

Indirect Coupling II

Geminal Coupling: ${}^2J_{AX}$ (2-bond Coupling)

Homonuclear, H–H, geminal coupling, ${}^2J_{HH}$, may be *observed* between geminal protons that are chemically inequivalent (they have different chemical shifts).

Note that the presence of a coupling does not indicate that observable resonance splittings will occur!

The value of geminal coupling constants in chemically equivalent groups can be determined using ${}^2\text{H}$ isotopic substitution. Although such information has clear value in terms of testing theory, the results have limited application to structural analysis.

Therefore, ${}^2J_{HH}$ may be observed if the chemically inequivalent protons that make of the geminal pair form a rigid fragment (limited conformational averaging), or more generally if the protons are diastereotopic (diastereomers are structural isomers that are *not* related as are an object and its mirror image).

The magnitude of ${}^2J_{HH}$, has three major influences:

- geminal bond angle
- hybridization of the carbon atom
- carbon substituents

Bond Angle dependence of ${}^2J_{AX}$

An increase in the H–C–H bond angle increases the s-character of the orbital and leads to a positive increase in the value of the coupling – note that this may act to decrease the magnitude of the coupling.

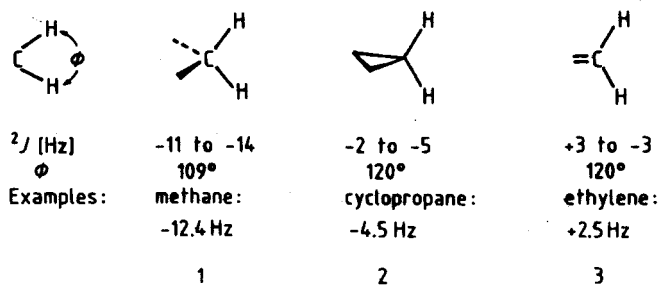


Figure 3-1 from Friebolin

$^2J_{AX}$ and Substituent Effects

Substitution of an electronegative atom in the α -position produces a positive shift in $^2J_{HH}$, i.e., decreases the magnitude of the coupling.

Substitution of an electronegative atom in the β -position leads to a negative shift in $^2J_{HH}$, i.e., increases the magnitude of the shift.

Molecule	$^2J_{HH}$
CH ₄	-12.4
CH ₃ OH	-10.8
CH ₃ Cl	-10.8
CH ₃ F	-19.6
CH ₂ Cl ₂	-7.5
CH ₂ O	+41.0

Vicinal Coupling: $^3J_{AX}$ (3-bond Coupling)

The most useful commonly measured coupling from a structural perspective is the vicinal coupling.

The original theoretical framework was established by Karplus. The theory develops predictions based on the interaction nuclear spins and the electron spins, recall that s-orbitals have nonvanishing probability at the nucleus – this interaction is named the *contact term*.

Karplus Analysis

Karplus, M. (1959) Contact Electron-Spin Coupling of Nuclear Magnetic Moments. *J. Chem. Phys.* **30**, 11-15.

The 1959 publication by Karplus establishes the link between the magnitude of $^3J_{AX}$ and the *dihedral angle* formed between the two H–C bond vectors.

$$^3J_{HH'} = A_{HH'} = \begin{cases} 8.5 \cos^2 \phi - 0.28; & 0^\circ \leq \phi \leq 90^\circ \\ 9.5 \cos^2 \phi - 0.28; & 90^\circ \leq \phi \leq 180^\circ \end{cases}$$

Any plot of ${}^3J_{AX}$ versus the dihedral angle is known as a *Karplus curve*.

The figure from the Friebolin text shows a plot of the original expression versus the dihedral angle – the hatched region depicts the experimentally observed range:

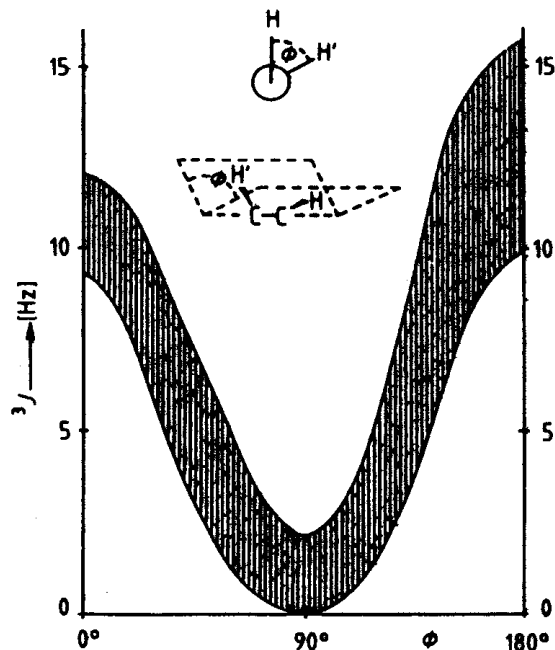


Figure 3-2 from Friebolin

Karplus, M. (1959) Contact Electron-Spin Coupling of Nuclear Magnetic Moments. *J. Chem. Phys.* **30**, 11-15.

$${}^3J_{HH'} = A_{HH'} = \begin{cases} 8.5 \cos^2 \phi - 0.28; & 0^\circ \leq \phi \leq 90^\circ \\ 9.5 \cos^2 \phi - 0.28; & 90^\circ \leq \phi \leq 180^\circ \end{cases}$$

Karplus later provided a more accurate expression for the structural relationship between the vicinal coupling constant and the dihedral angle:

Karplus, M. (1963) Vicinal Proton Coupling in Nuclear Magnetic Resonance. *J. Am. Chem. Soc.* **85**, 2870-2871.

$${}^3J_{HH'} = A + B \cos \phi + C \cos 2\phi$$

$$A = 4.22; B = -0.5; C = 4.5$$

The final paragraph of the 1963 Karplus paper provides some key (sage) advice:

Any structural analysis based on the dihedral-angle dependence of the vicinal coupling constants must take account of their variation as a function of other aspects of the molecular environment. Until extensive studies have been made to ascertain the qualitative details of these relationships, the most reliable results are to be expected from the comparison of closely related species. The introduction of empirical formulas for a particular series of compounds can be helpful in this regard. Furthermore, it is best if the solution to the structure problem under consideration depends not on the exact values of coupling constants, but only on the fact that certain couplings are "large" rather than "small" or *vice versa*. Certainly with our present knowledge, the person who attempts to estimate dihedral angles to an accuracy of one or two degrees does so at his own peril.

$^3J_{AX}$ and Substituent Effects

Alkanes

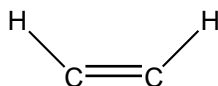
The relationship between 3J and the electronegativity of substituents is roughly linear, and depends upon the difference between the electronegativity of the substituent and that of hydrogen:

$$^3J = 8.0 - 0.8(E_X - E_H)$$

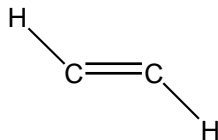
Substituent (X)	E_X	3J
H	2.2	8.0
Li	1.0	8.4
CH ₃	2.5	7.3
Cl	3.0	7.2
OR	3.5	7.0

Table 3-6 from Friebolin, H. (1998)

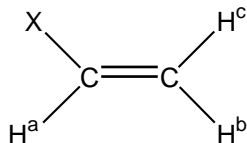
Alkenes



$$^3J_{cis} = 6 - 14 \text{ Hz}$$



$$^3J_{trans} = 14 - 20 \text{ Hz}$$



H^a and H^c are *trans*; H^a and H^b are *cis*

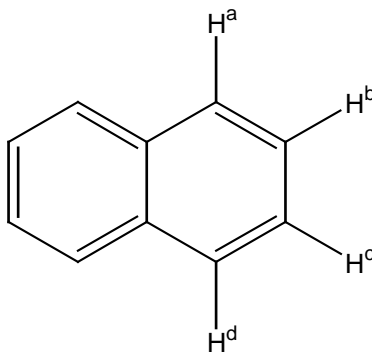
$${}^3J_{cis} = 11.7 - 4.7(E_X - E_H)$$

$${}^3J_{trans} = 19.0 - 3.3(E_X - E_H)$$

Substituent (X)	E_X	${}^3J_{cis}$	${}^3J_{trans}$
H	2.2	11.6	19.1
Li	1.0	19.3	23.9
Cl	3.0	7.3	14.6
OR	3.5	7.1	15.2
F	4.0	4.7	12.8

Coupling values from Gunther, H. (1987) *NMR Spectroscopy*, John Wiley and Sons, New York

Aromatics



$${}^3J(H^a, H^b) = 8.3 \text{ Hz}; \quad {}^3J(H^a, H^c) = 1.2 \text{ Hz}; \quad {}^3J(H^a, H^d) = 0.7 \text{ Hz}; \quad {}^3J(H^b, H^c) = 6.9 \text{ Hz}$$

	Benzene 3J	Range
3J_o	7.5	7 – 9
3J_m	1.4	1 – 3
3J_p	0.7	< 1

Table 3-9 from Friebolin, H. (1998)

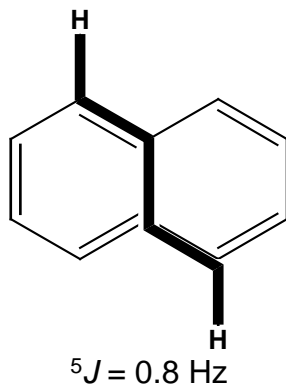
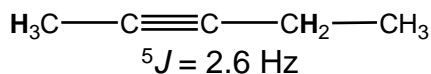
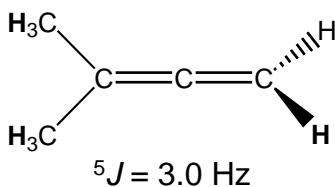
Long-Range Coupling

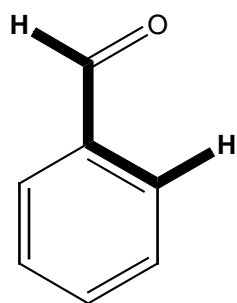
Long range J -coupling is defined between protons that are more than three bonds apart, i.e., 4 or sometimes 5 bonds apart. Such couplings are never completely vanishing and thus may be measured whenever the spectral resolution is sufficiently high.

As a general rule, J -couplings between protons with more than three intervening bonds are small, generally less than 1 Hz.

Long range coupling effects arise from two main effects: Interactions of H – C bonds with π -electrons of double and triple bonds and structural influences (sterically constrained W -configuration structures).

Examples:





${}^4J = 0.8 \text{ Hz}$



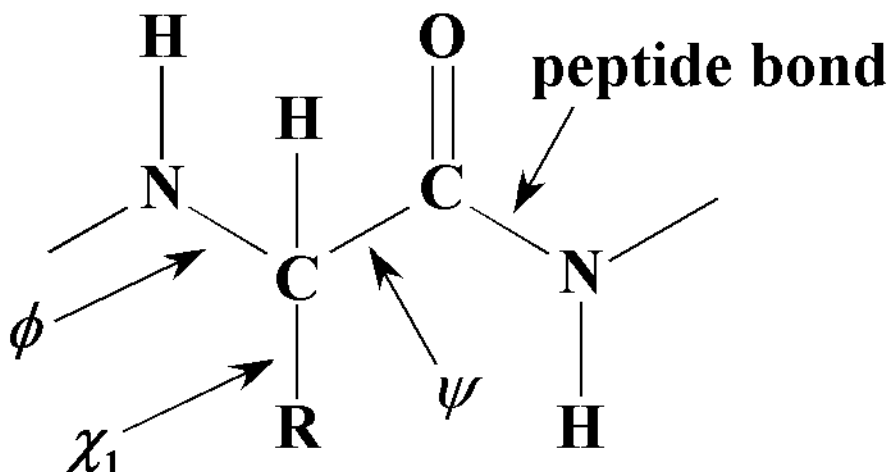
${}^4J = 1.1 \text{ Hz}$

Application to Biological Macromolecules I: Polypeptides

Bystrov, V.F. (1976) Spin-Spin Coupling and the Conformational States of Peptide Systems. *Prog. Nucl. Magn. Reson. Spectrosc.* **10**, 41-82.

Pardi, A., Billeter, M. and Wüthrich, K. (1984) Calibration of the Angular Dependence of the Amide Proton-C α Proton Coupling Constants, $^3J_{\text{HN}\alpha}$, in a Globular Protein. Use of $^3J_{\text{HN}\alpha}$ for Identification of Helical Secondary Structure. *J. Mol. Biol.* **180**, 741-751.

Wagner, G., Bruan, W., Havel, T.F., Schaumann, T. Gö, N. Wüthrich, K. (1987) Protein Structures in Solution by Nuclear Magnetic Resonance and Distance Geometry. The Polypeptide Fold of the Basic Pancreatic Trypsin Inhibitor Determined Using Two Different Algorithms, DISGEO and DISMAN. *J. Mol. Biol.* **196**, 611-639.



Vicinal coupling constants are related to the peptide dihedral angles as defined below:

Coupling Constant	Dihedral Angle	Atoms Involved
$^3J_{\text{H}^{\text{N}}\text{H}^{\alpha}}$	ϕ	$\text{H}^{\text{N}} - \text{N} - \text{C}^{\alpha} - \text{H}^{\alpha}$
$^3J_{\text{H}^{\alpha}\text{H}^{\beta}}$	χ_1	$\text{H}^{\alpha} - \text{C}^{\alpha} - \text{C}^{\beta} - \text{H}^{\beta}$

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

Note that $\cos^2 \theta = \frac{1}{2}(1 + \cos(2\theta))$...i.e., the expression is formally identical to the expression as defined by Karplus.

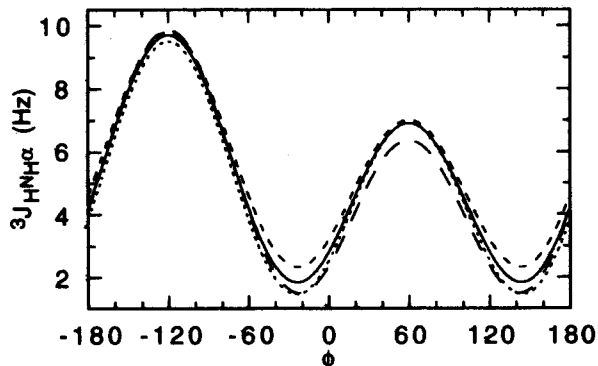


FIGURE 8.8 The Karplus curve describing the variation of ${}^3J_{\text{H}^N\text{H}^\alpha}$ with backbone dihedral angle ϕ . The dihedral angle between ${}^1\text{H}^N$ and ${}^1\text{H}^\alpha$ is given by $\theta = \phi - 60^\circ$. The four curves shown were calculated using [8.2] with the constants A , B , and C , as given in Table 8.1; (—) $A = 6.4$, $B = -1.4$, $C = 1.9$; (---) $A = 6.0$, $B = -1.4$, $C = 2.4$; (⋯) $A = 6.7$, $B = -1.3$, $C = 1.5$; (---) $A = 6.51$, $B = -1.76$, $C = 1.6$.

Figure 8.8 from Cavanagh, J., Fairbrother, W.J., Palmer III, A.G. and Skelton, N.J. (1996) *Protein NMR Spectroscopy*, Academic Press, New York.

Note that the 3J values *do not* map uniquely on to conformational space, i.e., a measured coupling constant of 5 Hz could correspond to a ϕ -angle of -170° , -60° , $+40^\circ$ or $+80^\circ$

Application to Biological Macromolecules II: Nucleic Acids

Altona, C. (1982) Conformational Analysis in Nucleic Acids. Determination of Backbone Geometry of Single-Helical RNA and DNA in Aqueous Solution. *Rec. Trav. Chim. Pays-Bas* **101**, 413-433.

$${}^3J_{\text{HH}} = 13.7 \cos^2 \phi - 0.73 \cos \phi + \sum_i \Delta\chi_i \left[0.56 - 2.47 \cos^2 (z_i \phi + 16.9 |\chi_i|) \right]$$

wherein $\Delta\chi_i$ is the electronegativity difference between some substituent i and H and z_i is an orientation factor that takes the value of ± 1 depending on the position of the substituent.

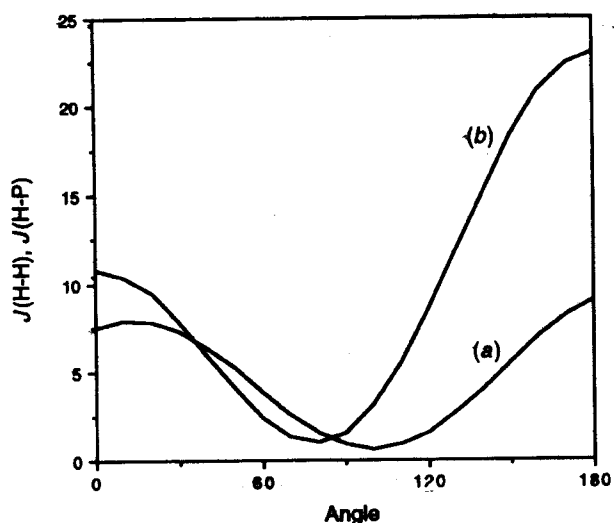


Figure 5-12
Two Karplus curves (coupling constant vs. dihedral angle between the spins involved) are shown. Curve (a) is for the HCOP coupling; curve (b) is for a HCCH coupling, such as that between the H1' and H2'. Both curves were calculated from the equations given in the text, [Derived by Altona 1982.]

Figure 5-12 from Bloomfield, V.A., Crothers, D.M. and Tinoco Jr., I. (2000) *Nucleic Acids*, University Science Books, Sausalito, CA.

Direct Heteronuclear Coupling: $^1J_{\text{HC}}$

s-orbital Character

The magnitude of the direct H–C coupling depends upon the percentage of s-orbital character in the H–C bond.

	$\text{H}_3\text{C} - \text{CH}_3$	$\text{H}_2\text{C} = \text{CH}_2$	C_6H_6	$\text{HC} \equiv \text{CH}$
Hybridization	sp^3	sp^2	sp^2	sp
s-orbital fraction	0.25	0.33	0.33	0.50
$^1J_{\text{HC}}$	129.4	156.4	158.4	249.0

Table 3-11 from Friebolin, H. (1998)

Cycloalkanes

	$^1J_{\text{HC}}$
Cyclopropane	160.3
Cyclobutane	133.6
Cyclopentane	128.5
Cyclohexane	125.1
Cyclodecane	124.3

Table 3-12 from Friebolin, H. (1998)

Cycloalkenes

	$^1J_{\text{HC}}$
Cyclopropene	228.2
Cyclobutene	168.6
Cyclopentene	161.6
Cyclohexene	158.4
$\text{C}_n\text{H}_{2n-2}$ ($n > 6$)	156

Table 3-13 from Friebolin, H. (1998)

Substituent Effects on $^1J_{\text{HC}}$

Generally, electronegative substituents increase $^1J_{\text{HC}}$ while electropositive substituents decrease $^1J_{\text{HC}}$.

$^{13}\text{C}-\text{X}$	$^1J_{\text{HC}}$
F	149.1
Cl	150.0
OH	141.0
H	125.0
CH ₃	124.9
Li	98.0

Table 3-14 from Friebolin, H. (1998)