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AN EXTENSION OF MULTIPARAMETRIC KARPLUS EQUATION

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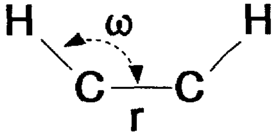
Abstract: Karplus equation was expanded to contain twelve terms including Mullay's group electronegativity for α- and β-substituents, H-C-C valence angles, C-C bond length, through-space interaction from the closest non-bonded group, and corrections for non-additivity of substituent effect.

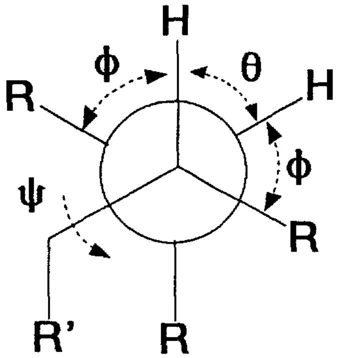
Karplus equation[1,2] has been repeatedly modified, notably by Pachler,[3] Altona,[4] and Gandour[5], but the accuracies of the improved equations remained, in our opinion, at the level of 0.7 to 0.8 Hz in terms of standard deviation of errors (*vide infra*). While these equations have been quite useful,[6] the high precision (0.1 Hz) in the experimental determination of $^3J_{HH}$ values renders further improvements in the equation highly desirable. We present below an extensive revision of Karplus equation.

Our attention is first directed to the two well-known contributors to $^3J_{HH}$ values, the dihedral angle θ between vicinal protons[2-4,7] and the electronegativity of substituent.[8] *Regarding the dihedral angle, there is clearly no a priori reason to* restrict the number of cosine terms to two. It seemed almost obvious from the beginning that the use of electronegativity of α-atom in the substituent, as has been practised before,[3,4] is not right and that some kind of group electronegativity should be used. After preliminary screening, we chose to adopt Mullay's electronegativity.[9]

In addition to these, the following three new effects are considered. *β-Effect* : Schaefer[10] has observed considerable increase in the J value when an electronegative group exists at β position of substituent in periplanar conformation relative to the coupling proton . *Structural effect* : Karplus[2] has long indicated that structural parameters like C-C and C-H bond lengths as well as C-C-H valence angles in the coupling system H-C-C-H may have some influence. *Through-space effect* : it is likely that not only the through-bond, but also the through-space interaction of non-bonded atoms or groups with the coupling proton gives rise to some changes in the coupling constant.

We began with an equation containing all conceivable forms of functions for the





above five effects, and arrived, after checking undesirable correlation among parameters and removing insignificant terms, at the following multi-term equation:

$$ {}^3J_{HH} = A\cos\theta + B\cos2\theta + C\cos3\theta + D\cos^2 2\theta + W(E\cos\theta\Sigma\Delta\chi_i\cos\phi_i + F\Sigma\Delta\chi_i\cos2\phi_i + G\Sigma\Delta\chi_i) + H\{(\omega_1 + \omega_2)/2 - 110\} + I(r_{C-C} - 1.5) + K\Sigma\Delta\chi^{\beta}_{j}\cos2\psi_j + Lr^{-4} + M \qquad (1) $$

where A to I, K to M, and W are adjustable parameters.

The first four cosine terms are all of considerable importance according to our statistical analysis. The next three terms contain χ_i, Mullay's group electronegativity of the i-th substituent R_i relative to that of hydrogen, and pertain to the effect of substituents directly attached to the H-C-C-H system (α-effect). ϕ_i is the dihedral angle between a coupling proton and R_i. The α-Effect is non-additive, hence this term is multiplied by an weighting factor W which changes with substitution pattern.

Structural effects are adequately described with H-C-C valence angle (ω_1 and ω_2) and C-C bond length (r_{C-C}). The next term corresponds to the β-effect, where $\Delta\chi^{\beta}_{j}$ is Mullay's group electronegativity of j-th β-substituent (e.g., R' in the drawing) relative to that of alkane, and ψ_j is the dihedral angle between a coupling proton and the j-th β-substituent.[11]

The penultimate term corresponds to the through-space effect, which we found to appear only when a coupling proton has a nonbonded group[12] within 3.3 A. The effect is best accounted for by the fourth inverse power of the distance r. Finally, a parameter M is added to correct for the overall non-additive effect.

When the parameters were optimized against a standard set of 198 experimentally observed coupling constants,[13] equation 1 gave a standard deviation of errors of 0.332 Hz.[14] A cautionary note is due here on the accuracies of modified equations. Accuracies are generally determined based on a standard set of data on which the parameters were optimized. The 'optimized accuracy' decreases upon recalculation against a different standard set. This situation is shown by the standard deviations of errors of about 0.8 Hz obtained on our standard set for the previously reported modified equations (Table I, the upper line). The performance of equation 1 also dropped when tested, without reoptimization of parameters, against a new set of experimental coupling constants collected from the papers published in *the Journal of American Chemical Society* and *the Journal of Organic Chemistry* during the year of 1988.[15] Nonetheless, the recalculated deviation of 0.50 Hz allows us to expect good performance of equation 1 (Table I, the lower line).

Table I. Standard Deviations of Errors (in Hz) in the Application of Karplus Equation and Its Modifications to Two Sets of Experimental $^3J_{HH}$ Coupling Constants[a]

	Karplus[b]	Pachler[c]	Altona[d]	Gandour[e]	Eq. 1
Standard set[f]	1.0559 (198)	0.7295 (198)	0.8351 (140)	0.8847 (69)	0.3318 (198)
JACS/JOC1988[g]	1.7764 (39)	0.7025 (39)	0.7619 (35)	-------	0.5002 (39)

[a] Number of experimental data are given in parenthesis. [b]Parameters in the original Karplus equation (ref. 2) were optimized against our standard set and used unchanged in the calculation of the JACS/JOC1988 set. [c] Ref. 3. [d] Ref. 4. [e] Ref. 5. [f] Footnote 13. [g] Footnote 15.

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(11) The β-effect is considered to appear only when a β-substituent is more electronegative than alkyl and takes periplanar conformation to a coupling proton, and when $\cos 2\psi$ is positive. Further details will be given in a full account of this work.

(12) 'Group' is used as the same meaning as united atom: Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S. Jr.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765.

(13) The standard set of observed coupling constants was collected from literature and consists of those values measured in $CDCl_3$ or CCl_4 and those compounds which can be subjected to geometry optimization with MM2/MMP2(85) program [Allinger, N. L. (converted by Buda, A. B.) *QCPE Bull*. **1987**, 7, 141]. The optimized parameters are as follows: A = -1.2246 , B = 5.0935, C = -0.1055, D = 0.5711, E = 0.8319, F = 0.0433, G = 0.0345, H = -0.2058, I = -8.9222, K = 0.1438, L(carbon) = -8.9395, L(oxygen) = 6.9202, M = 7.5075 (mono-subsitution on H-C-C-H system), 7.0306 (1,1-di), 6.4793 (1,2-di), 6.5432 (tri), 5.5319 (tetra), W = 1.00 (mono), 2.55 (1,1-di), 1.16 (1,2-di), 2.29 (tri), 1.40 (tetra). $\Delta\chi^{\beta}$ for N lone pair = -6.0493. Units used in equation 1 are Å for distances and degrees for angles. In the final adjustment, the following weighting factors were given to the observed coupling constants in the standard set: 0.5 for the constants reported before 1969, 1.0 for those reported between 1970 and 1979, and 2.0 for those reported after 1980.

(14) A FORTRAN-77 program (3JHHM) is written for calculating $^3J_{HH}$ values using equation 1 and will be shortly submitted to QCPE.

(15) Restricted to those data which were measured in $CDCl_3$ on molecules having no more than 18 rotamers and calculable with MM2/MMP2(85).

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