

A Desktop Calculator for the Karplus Equation

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The Macintosh program SWEET J solves equations of the Karplus type both numerically and graphically. Users of the program can change the coefficients to fit particular classes of chemical compounds. The Karplus–Altona equation is also implemented, which takes into account both the electronegativity and the orientation of the substituents on the fragment H–C–C–H. The program has many features which make it extremely easy to use: the fragment under observation is displayed in the Newman projection; the dihedral angle can be changed with the mouse; and the absolute configuration at stereogenic centers is ascertained by the computer. The executable program and its source code are available free.

INTRODUCTION

Scalar spin–spin coupling constant has been extensively used since its discovery for the important information it can provide on the electron distribution between two magnetically active nuclei. Karplus related the size of the vicinal coupling constant (3J) to the torsion angle between the coupled nuclei through the formula¹

$$^3J = A \cos^2 \theta + B \cos \theta + C \quad (1)$$

The above equation has been developed from valence bond calculations for the ethane molecule; the coefficients A , B , and C are to be adjusted empirically by comparison with molecules of known conformation. Equation 1 does not take into account other molecular parameters which affect the size of 3J to a lesser extent but are nonetheless important. Two alternatives are currently accepted to deal with these minor effects. A first approach fits the coefficients A , B , and C to specific bonds. For example, $^3J_{\text{H}^{\text{N}}, \text{H}^{\alpha}}$ in amino acids is described by the following equation³

$$^3J_{\text{H}^{\text{N}}, \text{H}^{\alpha}} = 6.4 \cos^2 \theta - 1.4 \cos \theta + 1.9 \quad (2)$$

while a different combination of coefficients deal with $^3J_{\text{H}^{\alpha}, \text{H}^{\beta}}$. Other combinations have been proposed for the relation between $^3J_{\text{CH}}$ and the torsion angles C–C–C–H⁴ and C–O–C–H,⁵ respectively. In most cases the parameters have been derived fitting measured coupling constants against X-ray crystallographic data.

For the sake of completeness it shall be remembered that Karplus himself proposed a “slightly more accurate” expression in 1963:²

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

While it is relatively easy to find in literature^{3–8} sets of parameters to substitute into eq 1, the opposite is true for eq 3. For this merely practical reason eq 3 will be ignored in the following.

The second approach explicitly takes into account the electronegativity of substituents and their relative position.⁶ Altona et al. derived the equation

$$^3J_{\text{H-H}} = P_1 \cos^2 \theta + P_2 \cos \theta + P_3 + \sum_i \{ \Delta\chi_i [P_4 + P_5 \cos^2 (\xi_i \theta + P_6 |\Delta\chi_i|)] \} \quad (4)$$

where the electronegativity of the substituent i is so defined:

$$\Delta\chi_i = \Delta\chi^{(\alpha\text{-atom})} - P_7 \sum \Delta\chi^{(\beta\text{-atoms})}$$

$$\Delta\chi_{\text{atom}} = \chi_{\text{atom}} - \chi_{\text{H}}$$

while the parameter ξ_i , which can take the values $+1$ or -1 , describes the orientation of the substituent i . Equation 4 was parametrized over 315 coupling constants of fragments H–C(sp³)–C(sp³)–H inside alicyclic molecules. These molecules were chosen for their conformational rigidity and the proton–proton torsion angles were determined via a General Valence Force Field method. The extrapolation of eq 4 to other compounds should not be extended to fragments other than H–C(sp³)–C(sp³)–H. This means, for example, that it cannot substitute eq 2 in the description of $^3J_{\text{H}^{\text{N}}, \text{H}^{\alpha}}$. Despite this limitation, eq 4 is evaluated as the most useful one for stereochemical and/or conformational purposes.¹¹

During the last few years the analysis of coupling constants has received increased attention.⁷ At the same time application of either eq 1 or eq 4 is far less widespread than it could be, for reasons which are easily understood. When either equation is solved for the dihedral angle it may furnish up to four answers, so a graphic approach is needed (see Figure 1). Furthermore the difficulties involved in calculation, though resolvable with pocket calculators, seem enough to discourage the average chemist. Computer programs which address this problem already exist. In the first category one can include molecular modeling programs, which may make use of the coupling information.^{8–10} A second category comprises small applications specific to the problem. To the best of my knowledge there exists only one member into the latter, namely the program ALTONA, written in 1990 by Cerda-García-Rojas et al.¹¹ This program has the undeniable advantages of simplicity and cheapness. Yet I was convinced that there were enough reasons to write a new, different program. These reasons may be summarized as follows: ALTONA only deals with eq 4 and not with eq 1; the program requires the values of ξ_i , directly from the user (which is not a trivial task for him or her) instead of deriving ξ_i by the structural formula; the program does not

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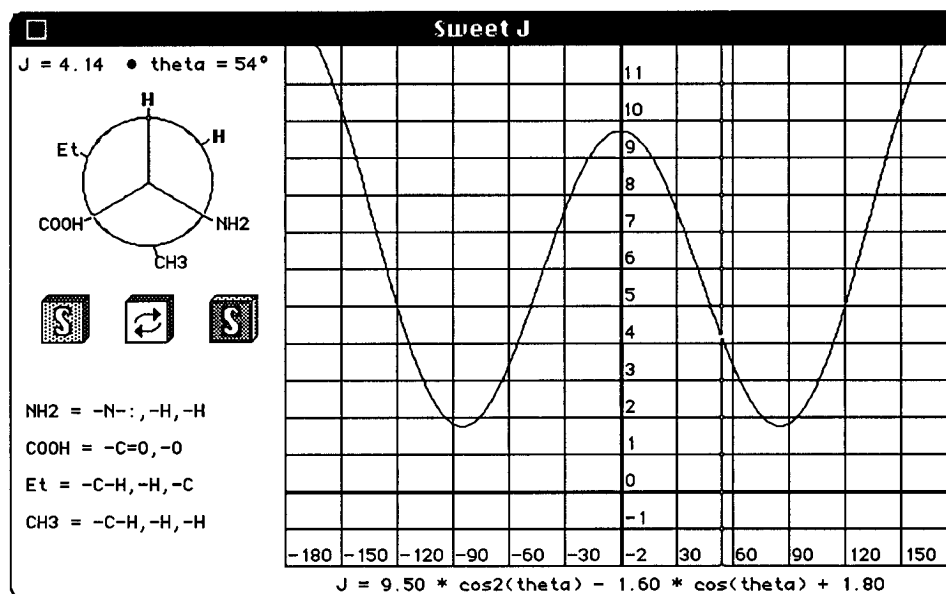


Figure 1. The program main window.

convert the values of the dihedral angle into a graphic representation of the molecular conformation; and the alpha-numerical user interface of ALTONA is cumbersome, and the user is forced to consult the instructions nearly every time he or she runs the program.

In the present paper I describe a new program, named Sweet J, written with the intent of overcoming the above limitations.

MATERIALS AND METHODS

Sweet J has been written in C and compiled with the Think C compiler.¹² Some relatively new features of the Macintosh environment, like color and cooperative multitasking, have been implemented without renouncing to compatibility with older computers. Final testing has been performed on a wide range of machines, from a Macintosh Plus with System 6 to a Power Macintosh with System 7.5.

Electronegativity values were taken from the Huggins scale,¹³ because the same scale was used to parametrize eq 4. All the constants in the program, namely the various coefficients in eq 4 and the values of electronegativities, are grouped into a header file, which facilitates modifications without changing the source code. Presently the following atoms are included: H, C, N, O, F, Si, P, S, Cl, Br, and I. When Sweet J checks the autoconsistency of formulas, hydrogen and halogens are treated as monovalent while all the other atoms are treated as tetravalent, with the added rule that a valence can be filled by a lone pair (see Figure 2b for an example).

Values of the coefficients and the rules to determine the sign of ξ_i have been repeatedly reported elsewhere.^{6,11} They will not be reported here. From the practical point of view they can be ignored, like any other detail internal to the program algorithm.

Once finished, Sweet J has been compared to the cited program ALTONA, yielding identical numerical values.

RESULTS

The main window, shown in Figure 1, contains, excluding the title-bar and from left to right and top to bottom, the

following parts: the status line, the Newman projection, three square buttons, the substituent table, the plot, and the equation.

The status line contains the current value of the dihedral angle (called theta) and the corresponding value for the coupling constant, in Hz.

The Newman projection describes the fragment under study. Nuclei whose coupling is measured are written in bold face. They can be dragged with the mouse, causing rotation of the nearby atom and the changing of the torsion angle. The four substituents are represented with labels, assigned by the user.

The two buttons with a capital letter report the absolute configuration at the two atoms along the axis of the Newman projection. The button on the left refers to the fore atom and the one on the right to the back atom. Clicking one of these buttons will cause the inversion of the related chiral center. The central button interchanges the two atoms in space without affecting their configuration (in other words it rotates the molecule by 180°).

The substituent table explains the meaning of the labels. Clicking here will start the "Substituent Editor" (see below) inside which the substituents can be redefined.

The plot of the function is essential in practice. In fact one normally knows the value of 3J and wants to obtain the corresponding torsion angle. The plot points out that this problem may lead up to four solutions and shows where they are. A vertical line signals the current value of the torsion angle. Moving the line (dragging it with the mouse or using the arrow keys) will rotate the molecule.

The equation at the bottom of the window reports the actual values for the coefficients in eq 1. When the Alttona equation is implemented, the word "Alttona" appears in the same place. Clicking here will toggle between the Karplus and the Alttona equations. When switching to Karplus, the "Equation Manager" is also activated (see below).

At any time all the current choices can be saved into a file (command "File/Save as...") or recalled from a file (command "File/Open..."). Other menu commands either are equivalent to some of the mouse operations previously

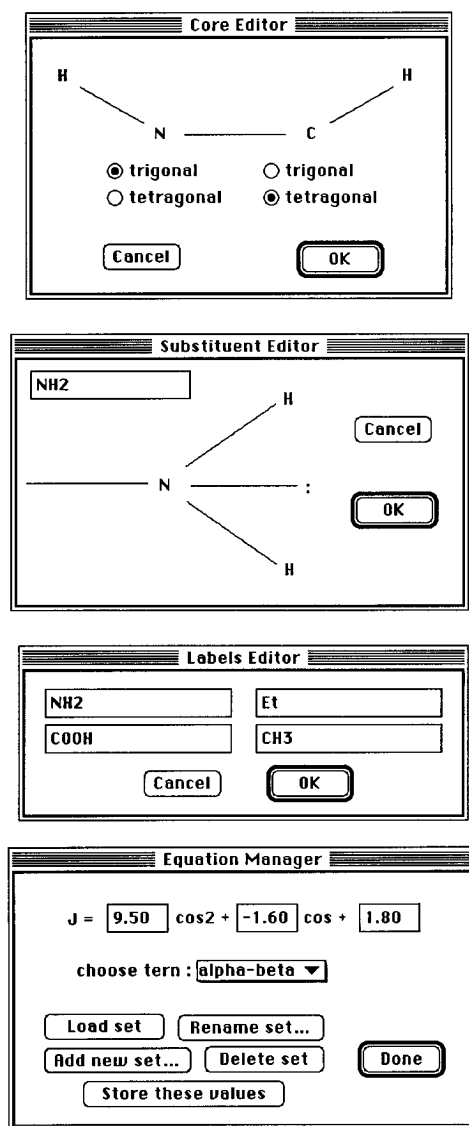


Figure 2. (a, top) Dialog for specifying the three bonds which define the dihedral angle. (b, near top) Dialog for specifying the structure and the name of a substituent. (c, near bottom) Alternative dialog to specify only the name of substituents. (d, bottom) Dialog for changing the coefficients of the Karplus equation.

described or launch one of the special editors, which are to be described.

Figure 2a shows the Core Editor window. If the user clicks on one of the four atomic symbols, a menu will appear to choose a different atom. Only tetravalent atoms (as defined in the Methods section of this paper) are allowed at the two central positions. The geometry of these inner nuclei can be trigonal or tetragonal. In the latter case they may be chiral centers. Sweet J automatically determines the absolute configuration of these centers from the nature of the substituent atoms in positions α and β , according to the Cahn, Ingold and Prelog rules.¹⁴ When two substituents differ in a more remote position, they can be distinguished by their labels. Sweet J assigns priority to the label which comes first in alphabetical order. If a core structure other than $\text{H}-\text{C}(\text{sp}^3)-\text{C}(\text{sp}^3)-\text{H}$ is specified, the program disables the use of the Altona equation.

Figure 2b shows the Substituent Editor window. Atomic symbols can be changed as in the previous case. The bonds represented horizontally can be changed by simply clicking

over them. The bond on the left can be single or double, while the horizontal one on the right can also be triple. If the first atom, the one on the left, has valence 1, the rest of the figure disappears. There are two reasons to specify the atoms in the substituents: to calculate the electronegativity of the substituent as required by eq 4 and to let the program determine the absolute configuration of the molecule. In case the user does not need either of these two functions, he can resort to the simpler Labels Editor depicted in Figure 2c.

The Equation Manager is shown in Figure 2d. It permits changing the coefficients in eq 1, storing these values for subsequent use, and recalling existing sets of values. The default values are taken from ref 6.

CONCLUSION

Writing a small application like Sweet J is a straightforward process. What is important to see is if it will bring chemists to a more frequent and accurate use of the Karplus equation(s). I am quite confident about this issue. In fact, comments that I receive from hundreds of colleagues from all over the world demonstrate that, from the user's point of view, the first requisite for a good software is simplicity. It was this last consideration which eventually persuaded me to write Sweet J. I make it available to everyone interested, in the form both of executable application and of source code. In this way it should be easy to port the program to other operative systems. The electronic address to Sweet J is <ftp://cacao.issecc.fi.cnr.it> (149.139.10.2).

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