Conformational analysis

What and why

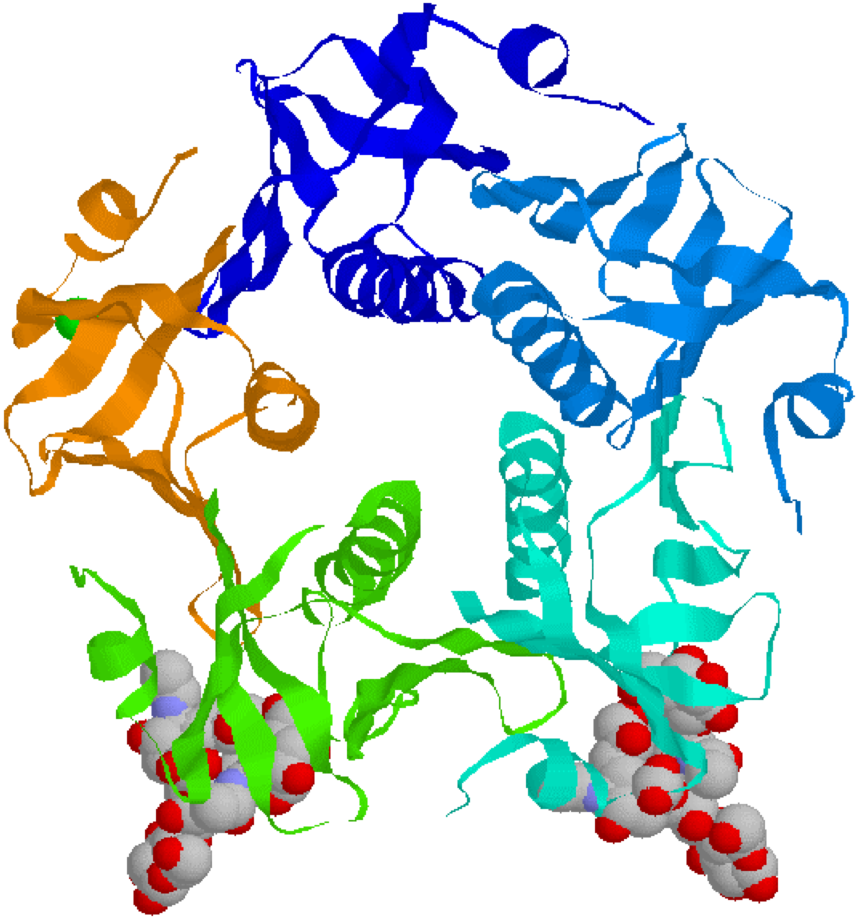
Theoretical methods

Experimental methods

Cholera toxin

THR PRO GLN ASN ILE THR ASP LEU CYS
ALA GLU TYR HIS ASN THR GLN ILE HIS
THR LEU ASN ASP LYS ILE PHE SER TYR
THR GLU SER LEU ALA ARG LYS ARG GLU
MET ALA ILE ILE THR PHE LYS ASN GLY
ALA THR PHE GLN VAL GLU VAL PRO GLY
SER GLN HIS ILE ASP SER GLN LYS LYS
ALA ILE GLU ARG MET LYS ASP THR LEU
ARG ILE ALA TYR LEU THR GLU ALA LYS
VAL GLU LYS LEU CYS VAL TRP ASN ASN
LYS THR PRO HIS ALA ILE ALA ALA ILE
SER MET ALA ASN

Cholera toxin



Purpose of conformational analyses

Gain insights into molecular interactions

Predict physical properties

As part of structure determination (stereochemistry)

Structure

primary structure – sequence

secondary structure – α-helix, β-sheet…

tertiary structure – β-barrel…

quaternary structure – dimer, trimer…

Conformers

The result of conformational analyses is a description of the three dimensional structure as one or more conformers.

A conformer is an idealized structure.

Often conformers only differ in torsion angles; *i. e.* rotamers.

The difference between **conformation** and **configuration** is the energy required for interconversion.

Theoretical approaches

Conformers with low energies are more abundant (→Boltzmann distribution)

The potential energy can be related to the three dimensional structure

Molecular mechanics or quantum mechanical methods can be used to find structures with low energy

Energy terms in MM

$V_{stretch}(r)=k_{stretch}\,(r-r_0)^2$

$V_{bend}(\theta)=k_{bend}(\theta-\theta_0)^2$

$V_{torsion}(\theta)=c_1\cos(\theta-\theta_0)+c_2\cos(2(\theta-\theta_0))+c_3\cos(3(\theta-\theta_0))$

$V_{vdW}(i,j)=A_iA_j(r_i+r_j)^{-12}-B_iB_j(r_i+r_j)^{-6}$

$V_{colomb}(i,j)=q_iq_j/\varepsilon r_{ij}$

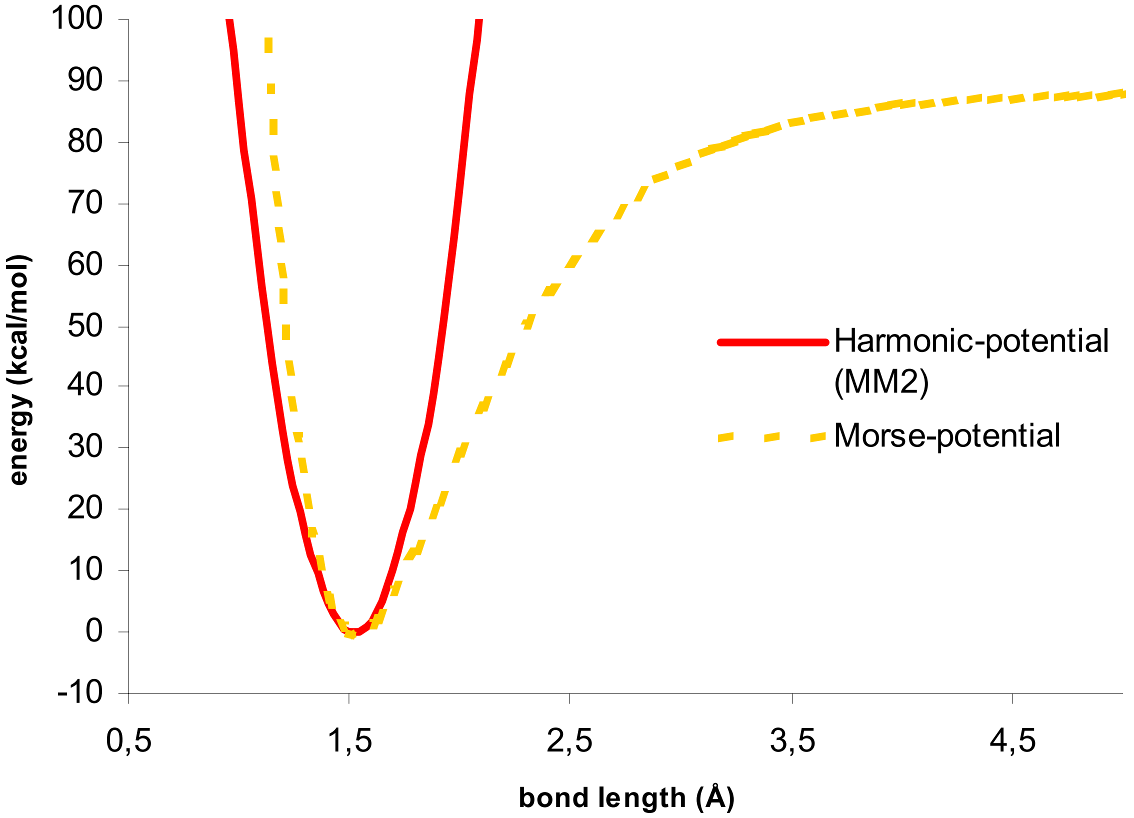
Atom types

Hydrogen: H s

Carbon: C sp - acetylene
C sp^2 ethene
C sp^3 - methane

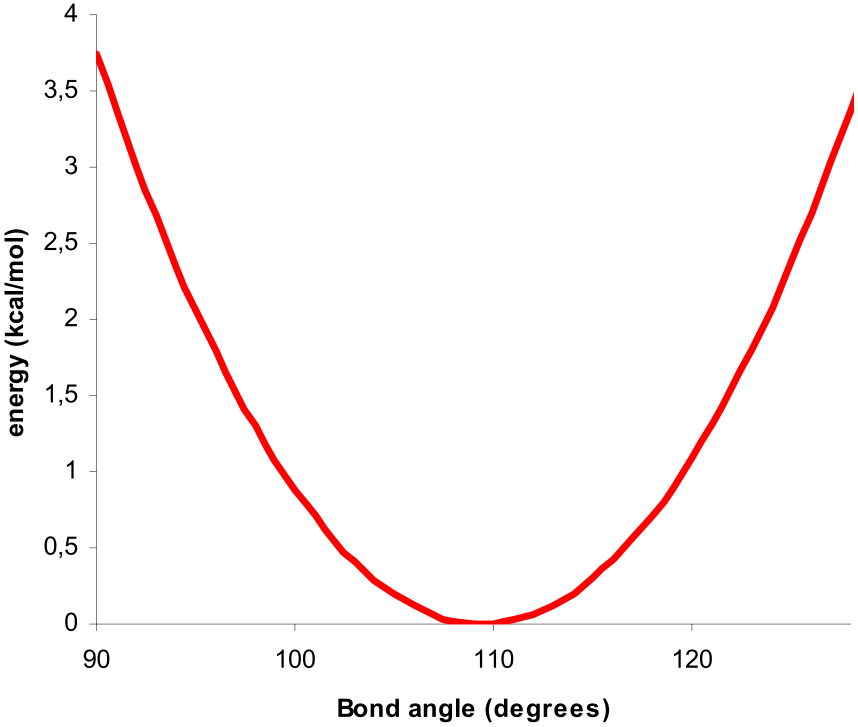
C sp^2 - conjugated
C sp^2 - aromatic

Bond length



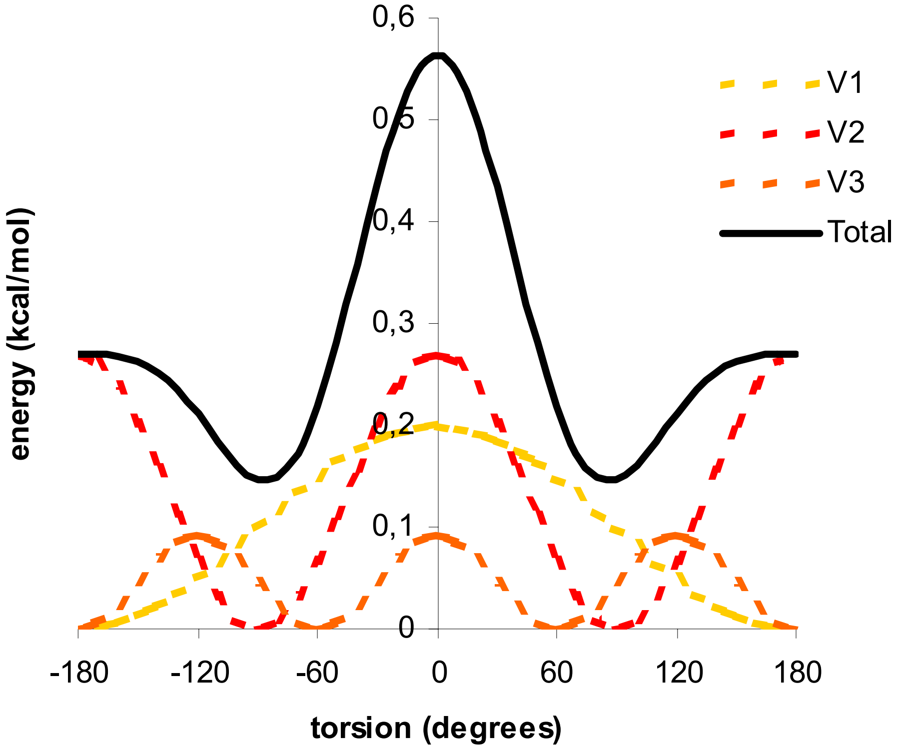
100
90
80
70
60
50
40
30
20
10
0
-10
energy (kcal/mol)
0,5
1,5
2,5
3,5
4,5
bond length (Å)
Harmonic-potential (MM2)
Morse-potential

Bond angles



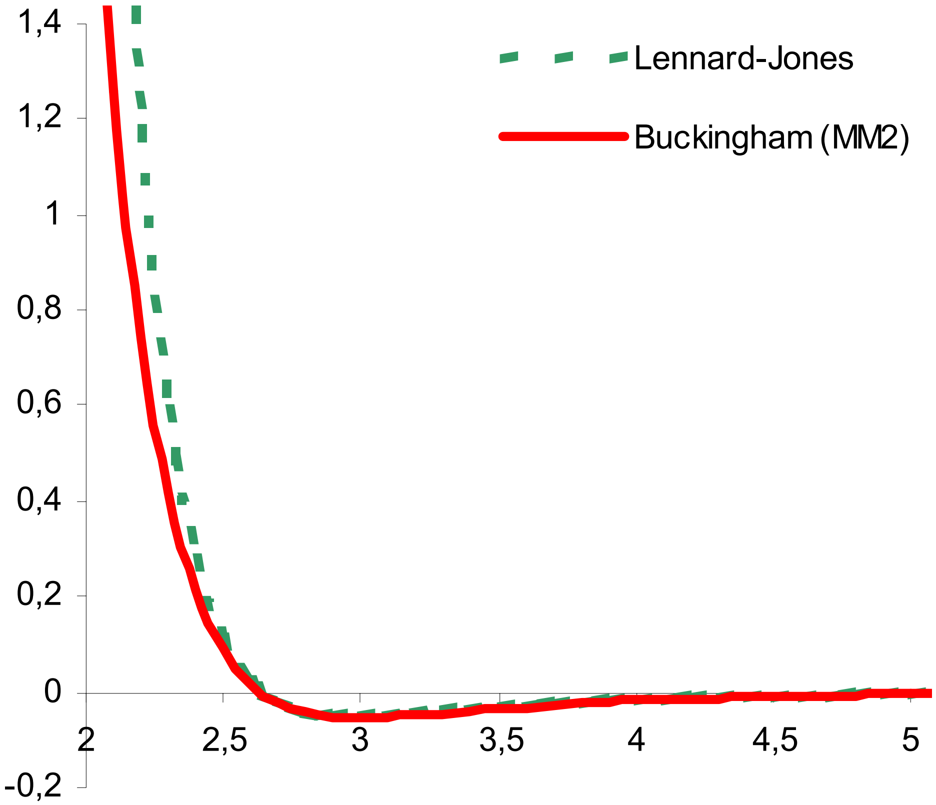
energy (kcal/mol)
4
3,5
3
2,5
2
1,5
1
0,5
0
90
100
110
120
Bond angle (degrees)

Torsion potential

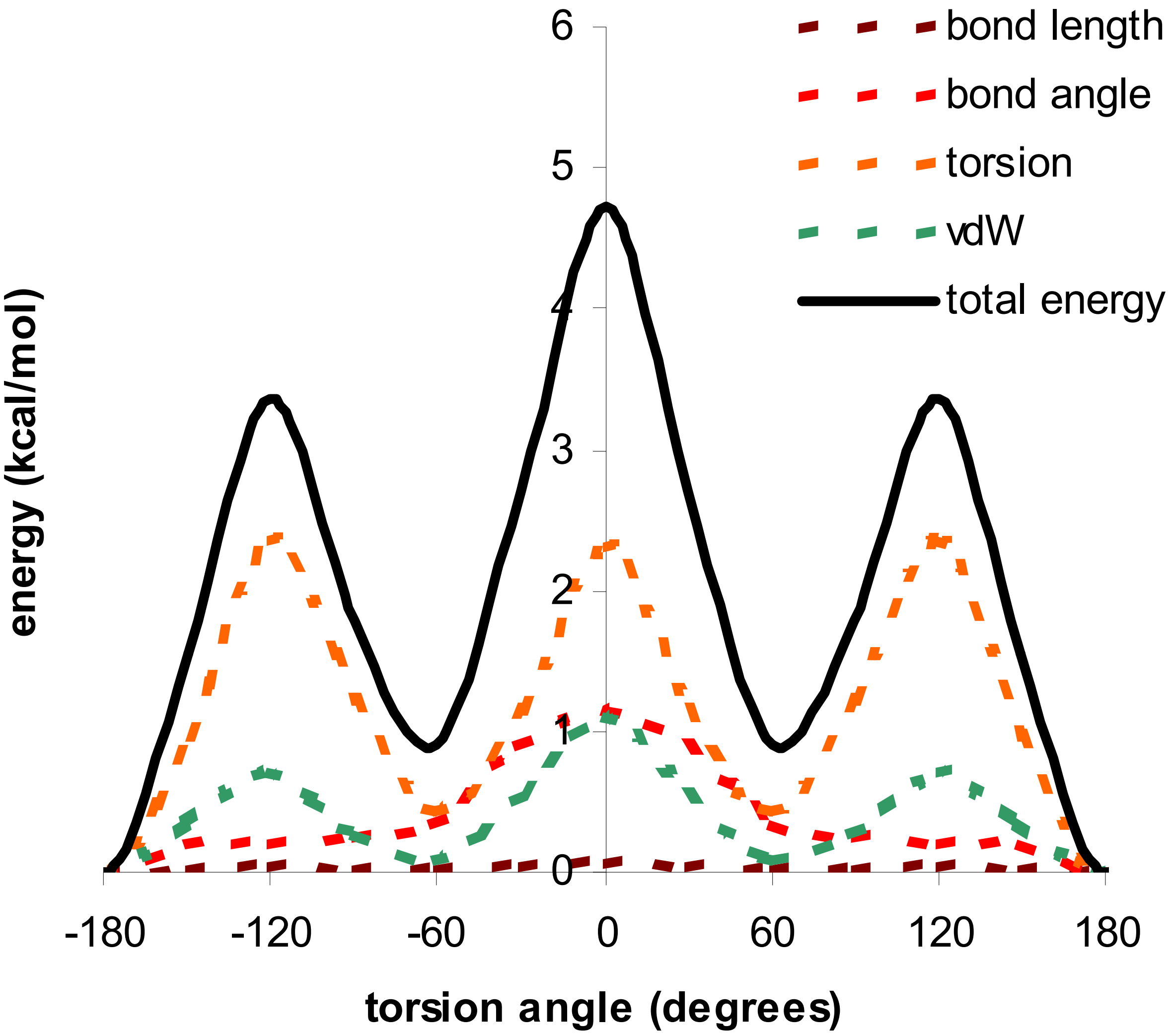


non-bonded interactions

(van der Waals and *core repulsion*)



Butane, MM2



6
5
4
3
2
1
0
-180
-120
-60
0
60
120
180
energy (kcal/mol)
torsion angle (degrees)
bond length
bond angle
torsion
vdW
total energy

Butane

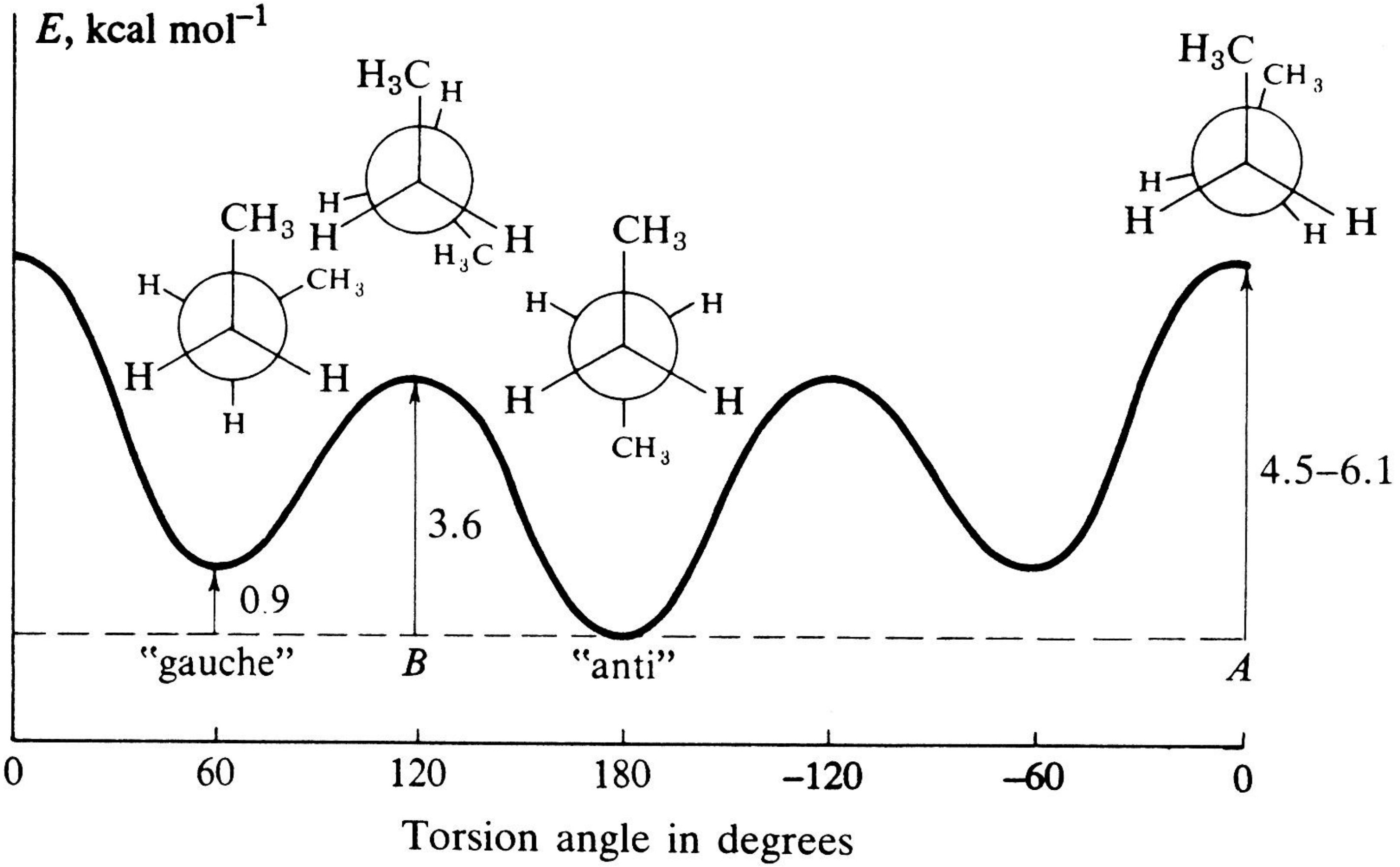


Figure 10.3. Potential energy of butane as a function of torsion angle.

What is calculated?

The energies that are obtained by geometry optimization are **not ΔH_f values**.

They can not be used to compare different molecules, *e.g.* with different functional groups!

They can be used for comparisons between conformers (assuming $T\Delta S=0$).

With bond increments ΔH_f can be estimated.

In many cases ΔH_f is a reasonable approximation of ΔG_f

What does the energy mean?

Proportion	$\Delta\Delta G^0$ (kcal/mol)
1:1	0
1:3	0.65
1:9	1.3
1:99	2.7
1:999	4.1

1% is the limit for detecting minor conformers by many experimental methods

Experimental methods

Solid state:

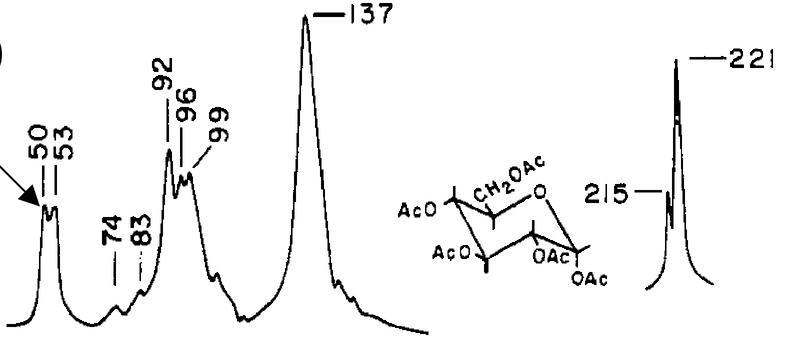
- Diffraction methods (X-ray or neutron)
- Solid state NMR (Chemical shift anisotropy)

Solution:

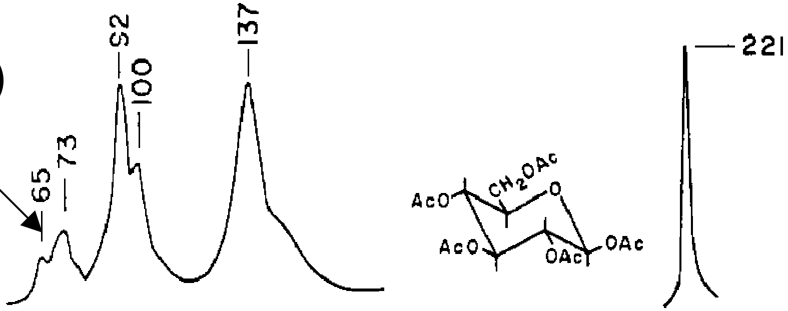
- NMR
  - NOE & dipolar couplings (distance)
  - Scalar coupling constants (torsion angles)
  - Relaxation (dynamics)

Torsion angle dependence of $^{3}J_{HH}$

H1 (^{3}J=3.2 Hz)



H1 (^{3}J≈8 Hz)



40 MHz, saturated $CHCl_3$ solution
Lemieux *et al.*, *J. Am. Chem. Soc.* **80** (1958) 6098-6105