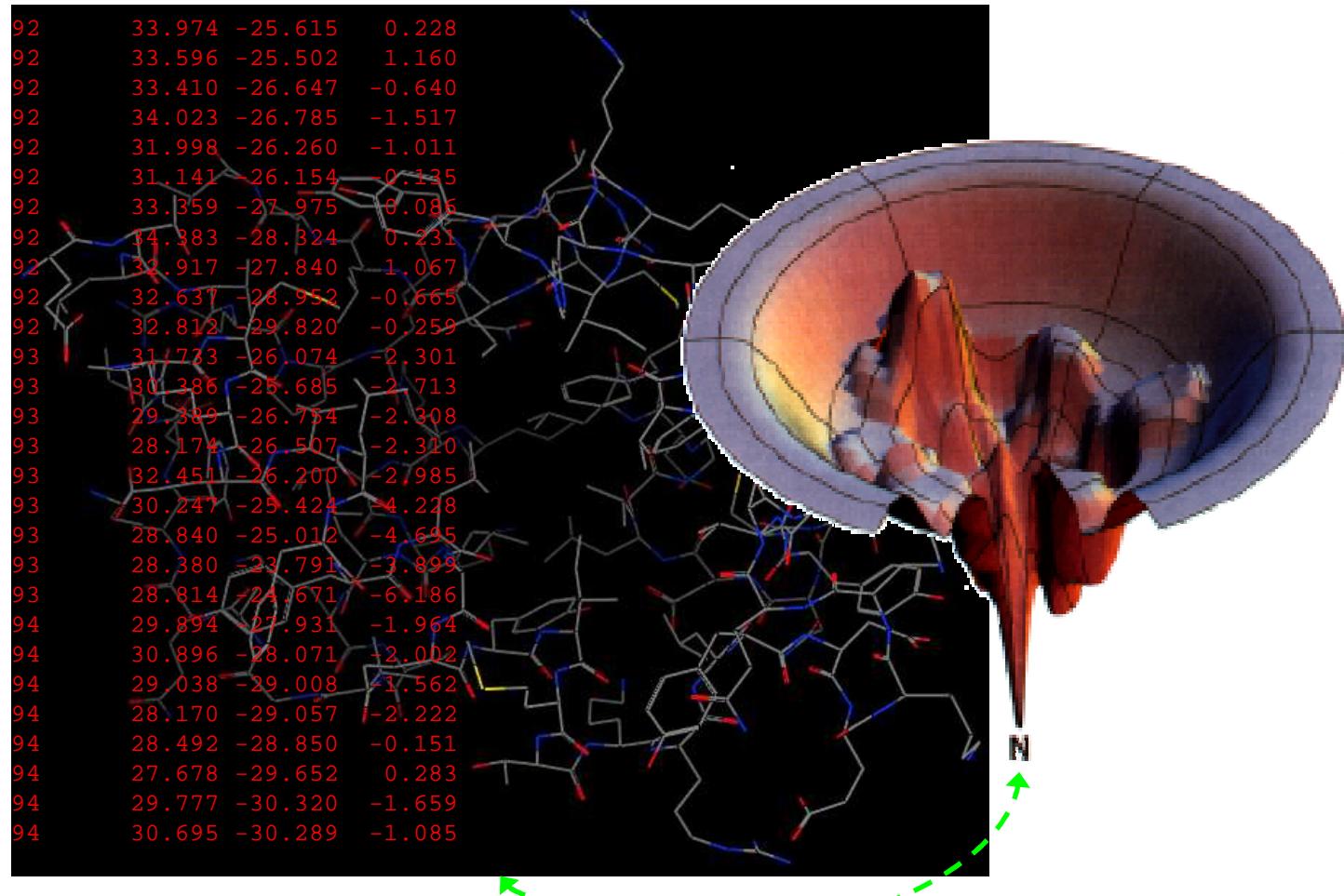




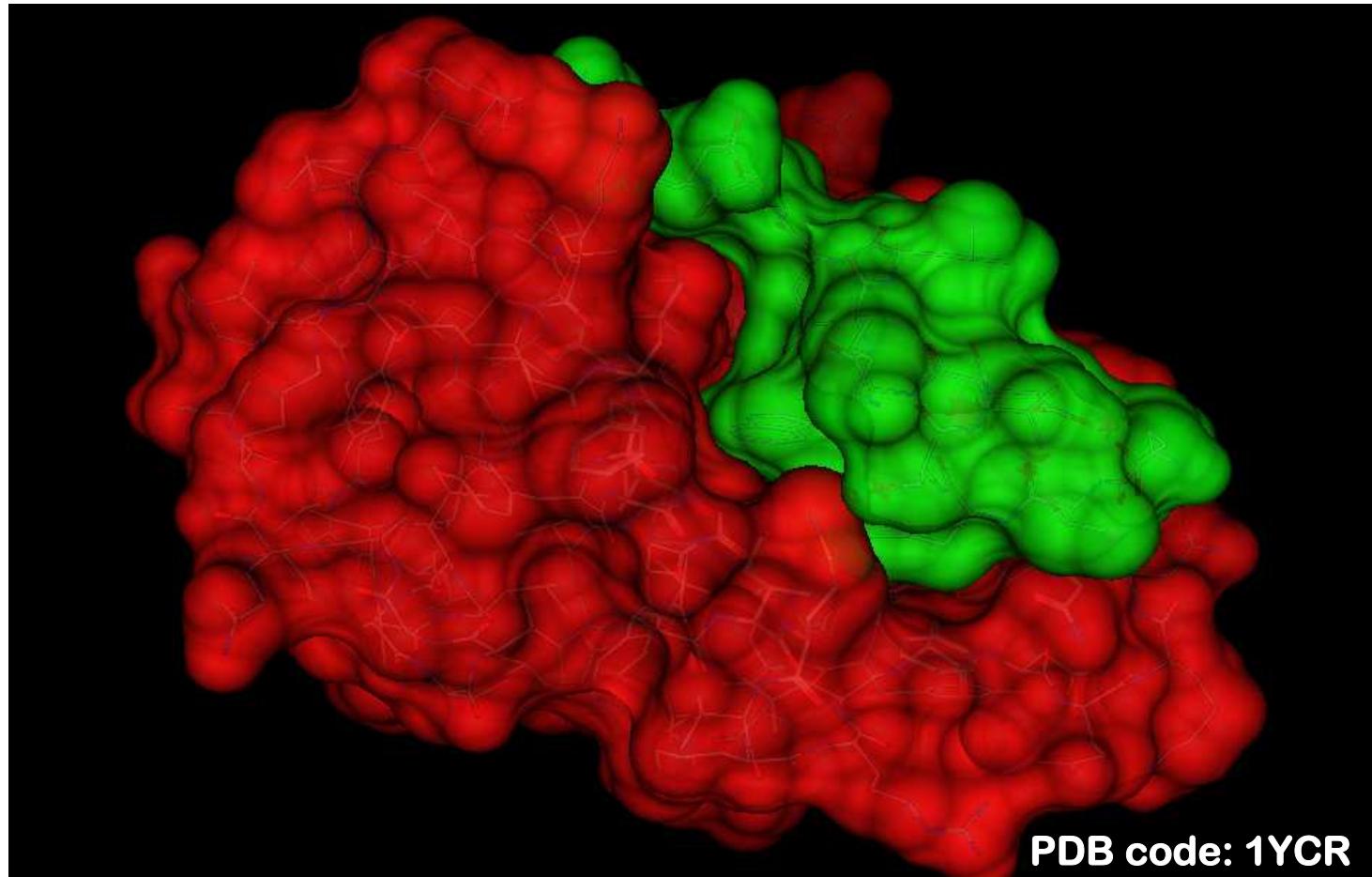
Would it be possible calculate the “stability” of a molecular structure starting from its Cartesian coordinates?

ATOM	1122	N	SER A	92	33.974	-25.615	0.228
ATOM	1123	H	SER A	92	33.596	-25.502	1.160
ATOM	1124	CA	SER A	92	33.410	-26.647	-0.640
ATOM	1125	H	SER A	92	34.023	-26.785	-1.517
ATOM	1126	C	SER A	92	31.998	-26.260	-1.011
ATOM	1127	O	SER A	92	31.141	-26.154	0.135
ATOM	1128	CB	SER A	92	33.359	-27.975	0.086
ATOM	1129	H	SER A	92	34.383	-28.324	0.231
ATOM	1130	H	SER A	92	32.917	-27.840	1.067
ATOM	1131	OG	SER A	92	32.637	-28.952	-0.665
ATOM	1132	H	SER A	92	32.812	-29.820	-0.259
ATOM	1133	N	LEU A	93	31.733	-26.074	-2.301
ATOM	1134	CA	LEU A	93	30.386	-25.685	-2.713
ATOM	1135	C	LEU A	93	29.389	-26.754	-2.308
ATOM	1136	O	LEU A	93	28.174	-26.507	-2.310
ATOM	1137	HN	LEU A	93	32.451	-26.200	-2.985
ATOM	1138	CB	LEU A	93	30.247	-25.424	-4.228
ATOM	1139	CG	LEU A	93	28.840	-25.012	-4.695
ATOM	1140	CD1	LEU A	93	28.380	-23.791	-3.899
ATOM	1141	CD2	LEU A	93	28.814	-24.671	-6.186
ATOM	1142	N	LYS A	94	29.894	-27.931	-1.964
ATOM	1143	H	LYS A	94	30.896	-28.071	-2.002
ATOM	1144	CA	LYS A	94	29.038	-29.008	-1.562
ATOM	1145	H	LYS A	94	28.170	-29.057	-2.222
ATOM	1146	C	LYS A	94	28.492	-28.850	-0.151
ATOM	1147	O	LYS A	94	27.678	-29.652	0.283
ATOM	1148	CB	LYS A	94	29.777	-30.320	-1.659
ATOM	1149	H	LYS A	94	30.695	-30.289	-1.085





**... and consequently estimate the “stability”
of a particular protein-protein complex?**





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.

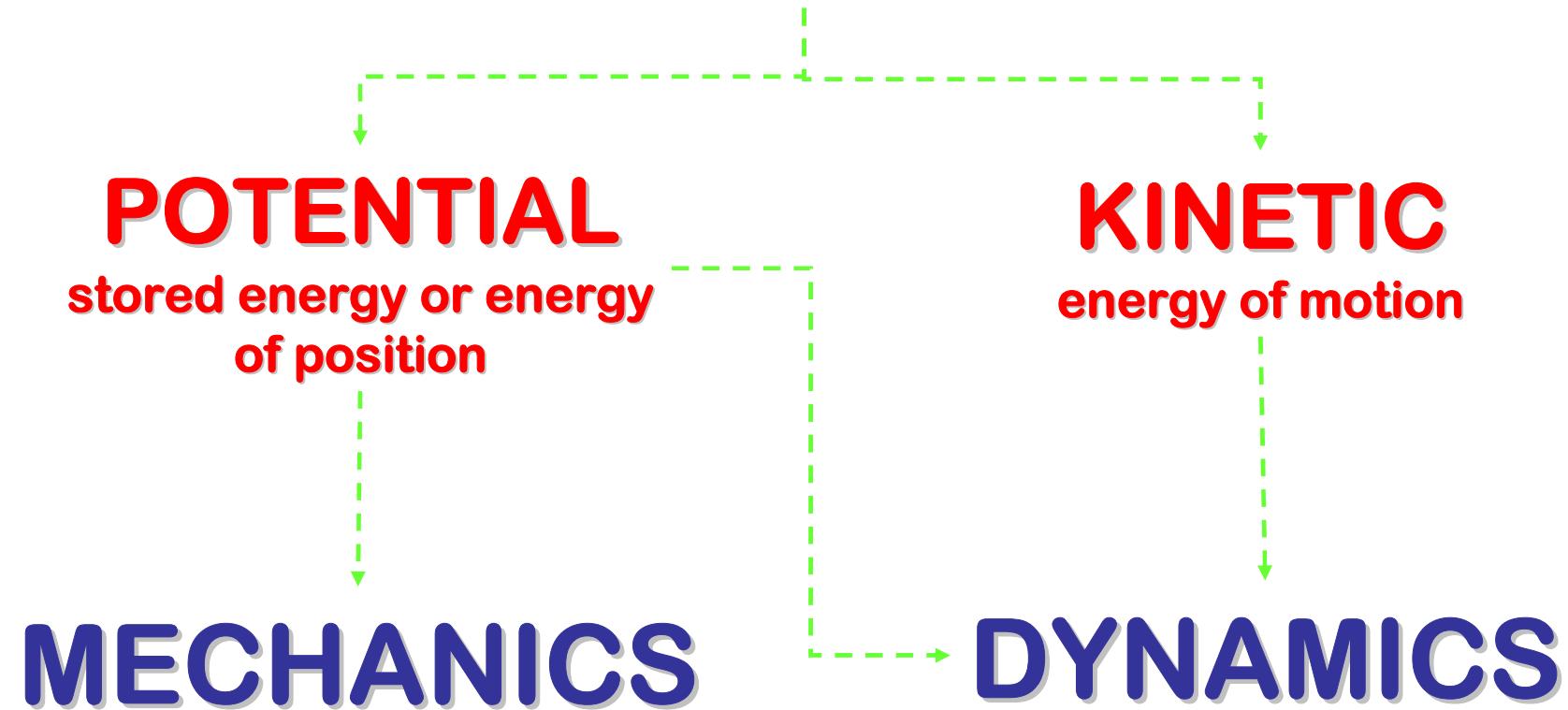
We can use the *energy* concept as a measure of the *stability* of a natural system.

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.



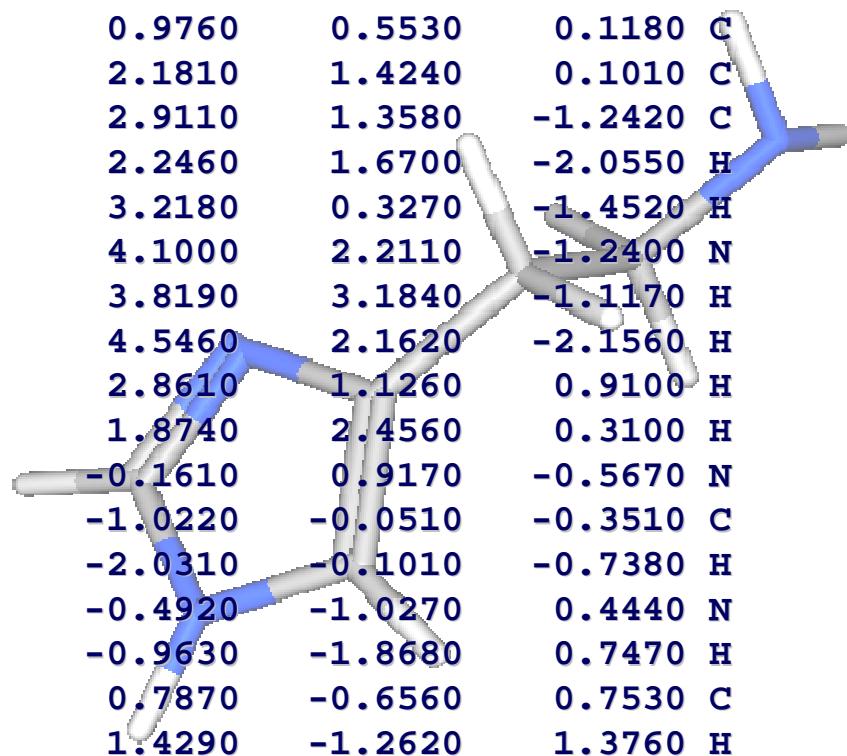
Back to stability concept:

All forms of energy fall under two categories:





Here what we need in the virtual world:

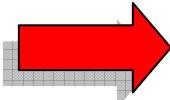
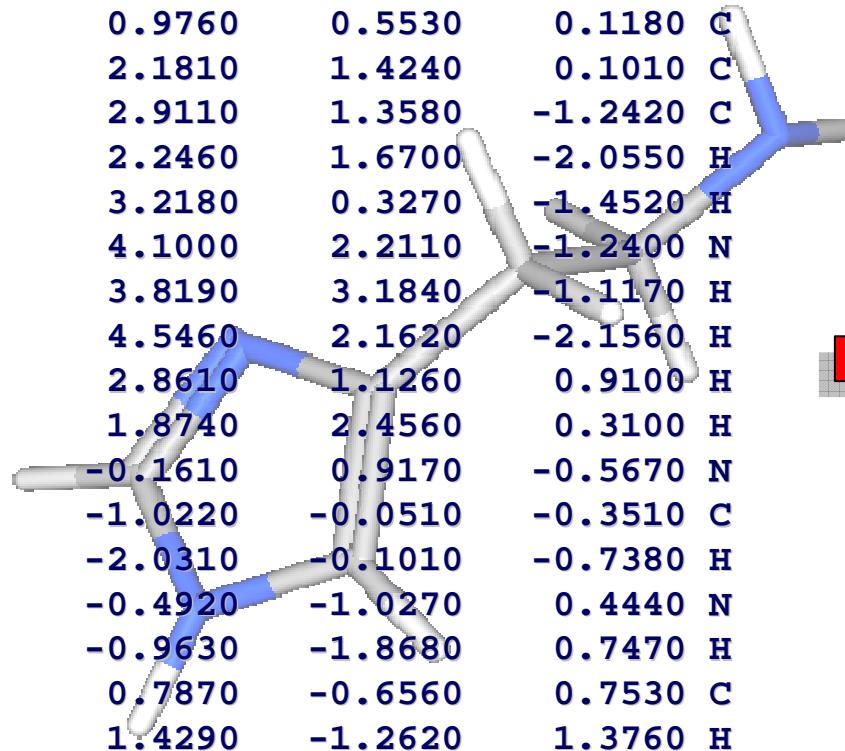


 kcal/mol



Actually, we have already an equation that does this:

Schrödinger equation



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

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.

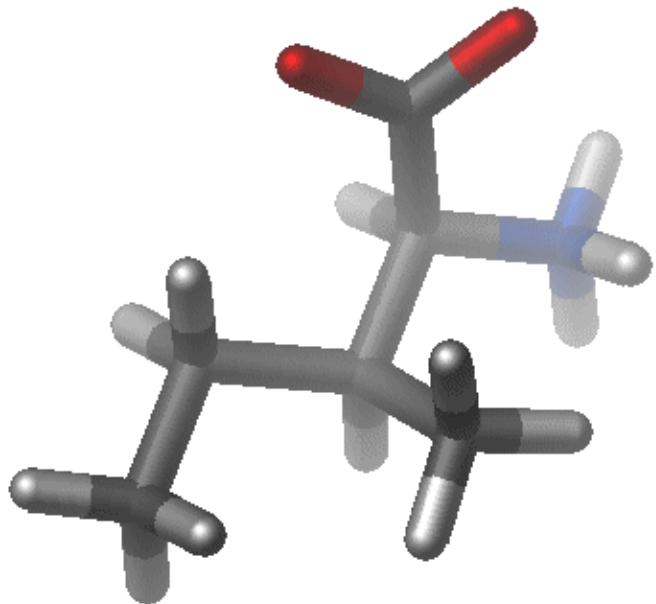
For more complex systems (i.e. many electron atoms/molecules) we need to make some simplifying assumptions/approximations and solve it numerically.

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



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

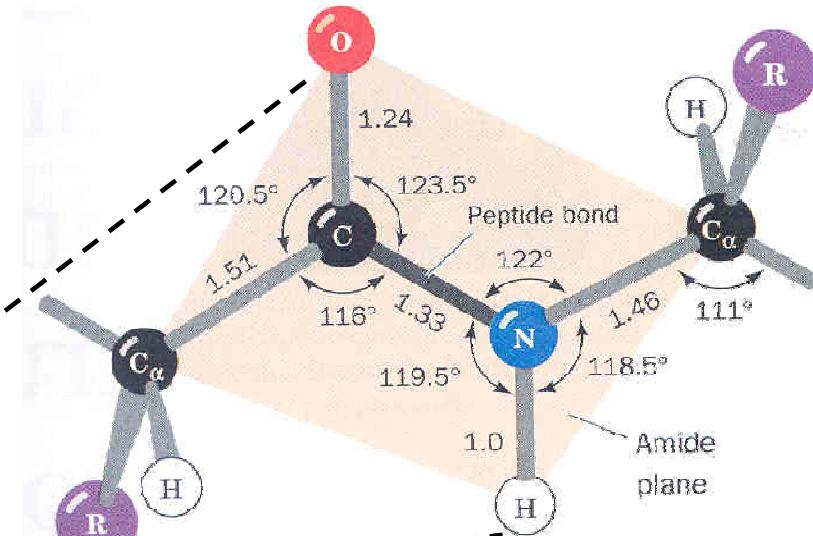
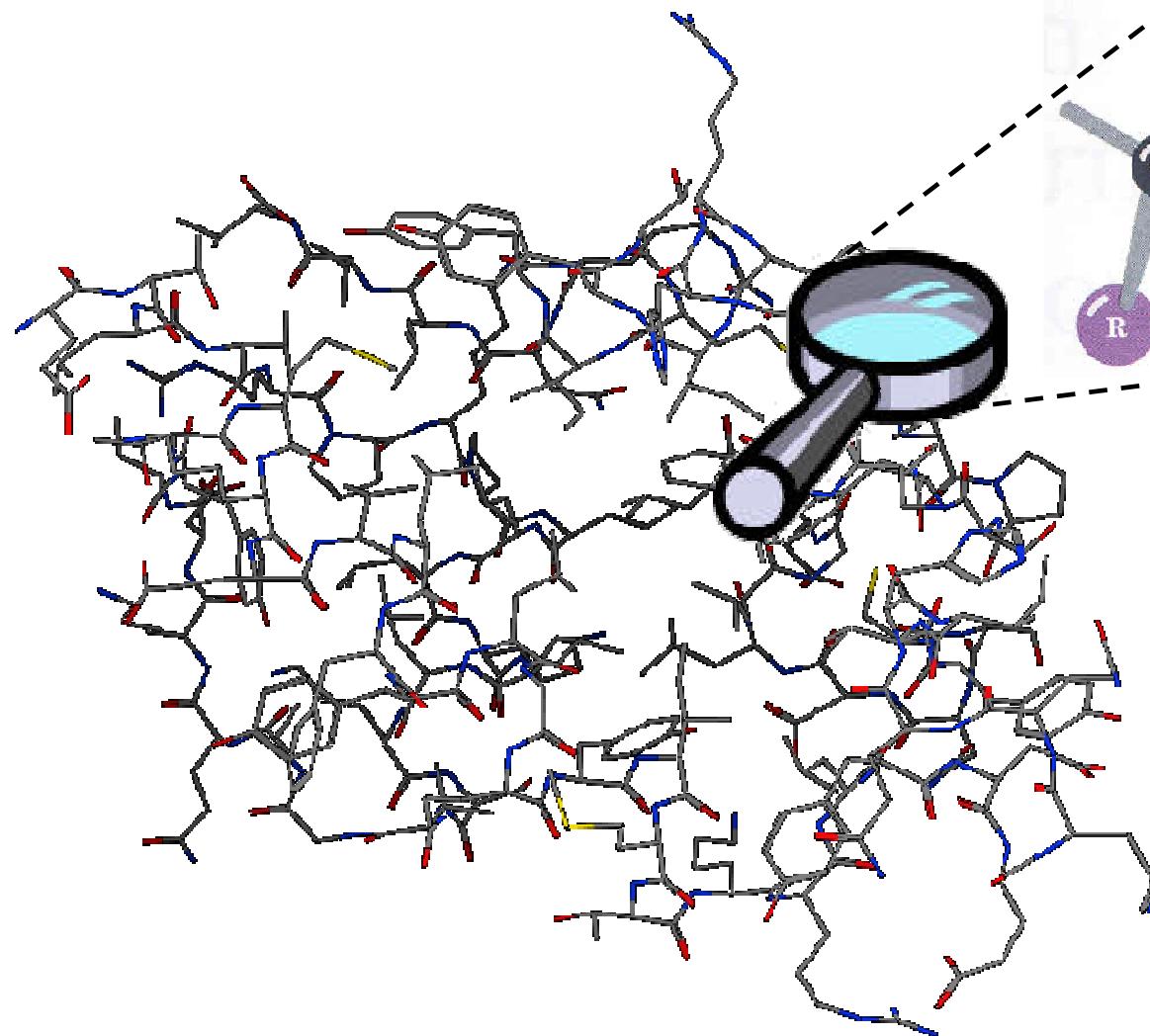
Where energy (potential) is stored inside a molecule? Mainly (but not only) here:

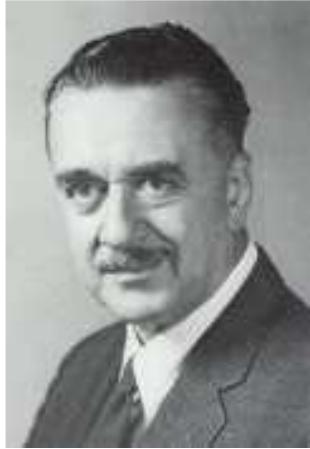


BOND ENERGIES

BOND ANGLE ENERGIES

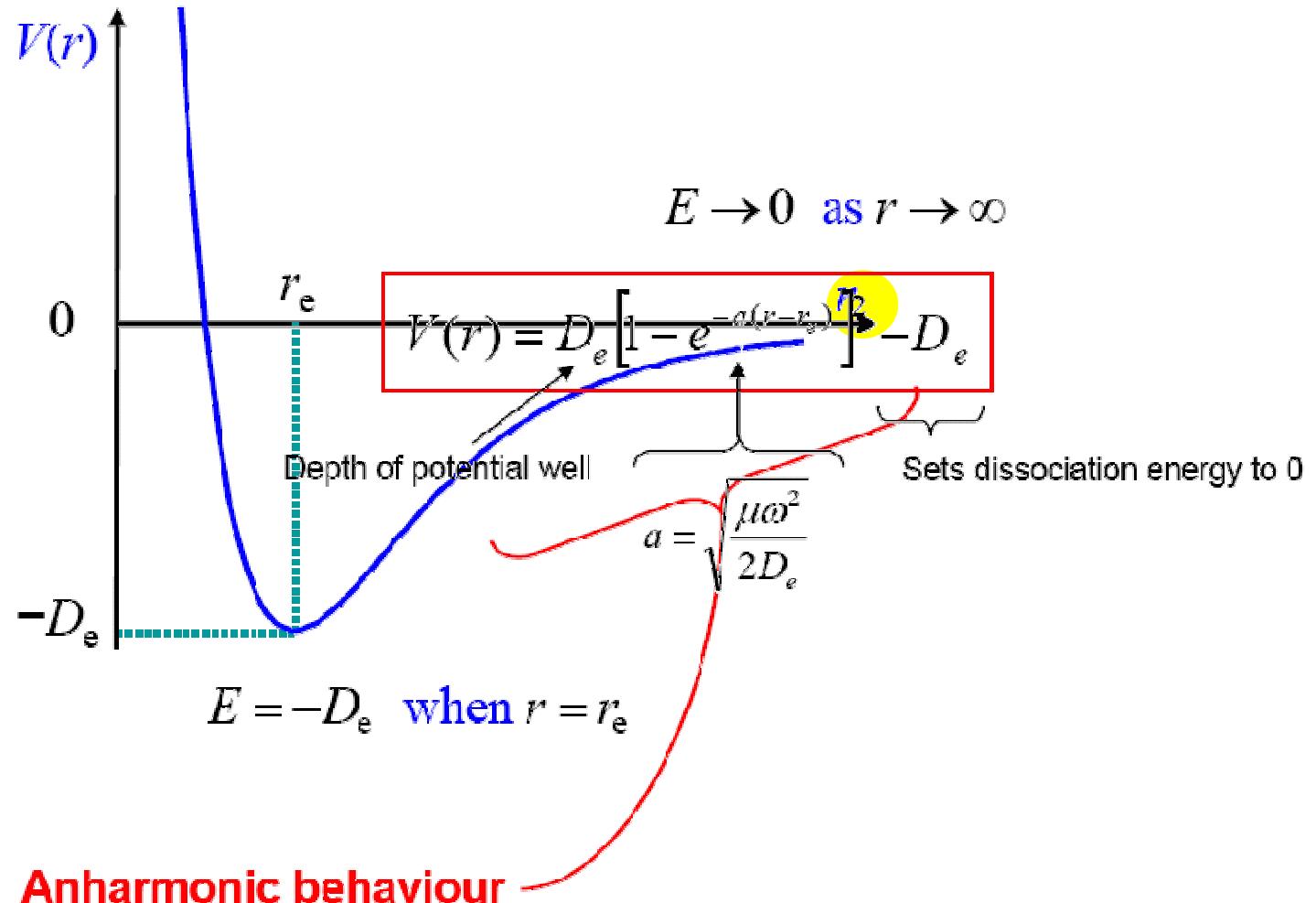
TORSION ANGLE ENERGIES





Do you remember the Morse's potential?

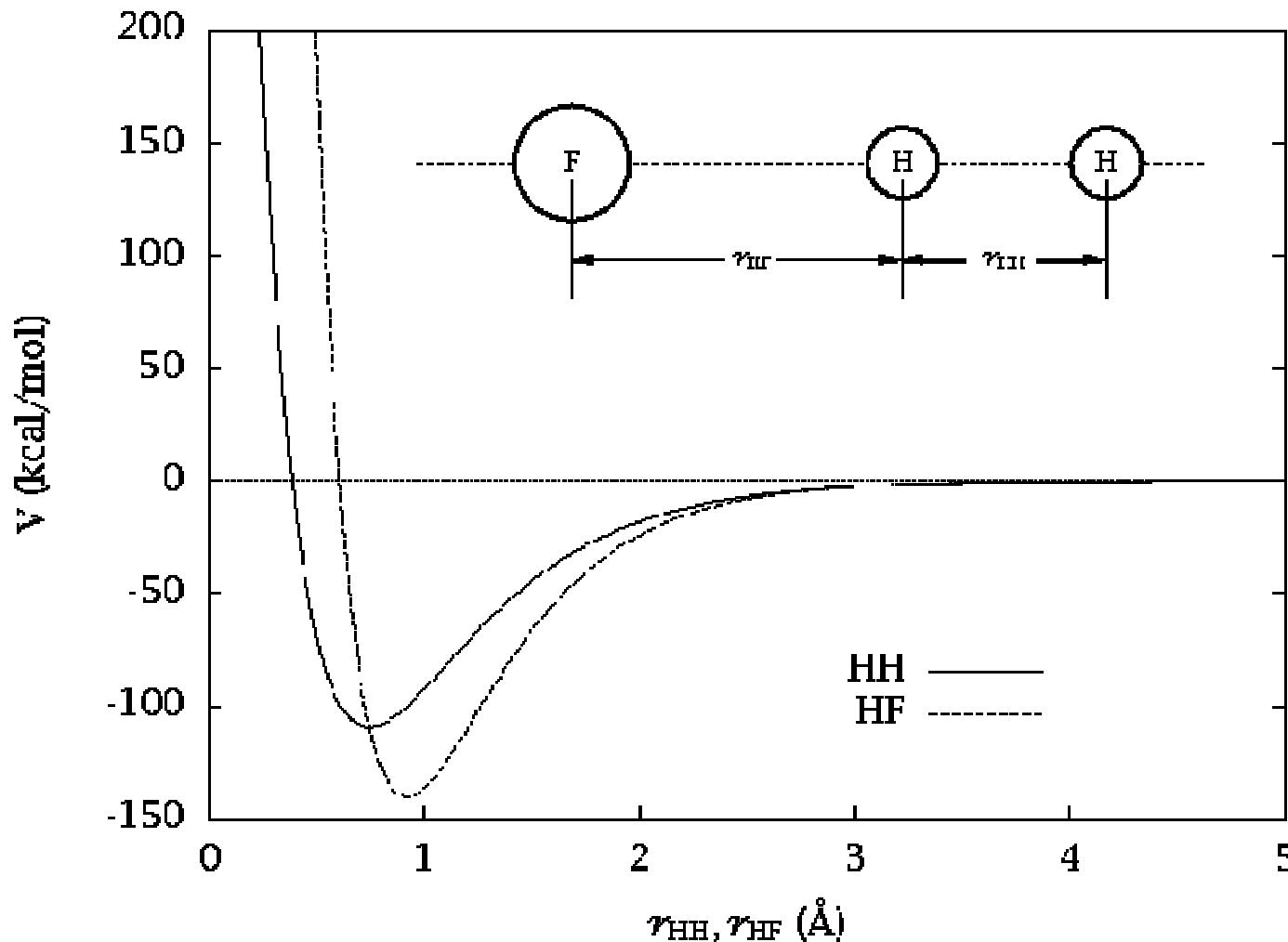
Philip McCord Morse



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



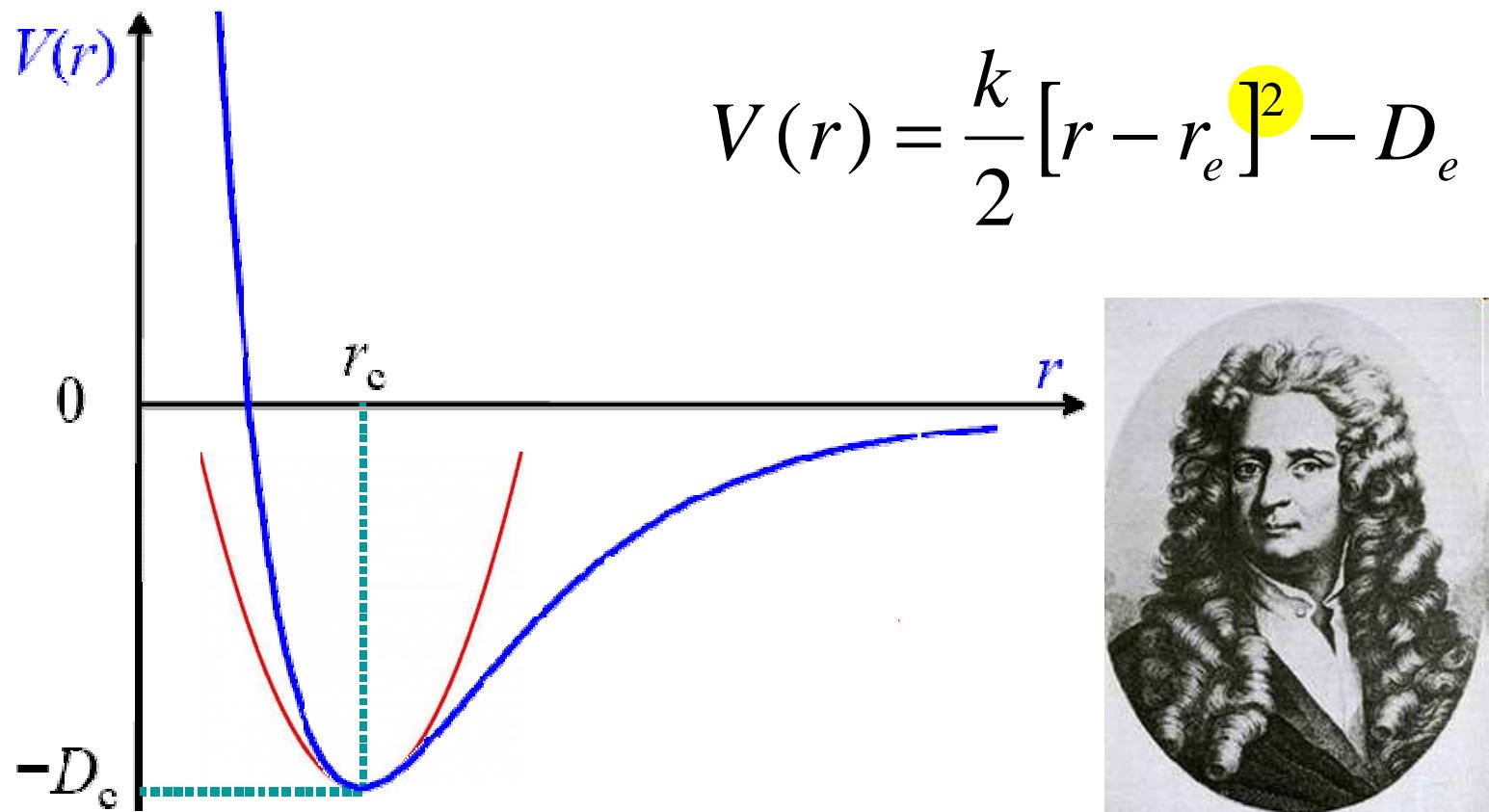
This is very interesting because we have different Morse's potentials corresponding to different kind of chemical bonds:





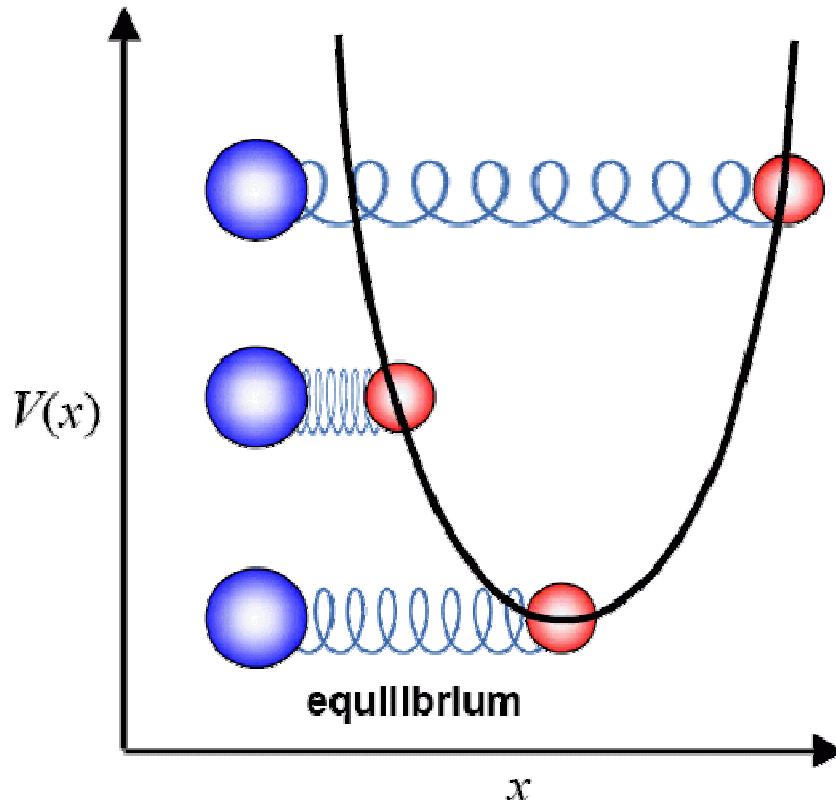
a brilliant comparison:

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





Robert Hooke



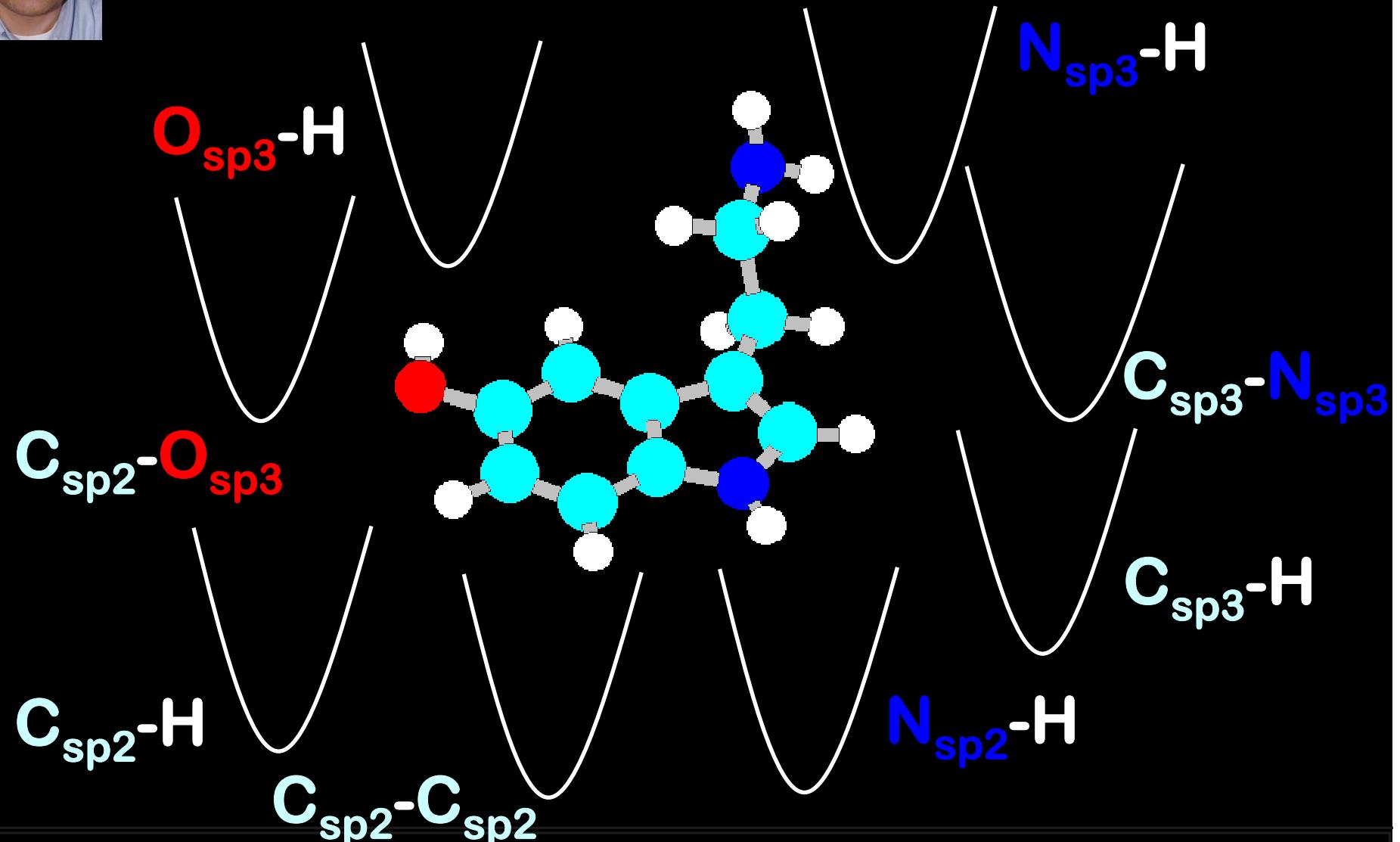
$$F = -kx$$

$$dV = Fdx = -kx dx$$

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

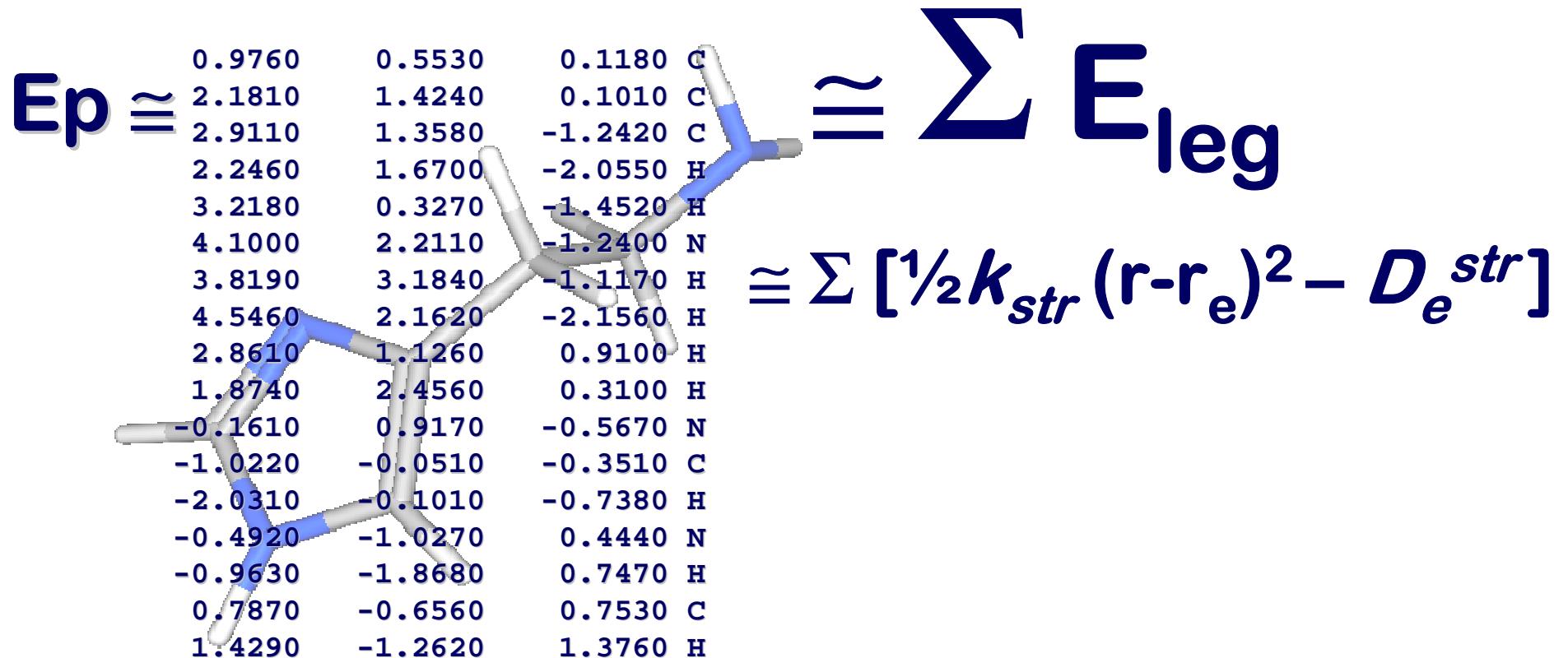


We can simplify like that: *one bond one parabola!*



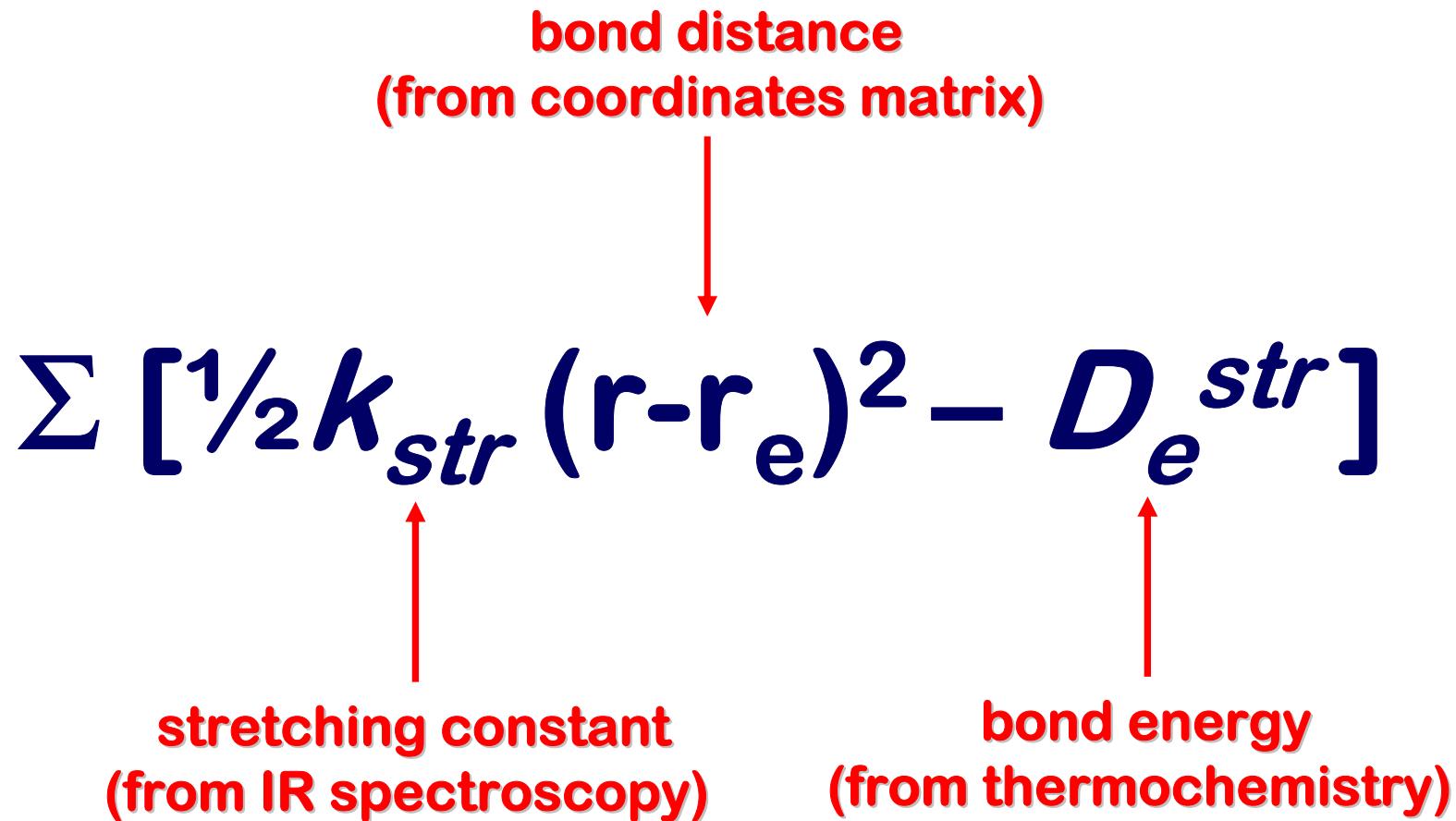


Force Field (FF): the empirical energy equation!



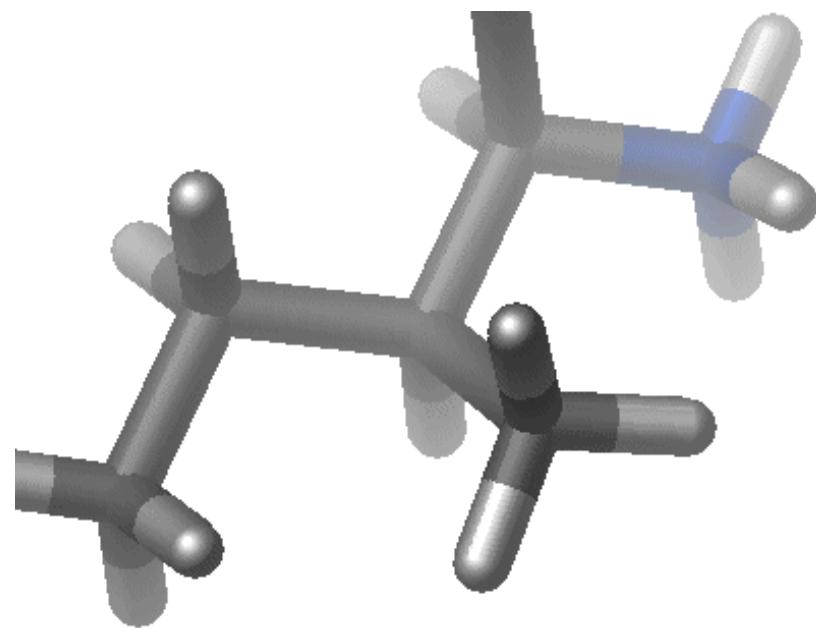
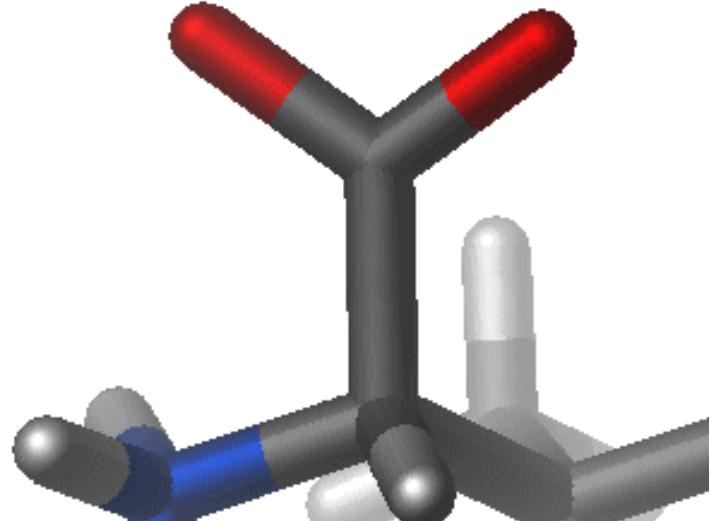


Force Field (FF) parameters: tabulated experimental values crucial to correctly solve FF equation.





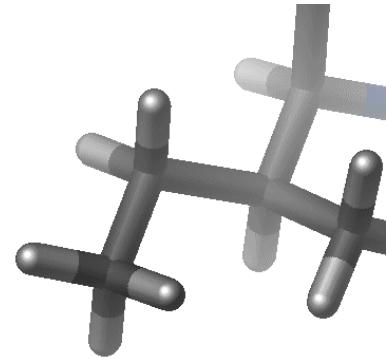
and after bond energy...



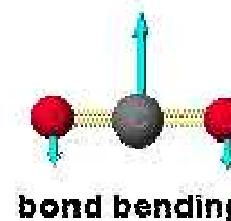


stretching... and bending!

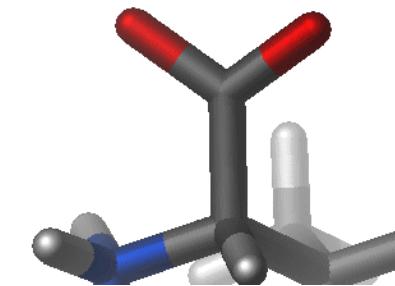
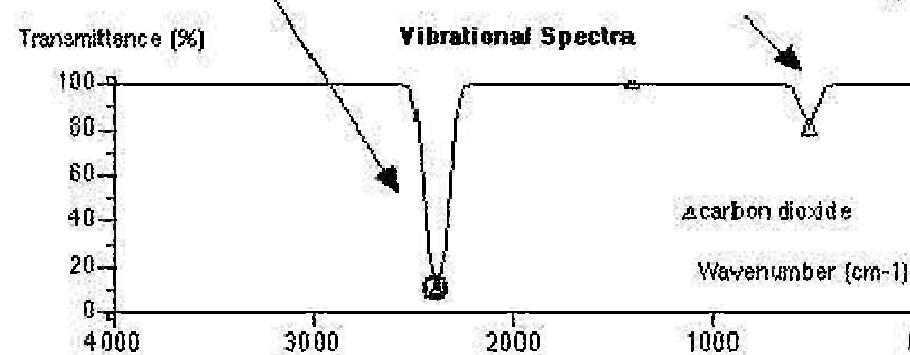
Carbon Dioxide - Infrared Absorption



bond stretching



bond bending

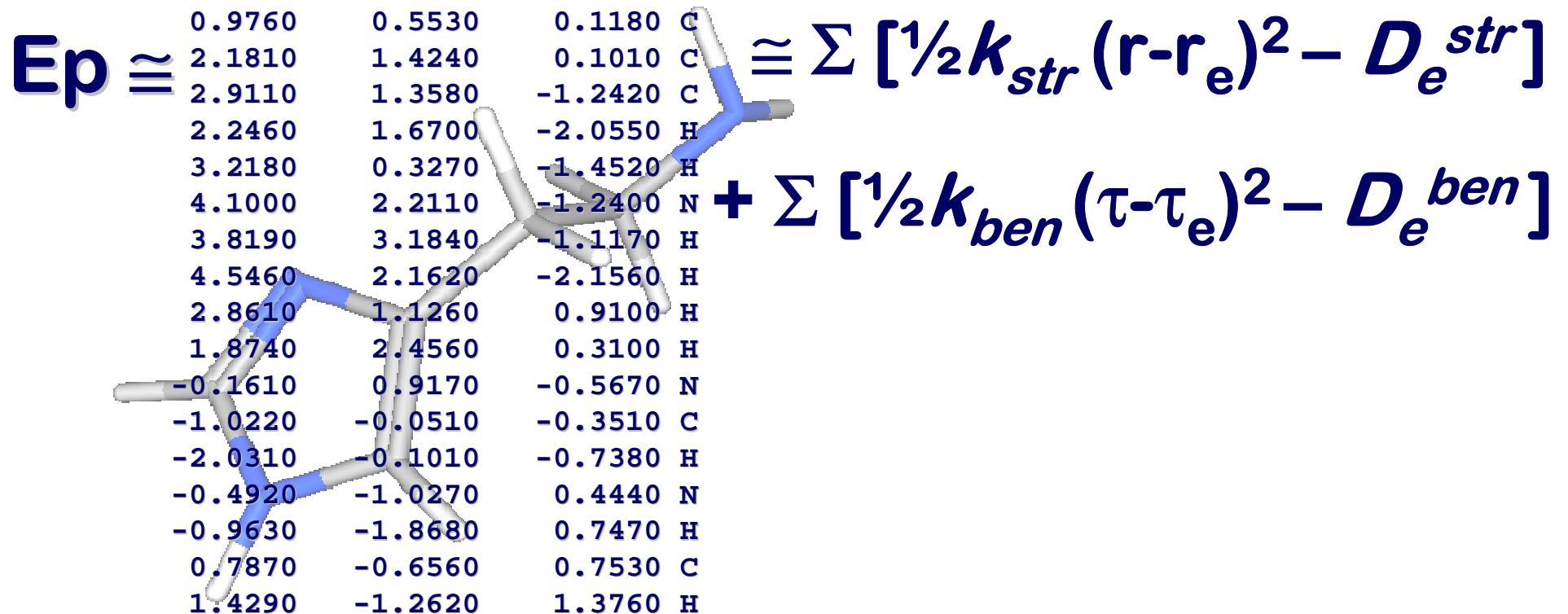


$$\approx \frac{1}{2}k_{str}(r-r_e)^2 - D_e^{str}$$

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



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





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

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

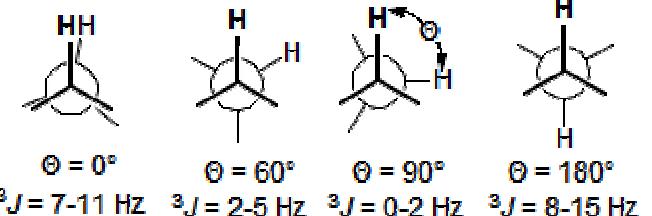
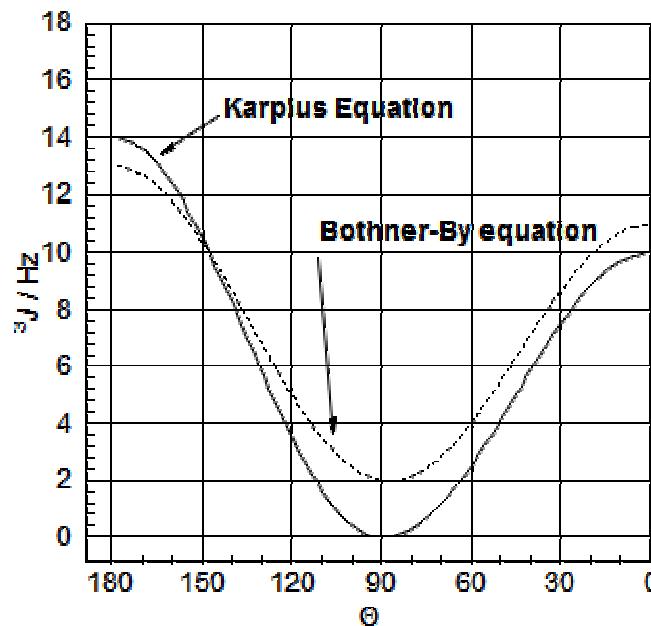
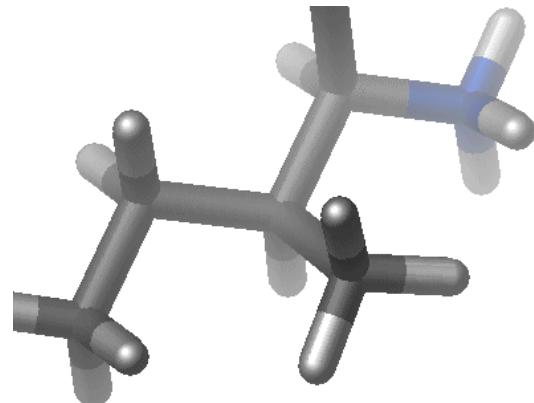
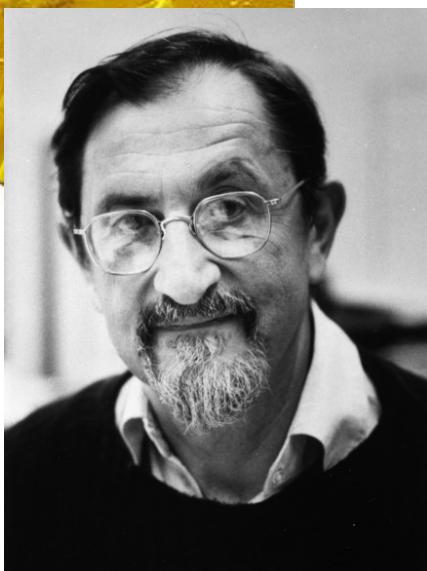
bond angle
(from coordinates matrix)

bending constant
(from IR spectroscopy)

bending energy
(from IR spectroscopy)



The most difficult energy contribution to parameterize:



Karplus Equation

$$^3J_{\text{HH}} = J_o \cdot \cos^2 \Theta - K$$
$$J_o = 14 \text{ (90-180°)}, J_o = 10 \text{ (0-90°)}, K = 0$$

Bothner-By equation

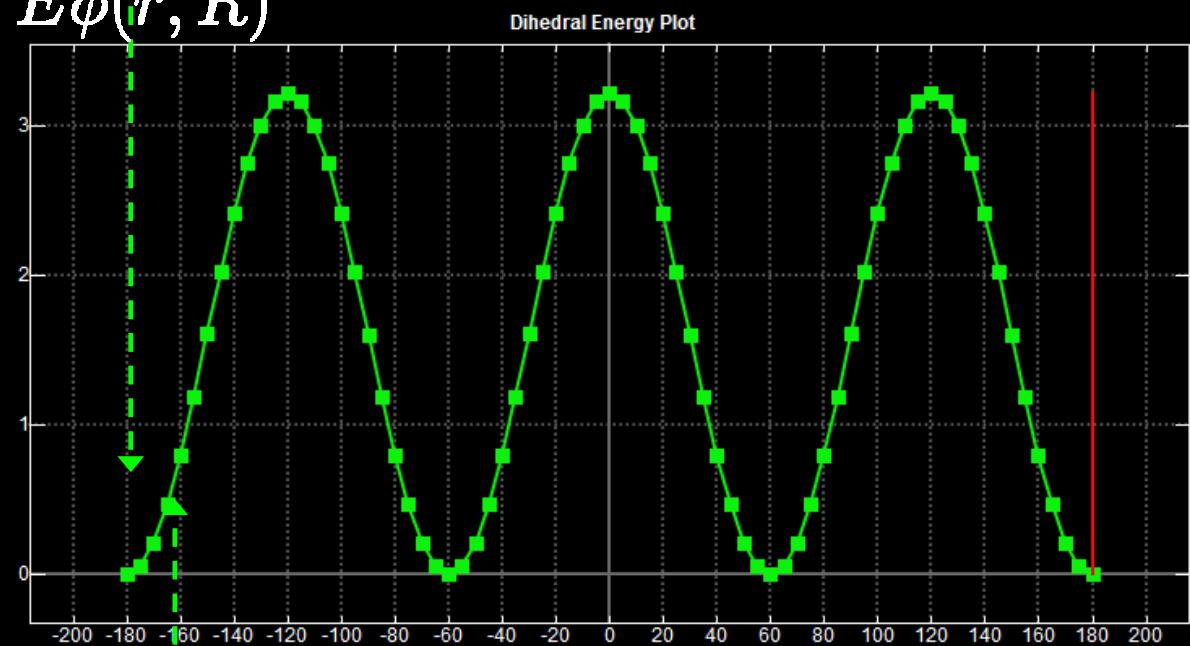
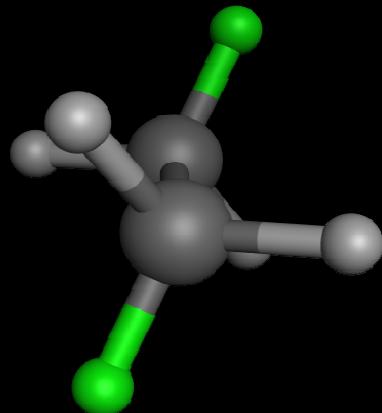
$$^3J_{\text{HH}} = 7 - \cos \Theta + 5 \cdot \cos 2\Theta$$



A possible strategy:

Schrödinger equation

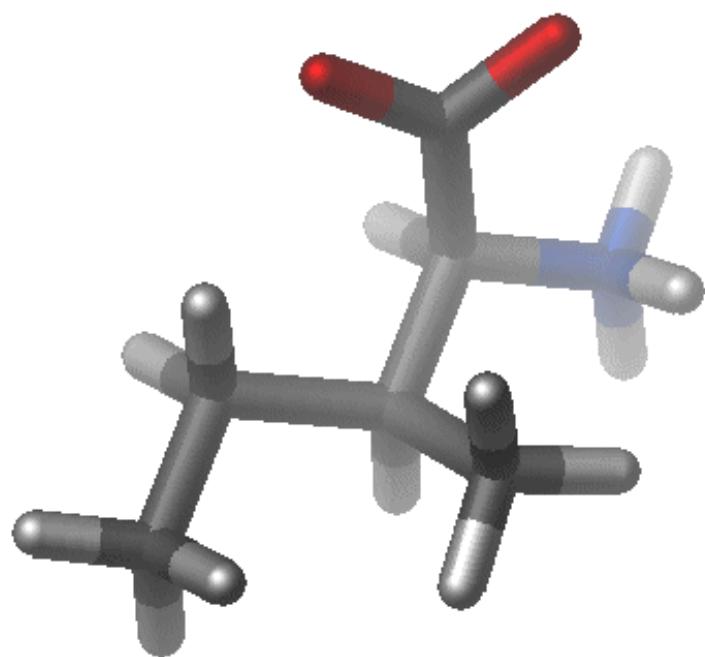
$$\hat{H}\phi(\vec{r}, \vec{R}) = E\phi(\vec{r}, \vec{R})$$



Best fitting

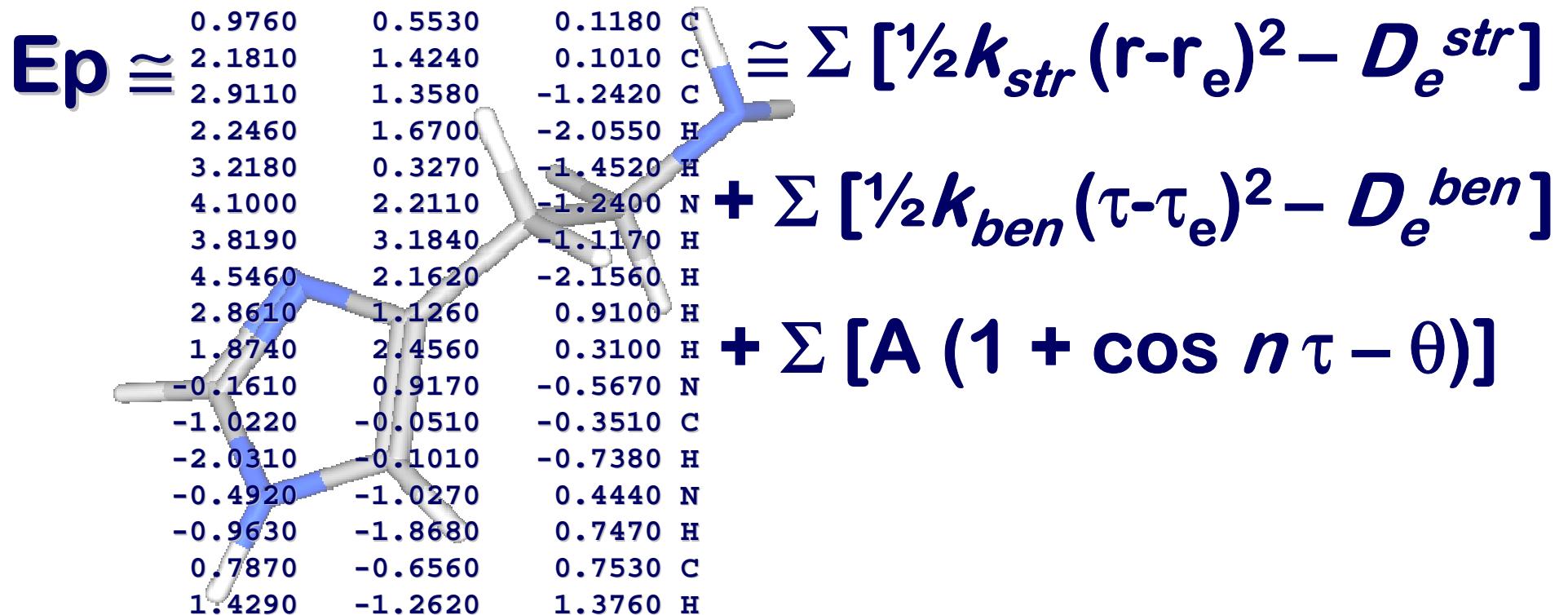
$$A [1 + \cos n \tau - \theta]$$

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



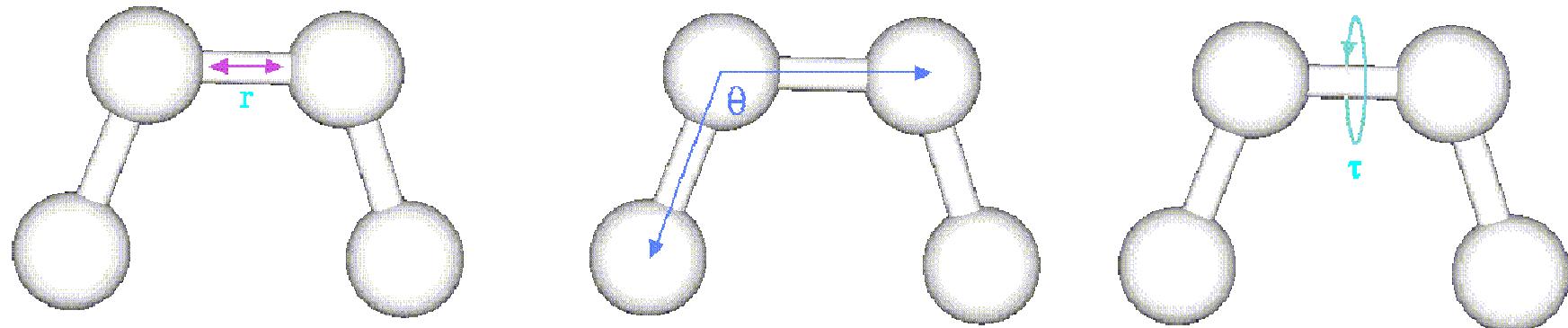


Force Field (FF): the empirical energy equation is growing...





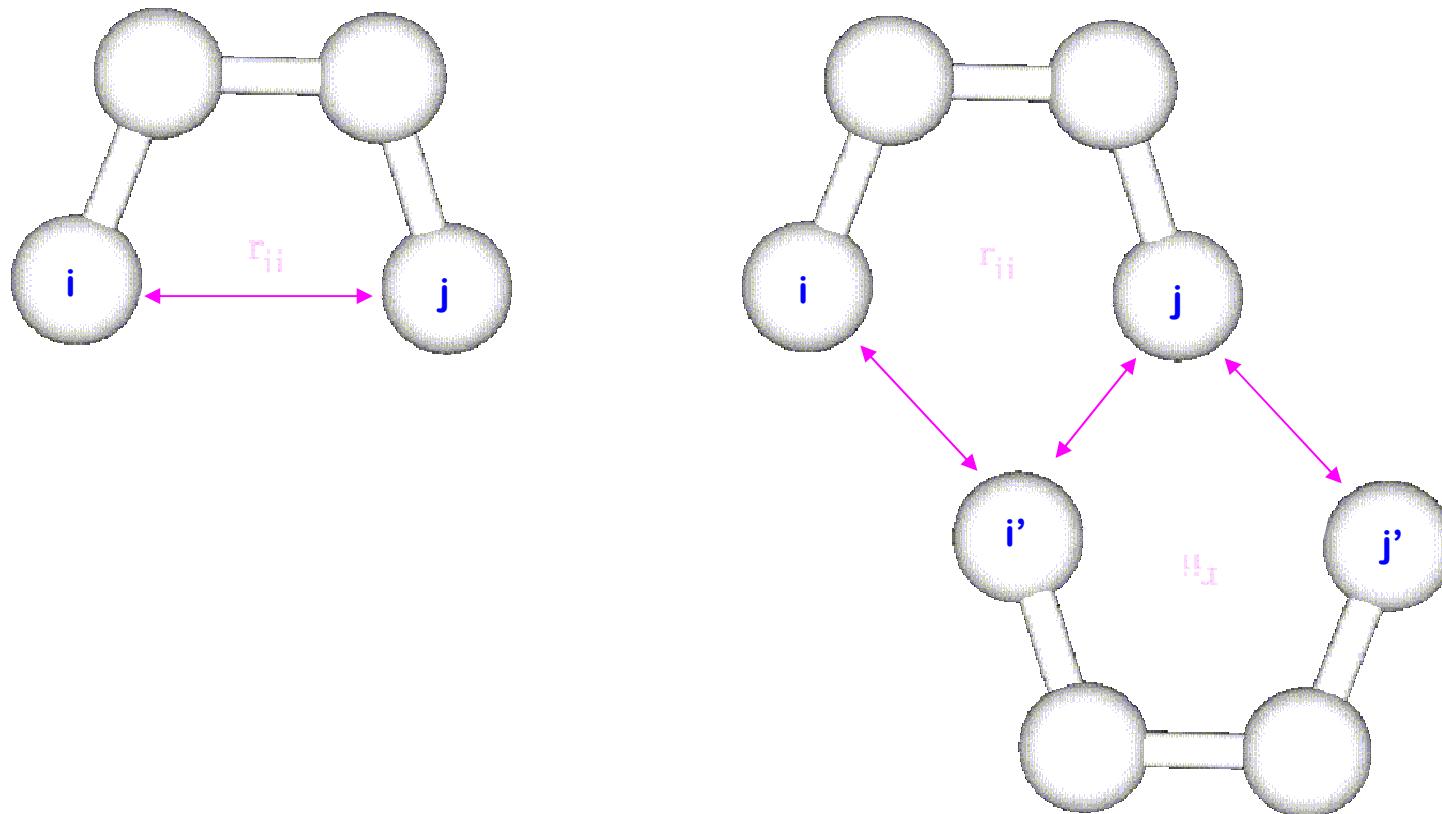
All variations of these potential energy contributions are related to the concept of chemical bond.



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



such as...



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

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

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

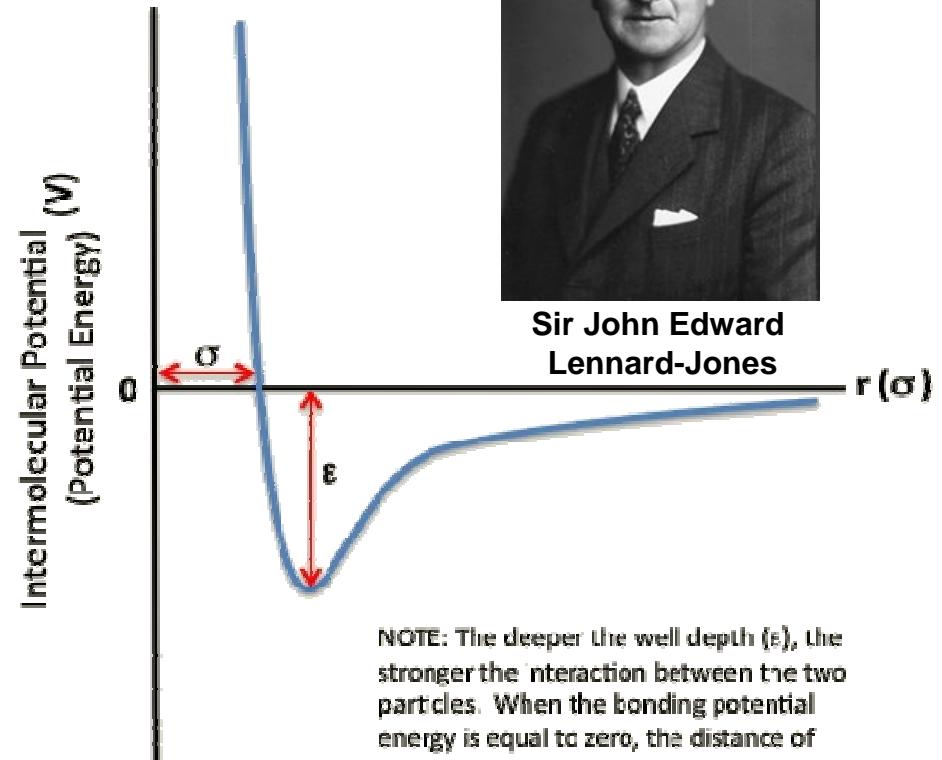
$\sum_{\substack{\text{nonbonded} \\ \text{pairs}}} \frac{q_i q_k}{4\pi\epsilon_0 r_{ik}}$



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.

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



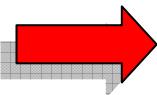
NOTE: The deeper the well depth (ϵ), the stronger the interaction between the two particles. When the bonding potential energy is equal to zero, the distance of separation, r , will be equal to σ .

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:

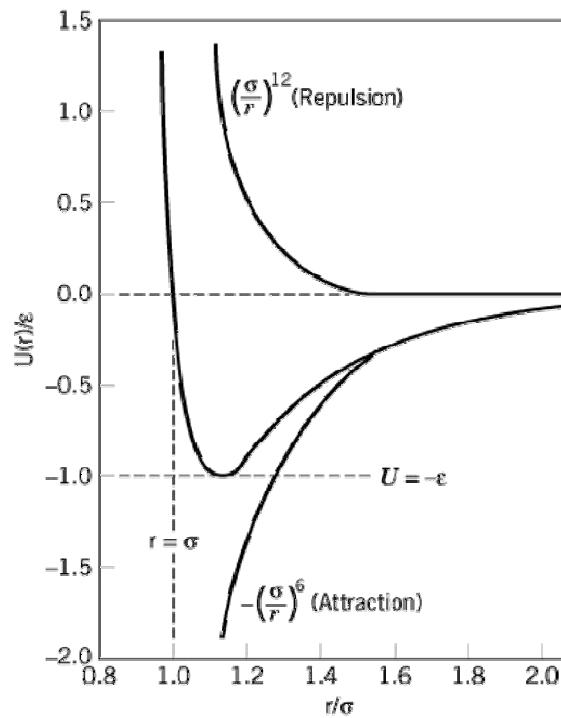
$$V(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$



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

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

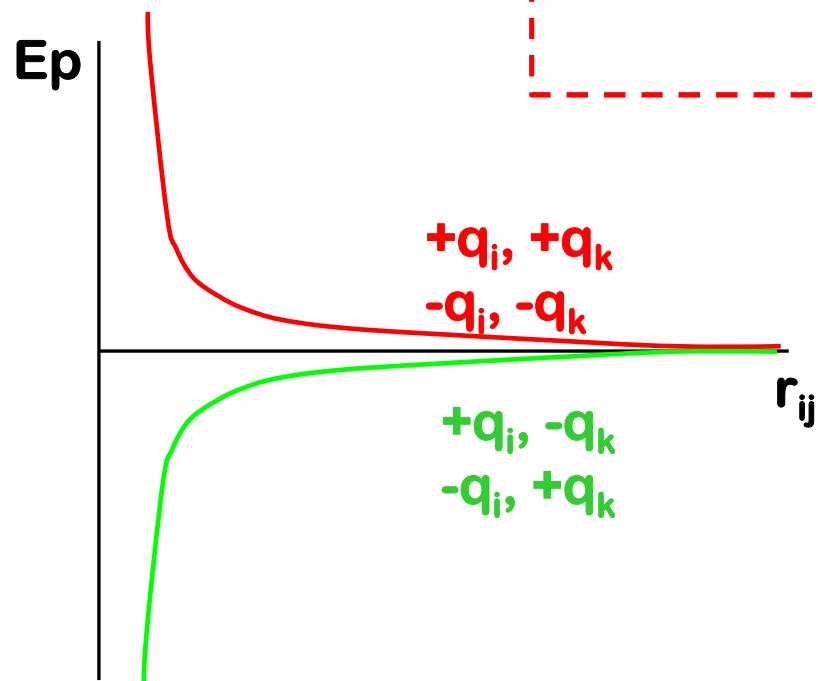
This form is a simplified formulation that is used by some simulation software packages:





and 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



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

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

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

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

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

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

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

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)

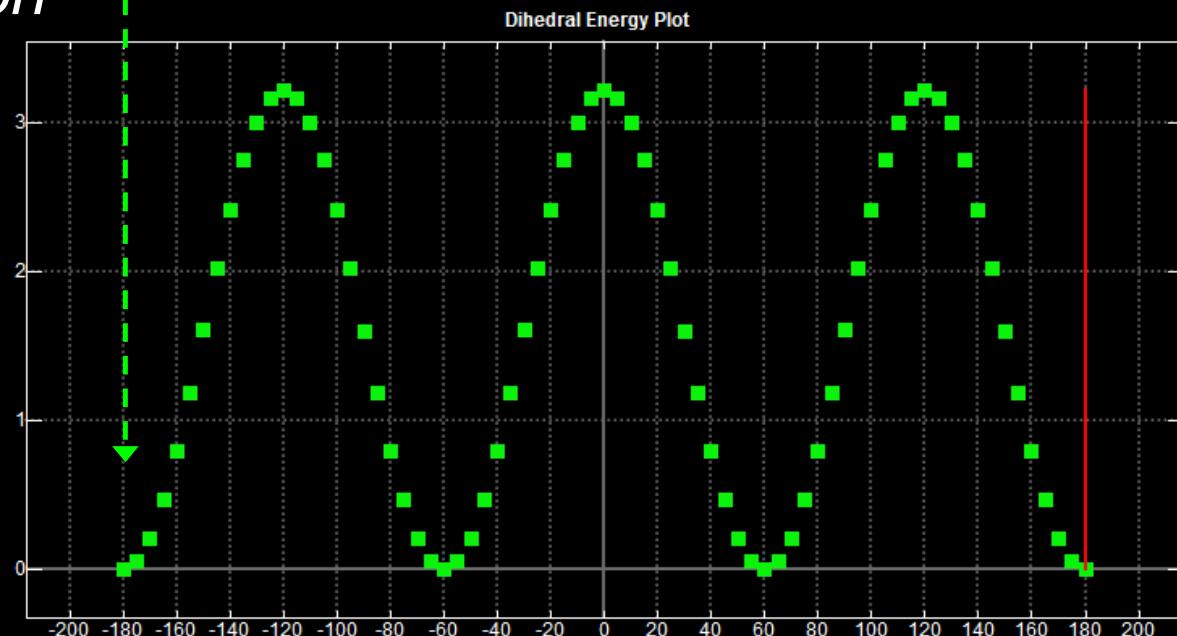
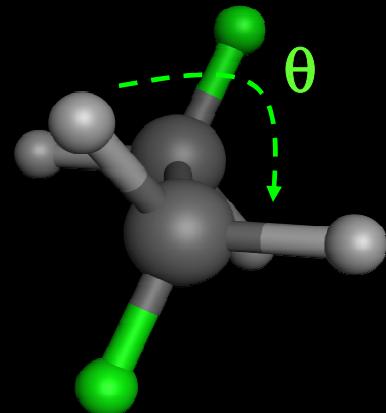
GROMOS: “Groningen Molecular Simulation” by van Gunsteren (1990)



If we have a measure of structure stability:
Now we have!

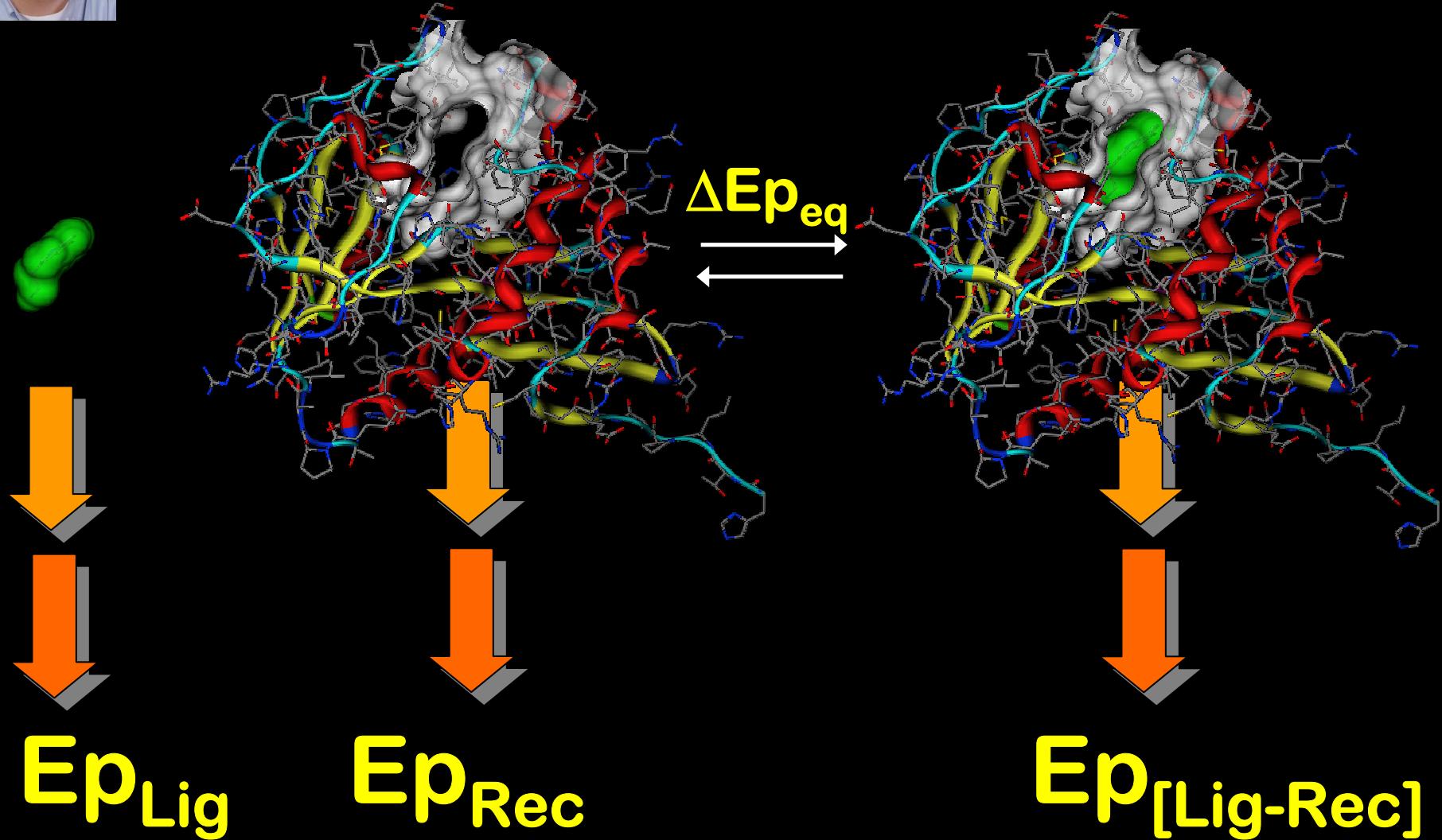
stability equation

FF equation





FF applications:





Did you understand which Ep contributions in responsible of the calculated ΔE_p ?

