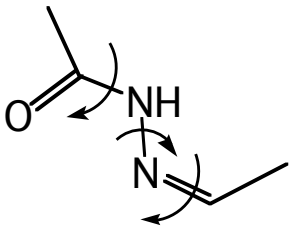
Comparison of analogy and optimized charges

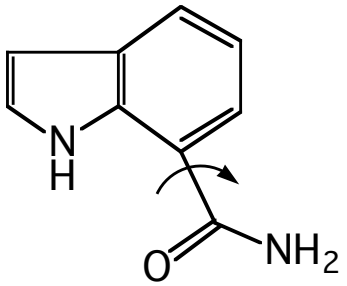
Name	Type	Analogy	Optimized
C1	CT3	-0.27	-0.27
H11	HA3	0.09	0.09
H12	HA3	0.09	0.09
H13	HA3	0.09	0.09
C2	C	0.51	0.58
O2	O	-0.51	-0.50
N3	NH1	-0.47	-0.32
H3	H	0.31	0.33
N4	NR1	0.16	-0.31
C5	CEL1	-0.15	-0.25
H51	HEL1	0.15	0.29
C6	CT3	-0.27	-0.09
H61	HA	0.09	0.09
H62	HA	0.09	0.09
H63	HA	0.09	0.09

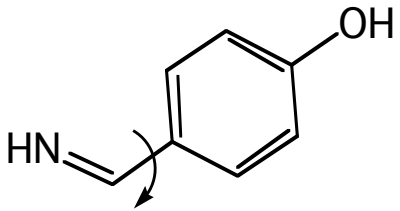


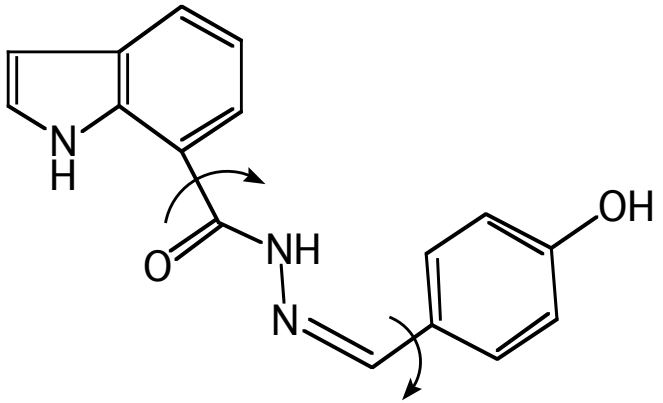
Dihedral optimization based on QM potential energy surfaces (HF/6-31G* or MP2/6-31G*).







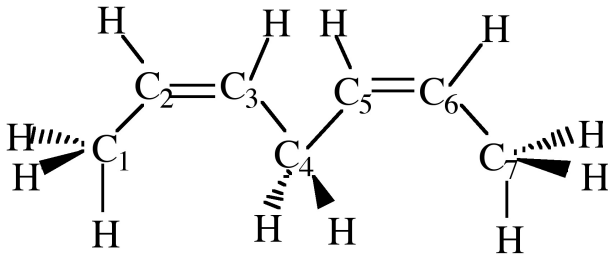


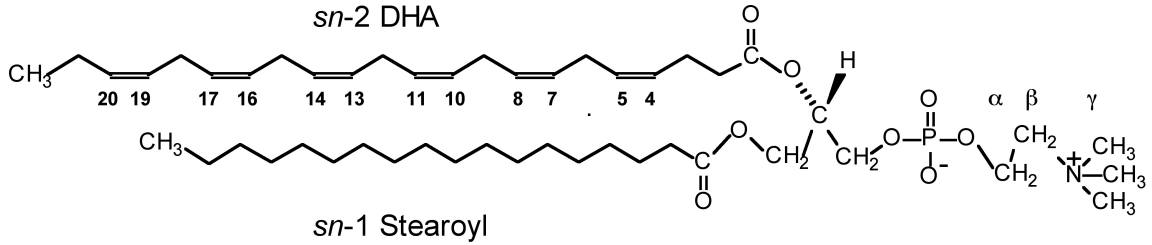


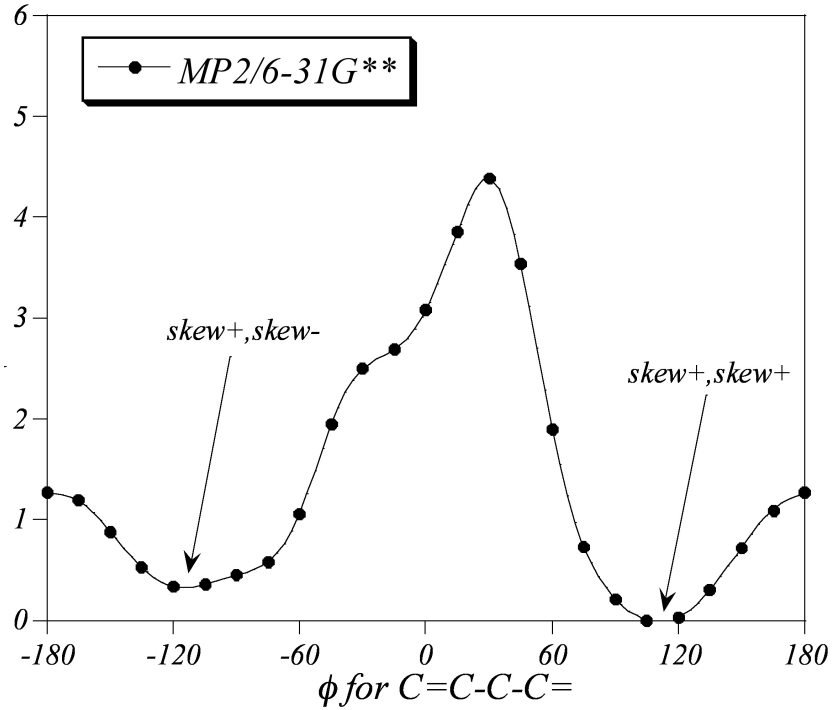
From MacKerell

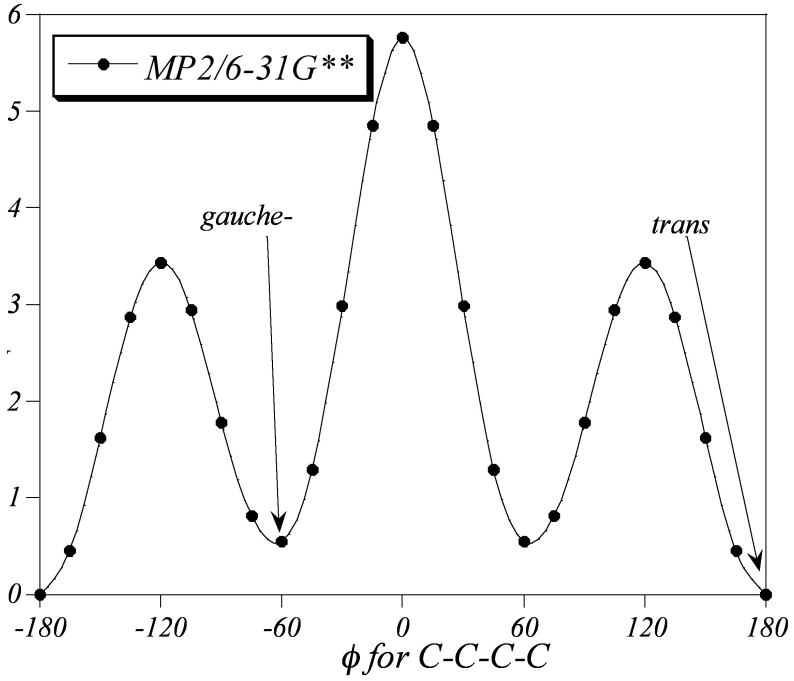
Parameterization of unsaturated lipids

- All C=C bonds are cis, what does rotation about neighboring single bonds look like?





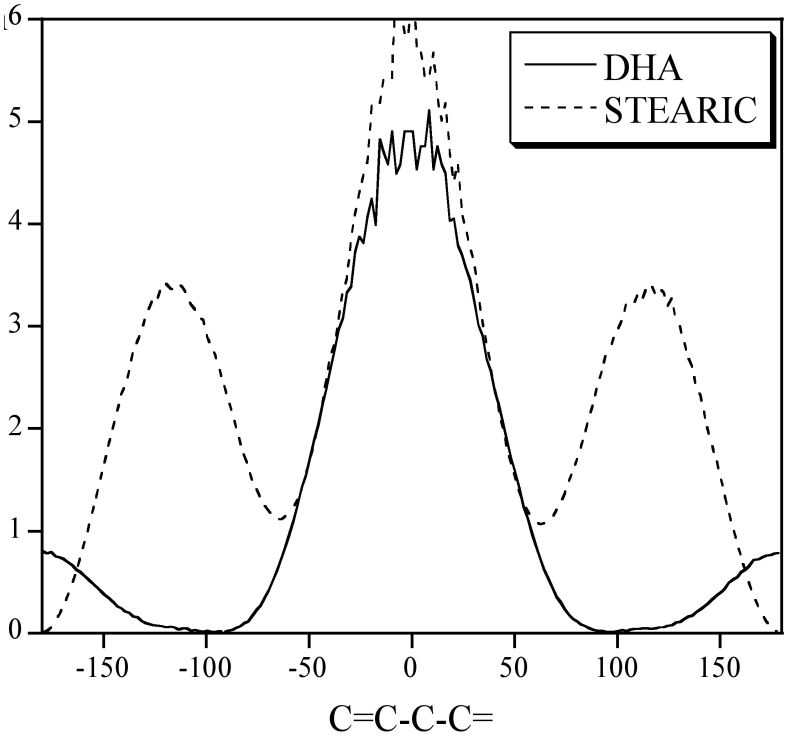


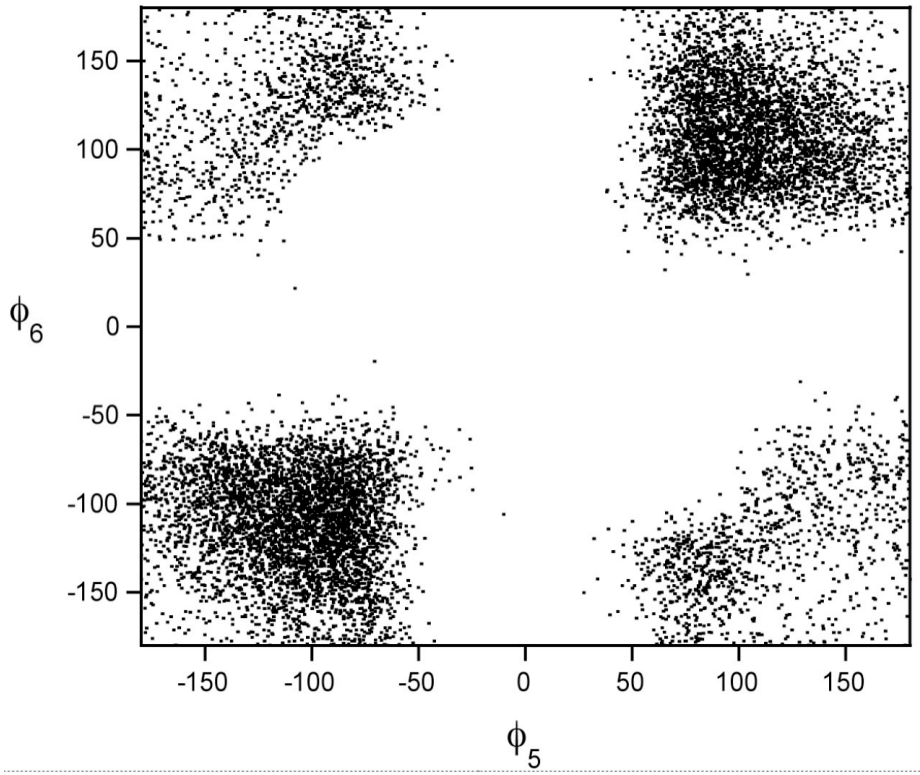


Courtesy of Scott Feller, Wabash College

DHA conformations from MD

- rotational barriers are extremely small
- many conformers are accessible w/ short lifetimes

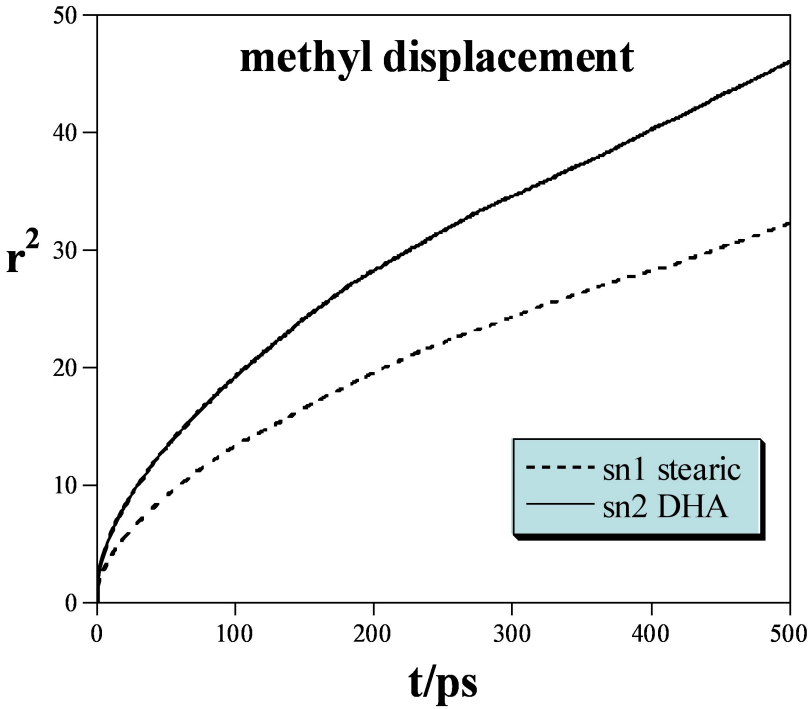


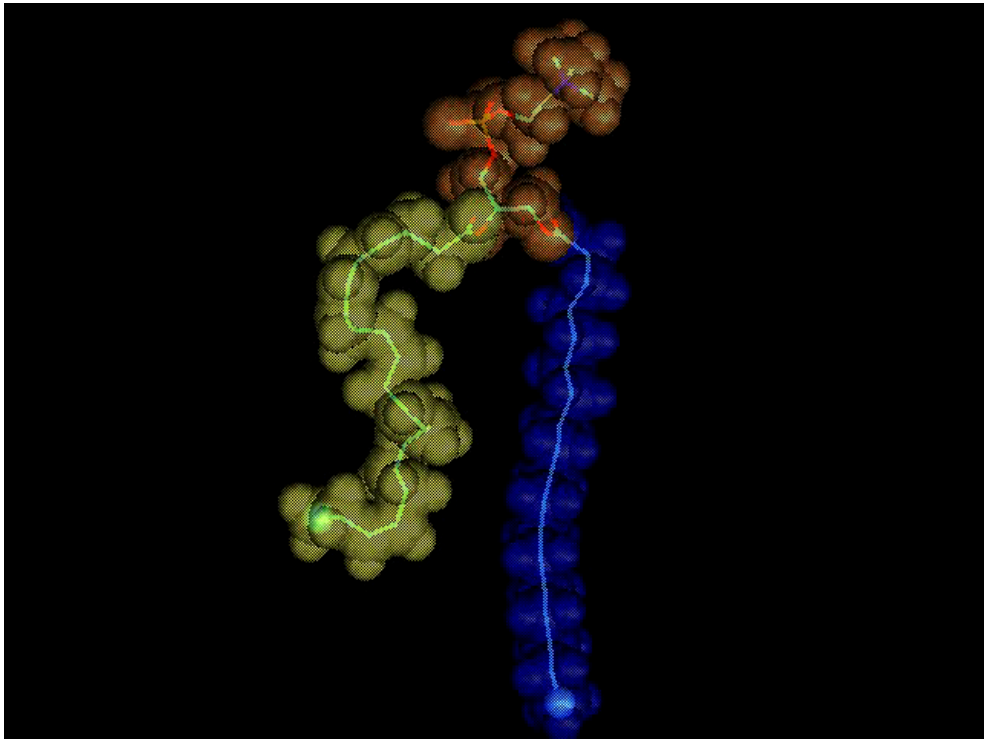


Courtesy of Scott Feller, Wabash College

Dynamics of saturated vs. polyunsaturated lipid chains

- *sn*1 stearic acid = blue
- *sn*2 DHA = yellow
- 500 ps of dynamics



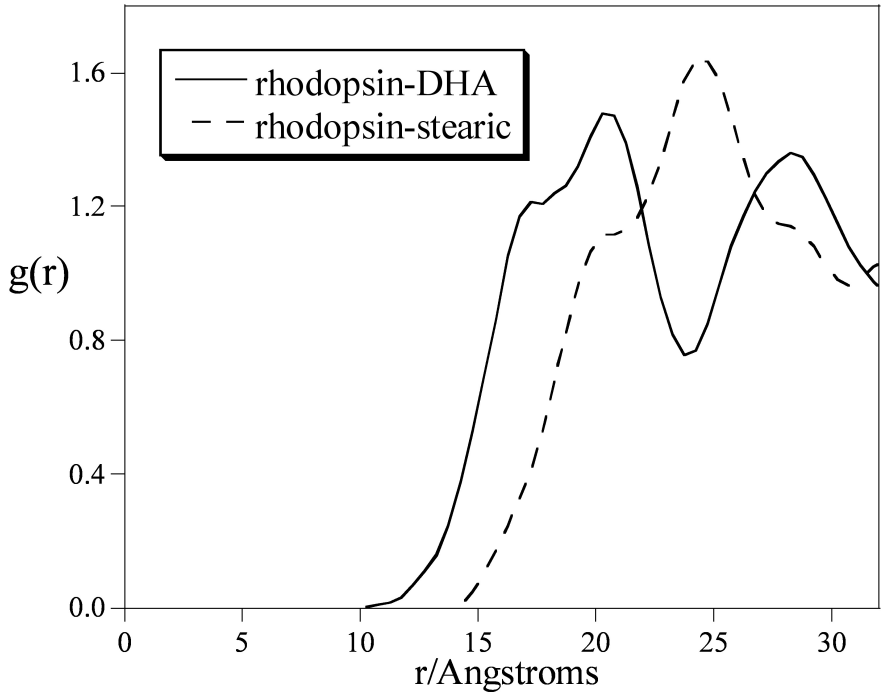


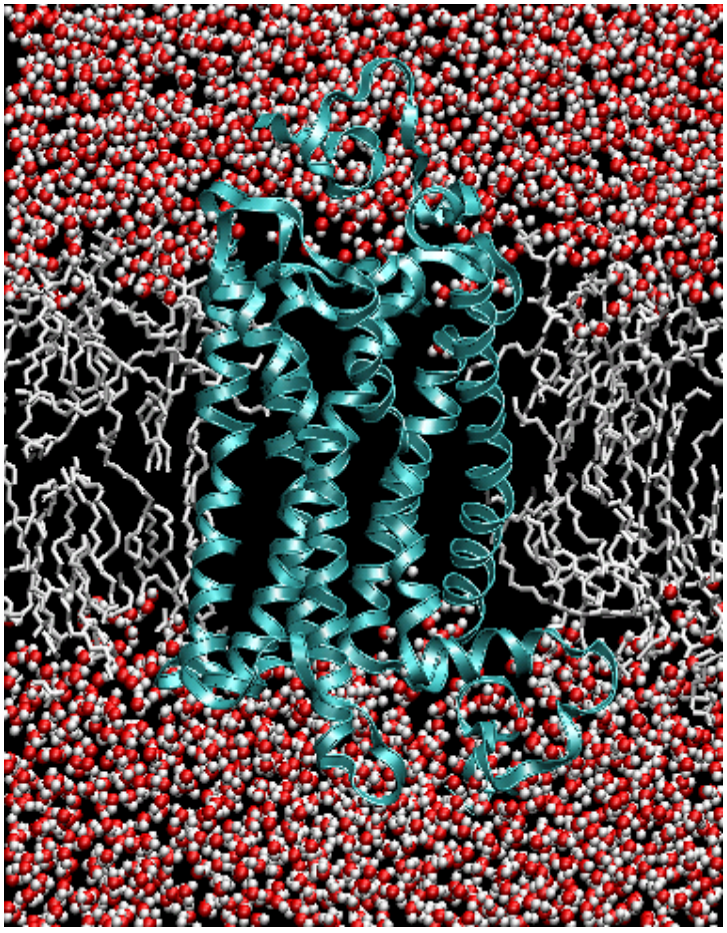
Movie courtesy of Mauricio Carrillo Tripp

Courtesy of Scott Feller, Wabash College

Lipid-protein interactions

- Radial distribution around protein shows distinct layering of acyl chains

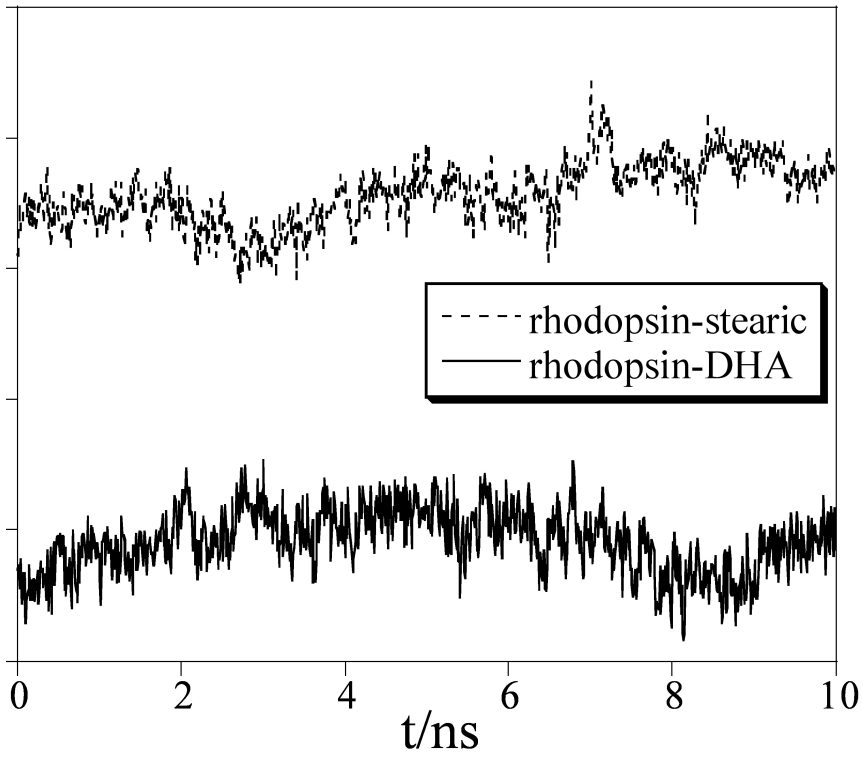




Courtesy of Scott Feller, Wabash College

Lipid-protein interactions

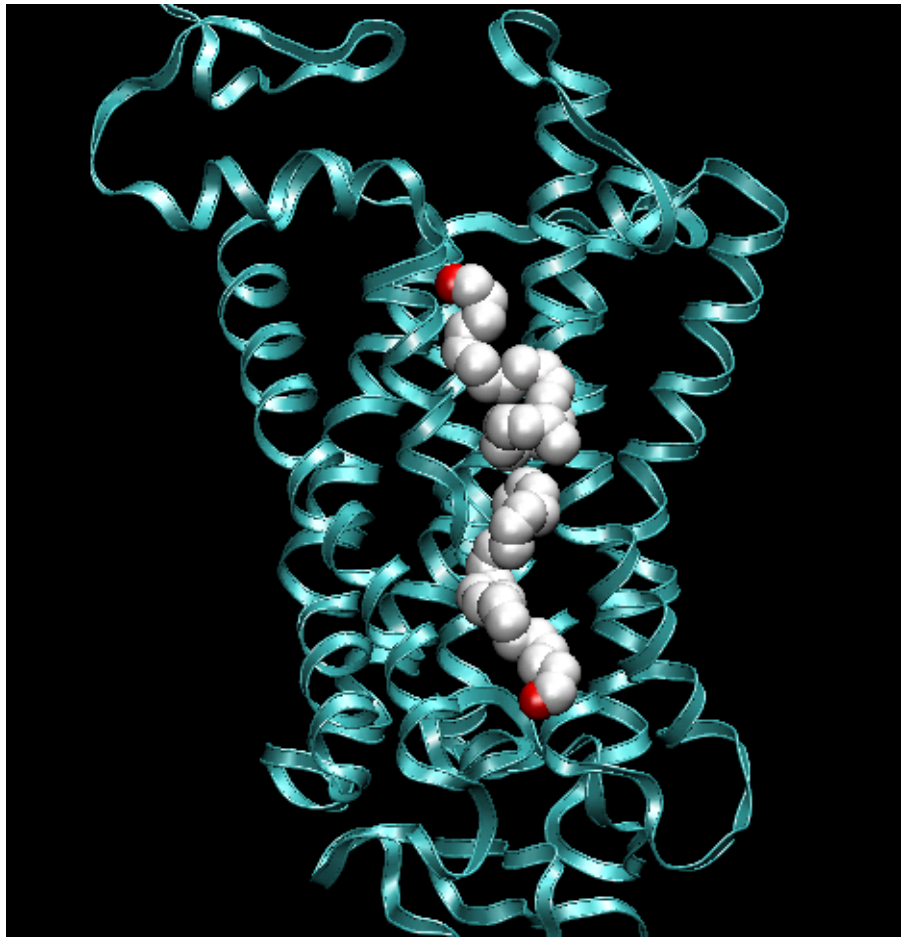
- Decomposition of non-bonded interaction shows rhodopsin is strongly attracted to unsaturated chain
- All hydrophobic residues are stabilized by DHA

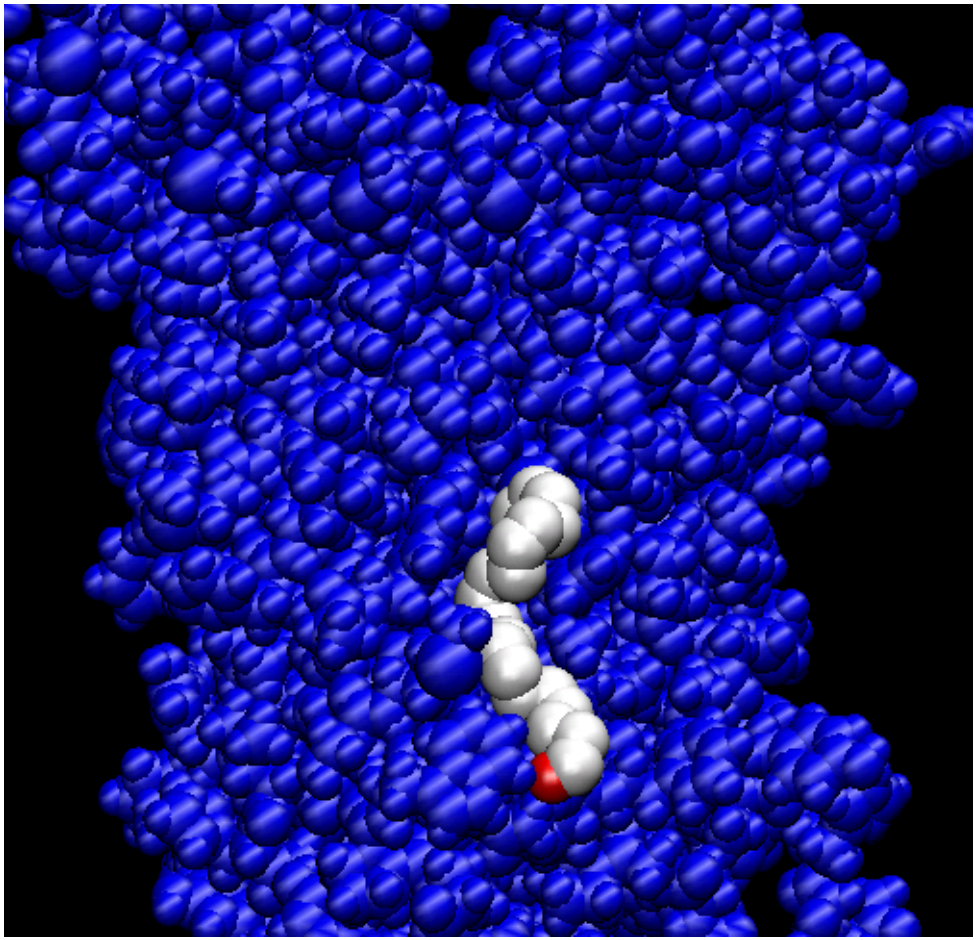


resname	U_{DHA}	$U_{stearic}$	ratio
PHE	-44.9	-22.6	2.0
ILE	-30.0	-10.1	3.0
VAL	-24.0	-9.6	2.5
LEU	-23.1	-13.0	1.8
MET	-22.8	-9.7	2.4
TYR	-18.6	-10.4	1.8
ALA	-11.4	-3.0	3.8
TRP	-10.3	-2.4	4.2

Courtesy of Scott Feller, Wabash College

Origin of protein:DHA attraction





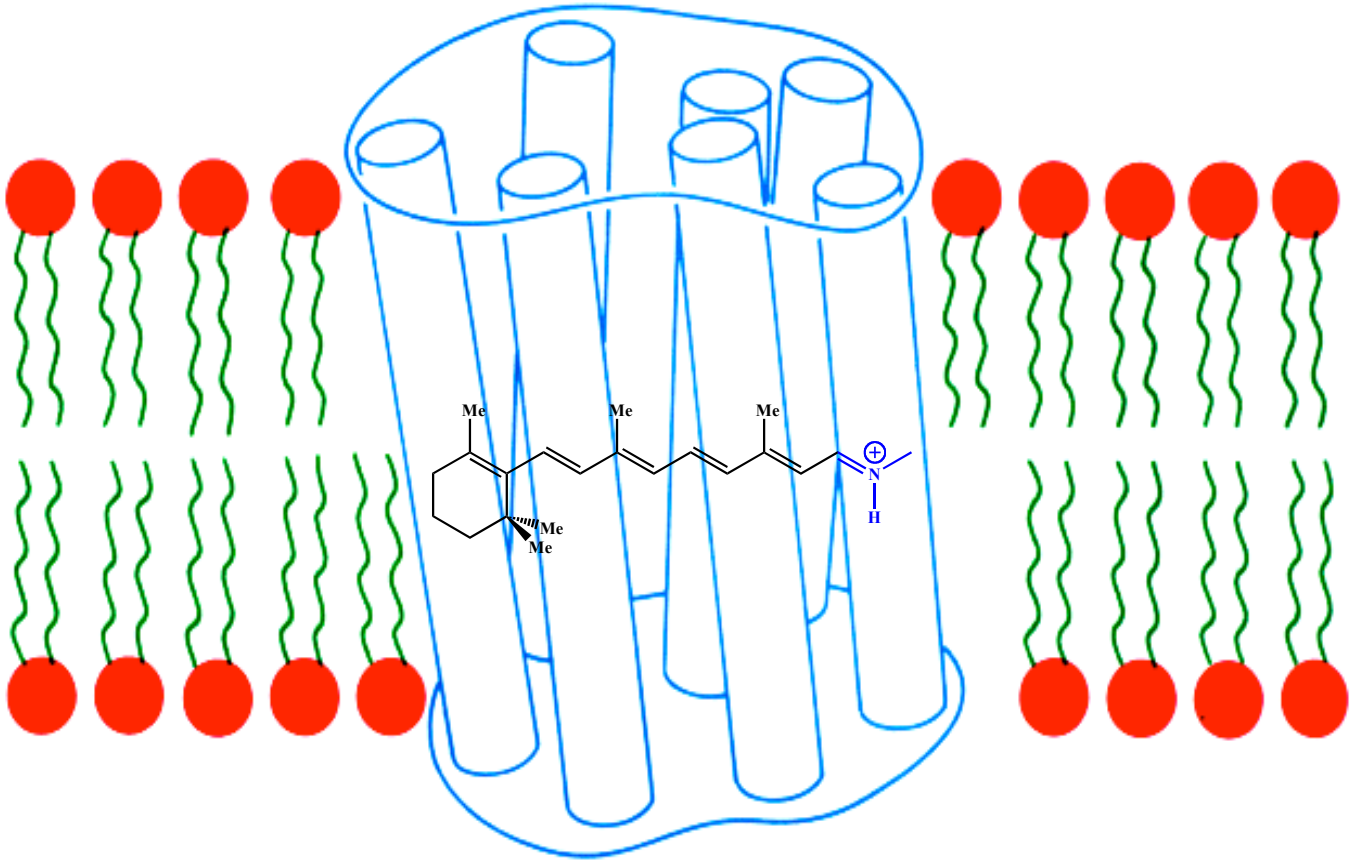
- Flexibility of the DHA chain allows solvation of the rough protein surface to occur with little intra-molecular energy cost

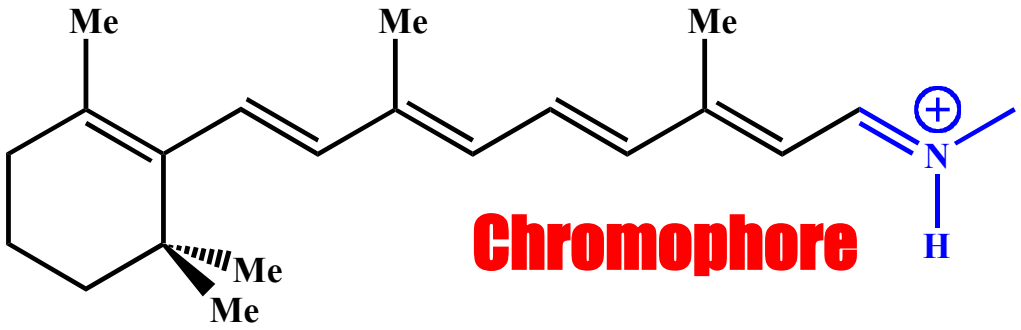
Courtesy of Scott Feller, Wabash College

Major Recent Developments

- New set of lipid force field parameters for CHARMM (CHARMM32^{+})
  - Pastor, B. Brooks, MacKerell
- Polarizable force field
  - Roux, MacKerell

Retinal Proteins -- Rhodopsins

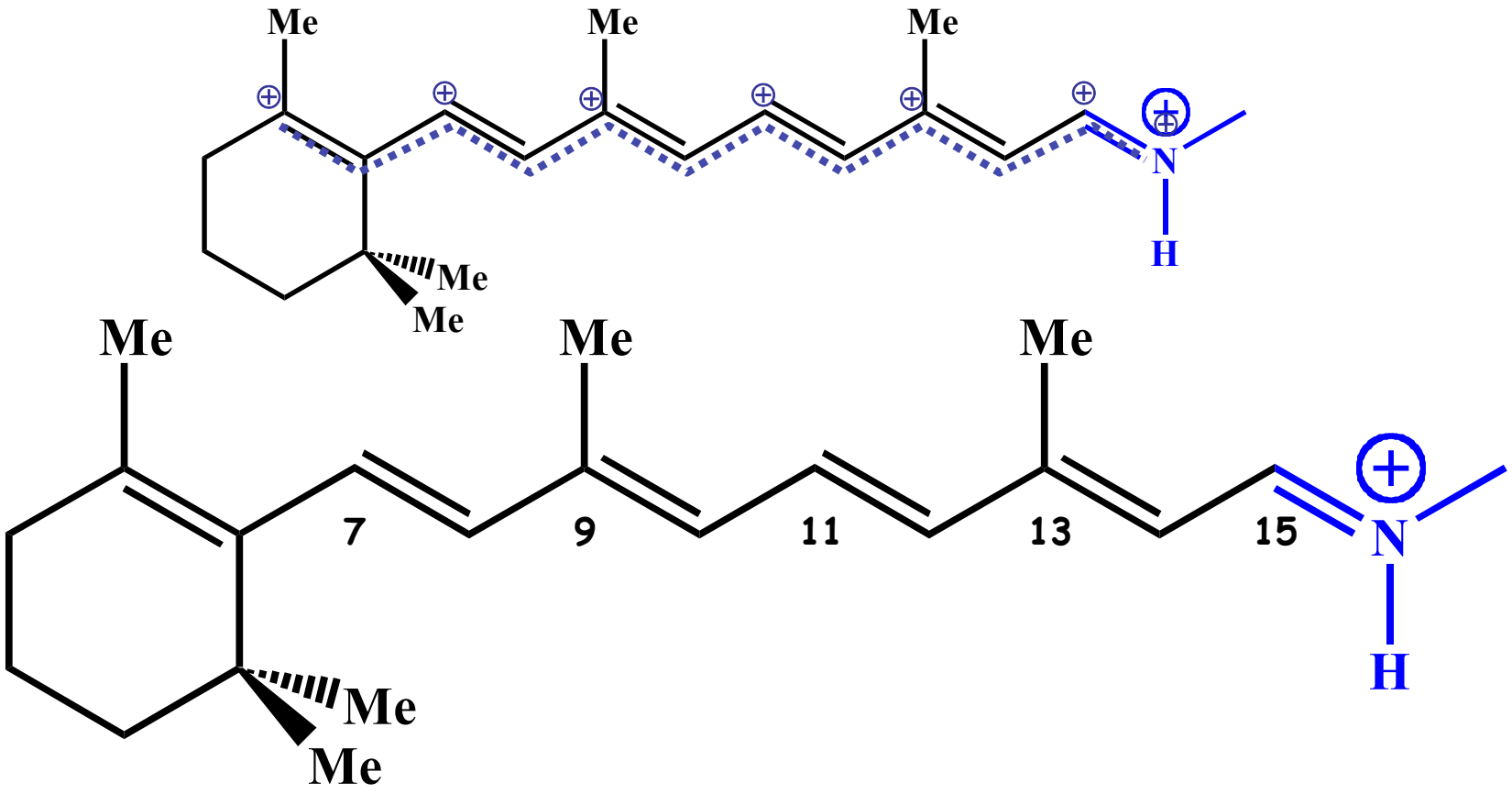




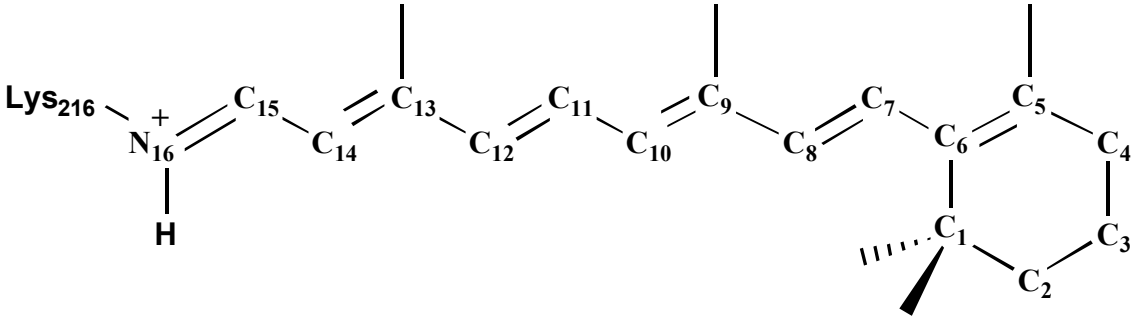
Chromophore

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

Unconventional chemistry



Isomerization Barriers in retinal



DFT/6-31G**

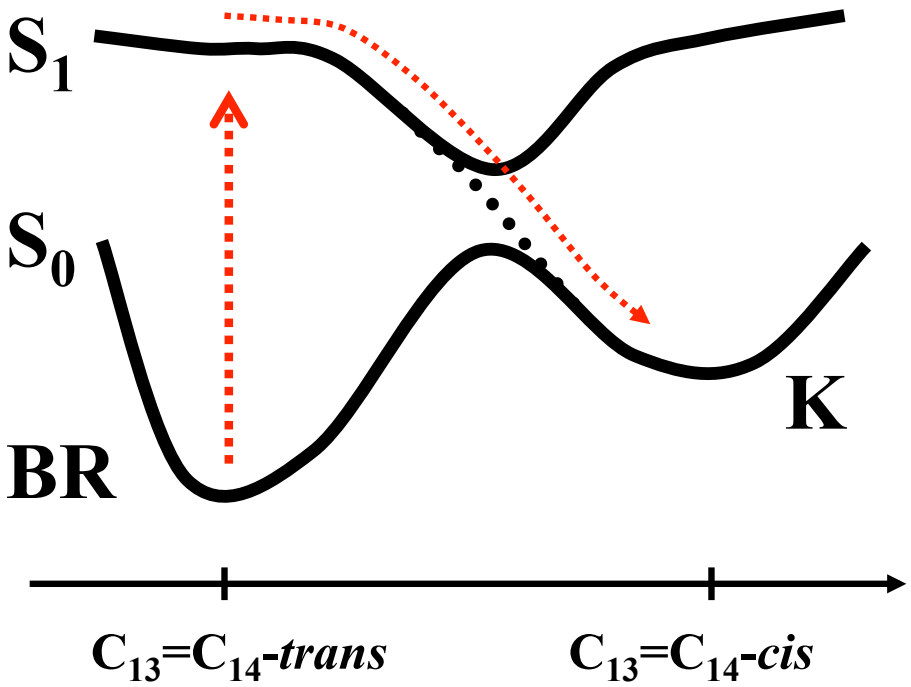
TABLE 2 The parameter set B used for the torsional potentials of the main polyene chain of the retinal Schiff base

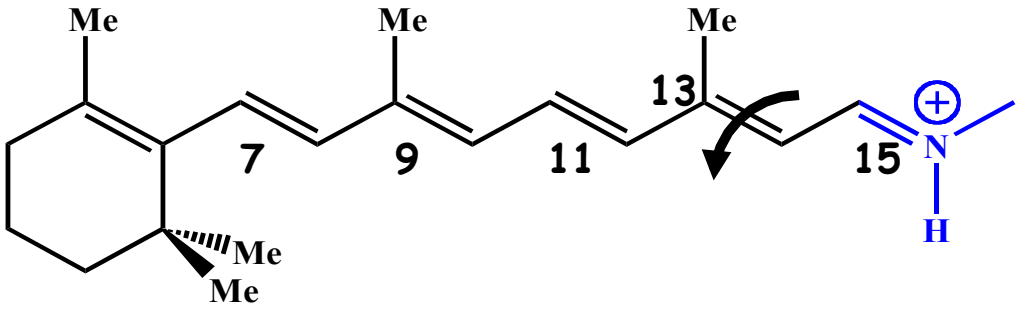
ϕ_i	k_i (kcal/mol)*	n_i	δ_i (deg)
$C_5{=}C_6{-}C_7{=}C_8$	11.24	2.0	180.00
$C_6{-}C_7{=}C_8{-}C_9$	39.98	2.0	180.00
$C_7{=}C_8{-}C_9{=}C_{10}$	17.03	2.0	180.00
$C_8{-}C_9{=}C_{10}{-}C_{11}$	37.28	2.0	180.00
$C_9{=}C_{10}{-}C_{11}{=}C_{12}$	22.50	2.0	180.00
$C_{10}{-}C_{11}{=}C_{12}{-}C_{13}$	35.08	2.0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

Tajkhorshid et al., 1999.

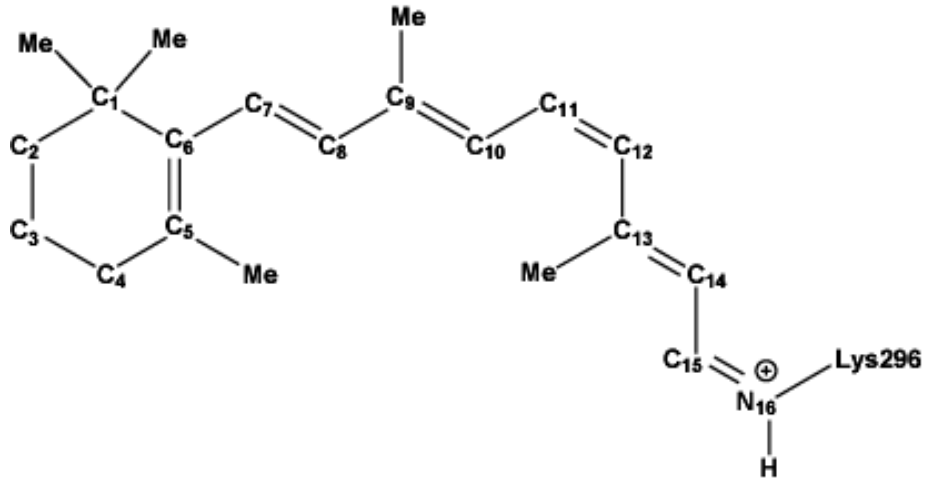
*$E_i^{\text{dihedral}} = (1/2)k_i[1 + \cos(n_i\varphi_i - \delta_i)]$.

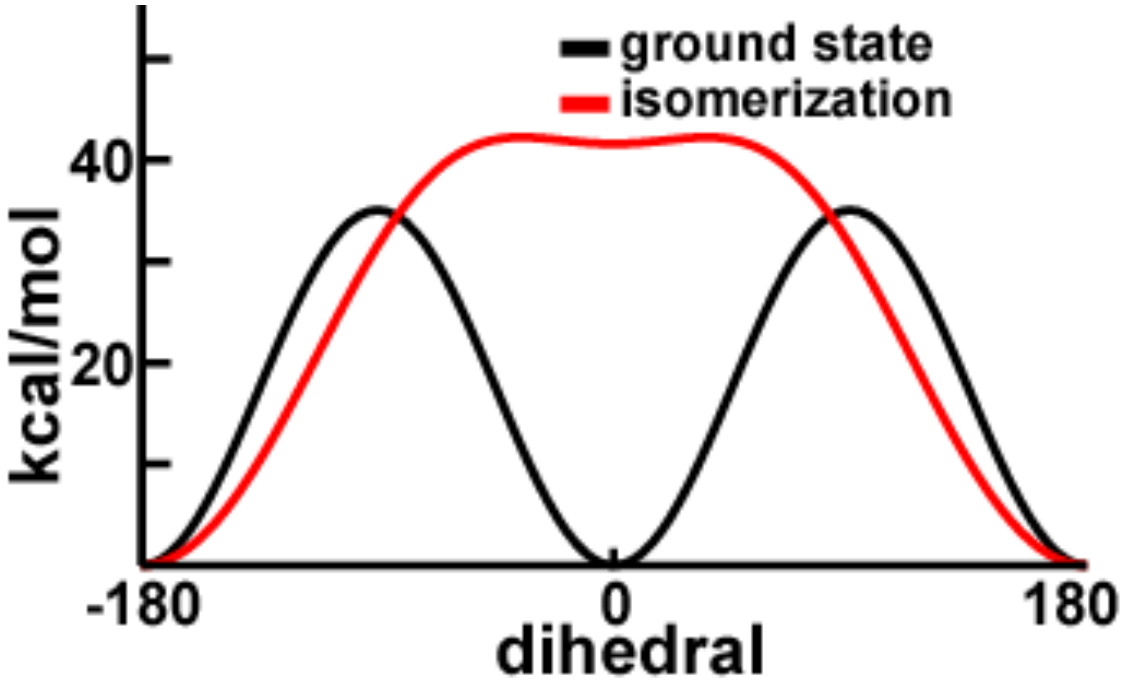
Coupling of electronic excitation and conformational change in bR





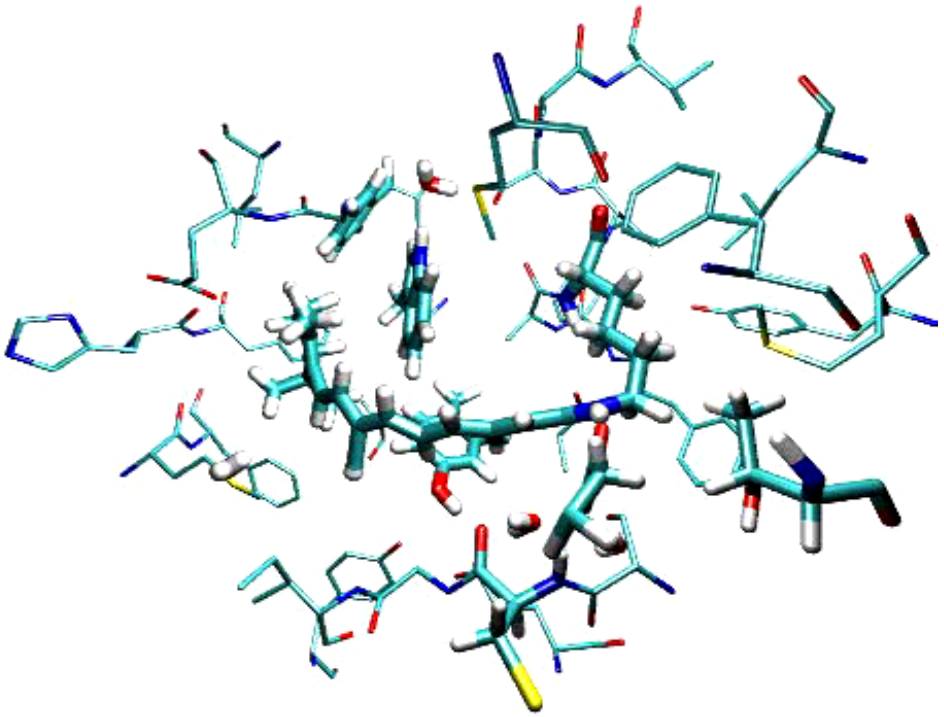
Inducing isomerization

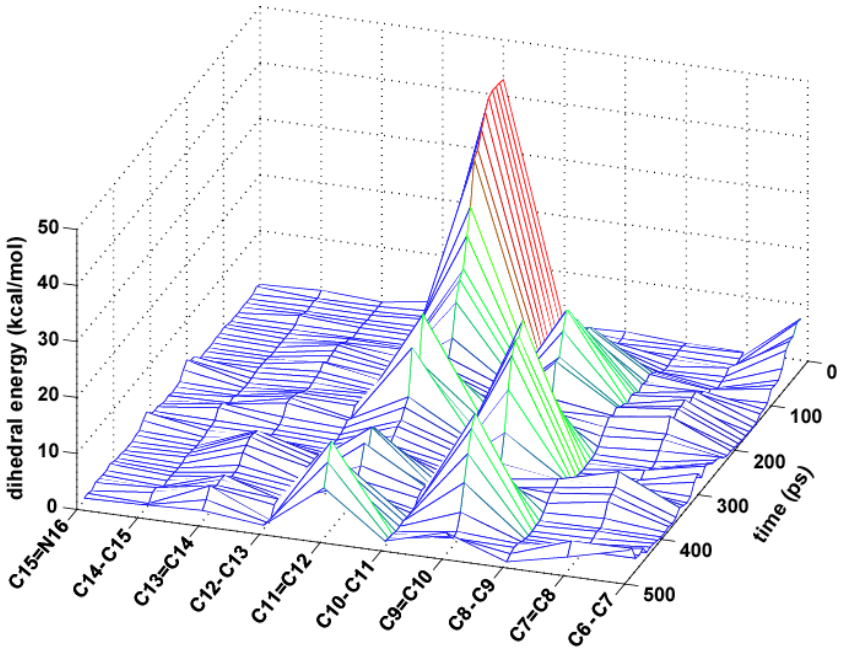




500 nm
~50 kcal/mole

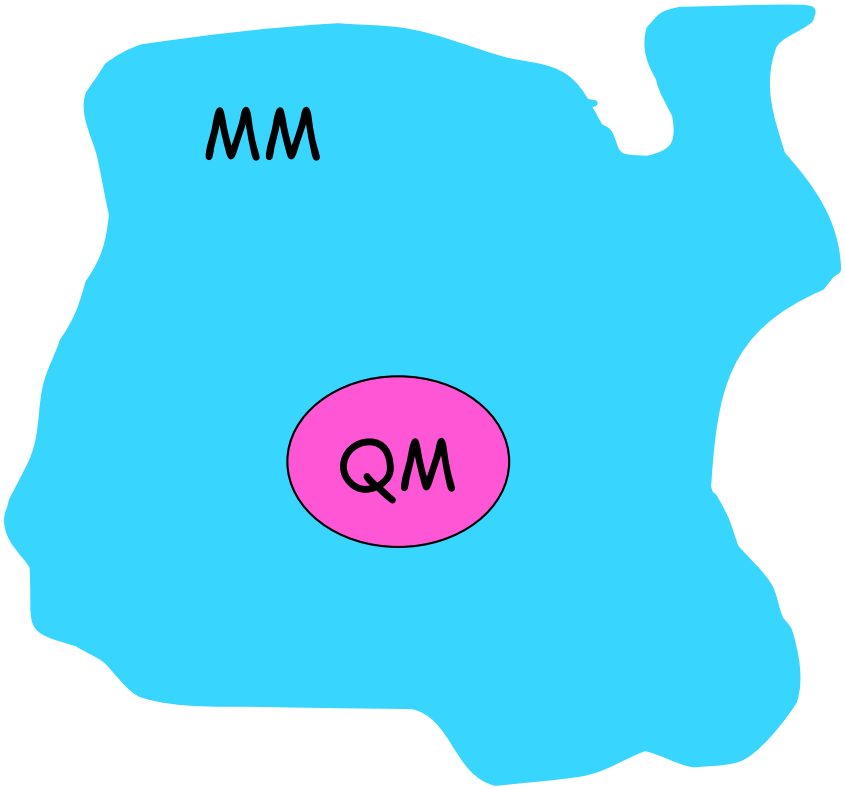
Classical Retinal Isomerization in Rhodopsin

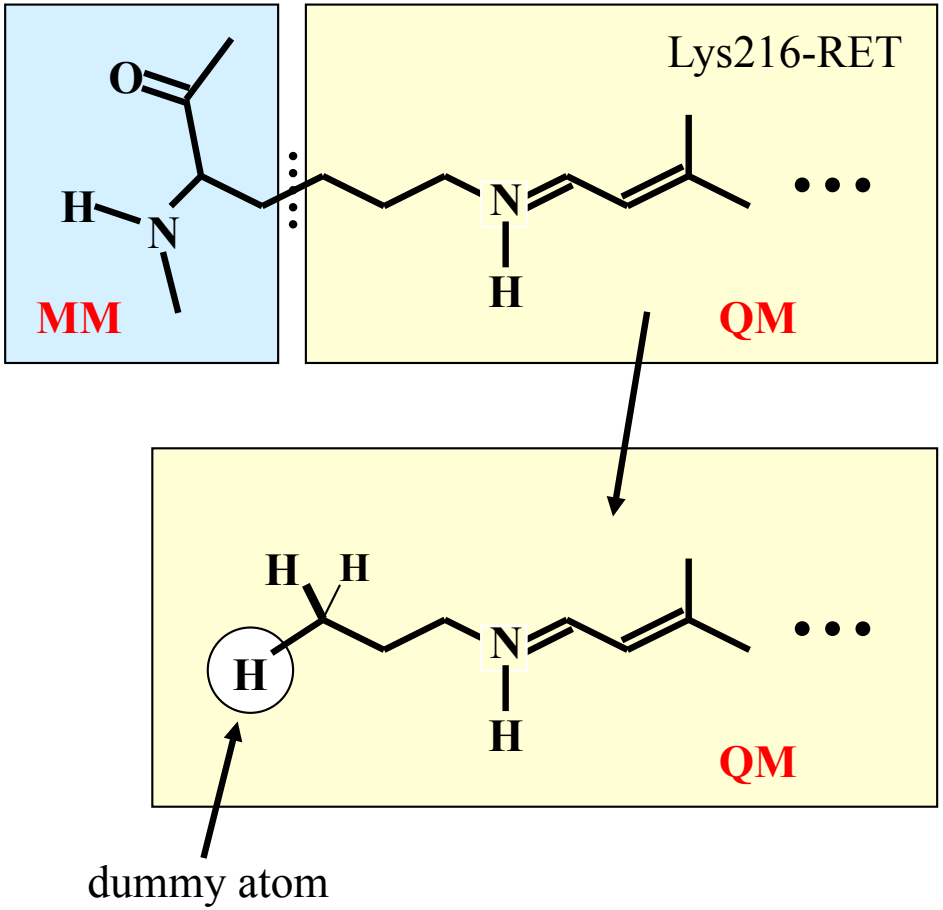




Twist Propagation

QM/MM calculations

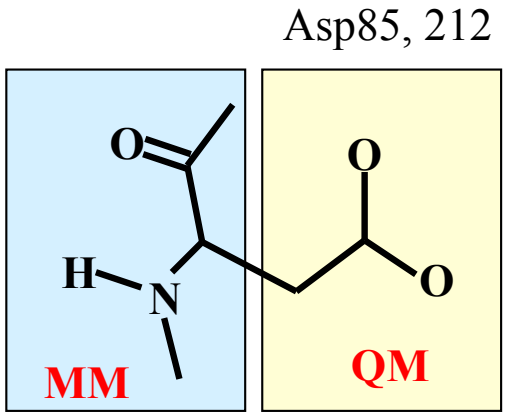




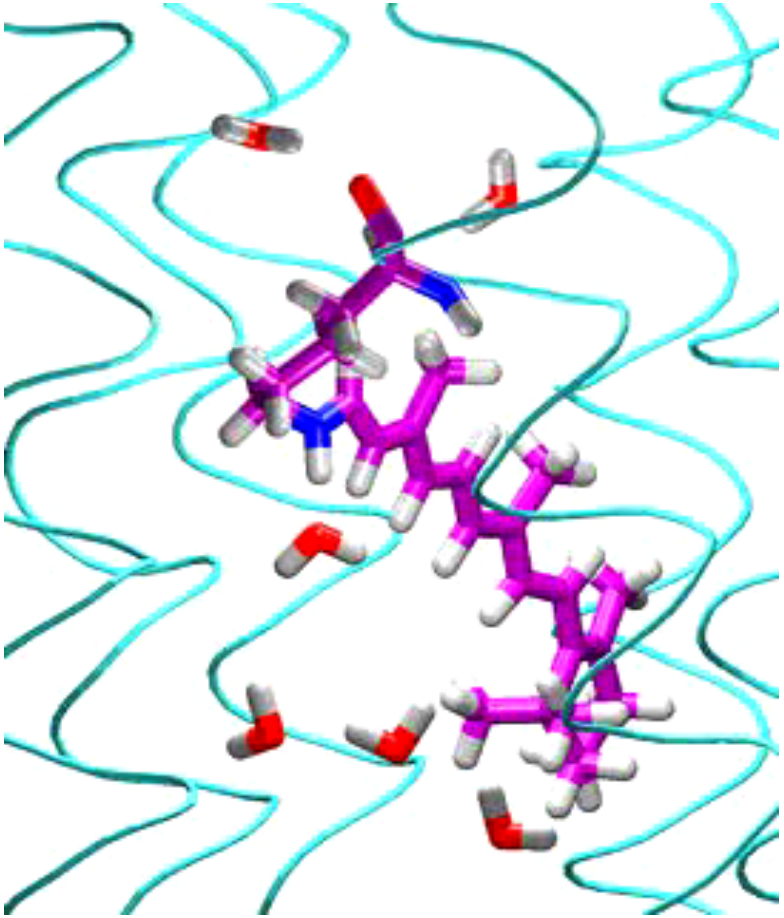
$$\hat{H} = \sum_i \frac{1}{2} p_i^2 + \sum_i \sum_A \frac{Z_A}{r_{iA}} + \sum_{i>j} \frac{1}{r_{ij}} + \sum_{A>B} \frac{Z_A Z_B}{r_{AB}}$$

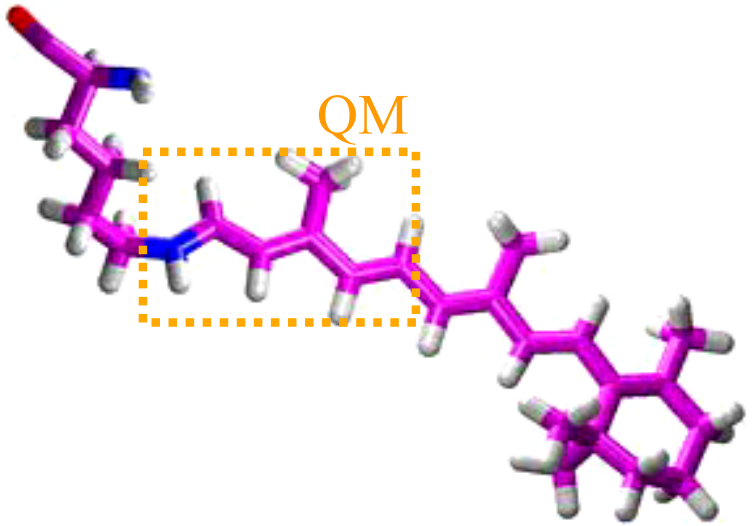
$$+ \sum_i \sum_p \frac{q_p}{r_{ip}} + \sum_A \sum_p \frac{Z_A q_p}{r_{Ap}}$$

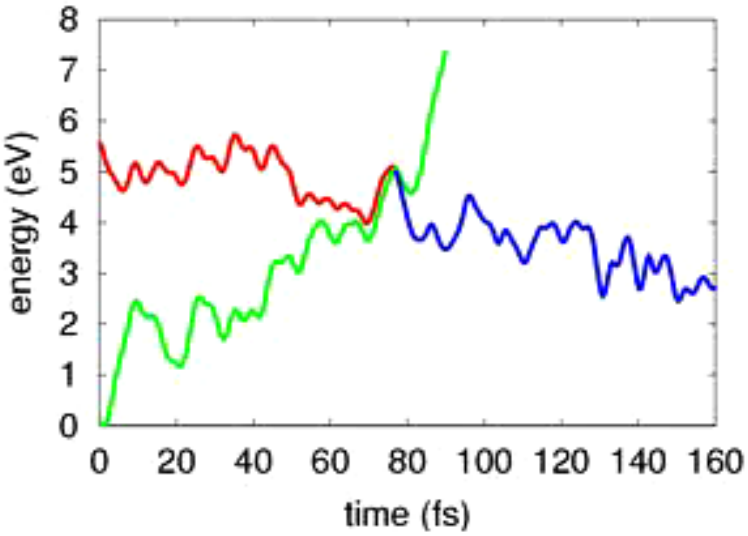
$$+ V_{QM-MM}^{MM} + V_{MM}^{MM}$$



Ab Initio QM/MM Excited State MD Simulation

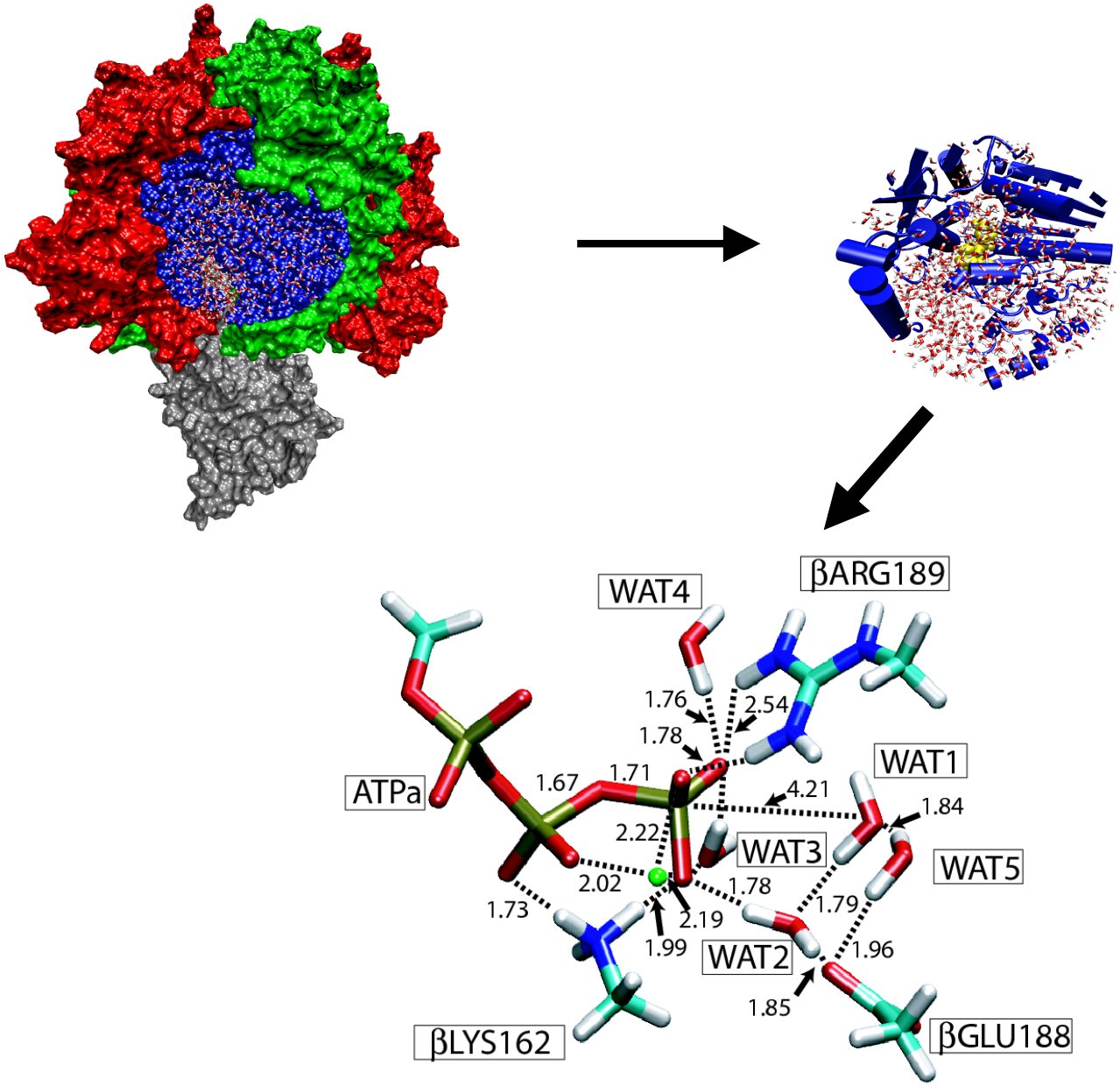






Quantum mechanical (QM) treatment of the chromophore, and force field (MM) treatment of the embedding protein

QM/MM calculation of ATP hydrolysis



Coarse grain modeling of lipids

150 particles

9 particles!