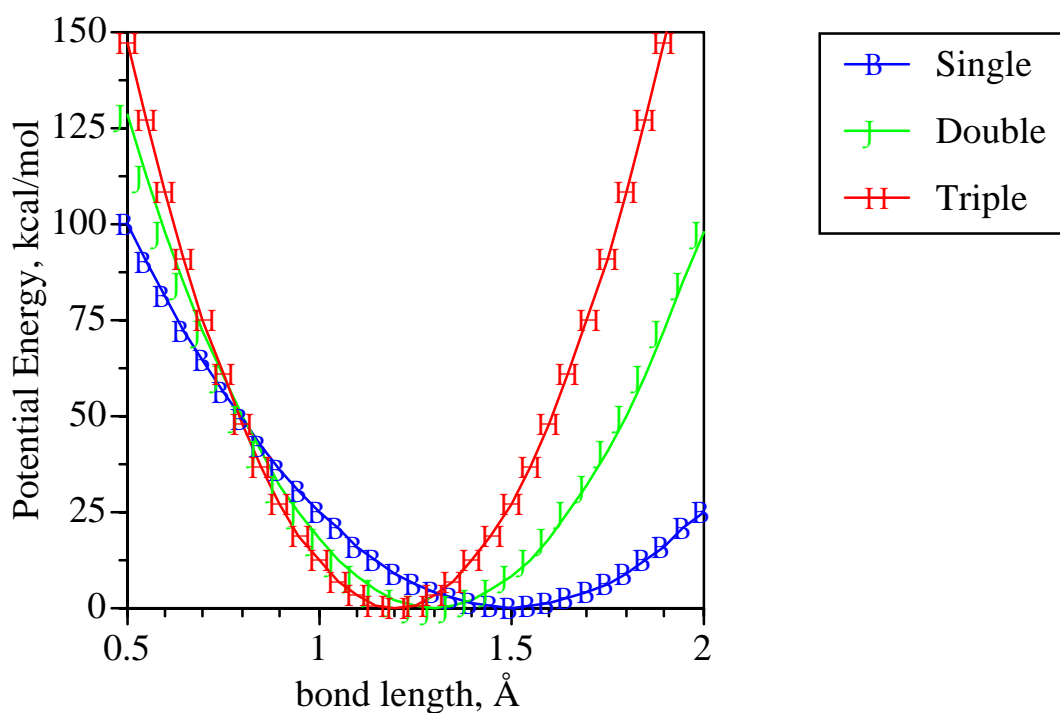


# Empirical Force Field Parameters

Theoretical Chemistry is based on the application of mathematical equations to describe the relationship of chemical structure to energy. This information, in combination with statistical mechanics, allows for, in principle, all properties of a system to be calculated. In practice, however, this is limited by the inability to calculate the energy of all possible conformations of a chemical system (note that a protein has ca.  $10^n$  conformations, where  $n$  is the number of amino acids). One way to overcome this limitation is the use of simple mathematical functions to treat the structure-energy relationship; this is the method of choice for the study of biological molecules, where the molecular weight of the molecules is large (> 10kDal) and the aqueous environment must be included. This type of approach is referred to as molecular mechanics or empirical force field calculations. However, the equation alone does not allow for computation of structure-energy relationships. In addition, parameters must be included in the mathematical equation. Different parameters allow for the same mathematical equation to be applied to different chemical entities. Further, the “quality” of these parameters dictate the validity of the computed structure-energy relationships. In this session an overview of empirical force field parameters along with the approach used in CHARMM to optimize those parameters will be presented.

$$E_{bond} = K_{bond} (b - b_o)^2$$

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	300 kcal/mole/Å <sup>2</sup>	1.2 Å



[http://www.pharmacy.umaryland.edu/~alex/www\\_alex/lectures/compchem\\_1.html](http://www.pharmacy.umaryland.edu/~alex/www_alex/lectures/compchem_1.html)

## **Empirical Force Field Parameter Sets**

### **Class I**

CHARMM(Foloppe & MacKerell, 2000; MacKerell & Banavali, 2000; MacKerell *et al.*, 1998; Schlenkrich *et al.*, 1996)

Proteins, nucleic acids, lipids, carbohydrates and a variety of small model compounds, including coenzymes

CHARMm (MSI)(Momany & Rone, 1992)

AMBER(Cornell *et al.*, 1995)

OPLS/AMBER(Jorgensen & Tirado-Rives, 1988; Pranata *et al.*, 1991)

ECEPP (Dunfield and others, JPC, 1978, 82:2609)

### **Class II**

CFF93 (Biosym)(Hwang *et al.*, 1994)

MM3(Lii & Allinger, 1991)

MMFF94 (Merck, Available in CHARMM)(Halgren, 1996)

DREIDING(Mayo *et al.*, 1990)

## Class I Potential Energy Function (CHARMM)

## Intramolecular

$$\sum_{\text{bonds}} K_b (b - b_o)^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_o)^2 + \sum_{\text{torsions}} K_\phi (1 + \cos(n\phi - \delta))$$

$$+ \sum_{\text{impropers}} K_\phi (\phi - \phi_o)^2 + \sum_{\text{Urey-Bradley}} K_{UB} (r_{1,3} - r_{1,3,o})^2$$

## Intermolecular

$$\sum_{\text{electrostatics}} \frac{q_i q_j}{r_{ij}} + \sum_{\text{VDW}} \epsilon_{ij} \left[ \left( \frac{R_{\text{min},ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{\text{min},ij}}{r_{ij}} \right)^6 \right]$$

## Parameter definitions

### Equilibrium terms

$b_o$ : bonds

$\theta_o$ : angles

$r_{1,3o}$ : Urey-Bradley

$\omega_o$ : impropers

$n$ : dihedral multiplicity

$\delta_o$ : dihedral phase

### Force constants

$K_b$ : bonds

$K_\theta$ : angles

$K_{UB}$ : Urey-Bradley

$K_\omega$ : impropers

$K_\phi$ : dihedral

### Intermolecular terms

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

$R_{min}$ : L-J radius ( $R_{min}/2$  in CHARMM)

#### Combining rules

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

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

$q_i$ : partial atomic charge

All possible terms used except Urey-Bradley and Impropers

constant dielectric of 1

no 1,4 scaling of vdW or electrostatic (except for special cases)

parameterize using infinite cutoffs (except for condensed phase calculations)

- (A) \* CHARMM example topology file
  - \*
- (B) 19 1
- (C) MASS 1 H 1.00800 H  
MASS 2 O 15.99900 O
- (D) DECL -C  
DECL -O  
DECL +N  
DECL +H  
DECL +CA
- (E) DEFA FIRS NTER LAST CTER
- (F) AUTOGENERATE ANGLES DIHEDRAL
- (G) RESI GLY 0.000
- (G1) GROUP
- (G2) ATOM N NH1 -0.35 H CA  
ATOM H H 0.25  
ATOM CA CH2E 0.10
- (G3) BOND N CA CA C C +N C O N H  
DOUBLE CA CB  
TRIPLE CB CG
- (G4) ANGL N CA C (optional)
- (G5) DIHE -C N CA C N CA C +N (optional)
- (G6) IMPH N -C CA H
- (G7) DONO H N
- (G8) ACCE O C
- (G9) IC -C CA \*N H 0.0000 0.00 180.00 0.00 0.0000  
IC -C N CA C 0.0000 0.00 180.00 0.00 0.0000

MacKerell, Parameter Notes

(G10) PATCH FIRST NONE LAST NONE

## PATCH residue

(H) PRES CTER -1.000  
(H1) DELE ATOM O  
(H2) ATOM C C 0.14  
      ATOM OT1 OC -0.57  
      ATOM OT2 OC -0.57  
(H3) BOND C OT1 C OT2  
      ANGL OT1 C OT2 (optional)  
      DIHE N CA C OT2 (optional)  
      IMPH C CA OT2 OT1  
(H4) ACCE OT1 C  
      ACCE OT2 C  
      IC N CA C OT2 0.0 0.0 180.0 0.0 0.0  
      IC OT2 CA \*C OT1 0.0 0.0 180.0 0.0 0.0  
  
(I) END

(A) \* CHARMM example parameter file  
\* (see documentation for more details)

(B) BOND

H O 500.0 1.00

(C) ANGLE (THETA)

H O H 100.0 104.51 20.0 1.70

(D) DIHEDRAL (PHI)

HT CT CT HT 10.0 3 180.0

X CT CT X 10.0 3 180.0

(E) IMPH

O C CT N 5.0 1 0.0

X C CT X 5.0 1 0.0

X X CT N 5.0 1 0.0

O X X N 5.0 1 0.0

(F) NBONDED nonbond-spec

H 0.00 -0.046 0.2245 0.00 -0.023 0.2245

O 0.00 -0.120 1.8000 0.00 -0.060 1.8000

(G) NBFIX

H O -0.30 1.50 -0.15 1.50

(H) HBONDS hbond terms (optional)

H O -0.00 1.00

(I) END

## Class II Potential Energy Function (CFF93)

## Intramolecular

$$\begin{aligned}
& \sum_{\text{bonds}} \left[ K_{b,2} (b - b_o)^2 + K_{b,3} (b - b_o)^3 + K_{b,4} (b - b_o)^4 \right] \\
& + \sum_{\text{angles}} \left[ K_{\theta,2} (\theta - \theta_o)^2 + K_{\theta,3} (\theta - \theta_o)^3 + K_{\theta,4} (\theta - \theta_o)^4 \right] \\
& + \sum_{\text{dihedrals}} \left[ K_{\phi,1} (1 - \cos \phi) + K_{\phi,2} (1 - \cos 2\phi) + K_{\phi,3} (1 - \cos 3\phi) \right] \\
& + \sum_{\text{impropers}} K_{\chi} \chi^2 \\
& + \sum_{\text{bonds}} \sum_{\text{bonds}'} K_{bb'} (b - b_o)(b' - b_o') + \sum_{\text{angles}} \sum_{\text{angles}'} K_{\theta\theta'} (\theta - \theta_o)(\theta' - \theta_o') \\
& + \sum_{\text{bonds}} \sum_{\text{angles}} K_{b\theta} (b - b_o)(\theta - \theta_o) \\
& + \sum_{\text{bonds}} \sum_{\text{dihedrals}} (b - b_o) \left[ K_{\phi,b1} \cos \phi + K_{\phi,b2} \cos 2\phi + K_{\phi,b3} \cos 3\phi \right] \\
& + \sum_{\text{bonds}'} \sum_{\text{dihedrals}'} (b' - b_o') \left[ K_{\phi,b'1} \cos \phi + K_{\phi,b'2} \cos 2\phi + K_{\phi,b'3} \cos 3\phi \right] \\
& + \sum_{\text{angles}} \sum_{\text{dihedrals}} (\theta - \theta_o) \left[ K_{\phi,\theta1} \cos \phi + K_{\phi,\theta2} \cos 2\phi + K_{\phi,\theta3} \cos 3\phi \right] \\
& + \sum_{\text{angles}} \sum_{\text{angles}'} \sum_{\text{dihedrals}} (\theta - \theta_o)(\theta' - \theta_o') \cos \phi
\end{aligned}$$

## Intermolecular

$$\sum_{\text{electrostatics}} \frac{q_i q_j}{r_{ij}} + \sum_{\text{VDW}} \epsilon_{ij} \left[ 2 \left( \frac{R_{\min,ij}}{r_{ij}} \right)^9 - 3 \left( \frac{R_{\min,ij}}{r_{ij}} \right)^6 \right]$$

## Polarizable (non-additive) Force Fields

Include explicit term in potential energy function to treat polarization of charge distribution by the environment.

Still under development.

PIPF (Gao and coworkers)

AMBER(Caldwell & Kollman, 1995)

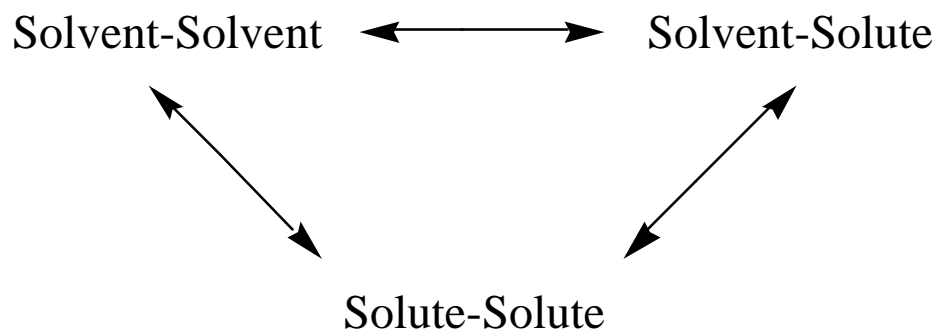
Friesner/Berne et al.(Stern *et al.*, 1999)

CHARMM (In progress)

# Self-Consistent Empirical Parameterization

Intramolecular  $\longleftrightarrow$  Intermolecular

"Interaction Triad"





## Extent of Parameter Optimization

Minimal: by analogy

- quick and dirty

- starting point

- adequate for:

  - internal terms excluding dihedrals

  - Lennard-Jones terms

Maximal: detailed parameter optimization

- time-consuming

- requires sufficient target data

## Choice based on ultimate target of the calculations

Minimal

- crude gas-phase modeling

- NMR and X-ray structure determination (assuming constraints will dominate the structure)

Maximal

- free energy calculations

- umbrella sampling

- mechanistic studies

- subtle environmental effects

## Manual vs. Automated Fitting Procedures

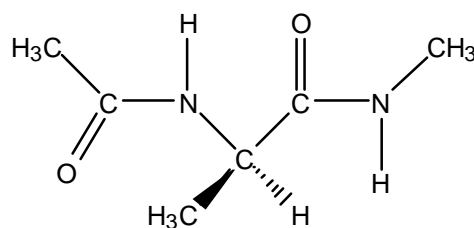
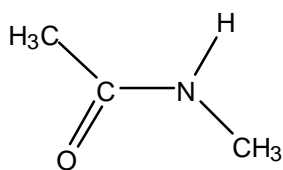
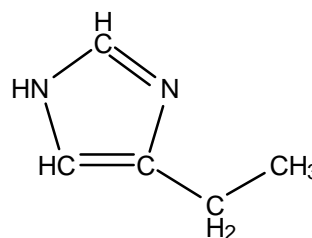
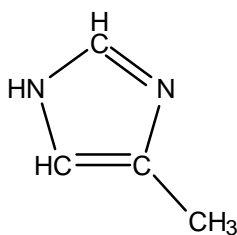
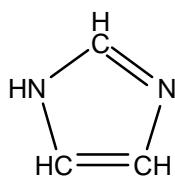
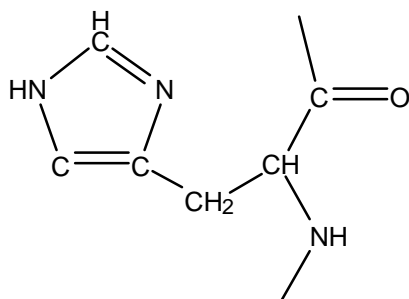
### Manual

- Focus on individual molecules or classes of molecule
- Hierarchical approach
- Physical Insights

### Automated

- Requires large set of target data
- Re-optimize as set expands
- Necessary for Class II/polarizable force fields???

## Selection of Appropriate Model Compounds



Protonation states

## Initial Guess of Parameters

### Hierarchical Approach

Create molecule based on analogy with already parameterized compounds

Assign new parameters as required and *annotate*

In CHARMM charges are flexible due to assignment in topology file

Test model compounds with respect to target data

*Only* adjust new parameters

Retest model compounds with respect to target data

Add new atom types if necessary

Continue optimization

Maintain quality of previously parameterized molecules while maximizing quality of new molecule.

# Intermolecular parameterization target data

## *Small molecule/local*

Interaction energies and geometries: *ab initio*, microwave, mass spectrometry

Dipole moments

*ab initio* electrostatic potentials

## *Condensed phase/global*

Heats of vaporization, solvation and sublimation

Crystal lattice parameters

Crystal survey data of non bonded interactions

Free energies of solvation

Molecular volumes (density), partial molar volumes

## Intermolecular Small Molecule/Local

Electrostatic: partial atomic charges

effective pair potentials: implicit inclusion of polarizability

explicit treatment of polarizability: future, \$\$\$

LJ parameters:

relative values of  $R_{\min}$  and epsilon for individual atoms (difficult)

## Target Data

### Experimental

Interaction enthalpies (mass spectrometry)

Interaction geometries (microwave)

Crystal interactions

dipole moments

### *Ab initio*

Mulliken Population Analysis

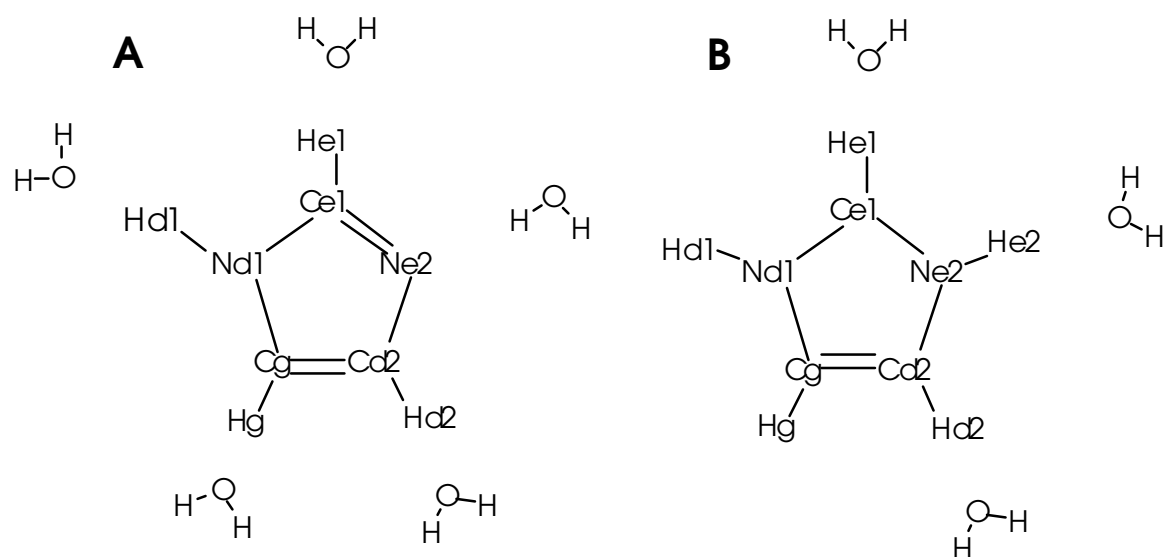
Electrostatic Potential Based(Chirlian & Francl, 1987; Singh & Kollman, 1984)

Chirlian and Francl: Gaussian Package POP=(CHELPG,DIPOLE)

RESP: restricted ESP(Cornell *et al.*, 1993)

Dimer Interaction Energies and Geometries Based(Jorgensen, 1986; MacKerell & Karplus, 1991)

Local polarization effects included in *ab initio* interaction data

Neutral Species (see imid\_wat.inp)

scale HF/6-31G\* *ab initio* interaction energies by 1.16

offset HF/6-31G\* *ab initio* minimum interaction distances by -0.1 to -0.2 Å

Charged Species

NO scaling of a.i. interaction energies

offset HF/6-31G\* *ab initio* minimum interaction distances by 0.0 to -0.1

Dimer Interactions

Interaction	6-31G*		Experimental Enthalpy	Empirical			
	Rmin	Emin		Rmin	Emin		
<u>Imidazole with Water</u>							
Ne2 to Water H	2.12	-7.26		1.90	-7.23		
Hd1 to Water O	2.07	-6.65		1.88	-6.58		
He1 to Water O	2.45	-2.44		2.22	-2.42		
Hg to Water O	2.51	-2.40		2.65	-1.49		
Hd2 to Water O	2.66	-0.99		2.63	-0.88		
<u>Imidazolium with Water</u>							
HD1 to Water O	1.85	-15.94	-14.8	1.76	-15.94		
HE1 to Water O	2.03	-12.28	-12.6	1.93	-12.28		
HD2 to Water O	2.13	-9.53	-12.3	2.12	-9.50		
<u>Imidazolium HD1 to Imidazole NE2</u>							
	6-31G*			Experimental Enthalpy	Empirical		
	Rmin	Angle	Emin		Rmin	Angle	Emin
parallel	1.87	132	-22.54	-23.7	1.83	130	-20.20

antiparallel	1.87	129	-22.70	1.83	134	-20.19
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Experimental, Moet-Ner, 1988.

## Intermolecular condensed phase/global

maximal approach to parameter optimization

final check of parameters

A) pure solvents: **LJ-parameters** (neat, pure liquid simulations)

heats of vaporization

molecular volumes

B) aqueous solution (free energy perturbation or solution phase simulations)

free energy of solvation, heats of solvation

molecular volumes (partial molar volumes)

C) crystals (crystal simulations)

heats of sublimation

lattice parameters

details of intramolecular and intermolecular geometries

See **imi20\_xtal\_uc.inp**, **imi20\_xtal\_uc\_ana.inp**, **l\_his\_xtal\_uc.inp** and **ace\_hisp\_xtal\_uc.inp**

## Intramolecular parameterization target data

Geometries: microwave, x-ray crystallography, electron diffraction, *ab initio*,  
crystal surveys of geometries

Vibrations: infrared, raman, *ab initio*

Conformational energies: microwave, *ab initio*

## Intramolecular Geometries

### Equilibrium bond lengths, angles and dihedral phase and multiplicity

#### Target data

- gas phase (microwave, electron diffraction)
- crystal (surveys preferable over single crystals)
- ab initio* (charged species, hydrogens)

#### Empirical, Experimental and *Ab initio* geometric parameters for Imidazole

Term	Emp.	Micro <sup>1</sup>	Neu. 20C <sup>2</sup>	Neu. -150C <sup>2</sup>	6-31G*
Bond lengths, Å					
CE1-NE2	1.356	1.364	1.359	1.355	1.361
CE1-ND1	1.316	1.314	1.330	1.333	1.296
NE2-CD2	1.379	1.377	1.387	1.378	1.363
ND1-CG	1.383	1.382	1.394	1.382	1.361
CG-CD2	1.359	1.364	1.375	1.369	1.358
HE1-CE1	1.092	1.079	1.099	1.088	1.070
HE2-NE2	0.999	0.998	1.052	1.064	1.000
HD2-CD2	1.081	1.079	1.091	1.091	1.070
HG-CG	1.083	1.079	1.091	1.084	1.071
Bond angles, degrees					
CE1-NE2-CD2	106.9	106.9	107.3	106.9	107.2
CE1-ND1-CG	105.3	104.9	105.3	105.1	106.0
ND1-CE1-NE2	111.8	112.0	111.6	111.8	111.1
NE2-CD2-CG	105.9	105.5	105.9	106.3	105.2
ND1-CG-CD2	110.2	110.7	109.9	109.8	110.5
HE1-CE1-NE2	124.5	125.5	124.6	124.3	124.5
HE2-NE2-CE1	126.5	126.2	127.2	127.0	126.4
HD2-CD2-NE2	124.5	121.9	123.1	123.7	123.1
HG-CG-CD2	129.6	127.9	128.0	128.2	126.1

The empirical, microwave and 6-31G\* structures are planar while the neutron crystal structures are not planar.

<sup>1</sup>Christen et al., 1982, <sup>2</sup>Craven et al., 1977.

Charmm Quick Commands or IC facility (see **imid\_min.inp**)

## Intramolecular flexibility

### Force constants: bonds, angles, dihedrals and impropers

#### Vibrational Spectra (see **imid\_vib.inp**)

IR

Raman

*ab initio* (see **imid\_gaussian\_vib.inp**)

scale HF/6-31G\* by 0.9(Florián & Johnson, 1994)

charged species

assignment of vibrational frequencies to internal coordinates(Pulay *et al.*,

1979)

#### Torsional surfaces (see **imid\_ethyl\_surf.inp**)

microwave

NMR

*ab initio*: angles vs. dihedral

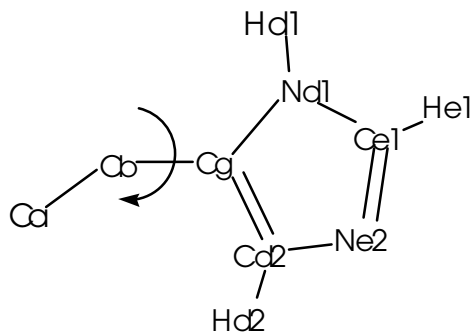
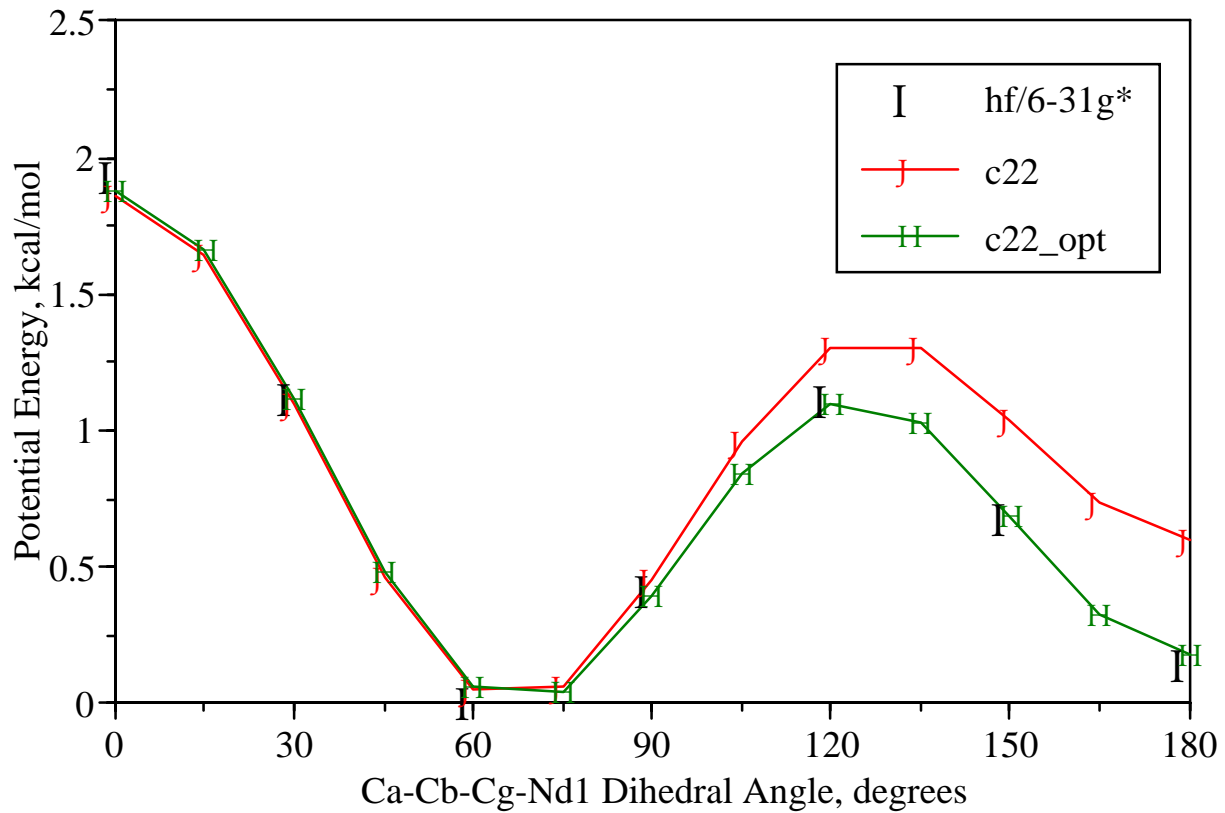
Include Urey-Bradley and Improper terms only if necessary to optimize vibrational spectra

## Experimental and Empirical Frequencies for Imidazole

Mode	Empirical Assignment	Empirical	Experimental	
1	N-H Wag (78), Ring Tor (12)	513	513	
2	Ring Tor (47), C-H Wag (39)	626	626	
3	Ring Tor (89)	674	658	
4	C-H Wag (95)	720	723	
5	Ring Tor (46), C-H Wag (30), N-H Wag (14)	837	809	
6	Ring Def (70), sC-N (22)	884	855	
7	Ring Def (70), sC-N (19)	888	890	
8	C-H Wag (95)	975	930	
9	sC-N (86)	1012	1055	
10	C-H Def (68), sC-C (24)	1076	1074	
11	C-H Def (59), sC-N (33)	1033	1127	
12	C-H Def (39), N-H Def.(24) sC-N (13)	1244	1160	
13	C-H Def (67), N-H Def (18) sC-N (11)	1160	1260	
14	sC-N (46), C-H Def (24) N-H Def (18)	1459	1330	
15	sC-N (49), C-H Def (22) N-H Def (20)	1503	1405	
16	sC-N (46), Ring Def (19) sC-C (16), N-H Def.	1579	1480	
17	sC-N (38), sC-C (27) Ring Def (23)	1589	1530	<b>4.1 %</b>
18	sC-H (99)	3059	3060	
19	sC-H (100)	3158	3135	
20	sC-H (100)	3165	3160	
21	sN-H (100)	3516	3518	<b>0.2 %</b>

Frequencies:  $\text{cm}^{-1}$ . Experimental assignments from Fan et al., 1986. Terms contributing 10 % or more to the potential energy distribution are given. Abbreviations: s, stretch, wag, out-of-plane wagging, tor, torsional rotation, def, in-plane angle deformation.

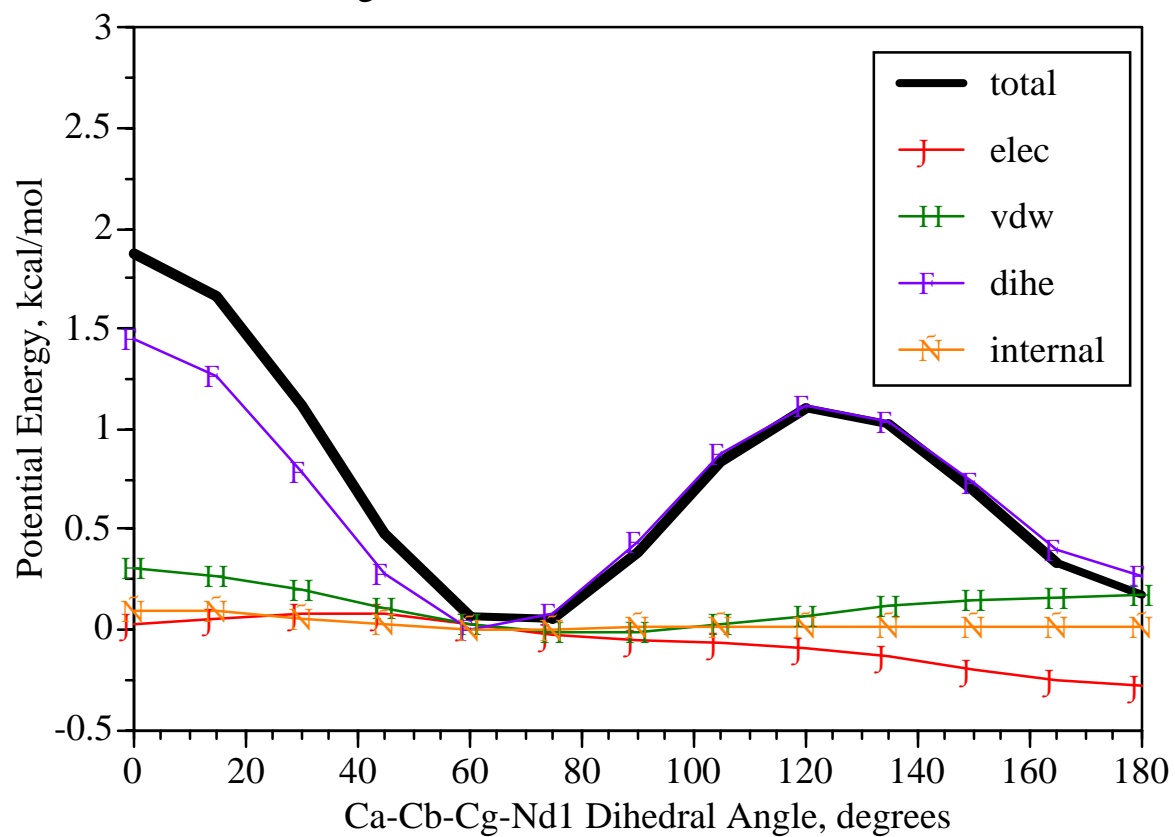
## CHARMM Vibran/MOLVIB facilities



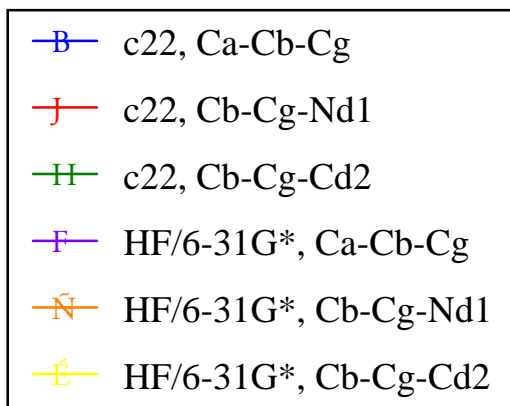
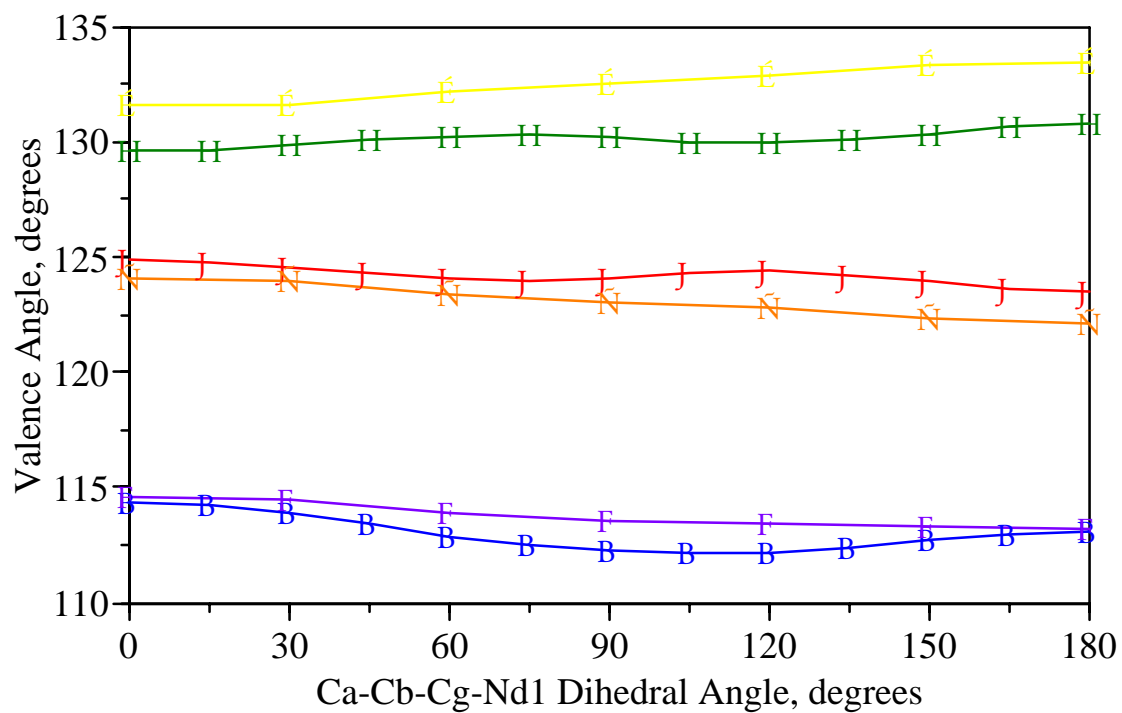
Also look at angles as a function of dihedral to test of deformation of molecule is properly treated; test of both force constants and relative contributions of different terms in the energy function to the surface.

CHARMM Constraints and IC or quick facilities

4-ethylimidazole, energy component contributions to the Ca-Cb-Cg-Nd1 torsion surface

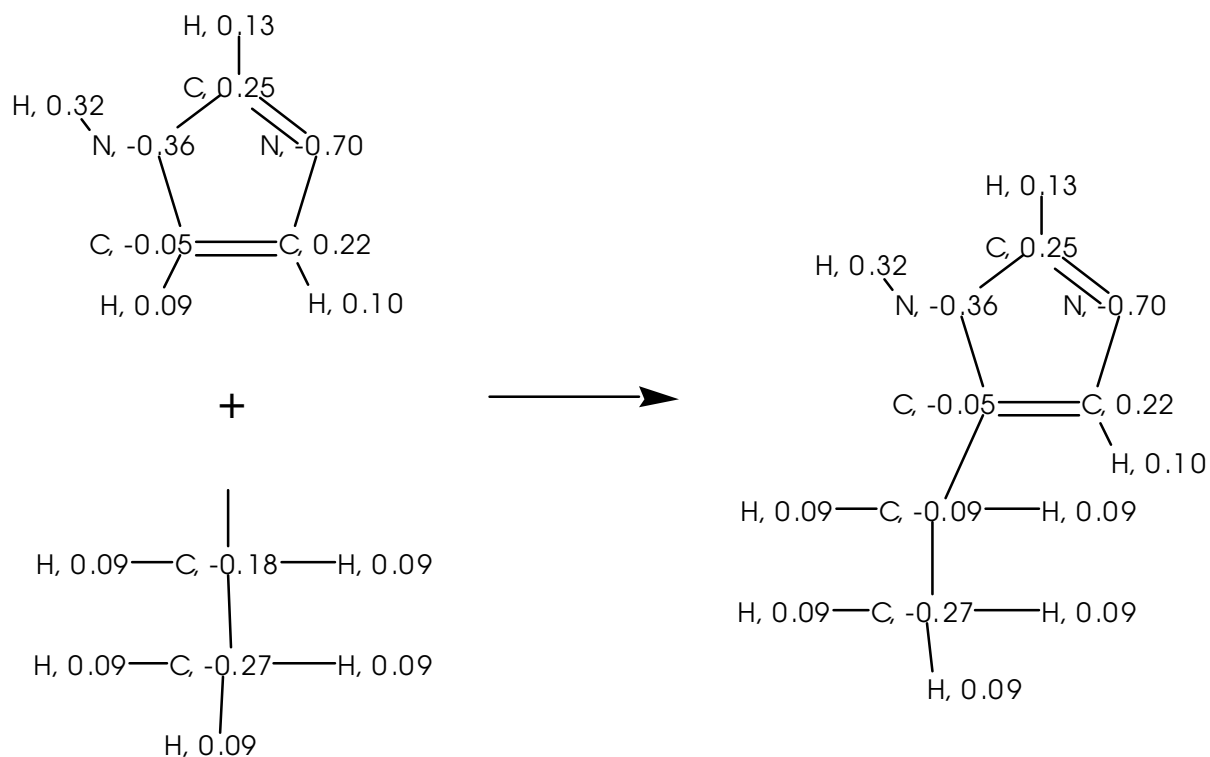


4-ethylimidazole, Valence angles as a function of the Ca-Cb-Cg-Nd1 dihedral angle.



## Combining model compounds into larger molecule

- 1) remove hydrogen create covalent bond between carbons  
(never terminate a model compound with a heteroatom, unless the heteroatom is a terminal atom in the final molecule)
- 2) move charge from deleted hydrogen into the carbon



## Test new linker

- 1) *Ab initio* surface at a reasonable level (HF/6-31G\*)
- 2) Reproduction of crystal structure

## Final testing

- 1) Condensed phase simulations not included in target data.
  - crystals
  - aqueous solution
  - pure solvent
- 2) Be alert during application work.

## Transition State Force Field Parameters(Eksterowicz & Houk, 1993)

Same approach as standard force field parameterization

Require target data for transition state of interest: *ab initio*

## Metal Force Field Parameterization(Hoops *et al.*, 1991)

Only Interaction parameters

Include Intramolecular terms

## Parameterization of QM atoms for QM/MM calculations

## Parameter References

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