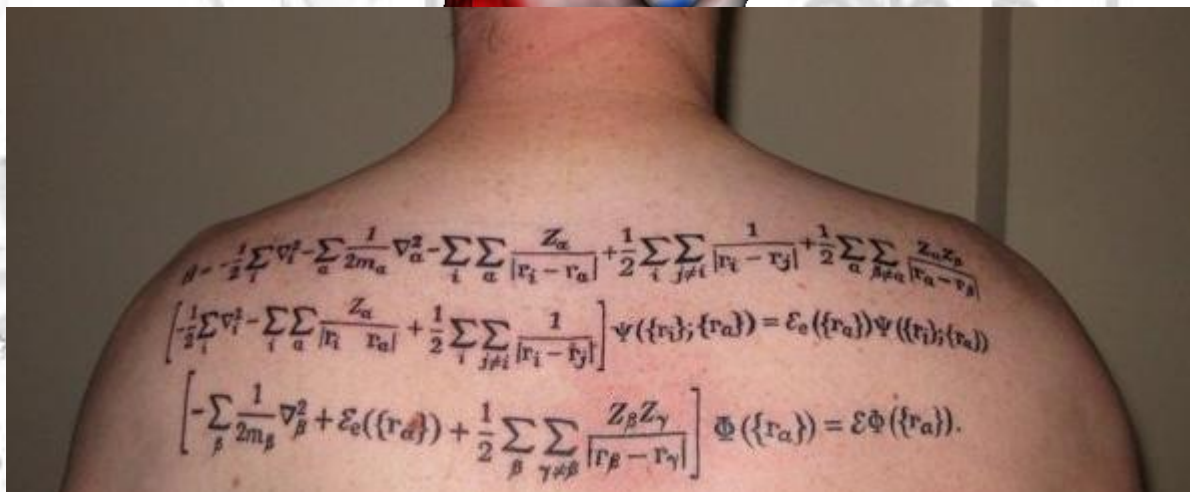
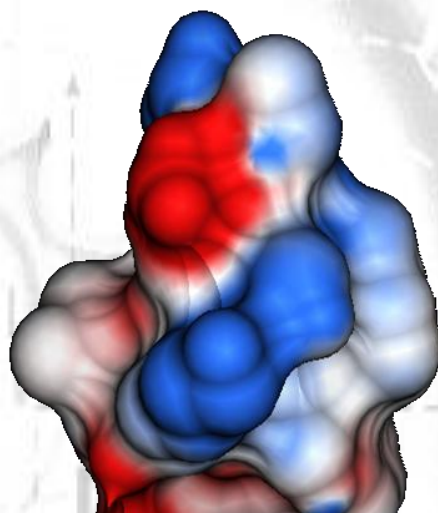


Molecular... energetics!





What we are still orphans:

- Virtualize molecular topology (shape and volume);
- Virtualize the generation of alternative conformers;
- Virtualize the evaluation of the stability of each conformer.



Back to stability concept:

Stability as a measure of the geometrical deformability of an object;

Rigidity as a measure of the reduction degree of the geometrical deformability of an object.



Back to stability concept:

Natural systems left to themselves move towards states of higher stability. For example, water flows down a hill or a ball rolls down a hill, if free to do so.

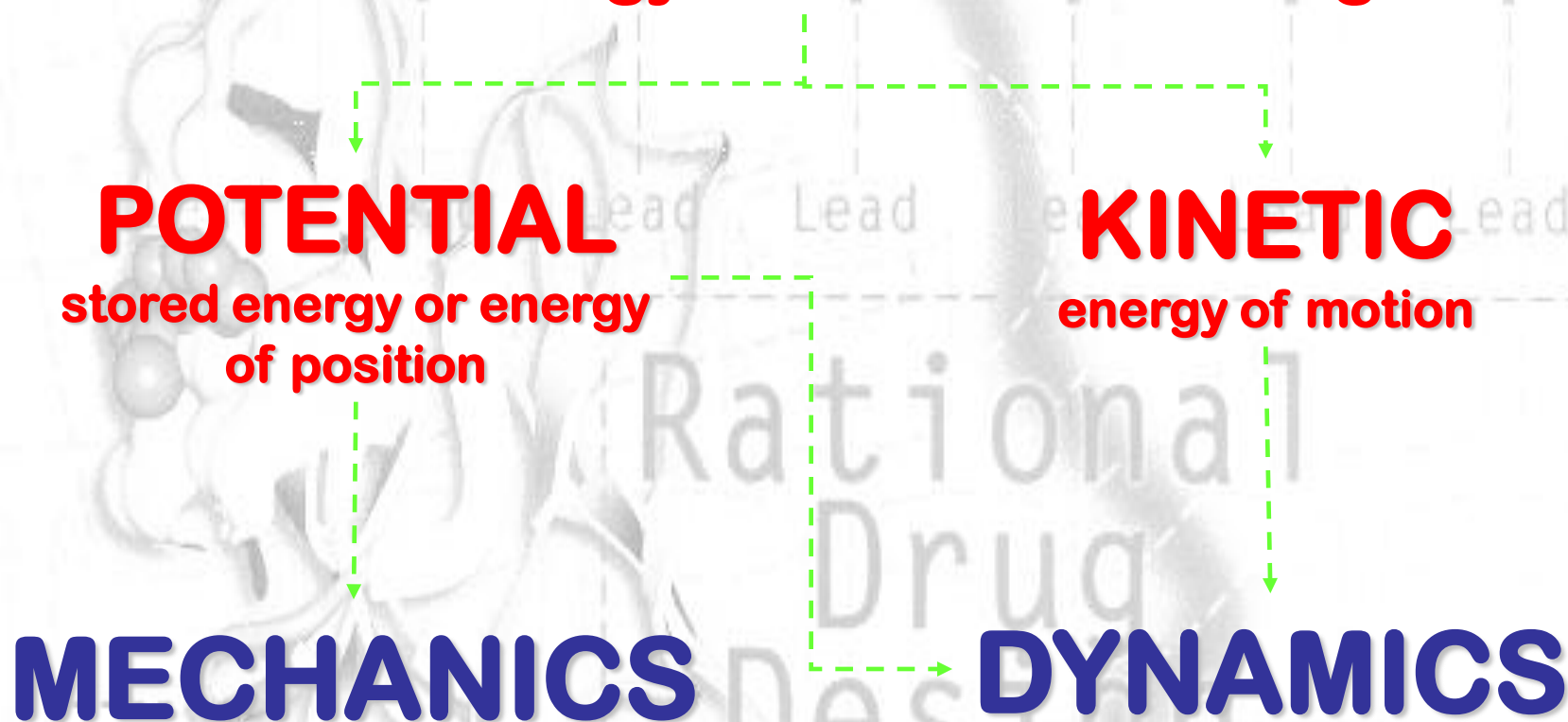
We can use the *energy* concept as a measure of the *stability* of a natural system.

As a rule, the lower the energy of a system, the more stable it is. As a result, left to themselves, systems attempt to reach the configuration with the lowest energy possible under a given set of constraints.



Back to stability concept:

All forms of energy fall under two categories:





Here what we need in the virtual world:

0.9760	0.5530	0.1180	C
2.1810	1.4240	0.1010	C
2.9110	1.3580	-1.2420	C
2.2460	1.6700	-2.0550	H
3.2180	0.3270	-1.4520	H
4.1000	2.2110	-1.2400	N
3.8190	3.1840	-1.1170	H
4.5460	2.1620	-2.1560	H
2.8610	1.1260	0.9100	H
1.8740	2.4560	0.3100	H
-0.1610	0.9170	-0.5670	N
-1.0220	-0.0510	-0.3510	C
-2.0310	-0.1010	-0.7380	H
-0.4920	-1.0270	0.4440	N
-0.9630	-1.8680	0.7470	H
0.7870	-0.6560	0.7530	C
1.4290	-1.2620	1.3760	H

→ **kcal/mol**



Actually, we have already an equation that does this:

Schrödinger equation

0.9760	0.5530	0.1180	C
2.1810	1.4240	0.1010	C
2.9110	1.3580	-1.2420	C
2.2460	1.6700	-2.0550	H
3.2180	0.3270	-1.4520	H
4.1000	2.2110	-1.2400	N
3.8190	3.1840	-1.1170	H
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2.8610	1.1260	0.9100	H
1.8740	2.4560	0.3100	H
-0.1610	0.9170	-0.5670	N
-1.0220	-0.0510	-0.3510	C
-2.0310	-0.1010	-0.7380	H
-0.4920	-1.0270	0.4440	N
-0.9630	-1.8680	0.7470	H
0.7870	-0.6560	0.7530	C
1.4290	-1.2620	1.3760	H



$$i\hbar \frac{\partial}{\partial t} \Psi(\mathbf{r}, t) = \left[\frac{-\hbar^2}{2m} \nabla^2 + V(\mathbf{r}, t) \right] \Psi(\mathbf{r}, t)$$

Time-dependent Schrödinger equation
(single non-relativistic particle)



Why we cannot simply use Schrödinger equation?

Schrödinger equation can only be solved exactly for the hydrogen atom.

For more complex systems (i.e. many electron atoms/molecules) we need to make some simplifying assumptions/approximations and solve it numerically.

The solution of the approximated Schrödinger equation is very time consuming and solvable only for a small ensemble of atoms.



Why we cannot simply use Schrödinger equation?

Schrödinger equation can only be solved exactly for the hydrogen atom.

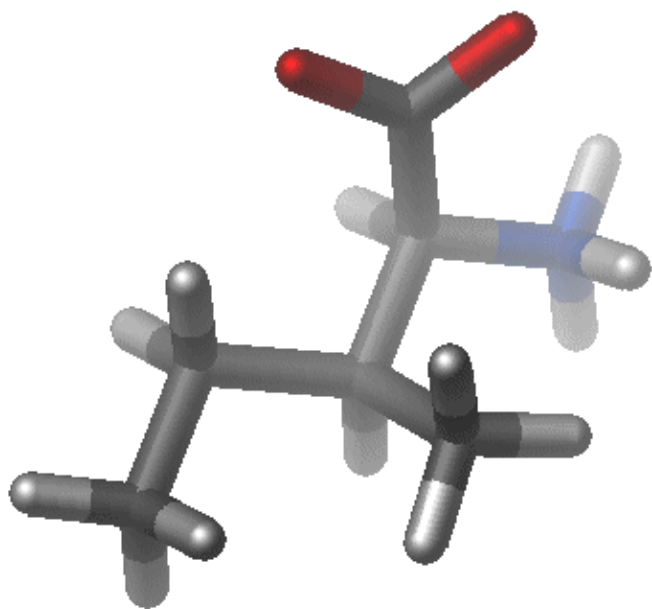
Lead Lead Lead Lead Lead Lead Lead

Rational
Drug
Design



And now? Let's try in another way...

Where energy (potential) is stored inside a molecule? Mainly (but not only) here:



BOND ENERGIES

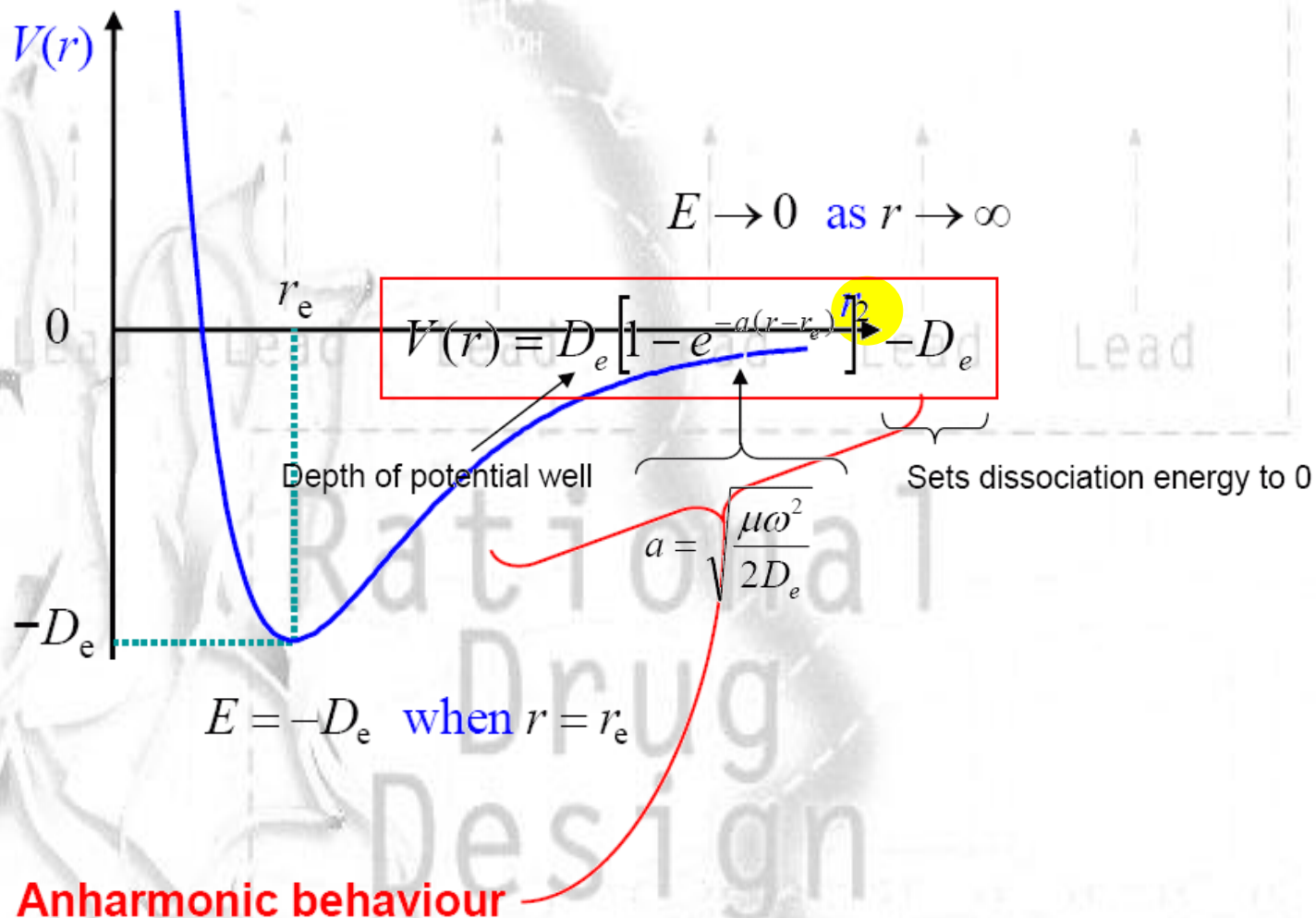
BOND ANGLE ENERGIES

TORSION ANGLE ENERGIES



Do you remember the Morse's potential?

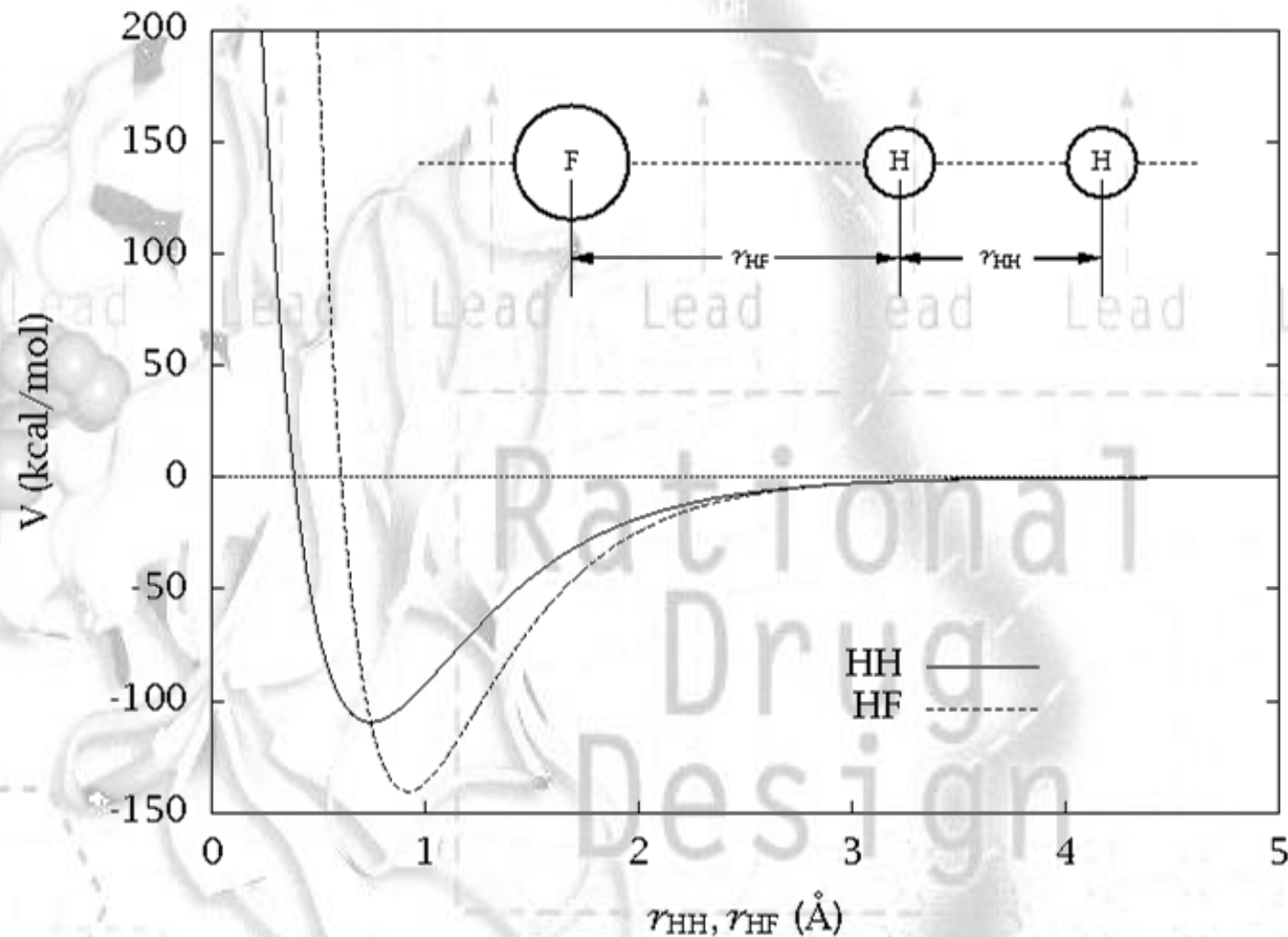
Philipp McCord Morse



P. M. Morse, Diatomic molecules according to the wave mechanics. II. Vibrational levels. *Phys. Rev.* 1929, 34, 57.



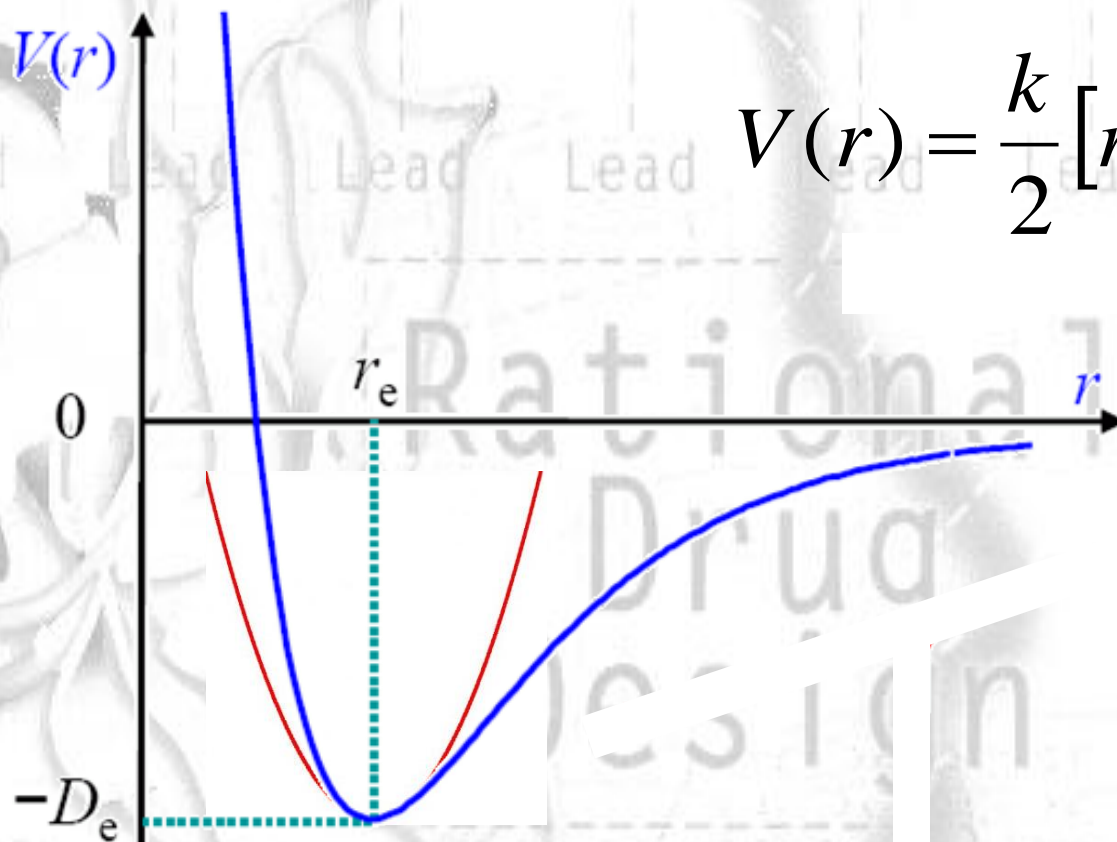
This is very interesting because we have different Morse's potentials corresponding to different kind of chemical bonds:



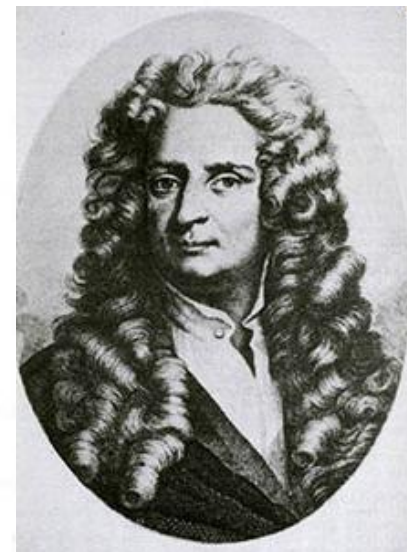


a brilliant comparison:

$$V(r) = D_e \left[1 - e^{-a(r-r_e)} \right]^2 - D_e$$

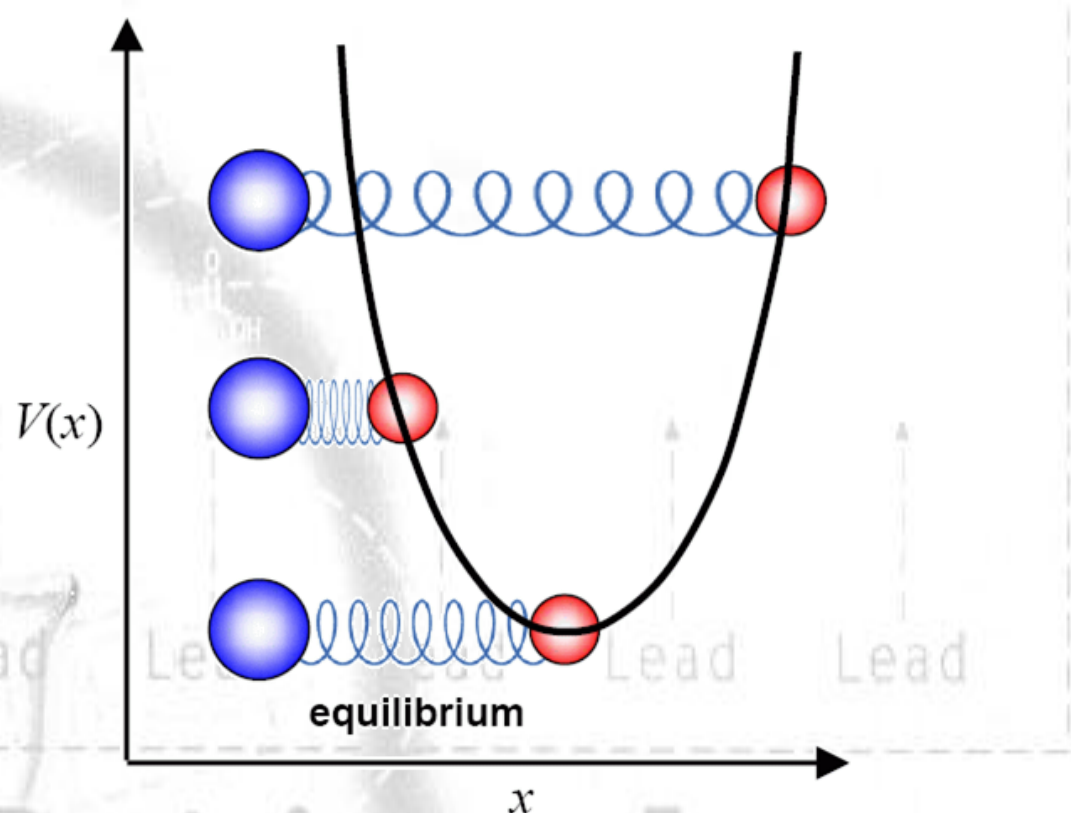


$$V(r) = \frac{k}{2} [r - r_e]^2 - D_e$$





Robert Hooke



... remember?

$$F = -kx$$

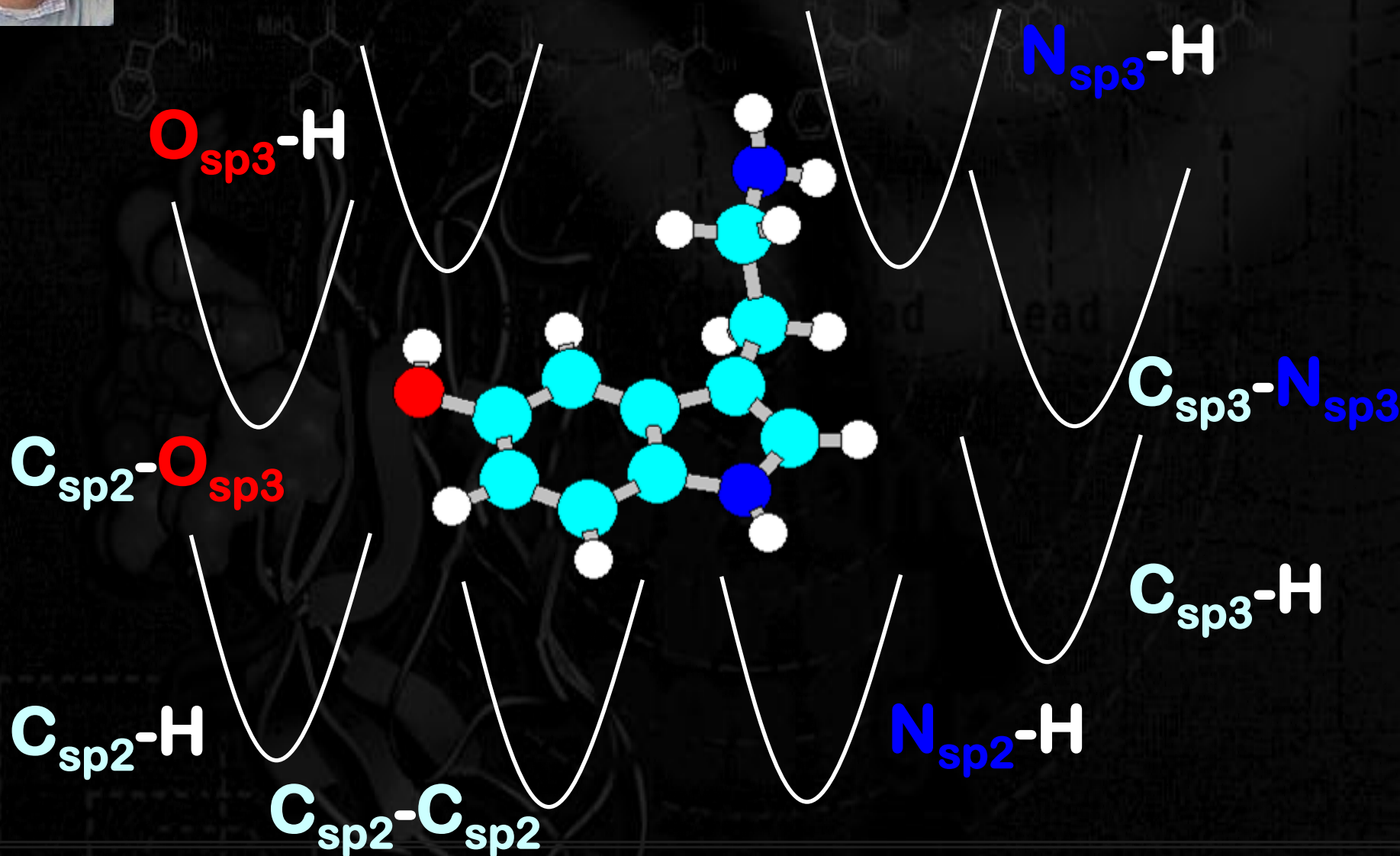
$$dV = Fdx = -kxdx$$

$$V(x) = \int -kxdx = -k \int xdx = -k \frac{1}{2} x^2$$





We can simplify like that: *one bond one parabola!*





Force Field (FF) parameters: tabulated experimental values crucial to correctly solve FF equation.

**bond distance
(from coordinates matrix)**



$$\Sigma \left[\frac{1}{2} k_{str} (r - r_e)^2 - D_e^{str} \right]$$

**stretching constant
(from IR spectroscopy)**



**bond energy
(from thermochemistry)**





Force Field (FF): the empirical energy equation!

$E_p \cong$

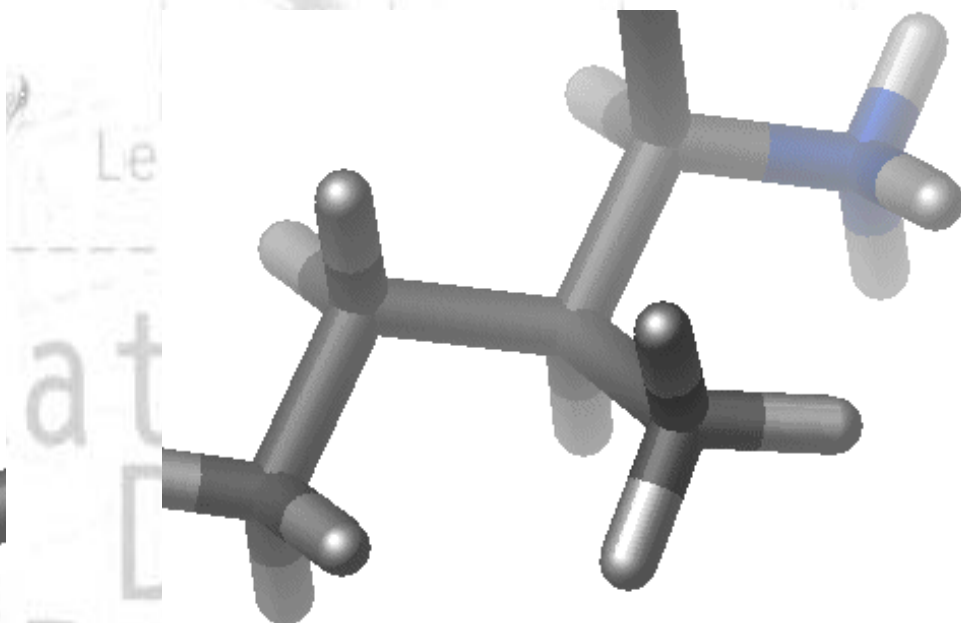
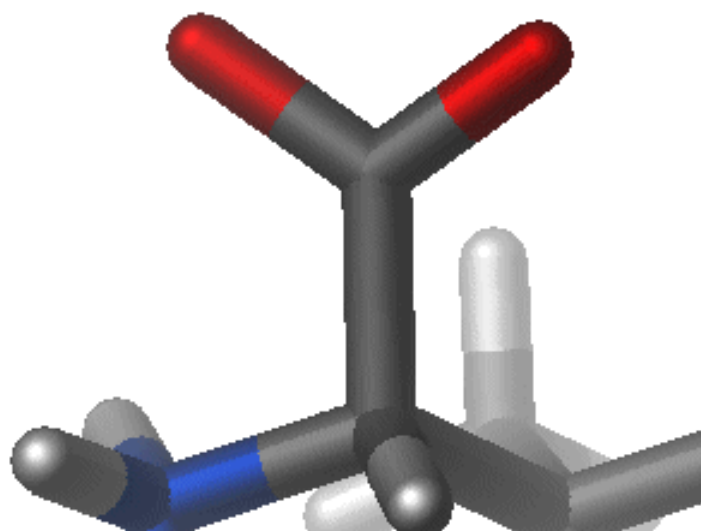
0.9760	0.5530	0.1180 C
2.1810	1.4240	0.1010 C
2.9110	1.3580	-1.2420 C
2.2460	1.6700	-2.0550 H
3.2180	0.3270	-1.4520 H
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3.8190	3.1840	-1.1170 H
4.5460	2.1620	-2.1560 H
2.8610	1.1260	0.9100 H
1.8740	2.4560	0.3100 H
-0.1610	0.9170	-0.5670 N
-1.0220	-0.0510	-0.3510 C
-2.0310	-0.1010	-0.7380 H
-0.4920	-1.0270	0.4440 N
-0.9630	-1.8680	0.7470 H
0.7870	-0.6560	0.7530 C
1.4290	-1.2620	1.3760 H

$\cong \sum E_{leg}$

$\cong \sum [\frac{1}{2}k_{str}(r-r_e)^2 - D_e^{str}]$



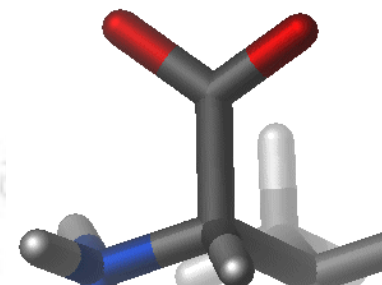
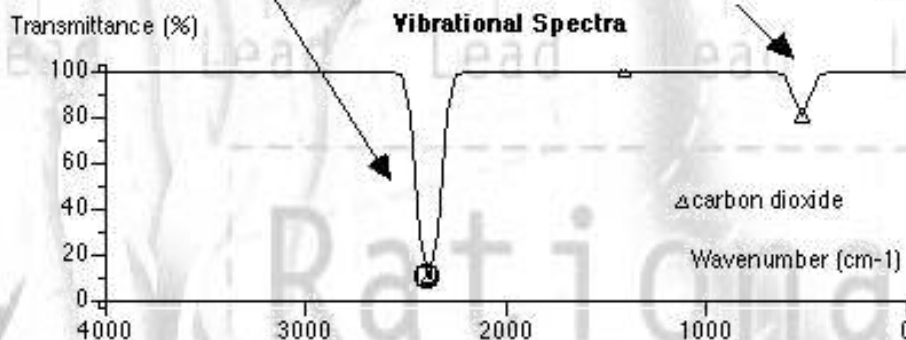
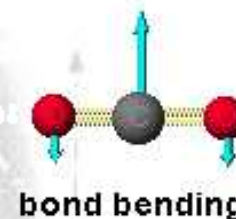
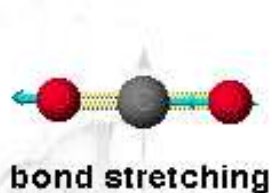
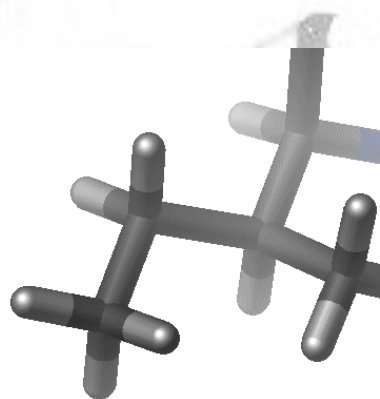
and after bond energy...





stretching... and bending!

Carbon Dioxide - Infrared Absorption



$$\cong \frac{1}{2}k_{str}(r-r_e)^2 - D_e^{str}$$

$$\cong \frac{1}{2}k_{ben}(\tau-\tau_e)^2 - D_e^{ben}$$



Force Field (FF): the empirical energy equation is growing...

$E_p \cong$

0.9760	0.5530	0.1180 C
2.1810	1.4240	0.1010 C
2.9110	1.3580	-1.2420 C
2.2460	1.6700	-2.0550 H
3.2180	0.3270	-1.4520 H
4.1000	2.2110	-1.2400 N
3.8190	3.1840	-1.1170 H
4.5460	2.1620	-2.1560 H
2.8610	1.1260	0.9100 H
1.8740	2.4560	0.3100 H
-0.1610	0.9170	-0.5670 N
-1.0220	-0.0510	-0.3510 C
-2.0310	-0.1010	-0.7380 H
-0.4920	-1.0270	0.4440 N
-0.9630	-1.8680	0.7470 H
0.7870	-0.6560	0.7530 C
1.4290	-1.2620	1.3760 H

$\cong \Sigma [\frac{1}{2}k_{str} (r-r_e)^2 - D_e^{str}]$
 $+ \Sigma [\frac{1}{2}k_{ben} (\tau-\tau_e)^2 - D_e^{ben}]$



Force Field (FF) parameters: tabulated experimental values crucial to correctly solve FF equation.

**bond angle
(from coordinates matrix)**



$$\Sigma [1/2 k_{ben} (\tau - \tau_e)^2 - D_e^{ben}]$$



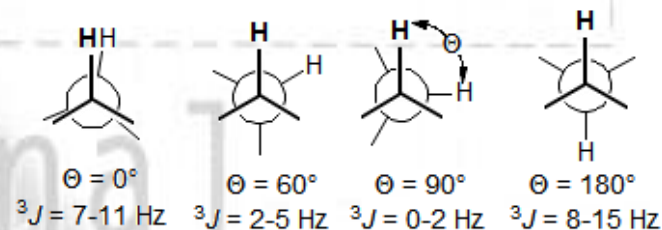
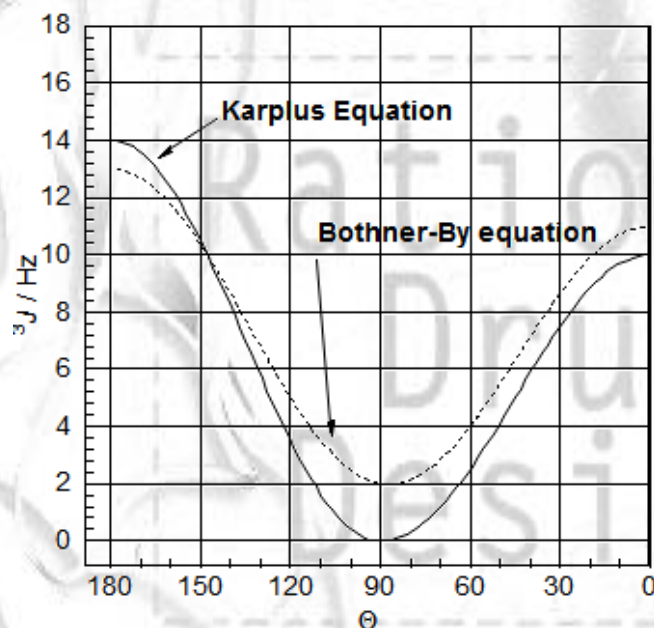
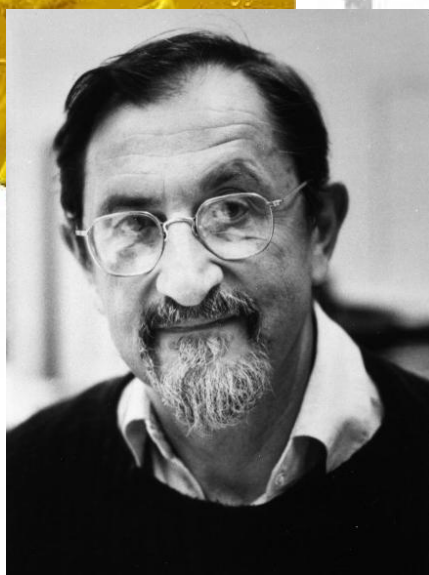
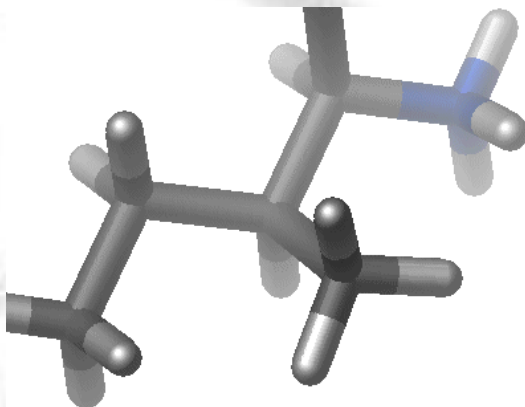
**bending constant
(from IR spectroscopy)**



**bending energy
(from IR spectroscopy)**



The most difficult energy contribution to parameterize:



Karplus Equation

$$^3J_{HH} = J_o \cdot \cos^2 \theta - K$$

$$J_o = 14 \text{ (90-180}^\circ\text{)}, J_o = 10 \text{ (0-90}^\circ\text{)}, K = 0$$

Bothner-By equation

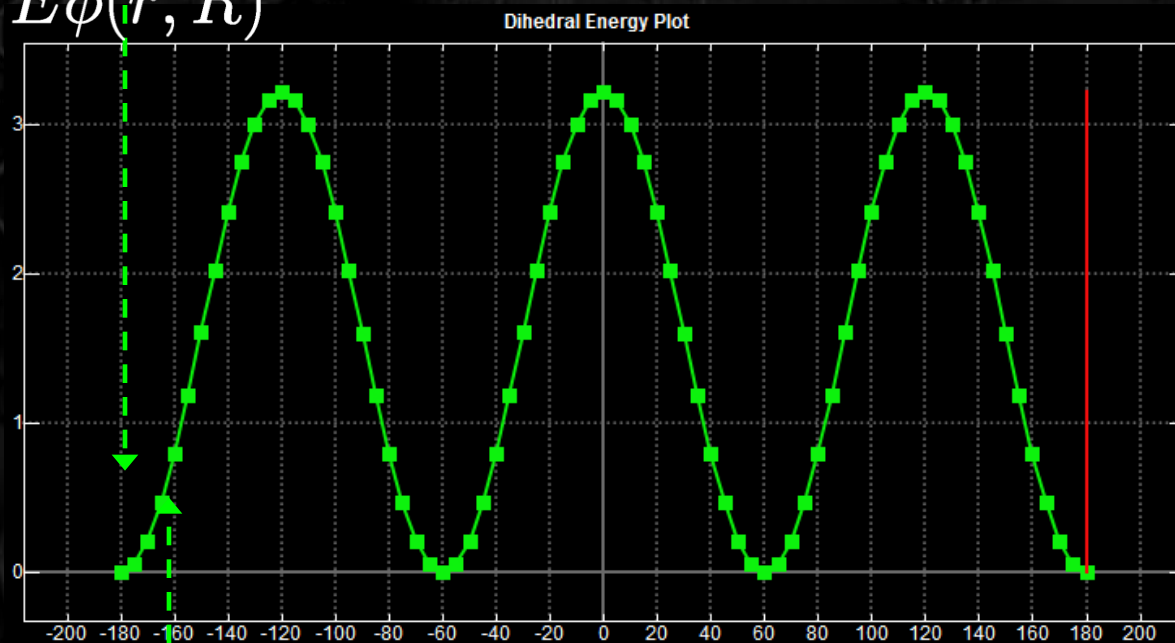
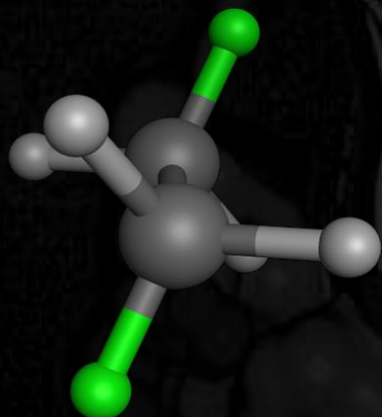
$$^3J_{HH} = 7 - \cos \theta + 5 \cdot \cos 2\theta$$



A possible strategy:

Schrödinger equation

$$\hat{H}\phi(\vec{r}, \vec{R}) = E\phi(\vec{r}, \vec{R})$$

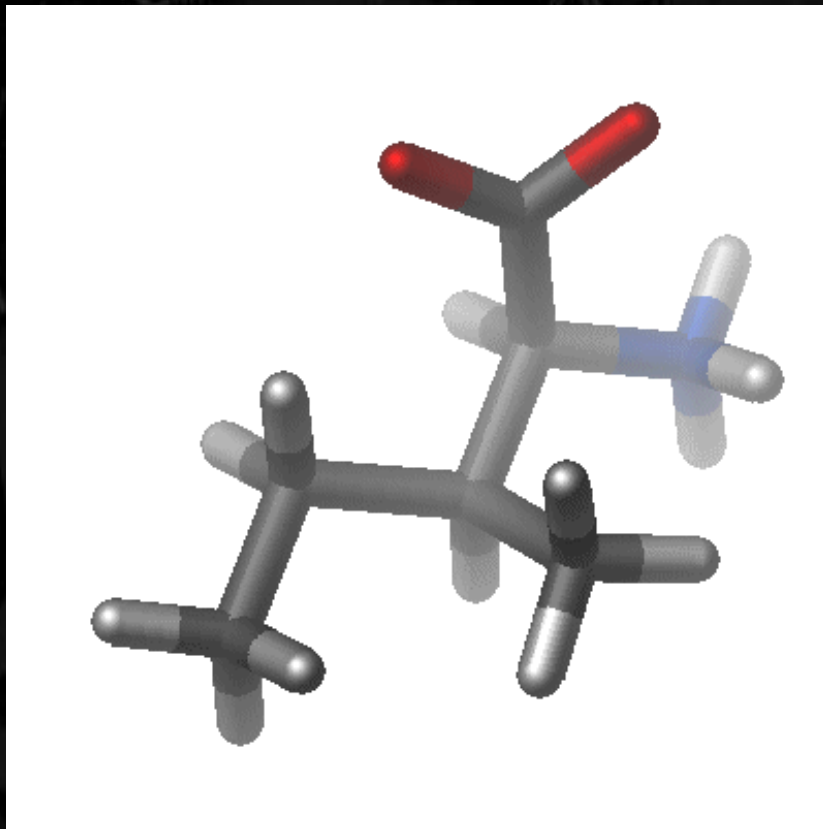


Best fitting

$$A [1 + \cos n \tau - \theta]$$

$$1.6 [1 + \cos \tau - 0]$$

$$E(\vec{R}) = \sum_{\text{bonded}} E_i(\vec{R})$$





Force Field (FF): the empirical energy equation is growing...

$E_p \cong$

0.9760	0.5530	0.1180 C
2.1810	1.4240	0.1010 C
2.9110	1.3580	-1.2420 C
2.2460	1.6700	-2.0550 H
3.2180	0.3270	-1.4520 H
4.1000	2.2110	-1.2400 N
3.8190	3.1840	-1.1170 H
4.5460	2.1620	-2.1560 H
2.8610	1.1260	0.9100 H
1.8740	2.4560	0.3100 H
-0.1610	0.9170	-0.5670 N
-1.0220	-0.0510	-0.3510 C
-2.0310	-0.1010	-0.7380 H
-0.4920	-1.0270	0.4440 N
-0.9630	-1.8680	0.7470 H
0.7870	-0.6560	0.7530 C
1.4290	-1.2620	1.3760 H

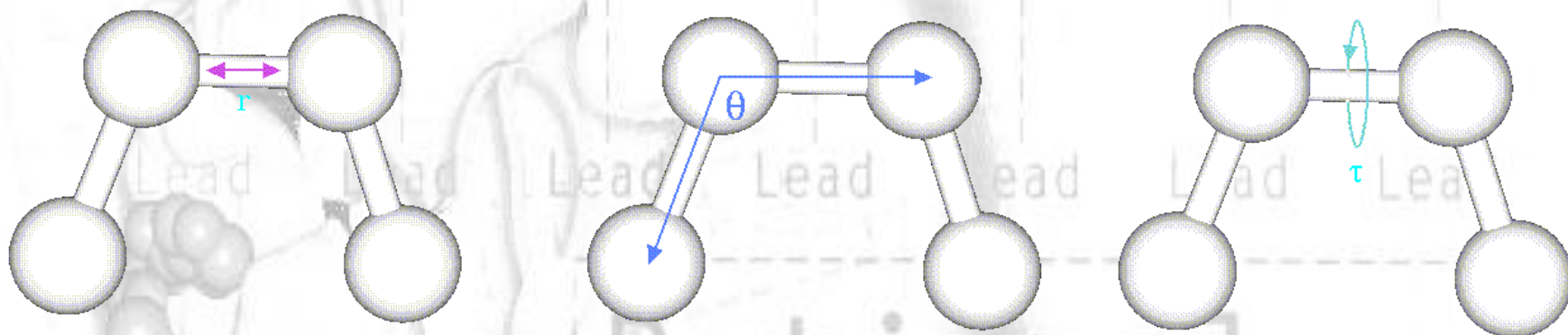
$\cong \sum [\frac{1}{2}k_{str}(r-r_e)^2 - D_e^{str}]$

$+ \sum [\frac{1}{2}k_{ben}(\tau-\tau_e)^2 - D_e^{ben}]$

$+ \sum [A(1 + \cos n\tau - \theta)]$



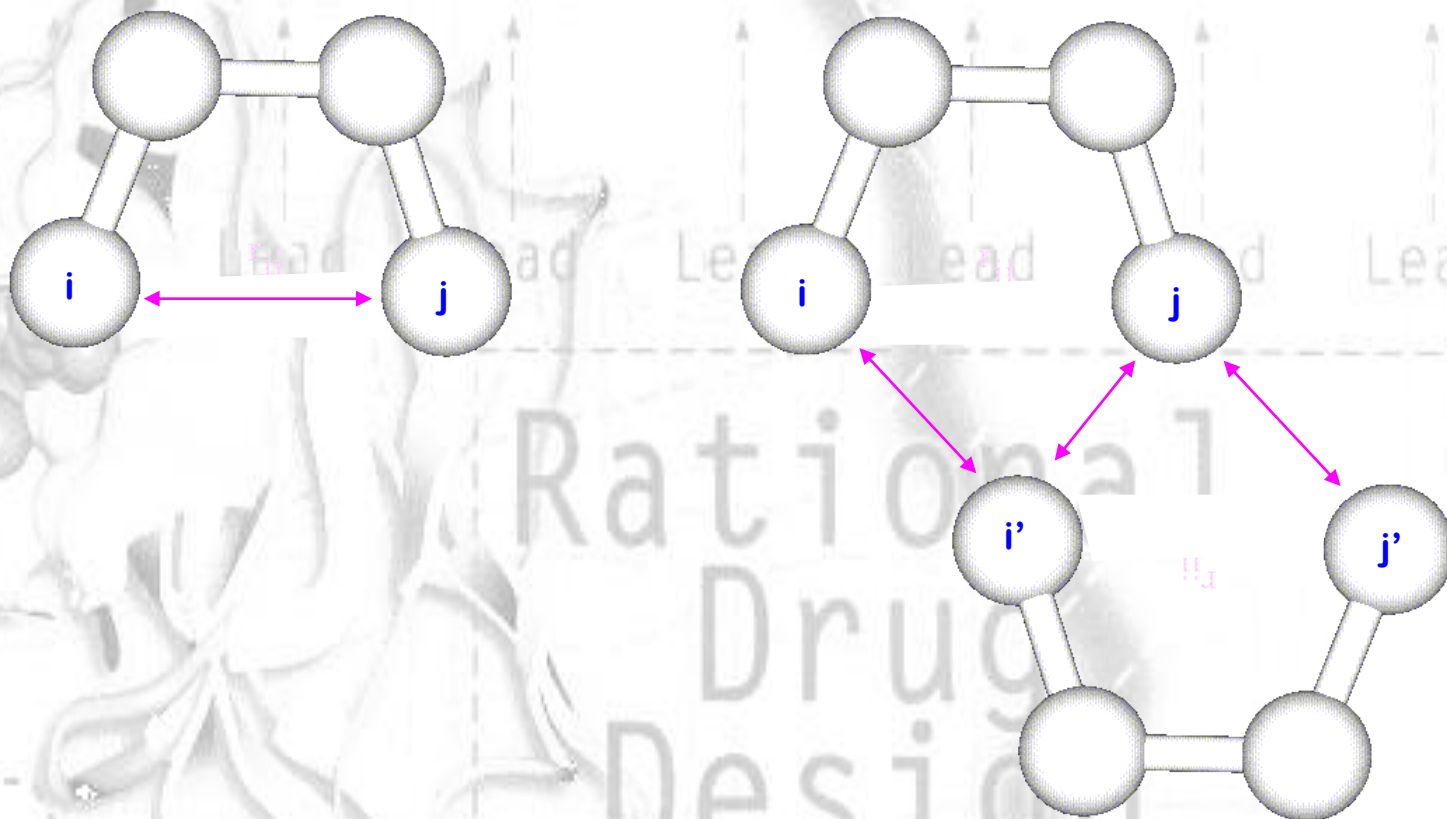
All variations of these potential energy contributions are related to the concept of chemical bond.



but there are other contributions to the potential energy inside a molecular system?



such as...



$$E(\vec{R}) = \sum_{\text{bonded}} E_i(\vec{R}) + \sum_{\text{non-bonded}} E_i(\vec{R})$$

$$E_{\text{non-bonded}} = E_{\text{van der Waals}} + E_{\text{electrostatic}}$$

$$\sum_{\text{nonbonded pairs}} \left(\frac{A_{ik}}{r_{ik}^{12}} - \frac{C_{ik}}{r_{ik}^6} \right)$$

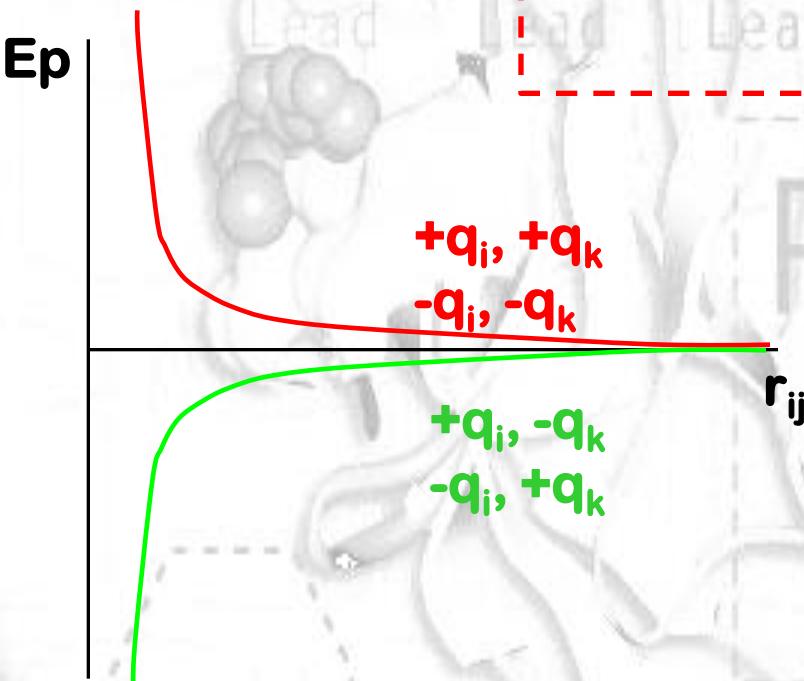
$$\sum_{\text{nonbonded pairs}} \frac{q_i q_k}{4\pi\epsilon_0 r_{ik}}$$



we can start with the electrostatic potential:

$$\sum_{\text{nonbonded pairs}} \frac{q_i q_k}{4\pi\epsilon_0 r_{ik}}$$

The electrostatic potential must be calculated among all atoms but not between those engaged in a chemical bond!



vacuum permittivity, permittivity of free space or electric constant:

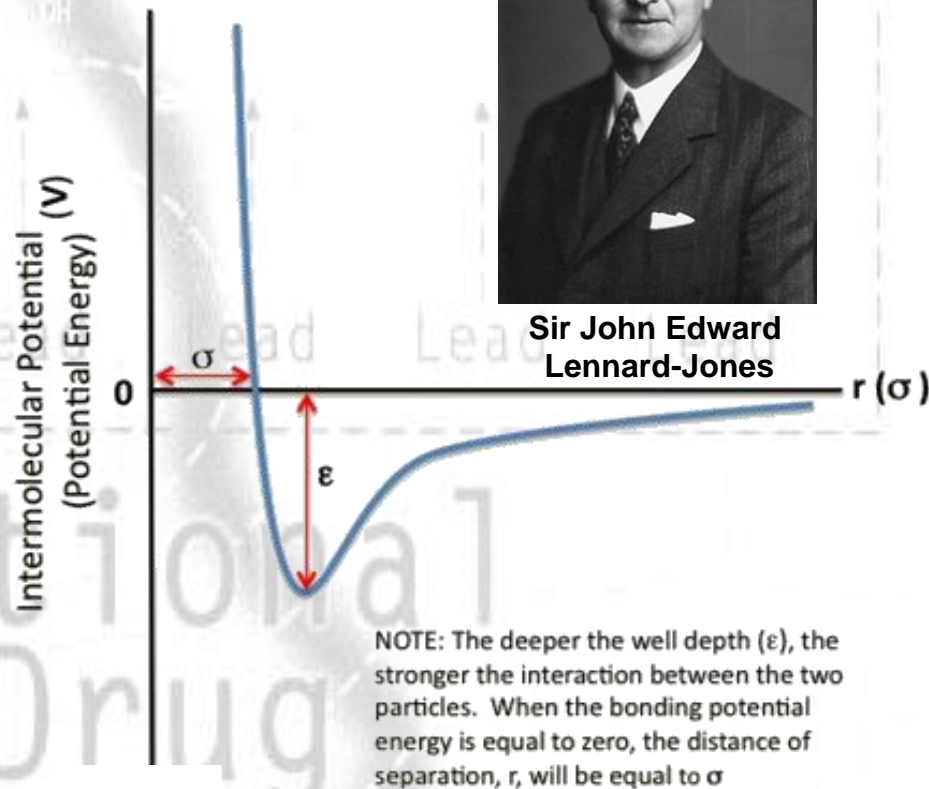
solvent	ϵ_r
vacuum	1
benzene	2.3
methanol	30
water	78.5



and van der Waals... or di Lennard-Jones... or 12-6 potential:

The Lennard-Jones potential is the best known and the most used of empirical potentials to describe the interatomic and intermolecular interactions.

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

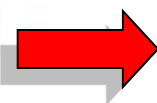


ϵ is a measure of how strongly the molecules attract each other.
 σ is the distance at which the intermolecular potential is zero.
 r is the distance of separation between both molecules.



van der Waals... or di Lennard-Jones... or 12-6 potential:

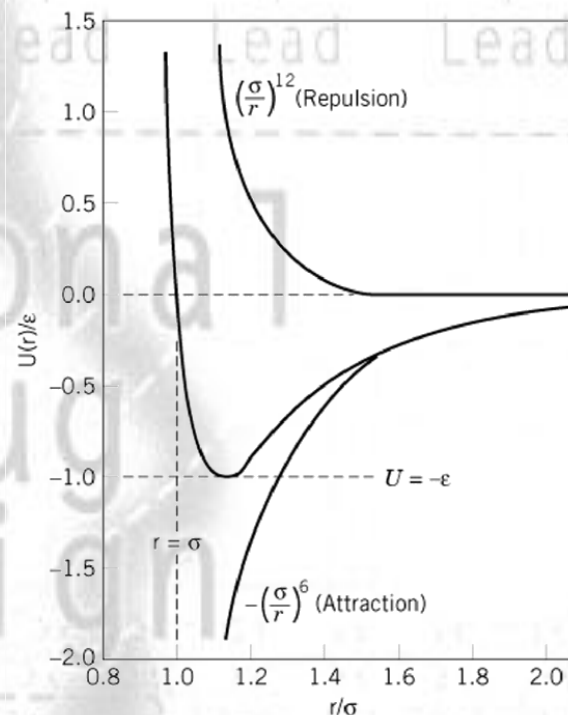
$$V(r) = 4\varepsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$



$$V(r) = \frac{A}{r^{12}} - \frac{B}{r^6}$$

where $A = 4\varepsilon\sigma^{12}$ and $B = 4\varepsilon\sigma^6$

This form is a simplified formulation that is used by some simulation software packages:





Force Field (FF): the empirical energy equation is growing...

$E_p \cong$

0.9760	0.5530	0.1180	C
2.1810	1.4240	0.1010	C
2.9110	1.3580	-1.2420	C
2.2460	1.6700	-2.0550	H
3.2180	0.3270	-1.4520	H
4.1000	2.2110	-1.2400	N
3.8190	3.1840	-1.1170	H
4.5460	2.1620	-2.1560	H
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1.8740	2.4560	0.3100	H
-0.1610	0.9170	-0.5670	N
-1.0220	-0.0510	-0.3510	C
-2.0310	-0.1010	-0.7380	H
-0.4920	-1.0270	0.4440	N
-0.9630	-1.8680	0.7470	H
0.7870	-0.6560	0.7530	C
1.4290	-1.2620	1.3760	H

 $\cong \sum [\frac{1}{2} k_{str} (r-r_e)^2 - D_e^{str}]$
 $+ \sum [\frac{1}{2} k_{ben} (\tau-\tau_e)^2 - D_e^{ben}]$
 $+ \sum [A (1 + \cos n \tau - \theta)]$
 $+ \sum_{\text{nonbonded pairs}} \left(\frac{A_{ik}}{r_{ik}^{12}} - \frac{C_{ik}}{r_{ik}^6} \right)$
 $+ \sum_{\text{nonbonded pairs}} \frac{q_i q_k}{4\pi\epsilon_0 r_{ik}}$

Specialization of the Force Fields:

Small organic molecules

MM2, MM3, MM4: by Allinger
(1977; 1989; 1996)

CFF93: “Central Force Field” by
Karplus (1979; 1994)

MMFF: “Merck Molecular Force
Field” by Halgren (1996)

Polisaccaride

PEF95SAC: by
Rasmussen (1997)

Metal complexes

SHAPES: by Allured
(1991)

Proteins and nucleotides

ECEPP: “Empirical Conformational
Energy Program for Peptides” by
Scheraga (1975)

CHARMm: “Chemistry at Harvard
Macromolecular Mechanics” by
Karplus (1983; 1996)

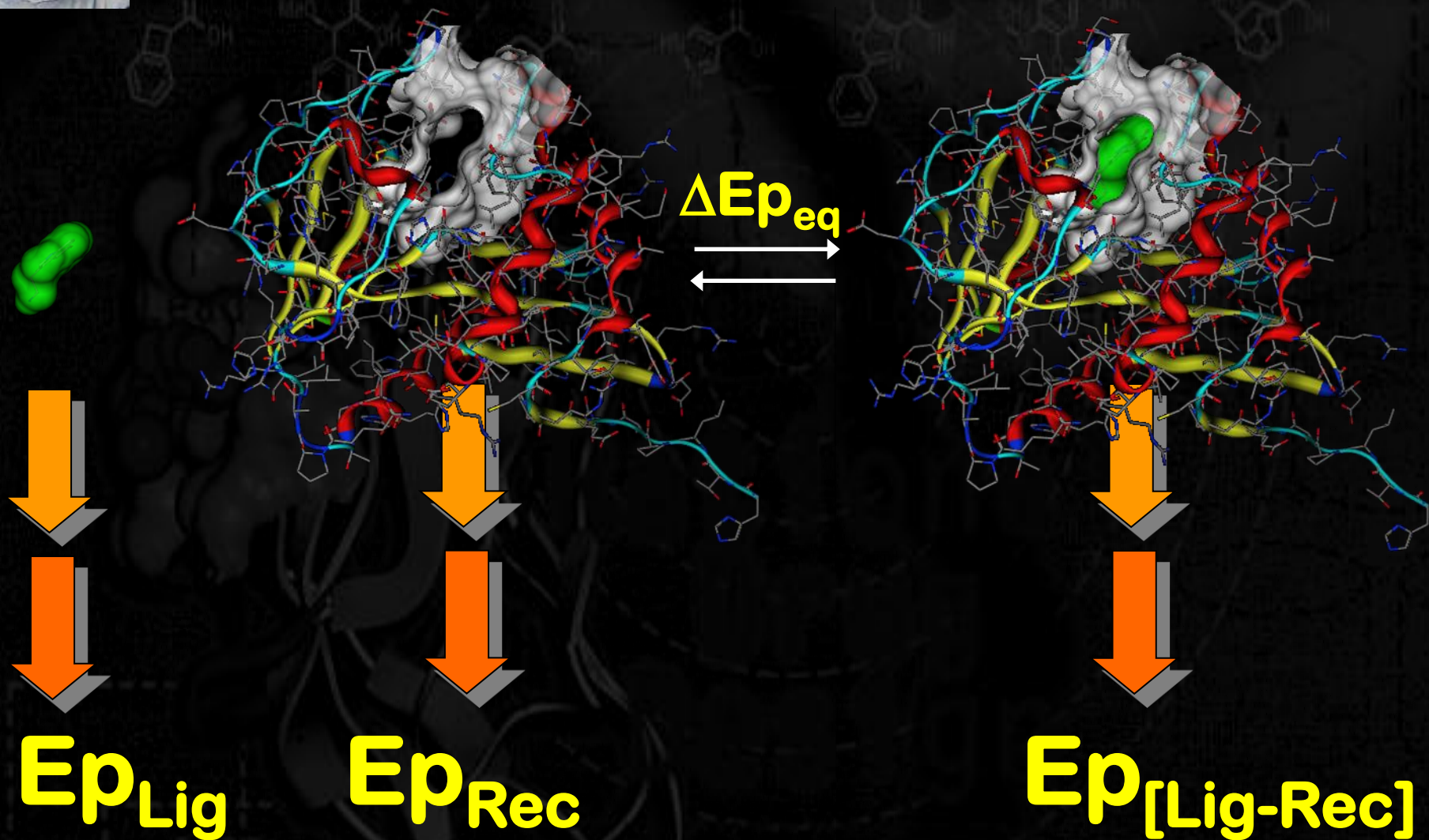
AMBER: “Assisted Model Building
with Energy Refinement” by Peter
Kollman (1984; 1995)

OPLS: “Optimised Potentials for
Liquid Simulations” by Jorgensen
(1988)

GROMOS: “Groningen Molecular
Simulation” by van Gunsteren (1990)

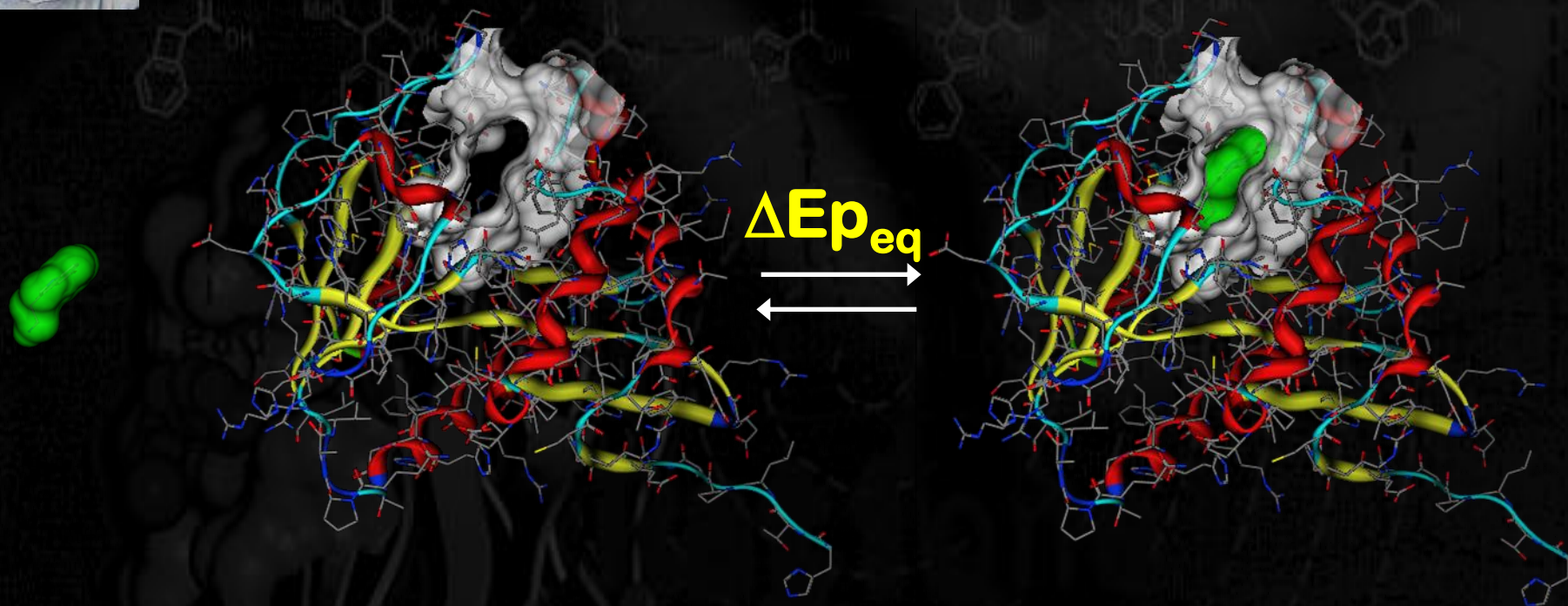


FF applications:





FF applications:

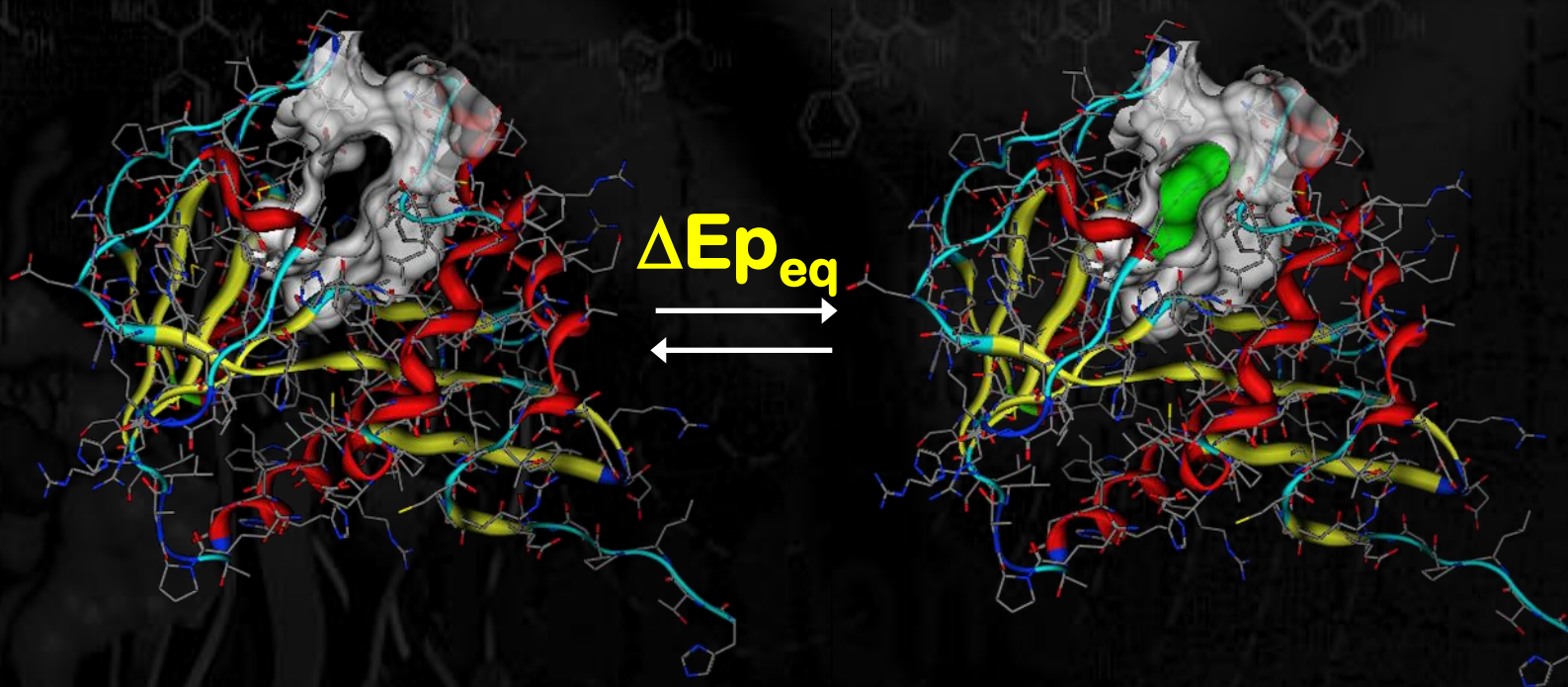


$\Delta E_{p_{eq}} > 0$
unfavorable

$\Delta E_{p_{eq}} < 0$
favorable



FF applications: *virtual screening*

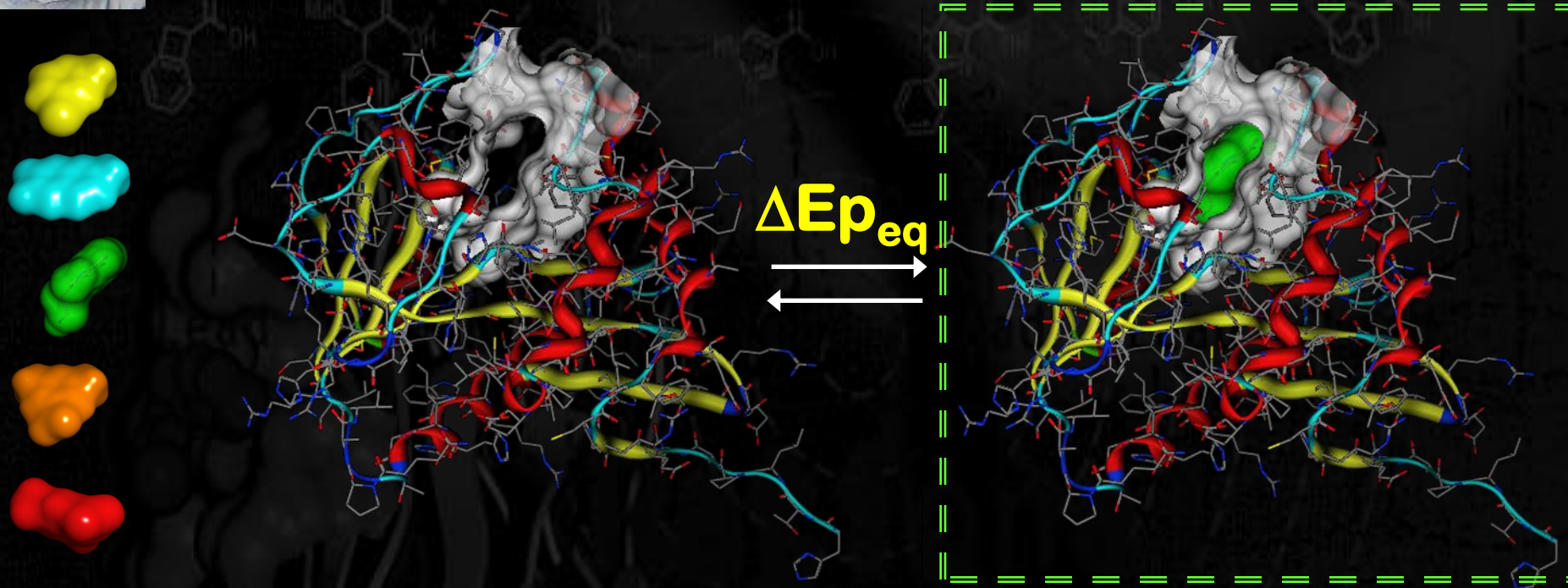


REMOVE
unfavorable

SELECT
favorable



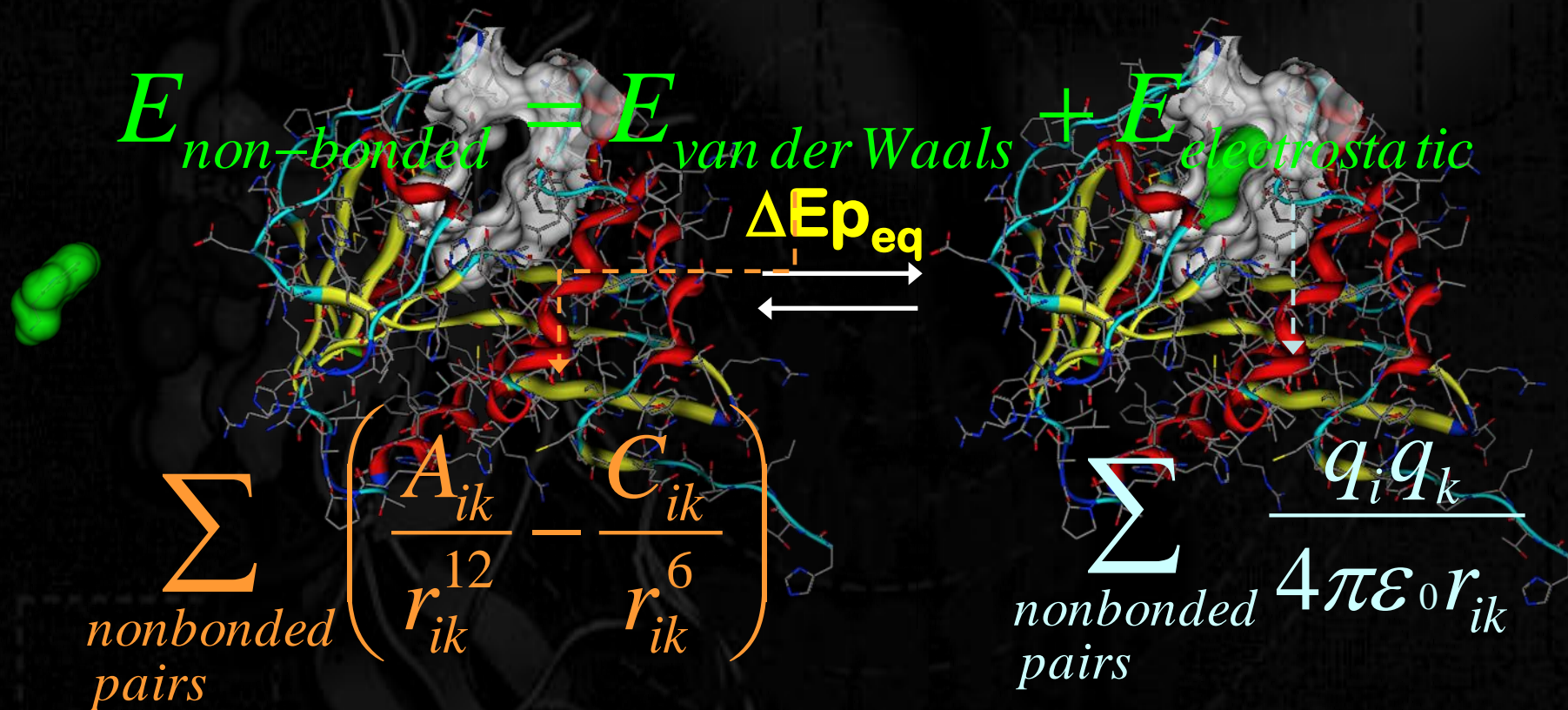
FF applications: what we need to perform this *virtual screening*?



**3D structures of the final state
(complexes)**



Did you understand which contributions are responsible of the calculated ΔE_p ?





Lead