

Origin of Chemical Shifts

BCMB/CHEM 8190

Empirical Properties of Chemical Shift

$$\nu_i \text{ (Hz)} = \gamma B_0 (1 - \sigma_i) / 2\pi$$

- The Larmor frequencies of nuclei depend on the electronic structure of the molecule and the electronic environments of the nuclei, and reflect the chemical properties
- The adjustments to the resonance frequencies to account for electronic structure and electronic shielding of nuclei from the magnetic field are embodied in the shielding constant, σ
- The values of σ are small (10^{-6}), and reduce the effective field strength by parts per million (ppm) ($B_{\text{eff}} = B_0(1-\sigma)$)

Measurements are made relative to a reference peak (TMS).
Offsets given in terms of δ in parts per million, ppm, + downfield.

$$\delta_i = (\sigma_{\text{ref}} - \sigma_i) \times 10^6$$

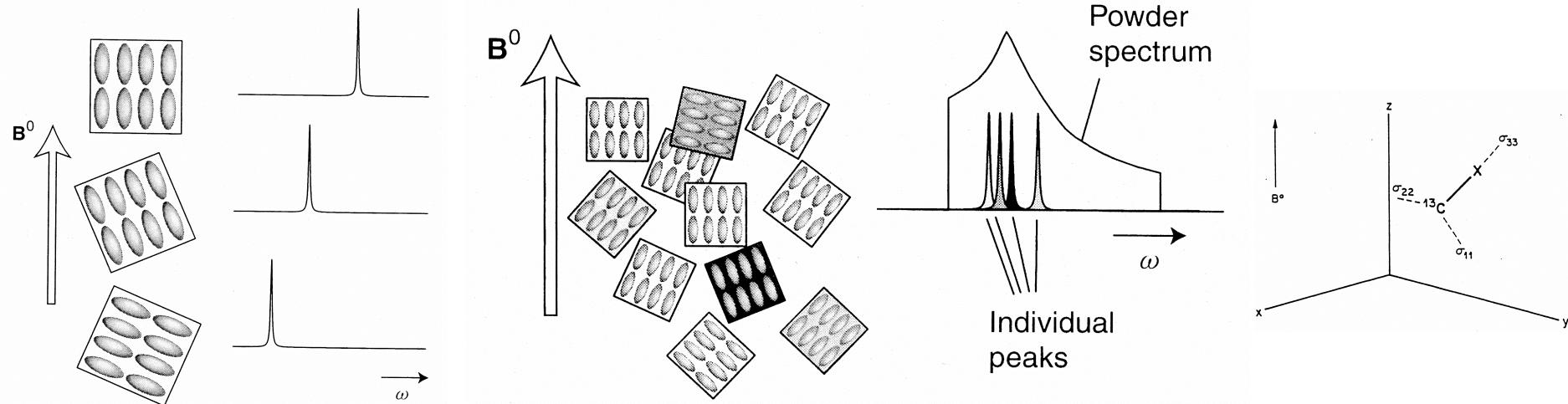
or

$$\delta_i = ((\nu_i - \nu_{\text{ref}}) / \nu_{\text{ref}}) \times 10^6$$

Ranges: ^1H , ^2H , 10 ppm; ^{13}C , ^{15}N , ^{31}P , 300 ppm; ^{19}F , 1000 ppm

Importance of Chemical Shifts and Their Origins

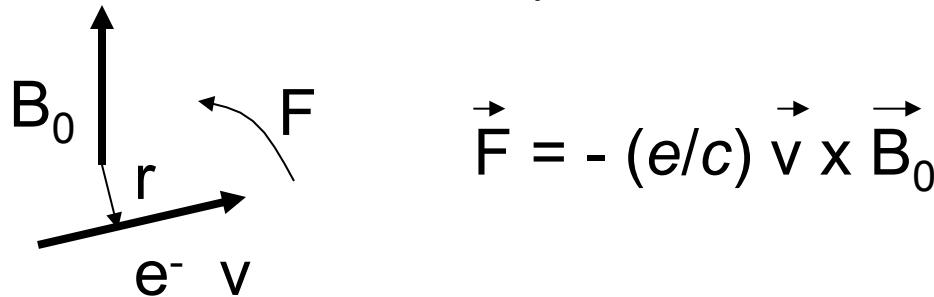
- Shieldings are tensor quantities: magnitudes depend on orientation to magnetic field (*chemical shift anisotropy*)
- In the solid state, different orientations give different shifts
- In solution (rapid molecular tumbling) an average value results
- However, in solution some orientation can be reintroduced in order to exploit available structural information
- Chemical shifts reflect chemical environment, so there is potentially lots of structural information in chemical shifts themselves if we can understand the relationship with structure



Ramsey's Equation for Chemical Shift

Reference: Webb, G. A. in "Nuclear Magnetic Shielding and Molecular Structure", J. A. Tossel, Ed., NATO Advanced Science Institutes Series (1993), 1-25.

- Classical explanation offered by *Ramsey's equation*: charged particles moving through a magnetic field (B_0) experience a force perpendicular to both B_0 and the particle trajectory
- So, electrons in the molecule (around the nucleus) precess



- The precessing charge generates its own magnetic field (B'), which happens to be in the *opposite* direction to B_0
$$\vec{B}' = -(e/c) (\vec{r} \times \vec{v}) / r^3 = -(e/cm) (\vec{r} \times \vec{p}) / r^3$$
- The opposing B' field reduces the effective B_0 field for the nucleus, so $B_{\text{eff}} < B_0$, and $B_{\text{eff}} = B_0(1-\sigma)$
- But, how does electronic structure dictate $B'?$ $\sigma?$ Need QM.

Some Quantum Mechanics Fundamentals

Expectation Values

- To find the value for some observable (i.e. B' , σ), quantum mechanically we calculate the *expectation value*
- Here, the expectation of some property ($\langle O \rangle$) is the result of some operator (\hat{O}) operating on an appropriate wavefunction (ψ) multiplied (on the left) by the complex conjugate of the wavefunction (ψ^*), integrated over all space

$$\langle O \rangle = \langle \psi | \hat{O} | \psi \rangle = \int \psi^* \hat{O} \psi \, d\tau \quad \hat{O} - \text{some operator} \quad \psi - \text{some wavefunction}$$

Wavefunctions

- For calculating B' and σ , (chemical systems) we'll need *electronic wavefunctions*
 - i.e. atomic electronic orbitals like $\psi = 1s, 2s, 2p_1, 2p_0, 2p_{-1}, \dots$
 - can write p orbitals as p_x, p_y, p_z (spatial representations) or $2p_1, 2p_0, 2p_{-1}$, (1, 0, -1 are magnetic quantum numbers m , p orbitals have total angular momentum of 1)

Some Quantum Mechanics Fundamentals

Wavefunctions

- For calculating spin systems we'll need *spin wavefunctions*
 $\psi = \alpha, \beta$ (single spins 1/2), $\alpha\alpha, \alpha\beta, \beta\alpha, \beta\beta$ (two spins 1/2)
 - for α and β , $m=+\frac{1}{2}$ and $m=-\frac{1}{2}$
 - for noninteracting spins, can just take products ($\alpha\alpha, \alpha\beta$, etc.)
- All of these wavefunctions are solutions to Schrödinger's equation
 - \hat{H} (Hamiltonian operator) operates on ψ to give back the energy (E) and ψ
 - a discrete set of energies and a discrete set of associated ψ s
- These wavefunctions must be *normalized*

$$\int \psi * \psi \, dt = \langle \psi | \psi \rangle = 1$$

- $\psi * \psi$, probability of finding our particle at some point in space
- so, sum of all probabilities (all space) should = 1

Some Quantum Mechanics Fundamentals

Operators

- The expectation value of the *Hamiltonian* operator is energy

$$\langle \psi | \hat{H} | \psi \rangle = E$$

- For electronic wavefunctions, the energy of interaction of the electrons with their environments are returned
- For spin wavefunctions, the energies of interaction of the nuclei with the magnetic field are returned

$$\hat{H}_z = -\hat{\mu} \cdot \mathbf{B}_0, \quad E_{z\alpha} = \langle \alpha | -\hat{\mu} \cdot \mathbf{B}_0 | \alpha \rangle, \quad E_{z\beta} = \langle \beta | -\hat{\mu} \cdot \mathbf{B}_0 | \beta \rangle$$

- Often the Hamiltonian can be understood by substituting operators (that operate on the wavefunctions) into a classical expression

$$\hat{\mu}_z = \gamma \hat{\mathbf{I}}_z \quad \mu_z = \gamma I_z = m\gamma\hbar \quad \leftarrow$$

- this gives us the quantum numbers $m=+\frac{1}{2}$ and $m=-\frac{1}{2}$, thus

$$E_{zm} = \langle \psi_m | -m\gamma\hbar B_0 | \psi_m \rangle = -m\gamma\hbar B_0 \langle \psi_m | \psi_m \rangle = -m\gamma\hbar B_0$$

Quantum Expression for B'

- For calculation of B' and σ , QM operators are needed
- Below are the classical expression for B' in terms of linear momentum (p) and the QM operator for linear momentum

$$B' = -(e/cm)(\vec{r} \times \vec{p})/r^3 = -e(\vec{r} \times \vec{p})/[r^3 cm] \quad \hat{\mathbf{p}}_0 = i\hbar(\partial/\partial x + \partial/\partial y + \partial/\partial z)$$

- One caveat: a charged particle in a magnetic field feels a force perpendicular to both B_0 and its trajectory, causing it to "curl"
- Solution: modify the linear momentum to recognize that the particle does not travel in a straight line, but curves (the "curl")

$$\vec{p} = \vec{p}_0 + e(\vec{B}_0 \times \vec{r})/(2c) = \vec{p}_0 + (e/c)\vec{A} \text{ where } \vec{A} = (\vec{B}_0 \times \vec{r})/2$$

- here \vec{A} is called the vector potential

- So, now the "corrected" classical expression for B' becomes

$$B' = -e(\vec{r} \times \vec{p}_0)/[r^3 cm] - e^2(\vec{r} \times \vec{A})/[r^3 c^2 m]$$

Quantum Expression for B'

- Quantum mechanically, calculate the expectation value from the following expression (ψ_0 are electronic wavefunctions)

$$B' = \langle \psi_0 | -e (\vec{r} \times \hat{\vec{p}}_0) / [r^3 cm] - e^2 (\vec{r} \times \hat{\vec{A}}) / [r^3 c^2 m] | \psi_0 \rangle$$

paramagnetic	diamagnetic
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- Are two parts to B' (and σ): paramagnetic and diamagnetic
 - Paramagnetic does not refer to paramagnetism or unpaired electrons
 - Diamagnetic part accounts for the induced circulation of electrons that shields the nucleus (so $B_{\text{eff}} < B_0$)
 - Paramagnetic part comes from change in the electronic wavefunctions
 - Paramagnetic component insignificant for hydrogen, but is important for heavier elements (is the cause of large chemical shift ranges)

Diamagnetic Shifts

- For H, only diamagnetic part important
- Only the diamagnetic, or "Lamb", term) explicitly includes B_0 , so, to first order, need only use this term in B' (B'_D)
- Rewrite the diamagnetic part in terms of \vec{B}_0 and \vec{r}

$$-e^2 (\vec{r} \times \hat{\vec{A}}) / [r^3 c^2 m] = -e^2 (\vec{r} \times \vec{B}_0 \times \vec{r}) / [2r^3 c^2 m] \text{ where } \vec{A} = (\vec{B}_0 \times \vec{r}) / 2$$

- So, B'_D is proportional to the applied magnetic field, as expected

$$B'_D = \langle \psi_0 | -e^2 (\vec{r} \times \vec{B}_0 \times \vec{r}) / [2r^3 c^2 m] | \psi_0 \rangle$$

- Cross product (see "Appendix" of Bloch equations lecture notes)

$$\vec{r} = [x \ y \ z] \quad (\vec{B}_0 \times \vec{r}) = [(\vec{B}_0 \times \vec{r})_x \ (\vec{B}_0 \times \vec{r})_y \ (\vec{B}_0 \times \vec{r})_z] \text{ and unit vectors } \vec{i}, \vec{j}, \vec{k}$$

$$\vec{r} \times (\vec{B}_0 \times \vec{r}) = [(\vec{i}(y(\vec{B}_0 \times \vec{r})_z - z(\vec{B}_0 \times \vec{r})_y) \ \vec{j}(z(\vec{B}_0 \times \vec{r})_x - x(\vec{B}_0 \times \vec{r})_z) \ \vec{k}(x(\vec{B}_0 \times \vec{r})_y - y(\vec{B}_0 \times \vec{r})_x)]$$

- B_0 is along z , so *only z component is significant*. Thus

$$\vec{r} \times (\vec{B}_0 \times \vec{r}) = [\vec{k} (x(\vec{B}_0 \times \vec{r})_y - y(\vec{B}_0 \times \vec{r})_x)]$$

Diamagnetic Shifts

$$\vec{r} \times (\vec{B}_0 \times \vec{r}) = [\vec{k} (x(\vec{B}_0 \times \vec{r})_y - y(\vec{B}_0 \times \vec{r})_x)]$$

- Now need the cross product $\vec{B}_0 \times \vec{r}$

$$\vec{B}_0 = [B_{0,x} \ B_{0,y} \ B_{0,z}] \quad \vec{r} = [x \ y \ z] \text{ and unit vectors } \vec{i}, \vec{j}, \vec{k}$$

$$\vec{B}_0 \times \vec{r} = [\vec{i}(\vec{B}_{0,y}z - \vec{B}_{0,z}y) \quad \vec{j}(\vec{B}_{0,z}x - \vec{B}_{0,x}z) \quad \vec{k}(\vec{B}_{0,x}y - \vec{B}_{0,y}x)]$$

- So

$$(\vec{B}_0 \times \vec{r})_y = \vec{j}(\vec{B}_{0,z}x - \vec{B}_{0,x}z) \quad (\vec{B}_0 \times \vec{r})_x = \vec{i}(\vec{B}_{0,y}z - \vec{B}_{0,z}y)$$

- Substitute

$$\begin{aligned}\vec{r} \times (\vec{B}_0 \times \vec{r}) &= [\vec{k} (x(\vec{j}(\vec{B}_{0,z}x - \vec{B}_{0,x}z)) - y(\vec{i}(\vec{B}_{0,y}z - \vec{B}_{0,z}y)))] \\ &= [x(\vec{B}_{0,z}x - \vec{B}_{0,x}z) - y(\vec{B}_{0,y}z - \vec{B}_{0,z}y)] = x(\vec{B}_{0,z}x) + y(\vec{B}_{0,z}y) = B_0(x^2 + y^2)\end{aligned}$$

- Finally

$$\begin{aligned}B'_D &= \langle \psi_0 | -e^2 (\vec{r} \times \vec{B}_0 \times \vec{r}) / [2r^3 c^2 m] | \psi_0 \rangle = \langle \psi_0 | -e^2 B_0 (x^2 + y^2) / [2r^3 c^2 m] | \psi_0 \rangle \\ &= -(e^2 / [2c^2 m]) B_0 \langle \psi_0 | (x^2 + y^2) / r^3 | \psi_0 \rangle\end{aligned}$$

Diamagnetic Shifts

$$B'_D = -(e^2 / [2c^2 m]) B_0 \langle \psi_0 | (x^2 + y^2) / r^3 | \psi_0 \rangle$$

- So, what does this predict?
- We now have a simple operator, $(x^2+y^2)/r^3$ that weights the probability density ($\langle \psi_0 | \psi_0 \rangle$)
- $(x^2+y^2)/r^3$ ($\sim 1/r$) *increases* as r (distance of electron from nucleus) decreases (as electron gets closer to nucleus)
- So, this predicts that B'_D (shielding of the nucleus by the magnetic fields generated by the precessing electrons) *increases* as electrons get closer to the nucleus (only s orbitals have electron density at nucleus)
- p,d, etc., have zero electron density at the nucleus

Predictions: depends on electron density near to nucleus
opposes magnetic field (shields)

Examples: He 2 1s electrons $\sigma = 59.93 \times 10^{-6}$

Ne 10 s electrons $\sigma = 547 \times 10^{-6}$

H ~2 1s electrons $\sigma = \sim 60 \times 10^{-6}$

HO- O withdraws ~10% ~6 ppm downfield

Paramagnetic Contribution to Shifts

- This comes from the first term in the quantum expression for B'

$$B' = \langle \psi_0 | -e (\vec{r} \times \hat{\vec{p}}_0) / [r^3 cm] | \psi_0 \rangle$$

- A variation of B' with B_0 is expected, but no explicit B_0 dependence in the operator as written
- The B_0 dependence is introduced when the nuclei are introduced into the magnetic field, because the electronic wavefunctions are perturbed/changed by the magnetic field
- So, a *second order perturbation*/correction is needed (perturbation theory)

$$\psi = \psi_0 + \psi' = \psi_0 + \sum_n \left(\langle \psi_n | \hat{H}' | \psi_0 \rangle / (E_n - E_0) \right) \psi_n$$

- Here, we add a correction factor, introducing changes to the Hamiltonian to account for the interactions of the electrons with the magnetic field, that we neglected to first order
- The correction factor mixes in wavefunctions for excited states
- Depends on the integral of the complex conjugate of the excited state wavefunction multiplied by the result of the corrected Hamiltonian operating on the ground state wavefunction
- Denominator is the energy gap (small differences make big contributions)

Paramagnetic Contribution to Shifts

- \hat{H}_0 is the Hamiltonian in the absence of a magnetic field

$$\hat{H}_0 = (1/(2m))\hat{\mathbf{p}}_0^2 + V$$

- includes operators representing kinetic energy ($K=p^2/2m$) and the strong electronic (Coulombic) interaction of the electron and nuclear charges (V)

- \hat{H} is the Hamiltonian in the presence of a magnetic field

$$\hat{H} = (1/(2m))(\hat{\mathbf{p}}_0 + (e/c)\hat{\mathbf{A}})^2 + V$$

- recall

$$\vec{p} = \vec{p}_0 + e(\vec{B}_0 \times \vec{r})/(2c) = \vec{p}_0 + (e/c)\vec{A} \text{ where } \vec{A} = (\vec{B}_0 \times \vec{r})/2$$

- so the \mathbf{p}_0^2 operator is rewritten as before, including the vector potential A , which *includes the B_0 dependence*

- \hat{H}' is the Hamiltonian that we will use, as it includes a linear dependence on B_0

$$\hat{H}' = (e/(2mc))\vec{A} \cdot \vec{\mathbf{p}}_0$$

- note that

$$(\vec{p}_0 + (e/c)\vec{A})^2 = \vec{p}_0^2 + 2\vec{p}_0(e/c)\vec{A} + ((e/c)\vec{A})^2$$

- so we're making a *first order approximation*, keeping only the linear B_0 dependence (which is what we expect for chemical shift, a linear B_0 dependence)

Paramagnetic term continued

- Expand $\vec{A} \cdot \vec{p}_0$ into a more useful form
$$\vec{A} \cdot \vec{p}_0 = ((\vec{B}_0 \times \vec{r})/2) \cdot \vec{p}_0 \equiv B_0 \cdot (\vec{r} \times \vec{p}_0)/2 = B_0 \hat{\mathbf{L}} \hbar / 2 = B_0 \hat{L}_z \hbar / 2$$
- the cross product $r \times p$ (distance \times linear momentum) is *angular momentum*
- The z projection operator, L_z , operating on atomic electronic wavefunctions, returns projections on the z axis
- Here L is the orbital angular momentum quantum number.
 - for s orbitals, L is 0
 - for p orbitals, L is 1, and $m = 1, 0$ and -1 ($2p_1, 2p_0, 2p_{-1}$, i.e. $2p_x, 2p_y, 2p_z$)
- If only s orbitals (hydrogen), paramagnetic term is insignificant
- Now we can rewrite the Hamiltonian
$$\hat{H}' = (e/(2mc)) \vec{A} \cdot \vec{p}_0 = (e/(2mc)) B_0 \hat{L}_z \hbar / 2 = B_0 e \hbar / (4mc) \hat{L}_z$$
- The corrected wavefunction now is

$$\begin{aligned}\psi &= \psi_0 + \psi' = \psi_0 + \sum_n \left(\langle \psi_n | \hat{H}' | \psi_0 \rangle / (E_n - E_0) \right) \psi_n \\ &= \psi_0 + B_0 e \hbar / (4mc) \sum_n \left(\langle \psi_n | \hat{L}_z | \psi_0 \rangle / (\Delta E) \right) \psi_n\end{aligned}$$

Paramagnetic term continued

- Here again is the expression for the paramagnetic term

$$B_p' = \langle \psi_0 | -e (\vec{r} \times \hat{\vec{p}}_0) / [r^3 cm] | \psi_0 \rangle$$

- The corrected expression now is

$$B_p' = \langle \psi_0 + \psi' | -e (\vec{r} \times \hat{\vec{p}}_0) / [r^3 cm] | \psi_0 + \psi' \rangle = \langle \psi_0 + \psi' | - (e/(cm)) \hat{L}_z / r^3 | \psi_0 + \psi' \rangle$$

- Now substitute in ψ'

$$B_p' = \langle \psi_0 + \psi' | - (e/(cm)) \hat{L}_z / r^3 | \psi_0 + \psi' \rangle$$

- Simplify ψ' and B' by getting rid of constants

$$B_p' \propto \langle \psi_0 + \psi' | \hat{L}_z / r^3 | \psi_0 + \psi' \rangle \quad \psi' \propto \sum_n \left(\langle \psi_n | \hat{L}_z | \psi_0 \rangle / (\Delta E) \right)$$

- Write B' , keeping only terms linear in B_0

$$B_p' \propto \sum_n [(\langle \psi_0 | \hat{L}_z | \psi_n \rangle \langle \psi_n | \hat{L}_z / r^3 | \psi_0 \rangle) / (\Delta E) + (\langle \psi_0 | \hat{L}_z / r^3 | \psi_n \rangle \langle \psi_n | \hat{L}_z | \psi_0 \rangle) / (\Delta E)]$$

- when the ΔE between the ground state orbitals and the excited state orbitals (that were mixed in) is small (i.e. low lying excited states), B' is big (responsible for large chemical shift ranges)
- for p orbitals, if all are equally occupied (spherical distribution), no effect (must be an asymmetric distribution)

Implications for Paramagnetic Term

$$B_p' \propto \sum_n [(\langle \psi_0 | \hat{L}_z | \psi_n \rangle \langle \psi_n | \hat{L}_z / r^3 | \psi_0 \rangle) / (\Delta E) + (\langle \psi_0 | \hat{L}_z / r^3 | \psi_n \rangle \langle \psi_n | \hat{L}_z | \psi_0 \rangle) / (\Delta E)]$$

- $B_p' \propto -\sigma_p$, so σ_p is negative (deshielding, opposite to σ_D)
- σ_p is zero unless $\hat{L}_z |\psi\rangle$ is finite
 - for instance, for "s" orbitals, $\hat{L}_z |s\rangle = 0$, so no contribution from paramagnetic term
 - so, chemical shift range for H is small
- $\hat{L}_z |\psi\rangle$ is finite for p orbitals, so σ_p is finite (when p orbitals are not equally occupied)
 - for ^{13}C , for instance, σ_p is finite (i.e. $\hat{L}_z |p_1\rangle = 1$, etc.)
 - for ^{13}C , ΔE can be small, so large chemical shift range
- Contributions of all p orbitals are summed, so if all are equally occupied, sum is zero (i.e. $\sum \hat{L}_z |p\rangle = 0$), so, no effect
 - in other words, electron distribution must be asymmetric
 - example: CH_4 , all p orbitals occupied (highly *shielded*, i.e. no deshielding from paramagnetic term)

^{13}C Example: Ethane vs Ethylene

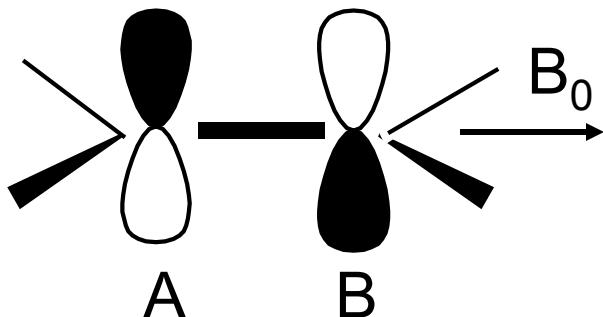
- For $\text{CH}_3\text{-CH}_3$, $\delta^{13}\text{C} = 6 \text{ ppm}$, for $\text{CH}_2=\text{CH}_2$, $\delta^{13}\text{C} = 123 \text{ ppm}$!
 - for $\text{CH}_3\text{-CH}_3$, nearly symmetrical use of p orbitals, so small σ_p
 - not so for $\text{CH}_2=\text{CH}_2$, where p orbitals are used for π orbitals (very asymmetrical)
- For both, σ_D is about the same ($\sim 200 \times 10^{-6}$)
- Consider our paramagnetic shielding contribution equation

$$\sigma_p \propto \sum_n [(\langle \psi_0 | \hat{\mathbf{L}}_z | \psi_n \rangle \langle \psi_n | \hat{\mathbf{L}}_z / r^3 | \psi_0 \rangle) / (\Delta E) + (\langle \psi_0 | \hat{\mathbf{L}}_z / r^3 | \psi_n \rangle \langle \psi_n | \hat{\mathbf{L}}_z | \psi_0 \rangle) / (\Delta E)]$$

-only consider ψ_n functions $2p_1$, $2p_0$, $2p_{-1}$ (s orbitals don't contribute significantly to σ_p)
-keep in mind ΔE in denominator: ΔE likely to be small, so will be important

- In ethylene, is a π bond between the C nuclei
 - the π bond is comprised of 2 p orbitals, one on each C nucleus (very different than the sp^2 bonds to the H nuclei)
 - the π bond tends to have low lying excited states (small ΔE)
 - the *occupied* π bond comes from the *sum of the two p orbitals* on the C atoms, but the first *excited state* (π^*) results from the *difference*
- Consider only the first excited state: $\pi^* = (1/\sqrt{2})(p_{1A} - p_{1B})$
 - fairly low lying, so ΔE likely to be small, and its contribution to σ_p large

Consider Field Parallel to C-C Bond



- Antisymmetric p orbitals of π^* bond: perpendicular to plane of other atoms (black - positive, white - negative)
- Here B_0 is parallel to C-C bond ("A" and "B" are carbons A and B)

- We have an expression for π^* that can be rewritten/expanded in terms of p_1 and p_{-1} (projections of angular momentum orbitals)

$$\pi^* = 1/\sqrt{2} (p_{xA} - p_{xB}) = 1/\sqrt{2} ((p_{1A} + p_{-1A}) - (p_{1B} + p_{-1B}))$$

- Note the following relationships

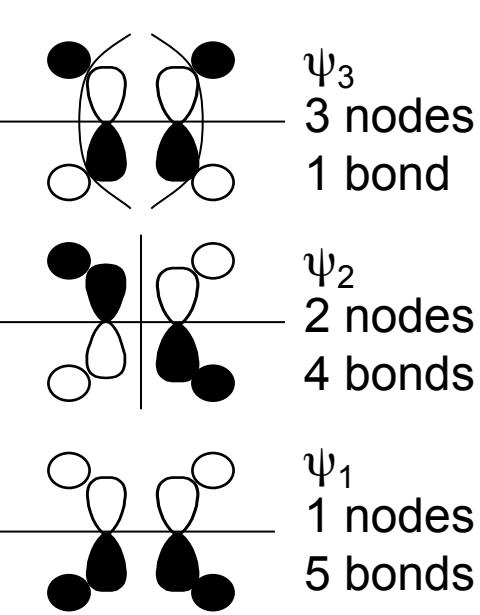
$$p_{xA} = (p_{1A} + p_{-1A}), \quad p_{yA} = (p_{1A} - p_{-1A}), \quad p_{xB} = (p_{1B} + p_{-1B}), \quad p_{yB} = (p_{1B} - p_{-1B})$$

- Now, operate on π^* with L_z operator: it returns projection of angular momentum on z axis (1 for p_{1A} , -1 for p_{-1A} , etc.)

$$\begin{aligned}\hat{L}_z |\pi^*\rangle &= \left(i\hbar/\sqrt{2}\right) (((1)p_{1A} + (-1)p_{-1A}) - ((1)p_{1B} + (-1)p_{-1B})) \\ &= \left(i\hbar/\sqrt{2}\right) ((p_{1A} - p_{-1A}) - (p_{1B} - p_{-1B})) \\ &= \left(i\hbar/\sqrt{2}\right) (p_{yA} - p_{yB}) \text{ antisymmetric combination of } p_y \text{ orbitals}\end{aligned}$$

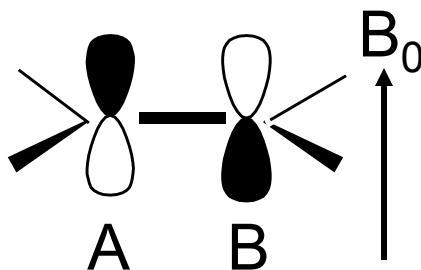
- So, when we evaluate $\langle \psi_0 | \hat{L}_z | \pi^* \rangle$, it will be finite if p_{yA} and p_{yB} are populated in ground state ψ_0 (so, look at ground state MOs)

Estimating Paramagnetic Contribution



- Ground state molecular orbitals for ethylene (in plane of atoms, p are p_y)
- Energies according to number of nodes
- Fill with electrons (2×6 for C, 4 for H = 16)
- 4 in $1s_C$, 2 in bonding p_0 (\perp to plane),
2 in C-C σ , 4 in C-H σ
- Implies can put 4 in MOs
- 2 go in ψ_1 , but is symmetric ($\langle \psi_0 | \hat{L}_z | \pi^* \rangle$ is zero)
- 2 go in ψ_2 , antisymmetric, so $\langle \psi_0 | \hat{L}_z | \pi^* \rangle$ is *finite*, so can attempt to calculate σ_p
- $\sigma_P = -(eh/(2\pi mc))^2 \langle (1/r^3) \rangle_{2p}$ etc. $\cong -200 \times 10^{-6}$
- Recall $\sigma_{c-c} = \sigma_D = 200 \times 10^{-6}$ also, so effects cancel approximately (i.e. expect big downfield shift)

σ Depends on Orientation in Magnetic Field

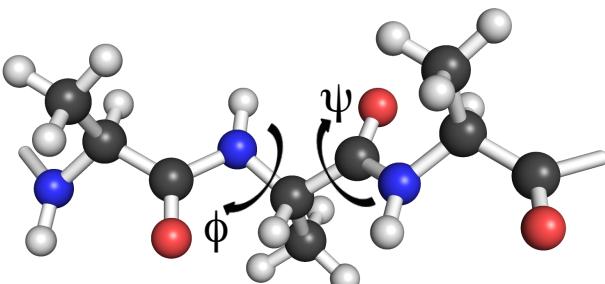


- Shieldings are tensor quantities: magnitudes depend on orientation to magnetic field (*chemical shift anisotropy*)
- What happens (ethylene) if B_0 is \perp to plane?
- Now antibonding (π^*) is made of p_z (p_0) orbitals
- $$\pi^* = 1/\sqrt{2}(p_{zA} - p_{zB}) = 1/\sqrt{2}(p_{0A} - p_{0B})$$
- Angular momentum projection on z is zero ($\hat{L}_z|p_0\rangle = 0$), $\sigma_p = 0$
- So, shielding in z direction is purely diamagnetic
- $$\sigma_z = \sigma_D + \sigma_p = \sigma_D + 0 = 200 \times 10^{-6}$$
- Summary: for B_0 along C-C bond (σ_x), $\sigma_p = \sigma_D$, so $\sigma_x = 0$, same for B_0 in plane perpendicular to C-C ($\sigma_y = 0$), and $\sigma_z = 200$
- Write as a tensor: isotropic shift = $1/3 \operatorname{Tr} \sigma \approx 70\text{-}100 \text{ ppm}$

σ (predicted)	σ (observed)
$\begin{bmatrix} 0 \\ 0 \\ 200 \end{bmatrix}$	$\begin{bmatrix} -20 \\ 120 \\ 200 \end{bmatrix}$

^1H of ethylene are significantly deshielded relative to ethane (5.84 vs 1.96 ppm). The deshielding is due to the paramagnetic B' effect of the π^* (remote group effect)

^{13}C Chemical Shift Calculations on Peptides



- Alpha and beta carbon chemical shifts are sensitive to structure, and reflect the magnitudes of ϕ and ψ angles in proteins
- Below: surface profiles of shielding constants for $^{13}\text{C}\alpha$ and $^{13}\text{C}\beta$ versus ϕ and ψ

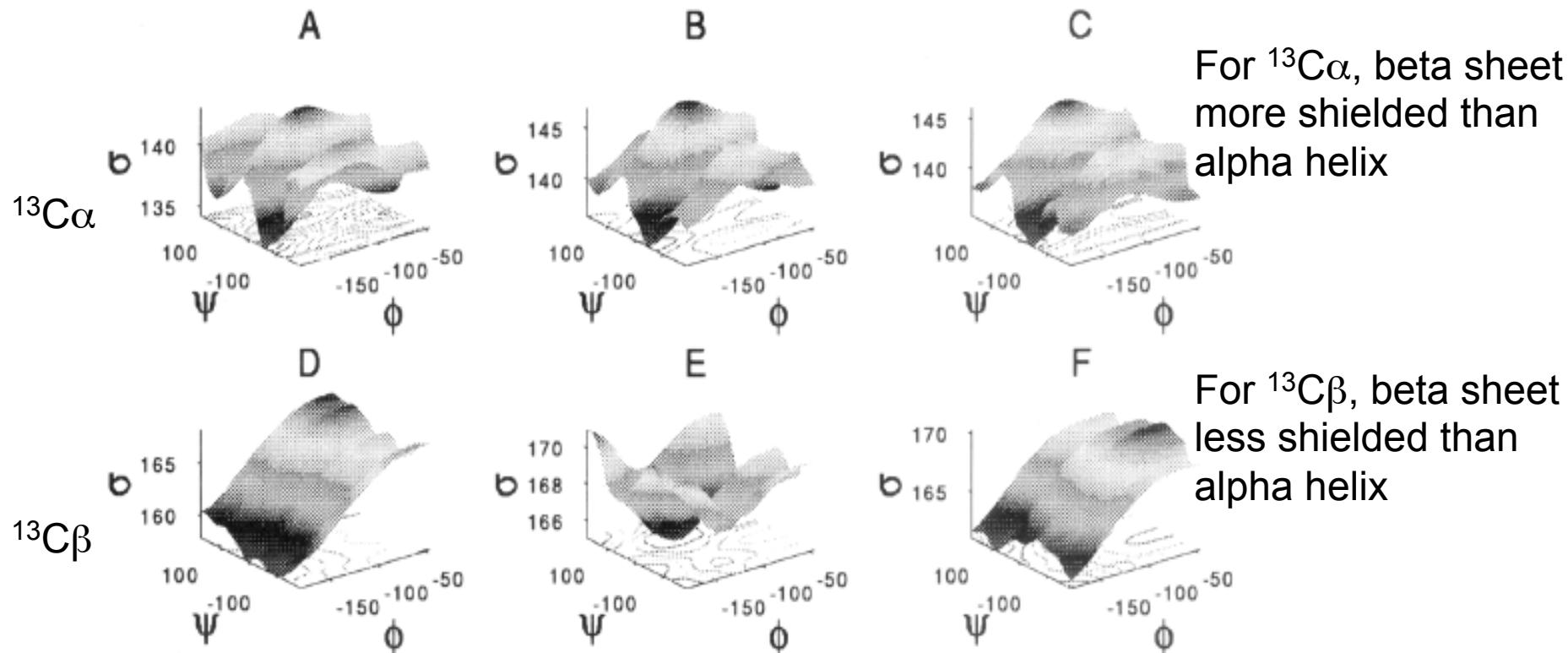
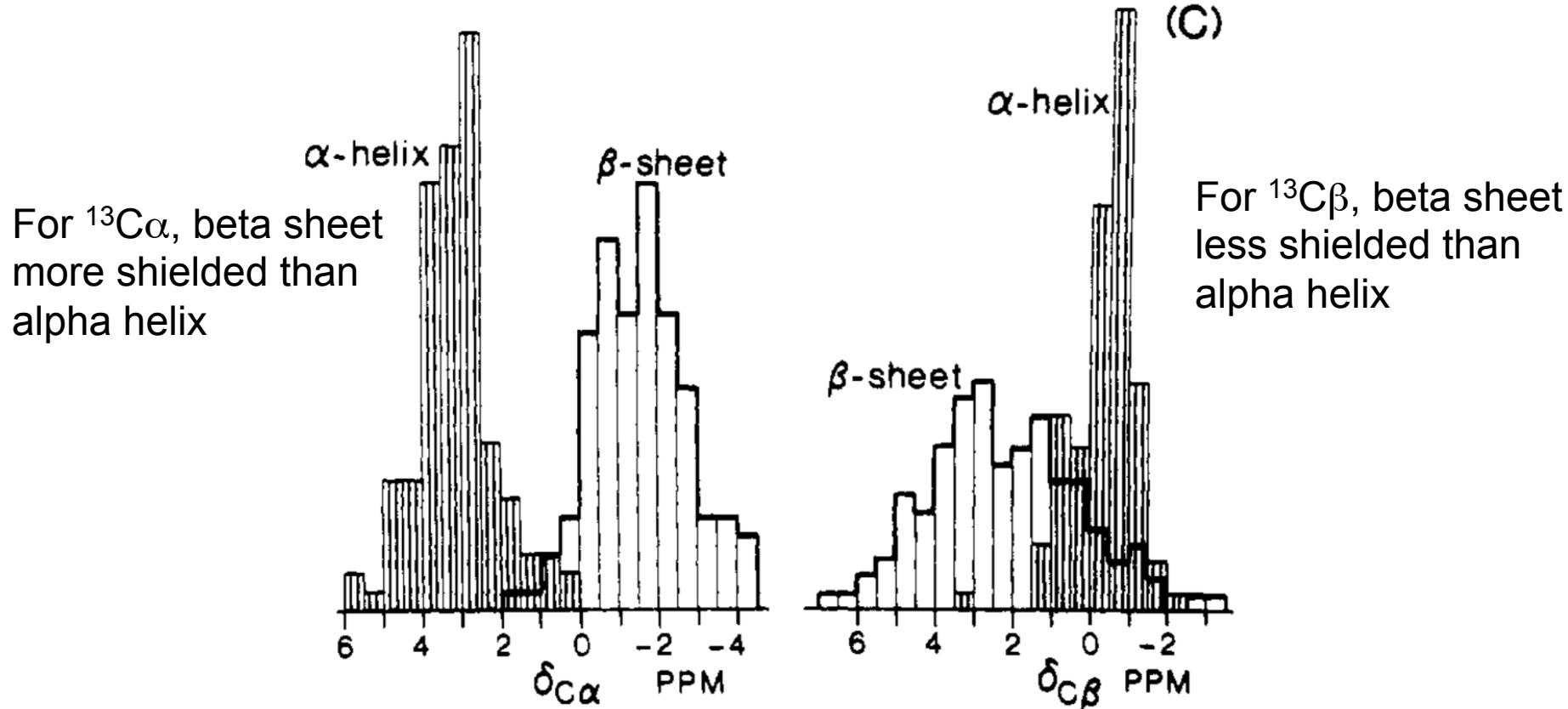


Figure 7. Calculated $^{13}\text{C}\alpha$ and $^{13}\text{C}\beta$ shieldings in formylvaline amide as a function of ϕ and ψ (at various χ^1 values): (A) C^α , $\chi^1 = 180^\circ$; (B) C^α , $\chi^1 = 60^\circ$; (C) C^α , $\chi^1 = -60^\circ$; (D) C^β , $\chi^1 = 180^\circ$; (E) C^β , $\chi^1 = 60^\circ$; (F) C^β , $\chi^1 = -60^\circ$.

α helix, -57, -47; β sheet, -139, 135; Oldfield and Dios, JACS, 116, 5307 (1994)

^{13}C shifts and Peptide Geometry

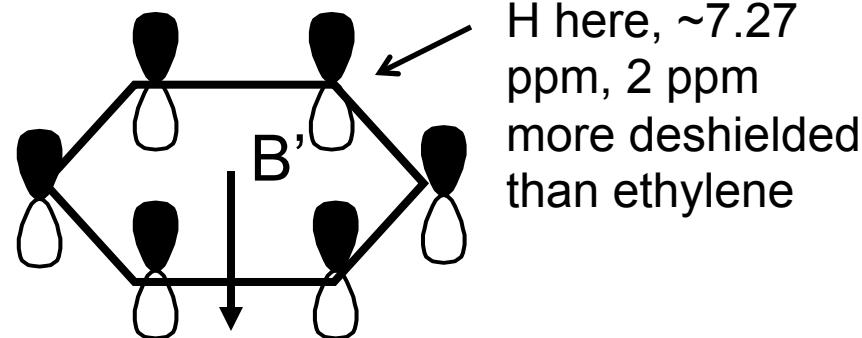
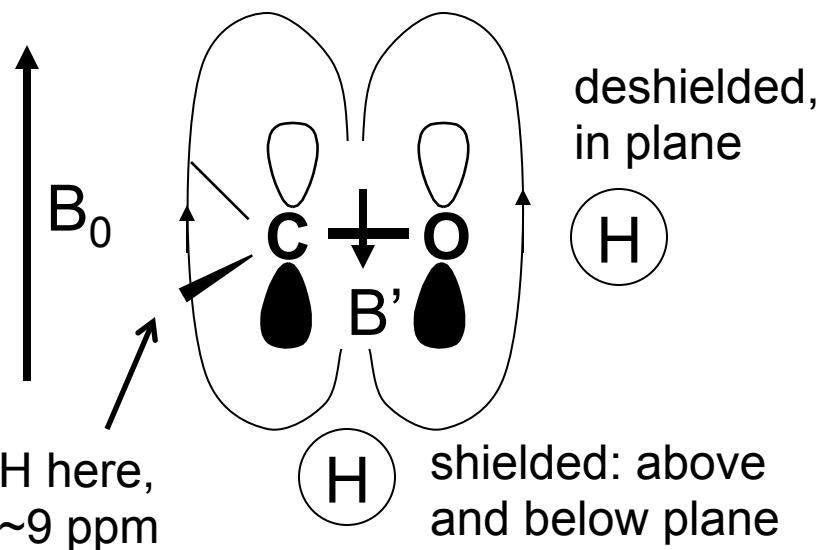
- Conclusions of calculations empirically verified
- Results led to important methods (Talos) to predict ϕ and ψ from $\delta^{13}\text{C}$



- Shifts relative to random coil with same amino acid
- Spera and Bax, JACS, 113, 5490 (1991)
- See also: Case, <http://www.scripps.edu/mb/case> (Shifts)
- See also: Wishart, <http://redpoll.pharmacy.ualberta.ca/shiftz>

Remote Group Effects

- Paramagnetic shielding effects arise from asymmetric electron distribution
- Nuclei near groups with large paramagnetic contributions to shielding can also be differentially shielded or deshielded, depending on their location



benzene does the same thing
(conjugated sets of bonds cause big effects, "ring current effect")

- $\sigma'_{\text{remote}} = \Delta\chi/r^3 (1-3\cos^2\theta)$: here $\Delta\chi$ is a measure of the magnitude of B' in B_0
- Johnson and Bovey, *J. Chem. Phys.*, **29**, 1012 (1958)

Shielding from a Benzene Ring

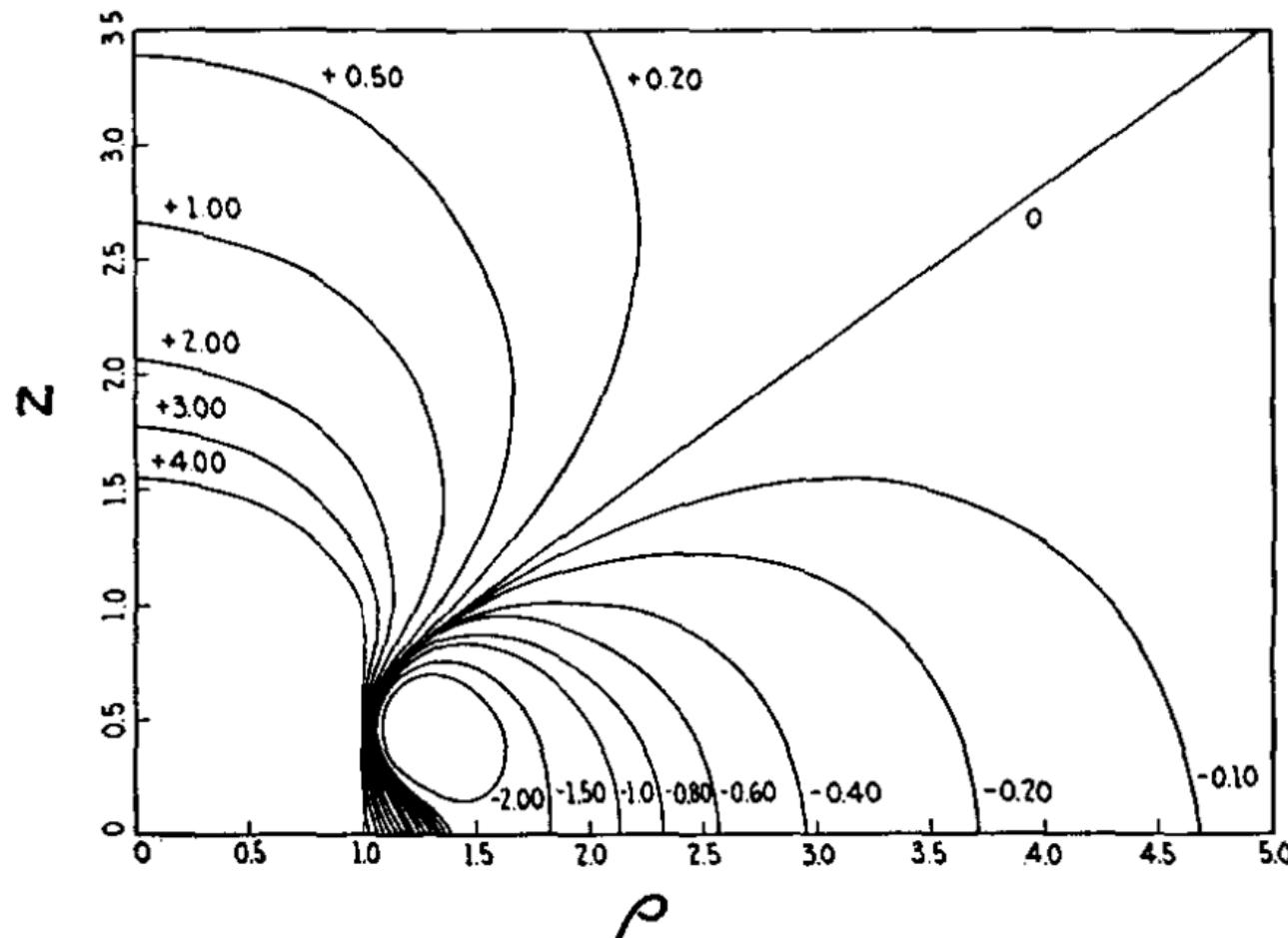


FIG. 1. "Isoshielding" lines in the neighborhood of a benzene ring. The plot represents one quadrant of a plane passing normally through the center of the ring. The lines represent the shift in the NMR shielding value which will be experienced by protons as a result of the magnetic field of the benzene ring.

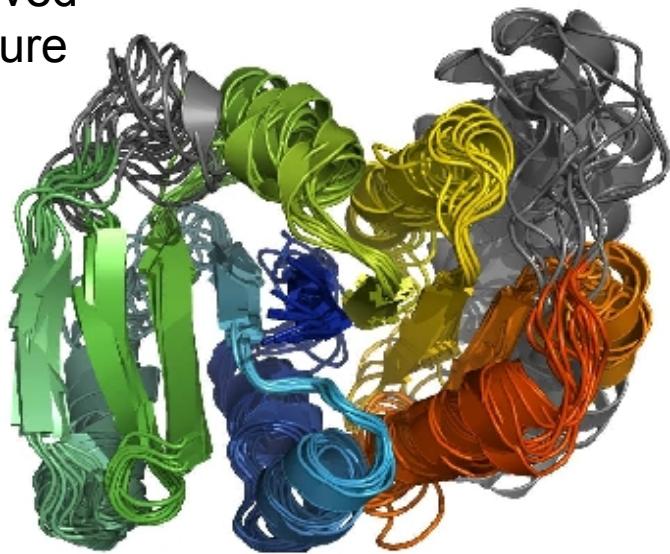
Recent Applications of Chemical Shift to Protein Structure Determination

- Shen Y, Bax A,
Protein backbone chemical shifts predicted from searching a database for torsion angle and sequence homology JOURNAL OF BIOMOLECULAR NMR 38: 289-302,2007
- Cavalli A, Salvatella X, Dobson CM, et al.
Protein structure determination from NMR chemical shifts PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 104: 9615-9620, 2007
- Shen Y, Lange O, Delaglio F, et al. Consistent blind protein structure generation from NMR chemical shift data, PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 105: 4685-4690, 2008
- Han, B., Liu, Y. F., Ginzinger, S. W. & Wishart, D. S. (2011). SHIFTX2: significantly improved protein chemical shift prediction. Journal of Biomolecular NMR 50, 43-57.

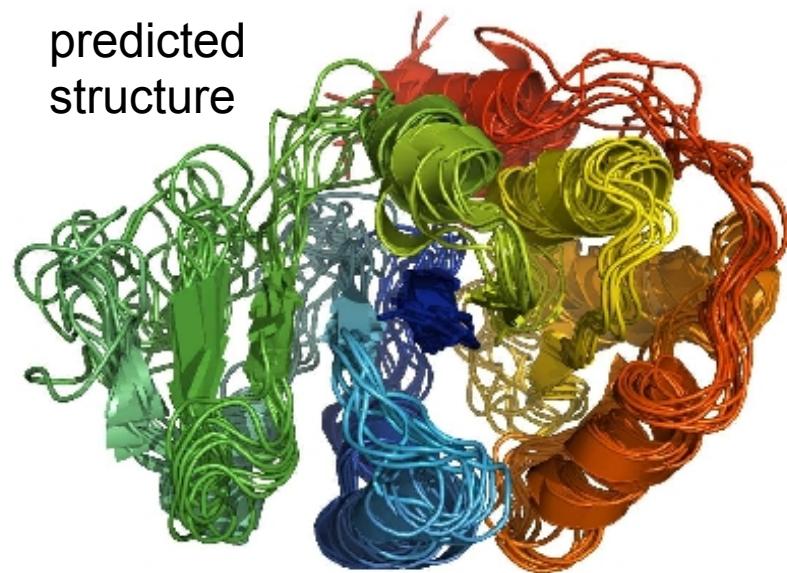
Other data can be combined with Chemical Shifts – Protein Targets now up to 25 kDa

- For small proteins, chemical shift data combined with other types of data (Residual Dipolar Couplings, RDC) can be used to "predict" structures to within good agreement with NMR structures determined traditionally (NOE based)

observed
structure



predicted
structure



Comparison of traditional NMR structure and predicted structure with chemical shift and RDC data.

Srivatsan, Lange, Rossi, et al. Science, 327:1014-1018, 2010