

A Graphical Tool for the Prediction of Vicinal Proton–Proton $^3J_{\text{HH}}$ Coupling Constants

Armando Navarro-Vázquez,* Juan Carlos Cobas, and Francisco Javier Sardina

Laboratorio Integral de Dinámica y Estructura de Biomoléculas, J. R. Carracido, Unidad asociada al CSIC, Universidad de Santiago de Compostela, Spain

Jorge Casanueva and Ernesto Díez

Facultad de Ciencias, C2, Departamento de Química Física Aplicada, Universidad Autónoma de Madrid, Madrid, 28049 Spain

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The easy to use and free available graphical tool MestRe-J, developed for Win-32 platforms, calculates the vicinal proton–proton coupling constants $^3J_{\text{HH}}$ from the torsion angle ϕ between the coupled protons for the two kinds of generalized Karplus equations developed by Altona's group as well as for equations from other authors. Besides the classical Haasnoot–de Leeuw–Altona equations, including individual substituent effects that depend on their relative Huggins's electronegativities $\Delta\chi$, the program incorporates the more recent and precise Díez–Altona–Donders equations. The substituent effects in these equations, that include effects of interactions between substituents, depend on substituent parameters λ optimized from the $^3J_{\text{HH}}$ couplings to methyl groups. Weighted time-averaged couplings can be calculated. The equations for $^3J_{\text{HH}}$ can be solved to provide the torsion angles ϕ .

INTRODUCTION

A very well-known stereochemistry fact is that the coupling constant $^3J_{\text{HH}}$ (hereafter J) between vicinal hydrogen atoms presents a strong dependence on the HCC'H' torsion angle ϕ between the two coupled nuclei showing maxima near 0° and 180° and minima near 90° and 270° as depicted in Figure 1. Hence, much valuable stereochemical information can be obtained from the proton NMR spectra.

After the pioneering work of Karplus, published 45 years ago¹ (eq 1 below), several other generalized Karplus equations² have been proposed for the torsional dependence on ϕ of J . Among these, Haasnoot–de Leeuw–Altona (HLA) equations³ (eqs 5 and 6 below) are by far the most widely used⁴ and have been implemented in several programs.^{4,5} Applications including other generalized Karplus equations are scarce which make their general use difficult for the common organic chemist. Such is the case of the more recent and precise Díez–Altona–Donders (DAD) equations^{2,6} developed by Altona's group.

Here we present the easy to use J pocket calculator MestRe-J for desktop PCs including several generalized Karplus equations. This work was inspired by the Balacco's SWEET-J program, designed for the Mac OS platform.⁴ We felt the necessity to provide a similar tool for Microsoft-Windows based machines. In addition, MestRe-J provides new capabilities such as the implementation of the DAD equations, the calculation of thermally average J couplings, an improved graphical interface, and a better integration with common desktop programs.

The implemented equations for the prediction of J are reviewed in the next section. The handling of these equations

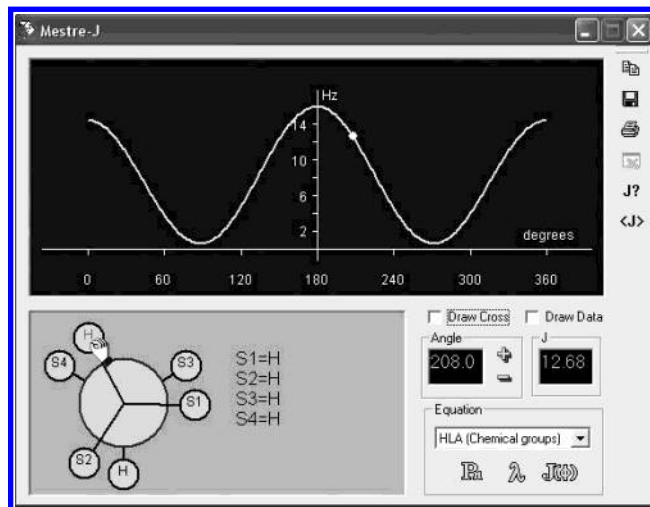


Figure 1. MestRe-J main window.

with MestRe-J is very easy though some of them can seem complicated.

EMPIRICAL EQUATIONS

The main factor that determines the magnitude of the J couplings is the dependence upon the torsion angle ϕ between the coupled protons. The angular dependence of J in ethane was described early by the Karplus¹ equation

$$J = A + B \cos \phi + C \cos 2\phi \quad (1)$$

derived from Valence Bond calculations. This equation with coefficients adjusted empirically for given classes of molecules of interest was for a long time the most important way to investigate the conformation of organic compounds in solution. The Karplus curve is symmetric around $\phi = 180^\circ$ (see Figure 1).

* Corresponding author phone: +34-981563100 ext 16231; fax: +34-981561028; e-mail: mestrec@usc.es.

The second important factor that affects to J is the electronegativity of substituents attached to the HCC'H' fragment in question. The effect depends on the relative positions of substituents with respect to the coupling protons. On the basis of theoretical Molecular Orbital (MO) calculations for monosubstituted ethanes $\text{CH}_3\text{CH}_2\text{X}$, Pachler⁷ proposed an extension of the Fourier series eq 2

$$J^X = A^X + B^X \cos\phi + C^X \cos 2\phi + D^X \sin\phi + E^X \sin 2\phi \quad (2)$$

where the terms $D^X \sin\phi$ and $E^X \sin 2\phi$ account for the substituent-induced asymmetry in the Karplus curve. The signs of the D^X and E^X values depend on the relative positions of the coupling protons and the X-substituent. This fact may be taken into account properly in equations using the notation proposed by Altona's group. The position of a substituent S_i on C or C' (see the Newman projection in Figure 1) is defined as being "positive", S_1 and S_3 , or "negative", S_2 and S_4 . Accordingly, a parameter ξ_i stands for +1 or -1 for the i th position. From MO calculations, Pachler arrives to a general equation for the couplings in saturated $\text{CHS}_1\text{S}_2-\text{C}'\text{H}'\text{S}_3\text{S}_4$ fragments.

$$J = A + a \sum \Delta\chi_i + (B + b \sum \Delta\chi_i) \cos\phi + (C + c \sum \Delta\chi_i) \cos 2\phi + d \sum \xi_i \Delta\chi_i \sin\phi + e \sum \xi_i \Delta\chi_i \sin 2\phi \quad (3)$$

This equation can be deduced from eq 2 by assuming that the effects upon J of substituents are additive and that the coefficients in eq 2 depend linearly on the $\Delta\chi_X$ Huggins's relative electronegativities⁸ of the α -atoms, i.e., the atoms of substituents bonded to the carbons of the HCC'H' fragment. $\Delta\chi_X$ is the electronegativity difference between an atom X and hydrogen.

$$\Delta\chi_X = \chi_X - \chi_H \quad (4)$$

Empirical parameters for eq 3 were derived from a least-squares treatment of 231 J values from 137 compounds giving a root-mean-square (rms) deviation σ of 0.65 Hz. The compounds included substituted ethanes and alicyclic as well as heterocyclic five- and six-membered ring compounds of various types.

Haasnoot, de Leeuw, and Altona³ introduced an equation (HLA equation) for J embodying a substituent-induced phase shift.

$$J = P_1 \cos 2\phi + P_2 \cos\phi + P_3 + \sum \Delta\chi_i (P_4 + P_5 \cos^2(\xi_i \phi + P_6 |\Delta\chi_i|)) \quad (5)$$

The parameters P_1-P_6 in this equation were empirically determined from a data set of 315 couplings. The σ deviation was 0.51 Hz. The data set was restricted to conformationally rigid structures, largely six-membered rings with holding groups, that can be assumed to exist in a single conformation. Norbornane- and norbornene-derivates were excluded from the data set due to the existence of extra contributions to J (Barfield effect⁹) from β -atoms, i.e., atoms bonded to α -atoms, and γ -atoms, i.e., atoms bonded to β -atoms. The data set was biased toward torsion angles about ca. 60° and 180° . The most frequently occurring α -atoms were C and O with a smaller number of N, S, halogens, Si, and Se. The

necessary torsion angles ϕ were determined via molecular mechanic methods supplemented by neutron-diffraction information.

In addition to the two important factors that determine the magnitude of the J couplings, the torsion angle ϕ and the nature of α -atoms, there is a series of secondary factors that influence J such as the nature and orientation of the β - and γ -atoms, the interactions between substituents, the changes in bond lengths and bond angles within the HCC'H' fragment (changes in local geometry), the rovibrational contributions, the contributions from large amplitude vibrations (torsional contributions), etc. A first order correction for the influence of β -atoms upon J was introduced using $\Delta\chi^{\text{group}}$ relative electronegativities in eq 5 (HLA β -effect equation) defined as

$$\Delta\chi_i^{\text{group}} = \Delta\chi_i^{\alpha\text{-atom}} - P_7 \sum \Delta\chi_j^{\beta\text{-atom}} \quad (6)$$

where the summation is over all the j th β -atoms attached to the α -atom in the i th position. The σ deviation decreases to 0.48 Hz when the β effects are included. To correct, in part, the effect upon J of the interactions between substituents, the parameters P_1-P_7 in eqs 5 and 6 were determined separately for fragments $\text{CH}_2\text{X}-\text{CH}_2\text{Y}$ (HLA two substituents equation, $\sigma = 0.37$ Hz), $\text{CH}_2\text{X}-\text{CHYZ}$ (HLA three substituents equation, $\sigma = 0.49$ Hz), and $\text{CHXY}-\text{CHZW}$ (HLA four substituents equation, $\sigma = 0.36$ Hz).

An equation for the prediction of J including interactions between substituents was formulated by Díez et al.⁶ as a truncated Fourier series in the torsion angle ϕ with coefficients expanded as Taylor series in substituent parameters λ . From the J^M couplings to methyl groups in CH_2XCH_3 and CHXYCH_3 molecules, Altona et al. derived a λ scale² of "substituent parameters" or "group electronegativities" (which may contain other factors besides electronegativity), using the equation

$$J^M = 7.836 - 0.594(\lambda_X + \lambda_Y) - 0.423(\lambda_X \cdot \lambda_Y) \quad (7)$$

A least-squares optimization of both the Fourier coefficients and the λ values in the Díez et al. equation was carried out by Donders et al. from a set of J values calculated by a reparametrized version of the Extended Hückel method.¹⁰ The coefficients in the Díez-Donders equation with Altona's λ scale, DAD equations, were empirically determined² from a data set of 299 couplings selected from the original data set of 315 couplings used for the parametrization of the HLA equations. The torsion angles ϕ were calculated with the aid of the MM2-85 force field.¹¹ A DAD equation with all cross terms zero except $S_{211} \sum \xi_i \lambda_i^2$

$$J = (C_{00} + C_{01} \sum \lambda_i) + C_{10} \cos\phi + (C_{20} + C_{21} \sum \lambda_i) \cos 2\phi + (S_{211} \sum \xi_i \lambda_i^2) \sin 2\phi \quad (8)$$

gives a σ deviation of 0.33 Hz. A DAD cross terms equation, as (8) but $C_{012}(\lambda_1 \lambda_2 + \lambda_3 \lambda_4)$, $C_{214}(\lambda_1 \lambda_4 + \lambda_2 \lambda_3) \cos 2\phi$, and a small 3-fold term $C_{30} \cos 3\phi$ added

$$J = [C_{00} + C_{01} \sum \lambda_i + C_{012}(\lambda_1 \lambda_2 + \lambda_3 \lambda_4)] + C_{10} \cos\phi + [C_{20} + C_{21} \sum \lambda_i + C_{214}(\lambda_1 \lambda_4 + \lambda_2 \lambda_3)] \cos 2\phi + C_{30} \cos 3\phi + (S_{211} \sum \xi_i \lambda_i^2) \sin 2\phi \quad (9)$$

provides a σ deviation of 0.31 Hz. When the HLA eq 5 is parametrized using Altona's λ_i , instead of $\Delta\chi_i$, the resulting σ deviation amounts to 0.36 Hz.

Various other equations for the prediction of the J coupling have been proposed. Colucci, Jungk, and Gandour¹² (CJG equation) defined substituent parameters ΔS_X that are related to the J^X couplings in monosubstituted ethanes $\text{CH}_3\text{—CH}_2\text{X}$

$$\Delta S_X = 4 \cdot (8.17 - J^X) \quad (10)$$

and used these values to parametrize their proposed equation

$$J = A + B\cos\phi + C\cos 2\phi + \cos\phi[(\Delta S_1 + \Delta S_3)\cos(\phi + 120) + (\Delta S_2 + \Delta S_4)\cos(\phi - 120)] \quad (11)$$

The large standard deviation encountered, 0.77 Hz, was not encouraging. The parameters A , B , and C were determined from 49 couplings in 19 conformationally rigid molecules including 8 norbornene derivatives.

Based on simple MO theory, Barfield and Smith¹³ derived an explicit expression for J (BS equation) in terms of ϕ and the two internal bond angles θ_1 , HCC' , and θ_2 , $\text{CC}'\text{H}'$

$$J = c_a a(\theta_1, \theta_2) \cos^2 \phi + [c_{b1} b_1(\theta_1, \theta_2) + c_{b2} b_2(\theta_1, \theta_2) + c_{b3} b_3(\theta_1, \theta_2)] \cos \phi + C \quad (12)$$

where $a(\theta_1, \theta_2)$, $b_1(\theta_1, \theta_2)$, $b_2(\theta_1, \theta_2)$, and $b_3(\theta_1, \theta_2)$ are trigonometric functions on θ_1 and θ_2 . The coefficients c_a , c_{b1} , c_{b2} , c_{b3} , and C were determined from 26 couplings in 8 rigid unsubstituted molecules. The σ deviation of the fit was 0.78 Hz.

Rapid interconversion between conformers, as it is usually the case for substituted ethanes at room temperature, yields weighted time averaged $\langle J \rangle$ coupling

$$\langle J \rangle = \int_0^{2\pi} J(\phi) P(\phi, T) d\phi \quad (13)$$

where $P(\phi, T)$ is the conformer density distribution. This can be calculated classically from the potential energy function $V(\phi)$ by assuming a Boltzmann distribution ignoring entropy effects

$$P(\phi, T) = \frac{\exp(-V(\phi)/RT)}{\int_0^{2\pi} \exp(-V(\phi)/RT) d\phi} \quad (14)$$

The potential $V(\phi)$ can be expressed as a truncated Fourier series

$$V(\phi) = V_0 + \sum_{i=1}^n (V_{ci} \cos i\phi + V_{si} \sin i\phi) \quad (15)$$

A customary simplifying procedure to obtain conformational information is to reduce the problem to a case of rapid equilibrium between the most stable conformers, i.e., the three staggered conformers in the case of ethane derivatives

$$\langle J \rangle = \sum x_i J_i = \frac{\sum J_i \exp(-E_i/RT)}{\sum \exp(-E_i/RT)} \quad (16)$$

where J_i , x_i , and E_i are the J coupling, the mole fraction ($\sum x_i = 1$), and the energy ($E_i = 0$ for the most stable conformer)

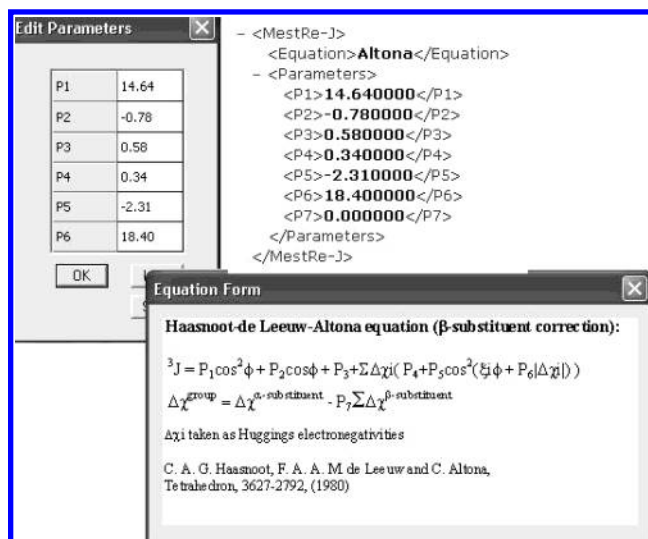


Figure 2. Parameter Edition Dialogue, XML file for parameter storing, and Equation Info Window.

of the i th conformer. This approximation introduces serious errors when the barriers that separate the minima in the potential energy functions are low.¹⁴

MATERIALS AND METHODS

MestRe-J is a native Win32 application that runs under all the Windows flavors.¹⁵ It has been developed using the Microsoft Foundation Classes (MFC's)¹⁶ as provided by the Visual C++ 6.0 compiler. Some graphical utilities have been taken from the CodeProject Web site.¹⁷

The program can be freely downloaded from the following URL: <http://www.mestrec.com/MestRe-J.html>.

RESULTS AND DISCUSSION

MestRe-J Description. The main window of MestRe-J is split into two panes (see Figure 1): the top pane displays the J values plotted against the torsion angle ϕ in degrees, whereas the bottom pane shows a Newman projection used to interactively set the substituents and the angle ϕ . The equation to be used may be chosen on the combo box inside the "Equation" group box. In addition, the program provides a toolbar at the right side for standard operations such as printing, saving, and exporting through the Windows clipboard as well as for obtaining the possible torsion angles for a given J value and for calculating their average couplings.

The parameter list for each equation can be customized using the P_n button in the "Equation" group box and exported to disk as an XML file for later use (Figure 2), thus allowing the use of custom parametrization. Finally, the $J(\phi)$ tool can be used to display essential information on the active equation.

Once the equation to be used is chosen the substituents may be set at the Newman projection showing the correct stereochemistry. Otherwise the calculated J values will be, in general, erroneous. To avoid mistakes the Newman projection for the coupling to be predicted must be drawn previously. The Newman projection represents the geometry of the $\text{CHS}_1\text{S}_2\text{—CHS}_3\text{S}_4$ fragment looking along the C—C bond. The carbon atom nearer the eye is shown as a point, and a coupled hydrogen H and the substituents S_1 and S_2



Figure 3. Choosing α - and β -atoms for HLA equations.

are attached to that forward carbon. The configuration about that forward carbon atom is fixed. The projected valence angle between H and S_1 amounts to approximately $+120^\circ$, counting clockwise from the coupled H as illustrated in Figure 1. The angle between H and S_2 amounts to about 240° . The rear carbon atom is immediately behind the near carbon atom, and a coupled H and the substituents S_3 and S_4 are attached to that farther carbon atom. It is important to realize that the positions of S_3 and S_4 are equivalent to those of S_1 and S_2 , respectively. This can be easily checked after rotation of 180° around an axis perpendicular to the C—C bond. The position of substituents is taken into account in equations by the parameter ξ_i , but, from a practical point of view when using MestRe-J, this can be ignored since it is determined automatically by the program.

The substituents are set in the Newman projection successively. The user may place the cursor over a given position, S_1 to S_4 , and double click when the cursor changes its shape to λ (for the DAD eqs 8 and 9 and also for the HLA eq 5 with λ instead of $\Delta\chi$ parameters), to χ (for the HLA eqs 5 and 6), or to ΔS (for the CJG eq 11). In the case of DAD and HLA equations, using λ parameters, a list with 62 different substituents is provided. The λ substituent parameter values given for the solvent CDCl_3 can be used for common organic solvents such as acetone- d_6 , CD_3CN , and DMSO. For the solvent D_2O , some λ values differ from those for the solvent CDCl_3 in cases where the substituent α -atom carries at least one nonconjugated lone pair of electrons that can readily act as a hydrogen bond acceptor. In the case of the CJG equation, using ΔS parameters, a more reduced list of 39 substituents is provided. This list contains less common substituents than the list for λ . In the case of the HLA equations, using $\Delta\chi$ relative Hugging's electronegativities, the user builds up the substituent selecting the α -atom and the β -atoms (Figure 3). The calculated "group electronegativity" is shown in the box. If desired, the user can overpass the calculated values, entering his/her own value in the edit box. In the case of the BS eq 12, the substituent effects are not accounted for explicitly, but J depends on the HCC bond angles θ_1 and θ_2 . When the BS equation is selected the H—C bonds are displayed in red, and when the mouse hovers over one of them, a double click will allow the user to input a new value for the bond angle.

Changing and Finding Torsional Angles. The proton—proton torsion angle ϕ is defined in the usual way, i.e., $0^\circ \leq \phi < 360^\circ$. There are three ways the user can change the dihedral angle: by moving the mouse wheel up and down,

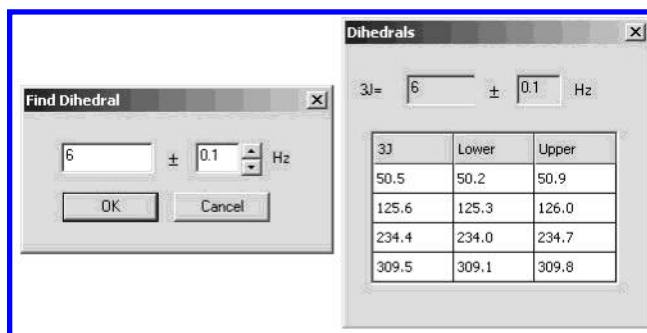


Figure 4. The "find dihedrals" tool.

by clicking on the plus and minus buttons in the Angle check box, or by pressing on the Angle LED-like control and entering a specific value. As the torsion angle gets modified, the J curve and the Angle and J LED-like controls are continuously refreshed. Finally, pressing with the right mouse button on the J curve will display the J and ϕ values at the mouse cursor point.

When the J value is known and the user wants to obtain the corresponding torsion angle ϕ , there can be up to four solutions. All the possible torsion angles for a given J can be displayed by pressing on the $\phi?$ button on the right side toolbar. After introducing the J value and the estimated error all possible solutions will be marked as red circles over the $J(\phi)$ curve. Pressing with the left mouse button over this circle will show a tooltip with the J value and the dihedral interval corresponding to the introduced error, whereas pressing with the right mouse button will show a table with all the information (Figure 4).

Averaged Coupling Constants. MestRe-J includes the calculation of weighted time average $\langle J \rangle$ couplings from the torsion angles and energies for the most stable conformers, eq 16, or from the Fourier potential $V(\phi)$ given by eq 15. In the latter case the conformer density distribution $P(\phi, T)$, eq 14, and the average $\langle J \rangle$, eq 13, are calculated using also eq 16 for 360 conformers. To get the averaged $\langle J \rangle$, the user has to click the $\langle J \rangle$ button on the right side toolbar. A dialogue will be opened where the potential energy curve in kcal/mol versus the HCC'H' torsion angle is displayed. To modify the shape of the curve the user must click on the V button and enter appropriate values for each term. For instance in Figure 5 a 3-fold potential with an energy barrier of 3 kcal/mol is defined.

Another option is to enter a discrete number of conformers. Pressing the E button will open a new dialogue in which the user can enter dihedral angles and relative energies for the chosen number of conformers. This can be accomplished also by loading a text file from the disk containing dihedral angles and energies in two separate columns. If the number of conformers is less than 24, each conformer will be shown on a screen as a rectangular box, otherwise a continuous line will be drawn.

Desktop Integration. We believe that modern applications should provide easy exporting of the results, i.e., by using the clipboard memory and standard protocols. Thus, MestRe-J allows easy printing and data exporting. These options are available in the right side toolbar. In addition to printing through a standard windows printing dialogue, it is possible to export the $J(\phi)$ curve to the clipboard memory or save it to disk, as an enhanced Windows metafile (EMF), a format

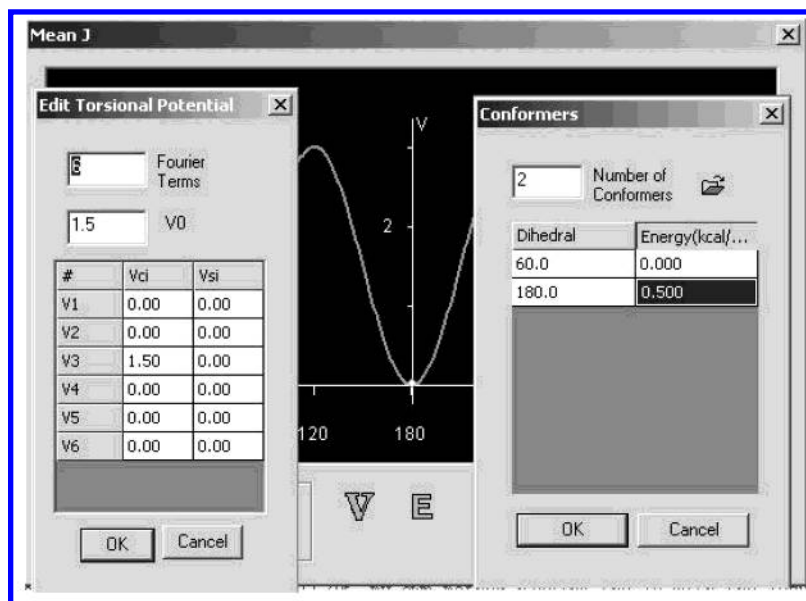


Figure 5. Calculating averaged coupling constants.

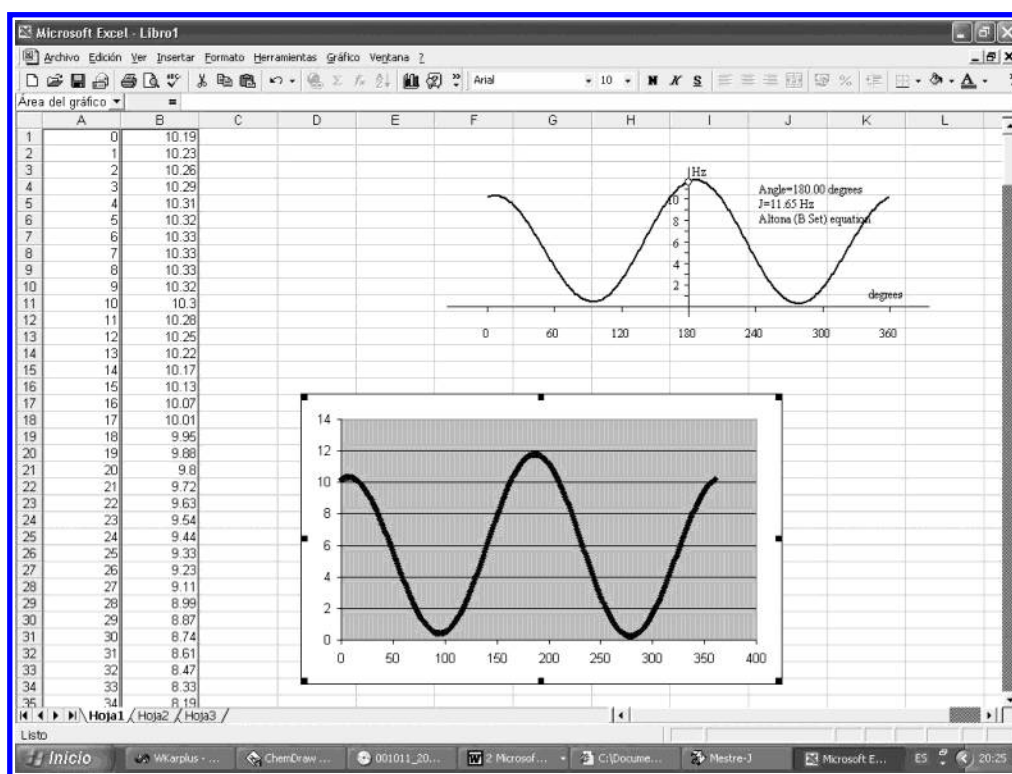


Figure 6. Exporting graphics and data to Excel.

that preserves the digital resolution inherent in the data. Finally, the curve data can be exported to a spreadsheet programs such as Excel as a table of ϕ angle values versus J values (Figure 6).

Application. MestRe-J makes very easy the calculation of J couplings using the implemented generalized Karplus equations, but the user may be aware of the limitations that the parametrization process introduces in the performance of each equation (see the "Empirical Equation" section). The most precise of these equations, the DAD cross-terms eq 9, is directly applicable, with a σ deviation of 0.31 Hz, to those fragments $\text{CHS}_1\text{S}_2\text{—CHS}_3\text{S}_4$ with substituents of known λ parameters. Otherwise, the λ parameters may be determined from appropriate J^M couplings to methyl groups by means

of eq 7 or, when this approach is not possible, λ parameters from similar substituents may be used. The equation does not account explicitly for the effect upon J of changes in the bond angles HCC. Therefore, the predicted J values can show large deviations from the experimental ones for strained cyclic compounds, when substantial deviations of HCC angles from tetrahedral value occur, i.e., three- and four-membered rings and multicycles. In five-membered rings, large deviations appear when the contribution to J from the Barfield effect⁹ is important. The remaining DAD and HLA equations developed by Altona's group show the same limitations that the DAD cross-terms equation and the σ deviations are larger. However, the classical HLA eqs 5 and 6 present the advantage, in principle, that the used $\Delta\chi_i$

substituent parameters are known for any substituent. Notwithstanding, the λ values are known for all of the substituents which appear in the $\text{CHS}_1\text{S}_2\text{—CHS}_3\text{S}_4$ fragments in the data set of J couplings used to parametrize the generalized Karplus equations developed by Altona's group. Substituents with unknown λ values lie outside of this data set, and the J values calculated for them using any of each equations may be used with caution.

The CJG eq 11 was parametrized using a small and heterogeneous data set of couplings giving a large σ deviation of 0.77 Hz. Substituent parameters ΔS were calculated from the J^M couplings of 39 monosubstituted ethanes $\text{CH}_3\text{—CH}_2\text{X}$ by means of eq 10. Only a few substituents are common to both the ΔS and the λ scales, but using eq 7 the λ values can be calculated for those substituents of known ΔS and using eq 10 the ΔS values can be calculated for substituents of known λ .

The BS eq 12 accounts for contributions to J from changes in the bond angles HCC but not for contributions from substituent effects. Cyclopropane and cubane J couplings were included in the parametrization. Therefore, this equation can be applied to strained hydrocarbonated molecules being the σ deviation 0.78 Hz.

CONCLUSION

MestRe-J is a Win32 graphical tool for the prediction of J couplings presenting a modern and clean interface. The program is very easy to use displaying the Newman projection of the fragment under observation and a plot of the J values against the torsion angle HCC'H' . Graphics and data can be easily exported to other Windows applications.

MestRe-J implements the two kinds of generalized Karplus equations developed by Altona's group: the classical Haasnoot-de Leeuw-Altona equations and the more recent and precise Díez-Altona-Donders equations. The Colucci-Jungk-Gandour, the Barfield-Smith, and the Karplus equations are also implemented. All of these equations are described in the "Empirical Equations" section, and their performance and limitations are presented in the "Discussion" section. Users of the program can change both the values of coefficients in equations and substituent parameters.

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REFERENCES AND NOTES

- (1) (a) Karplus, M. Contact Electro-Spin Coupling of Nuclear Magnetic Moments. *J. Chem. Phys.* **1959**, *30*, 11–15. (b) Karplus, M. Vicinal Proton Coupling in Nuclear Magnetic Resonance. *J. Am. Chem. Soc.* **1963**, *85*, 2870–2871.
- (2) Altona, C. Vicinal Coupling Constants & Conformation of Biomolecules. *Encyclopedia of NMR*; Grant, D. M., Morris, R., Eds.; Wiley: New York, 1996; pp 4909–4923.
- (3) Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. The Relationship Between Proton-Proton NMR Coupling Constants and Substituent Electronegativities-I. An Empirical Generalization of the Karplus Equation. *Tetrahedron* **1980**, *36*, 2783–2792.
- (4) Balacco, G. A Desktop Calculator for the Karplus Equation. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 885–887.
- (5) Some molecular mechanics programs such as PCMODEL (a) incorporate HLA equations into their environment. There exists also the ALTONA program (b) but its interface is quite cumbersome. Also, there are programs designed for working with biomolecules such as MULDER (c) or AURELIA (d). (a) PCModel. Serena Software, Bloomington, IN. (b) Cerda-García-Rojas, C. M.; Zepeda, L. G.; Joseph-Nathan, P. A PC Program for Calculation of Dihedral Angles from ^1H NMR Data. *Tetrahedron Comput. Method.* **1990**, *3*, 113–118. (c) Padrtá, P.; Sklenár, V. Program Mulder – A tool for extracting torsion angles from NMR data. *J. Biomol. NMR.* **2002**, *24*, 339–349. (d) Neidig, K.-P.; Geyer, M.; Goerler, A.; Antz, C.; Saffrich, R.; Beneicke, W.; Kalbitzer, H. R. Aurelia, a program for computer aided analysis of multidimensional NMR spectra. *J. Biomol. NMR.* **1995**, *6*, 255–270.
- (6) Díez, E.; San-Fabián, J.; Guilleme, J.; Altona, C.; Donders L. A. Vicinal Proton-Proton Coupling Constants I. Formulation of an Equation Including Interactions Between Substituents. *Mol. Phys.* **1989**, *68*, 49–63.
- (7) (a) Pachler, K. G. R. Extended Hückel Theory MO Calculations of Proton-Proton Coupling Constants II. The Effect of Substituents on Vicinal Couplings in Monosubstituted Ethanes. *Tetrahedron* **1971**, *27*, 187–199. (b) Pachler, K. G. R. The Dependence of Vicinal Proton-Proton Coupling Constants on Dihedral Angle and Substituents. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1936–1940.
- (8) Huggins, M. L. Bond Energies and Polarities. *J. Am. Chem. Soc.* **1953**, *75*, 4123–4126.
- (9) Marshall, J. L.; Walter, S. R.; Barfield, M.; Marchand, A. P.; Marchand N. W.; Segre, A. L. Reasons for the non equivalence of exo-exo and endo-endo vicinal NMR coupling constants in norbornanes. *Tetrahedron* **1976**, *32*, 537–542.
- (10) Donders, L. A.; de Leeuw, F. A. A. M.; Altona, C. Relationship Between Proton-Proton NMR Coupling Constants and Substituent Electronegativities IV. An Extended Karplus Equation Accounting for Interactions Between Substituents and its Application to Coupling Constant Data Calculated by the Extended Hückel Method. *Magn. Reson. Chem.* **1989**, *27*, 556–563.
- (11) Allinger, N. L. Quantum Chemistry Program Exchange MMP(85). Indiana State University. 1985.
- (12) (a) Colucci, W. J.; Jungk, S. J.; Gandour, R. D. An Equation Utilizing Empirically Derived Substituent Constants for the Prediction of Vicinal Coupling Constants in Substituted Ethanes. *Magn. Reson. Chem.* **1985**, *23*, 335–343. (b) Colucci, W. J.; Gandour, R. D.; Mooberry, E. A. Conformational Analysis of Charged Flexible Molecules in Water by Application of a New Karplus Equation Combined with MM2 Computations: Conformations of Carnitine and Acetylcarnitine. *J. Am. Chem. Soc.* **1986**, *108*, 7141–7147.
- (13) (a) Barfield, M.; Smith, W. B. Internal H—C—C Angles Dependence of Vicinal ^1H - ^1H Coupling Constants. *J. Am. Chem. Soc.* **1992**, *114*, 1574–1581. (b) Smith, W. B.; Barfield, M. Predictions of $^3J(\text{HH})$ near 180° – Reparametrization of the $\text{sp}^3\text{—sp}^3$ equation. *Magn. Reson. Chem.* **1993**, *31*, 696–697.
- (14) Gil, V. M. S.; Varandas A. J. C. The Use of Vicinal H—H Coupling Constants in Rotational Isomerism Studies, I. *J. Magn. Reson.* **1981**, *43*, 28–39.
- (15) It is possible however, to run efficiently MestRe-J under i386-Linux using the wine emulator: <http://www.winehq.com>.
- (16) Microsoft. Microsoft Visual C++ Class Library Reference.
- (17) <http://www.codeproject.com>.

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