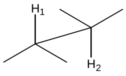
Guiding Conformational Searches with Experimental Information

CHEM8711/7711

Class Question

What type of experimental information shows conformational dependence?

NMR Coupling Constants



- ^{3}J
  - $\downarrow_1\downarrow_2 = \uparrow_1\uparrow_2$ but are not energetically equivalent to $\uparrow_1\downarrow_2 = \downarrow_1\uparrow_2$
  - Amount of coupling (energy difference between the above states) is determined by the ability of the spins to interact through intervening bonds
  - This interaction is affected by orbital overlap and has a torsional dependence as indicated by the Karplus equation

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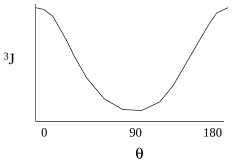
Karplus Equation



$^3J = A\cos^2\theta + B\cos\theta + C$

Values of A, B and C are dependent on the environment of the coupled nuclei, I have references for some

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Modeling Considerations

- Coupling constants observed in NMR spectra are usually consistent with more than one torsion angle
- The NMR timescale is slower than conformational changes of small molecules -> conformationally averaged values are observed

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Modeling Approaches

- Apply constraints (restraints) that force the model into a single conformation consistent with data
- Determine a population of conformers and verify that the Boltzman-weighted population would produce the correct experimental average observed (Glycoconj. J. 14, **1996**, 323-329)
- Model a time or ensemble-averaged population and add terms to the potential function that force the population toward the experimental average (JCAMD 8, **1994**, 29-40)

Class Exercise I

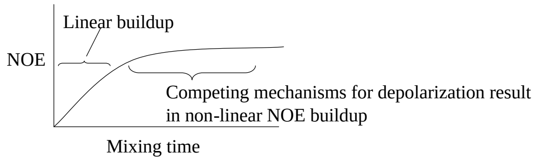
- Assume that A=7.76, B=-1.10 and C=1.40
- Use the following data to evaluate a realistic conformational distribution around the C2-C3 bond in pentane at an unknown temperature
  - ^3J = 6.0 Hz

NOE Enhancements

- NOE's result from cross-polarization
  - Example:
    - Irradiation of a particular ^1H nuclei changes the equilibrium distribution of spin states (more spins are promoted to the high spin state)
    - This change in ^1H polarization affects the distribution of spins for ^{13}C nuclei (more spins are demoted to the low spin state)
    - Subsequent irradiation of ^{13}C gives a stronger signal than without prior ^1H irradiation

Distance Dependence

- Polarization transfer is a through-space effect that drops off with the sixth power of the distance (NOE is proportional to r^{-6})
- Polarization transfer is also time dependent



Use of NOE's in Modeling

- Approach 1
  - A known distance in the molecule is used to calibrate the relationship between NOE buildup rate and distance (NOE = c r^{-6})
  - Exact distance values can be used as constraints during annealing or MD to drive the molecule's conformation toward one consistent with experiment
- Approach 2
  - NOE enhancements are assigned upper distance bounds
  - Upper limits on distances are used as constraints

Class Exercise II

- Given a C_1-H to C_4-H distance of 4 Å in 1-butanol, generate a conformation consistent with this information
- Defining restraints
  - Moe uses unique identifiers for every atom
    - Can get with variable = AtomPrompt [] by clicking on the atoms of interest
  - RestraintCreate ['distance',[[a1,a2]],value, weight]

Potential Problems

- What happens when there is more than one hydrogen at a given position?
- Constraints change the energy functions – a final minimization without constraints should always be done
- A small number of NOE-derived distances will not be sufficient to completely define the 3D shape of a molecule
- Modeling with NOE's is generally done repeatedly from different starting geometries to see if multiple structures consistent with the data are found

Reading

- First Edition
  - 8.6
  - 8.7-8.7.2, 8.7.4, 8.7.5
- Second Edition
  - 9.5
  - 9.6 (probably through 9.6.2, and 9.6.4, 9.6.5)