The Dependence of Vicinal Proton-Proton Coupling Constants on Molecular Structure

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Z. Naturforsch. **49a,** 815–818 (1994); received June 3, 1993

A modification of the Karplus equation is put forward, containing for mutually independent structural terms and four adjustable parameters. Among the new factors introduced in this modification are the distance between protons and Muallay's group electronegativity, used in the evaluation of the α-substituent effect. The new equation reproduces experimental NMR vicinal coupling constants with a standard deviation of about 0.6 Hz.

Introduction

An important discovery in 1959 [1] was that the vicinal protons coupling constant (J) depends on the orientation of the protons. This observation led to the Karplus equation [2]

$$J = A\cos\omega + B\cos 2\omega + E\,, \qquad (1)$$

where ω represents the dihedral angle between the coupling protons, and A, B, and E are adjustable parameters. This equation was for a long time the only means for investigating conformational problems of both theoreticians and experimentalists. Molecular-orbital approaches attained great success in interpretation of coupling constants of small molecules [3, 4]. Unfortunately, these theoretical calculations were not straightforwardly applicable to large molecules, which are of importance in conformational analysis. This was the main reason that (1) was revised by various investigators [5–8]. Among these proposed modifications, there is Pachler's equation [5]

$$J = A\cos\omega + B\sin\omega + C\cos 2\omega + D\sin 2\omega + E\,, \qquad (2)$$

where ω, as before, stands for the dihedral angle between coupling protons, and A, B, C, D, and E are adjustable parameters. Further improvements in this field were achieved by introducing some other structural factors that also influence the magnitude of coupling constants. The formula of Haasnoot et al., attained in 1980, is the most widely used expression for the calculation of coupling constants:

$$J = A\cos\omega + B\cos^2\omega + \sum \Delta E_i \times [C + D\cos(\xi\omega + E\,|\Delta E|)]\,, \qquad (3)$$

$$\Delta E_i = \Delta E_i^{\alpha} + F\,\Delta E_{ij}^{\beta}\,, \qquad (3\,a)$$

where ΔE_i^{α} stands for Huggins' electronegativity of the α-atom in the i-th substituent of the coupled H–C–C–H fragment, ΔE_{ij}^{β} is the electronegativity of the j-th β-atom in the i-th substituent, ξ_i amounts 1 or -1 depending on the orientation of i-th substituent, and A–F are adjustable parameters.

The standard deviation for te Karplus equation is about 0.7 Hz [9, 10], whereas that for (3) is about 0.5 Hz [8]. Experimental errors of determining coupling constants lie in the interval from 0.05 Hz (for data obtained after 1980) to 0.2 Hz (for data obtained before 1970). Another type of error arises from molecular mechanics calculation of the distribution of conformers.

One may conclude that the experimental values of coupling constants of vicinal protons were very well reproduced by (3). Another multiparametric formula for calculation of coupling constants was recently suggested by Osawa et al. [11, 12].

Although the accuracy of the Karplus equation was improved by its numerous modifications, its elegance and simplicity were reduced. Our idea was based on the assumption that it is possible to find out an equation, not so complex as that of Haasnoot et al. and Osawa et al., but which would reproduce experimental values of coupling constants with satisfactory accuracy. We supposed that besides the dihedral angle and the electronegativity of substituents, some other parameters influence the magnitude of the coupling constants.

Methodology

In our investigations, the interactive molecular mechanics program PC MODEL, version 4.0 [13],

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that involves an MMX force field [14, 15], was used for optimizing geometries. A variety of experimentally determined vicinal proton-proton coupling constants were available from literature. In order to minimize the errors that might appear from calculating rotamer energies, molecules which possess more than 15 rotamers were excluded from the consideration. Excluded were also those rotamers whose population is smaller then 0.1%. In this manner, a set of 288 coupling constants for 109 compounds was formed. The list of experimental data, compounds, results of calculations and literature information are available from the authors on request.

Results and Discussion

As already said, our aim was to find out parameters that influence the magnitude of the coupling constants. On the basis of the numerous experiments we concluded that it is the distance between the coupling protons (r). By exchanging in the second term of (1) ($\cos 2\omega$) by r, (4) was obtained. Equations (5)–(7) are the result of introducing the electronegativity and the number of substituents attached to the H–C–C–H fragment, whose influence on the coupling constants was already referred [8, 9, 16].

$$J = A\,r + B\cos\omega + E\,, \tag{4}$$

$$J = A\,r + B\cos\omega + C\sum \Delta E_i^{\alpha} + E\,, \tag{5}$$

$$J = A\,r + B\cos\omega + C\sum \Delta E_i^{\alpha} + D\,n + E\,, \tag{6}$$

$$J = A\,r + B\cos\omega + C\sum \Delta E_i^{\alpha} + D\,n\,. \tag{7}$$

In the equations above, r and ω represent the distance and the dihedral angle, respectively, between coupling protons, $\sum E_i^{\alpha}$ stands for Mually's sum of electronegativities [17], whereas n represents the number of substituents that are bonded to α-C atoms, other than hydrogen. Here, as before, $A-E$ stand for adjustable parameters. These constants were determined by least squares root fitting, and their values are shown in Table 1. The quality of the coupling constant patterns is conveniently judged by the root-mean square criterion RMS (standard deviation).

Table 1 shows that the equations which we suggested, (5), (6) and (7), possess a smaller value for RMS than that of Karplus (1), Pachler (2) and Haasnoot et al. (3). It is obvious that (6) and (7) are very similar in quality, meaning that the term E in (6) is not necessary.

In order to compare the quality of the formulas examined, the F-test was performed. The critical value of the F-parameter for 287 degrees of freedom and the confidence level of 95% was determined by interpolation. It amounts 1.22 [18]. The results of this test show that (6) and (7) are significantly better than (1) and (2).

This confirms our supposition that introducing the distance between the coupling protons r improves the quality of the calculated coupling constants. According to the F-test, the value of the parameter F for (3) and (7) is within the limits of statistically significant improvement. In addition to this, (7) contains a smaller number of parameters, what contributes to its successful use in the calculation of coupling constants.

It is of interest to examine the importance of each term in (7). The order of contributions of the terms was determined by excluding each term, one by one,

Table 1. Adjustable parameters and standard deviations for the Karplus equation (1) and its modifications (2)–(7). Parameter D has the values a, b, c, d, and e that correspond to the mono, 1,1-di, 1,2-di, tri and tetra substituted molecular fragments, respectively.

Eq.	A	B	C	D	E	RMS
(1)	−2.4673	6.0845			7.3613	0.758
(2)	9.7991	7.1685	14.7046	−5.4947	−6.2269	0.755
(3)						0.708
(4)	4.7334	9.8426	−13.6713			0.722
(5)	4.8986	9.6926	−0.0929		−13.4208	0.704
(6)	4.7412	9.9970	−0.4529	−335.9282 [a] −355.3330 [b] −355.1948 [c] −353.9072 [d] −353.9471 [e]	−343.7747	0.627
(7)	4.7412	9.9970	−0.4529	−12.1534 [a] −11.5582 [b] −11.4201 [c] −10.1325 [d] −10.1723 [e]		0.628

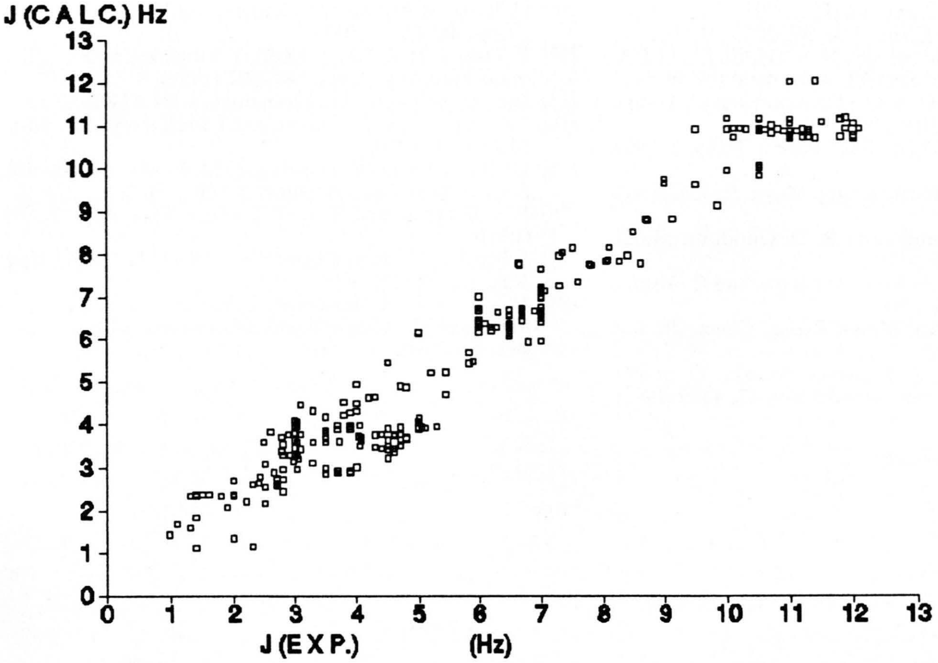

Fig. 1.
Comparison between the experimental and calculated (7) vicinal coupling constants.

Table 2. *F*-quotients for (1)–(7).

	(1)	(2)	(3)	(4)	(5)	(6)
(2)	1.00					
(3)	1.15	1.14				
(4)	1.10	1.09	1.04			
(5)	1.16	1.15	1.01	1.05		
(6)	1.46	1.45	1.27	1.33	1.26	
(7)	1.46	1.45	1.27	1.32	1.26	1

Table 3. Relative importance of linear terms in (7).

Term	*F*-test	RMS
$\sum E_i^\alpha$	1.22	0.694
r	1.69	0.817
n	2.72	1.035
$\cos \omega$	3.07	1.101

and reoptimizing the remaining set of parameters. The importance of some particular term was estimated on the basis of *F*-quotients and the root mean square criterion (Table 3). A term is important if the accuracy of the remaining formula is significantly lowered (in the statistical sense of the word) [18].

It is seen from Table 3 that the dihedral angle between coupling protons and the number of substituents are the most important factors influencing the magnitude of the coupling constants. The contribution of the distance between coupling protons is of lesser importance, whereas the influence of the electronegativities of the substituents, bonded to α-C atom, is only of marginal statistical importance.

Figure 1 illustrates how the coupling constants calculated according to (7) correlate with the observed ones. It is obvious that the points are uniformly distributed over the entire range from 1 Hz to 13 Hz. That is, certainly, the consequence of our procedure of taking all significantly populated rotamers into account.

Equation (7) is a modification of Karplus' formula that is distinguished by a relatively small number of terms with retained satisfactory accuracy. In addition to this, all necessary data for its application are easy to determine. Although (7) does not include the dependence of the vicinal proton-proton coupling constants on all existing conformational factors, it appears to be a successful and useful approximation for serving all stereochemical needs.

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