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 \( \alpha \)-substituent effect. The new equation reproduces experimental NMR vicinal coupling constants with a standard deviation of about 0.6 Hz.

\[ J = A \cos \omega + B \cos 2 \omega + E, \]  
\[ \Delta E_i = \Delta E_i^0 + F \Delta E_i^E, \]  

where \( \Delta E_i \) stands for Huggins' electronegativity of the \( \alpha \)-atom in the \( i \)-th substituent of the coupled \( \text{H-C-C-H} \) fragment, \( \Delta E_i^E \) is the electronegativity of the \( j \)-th \( \beta \)-atom in the \( i \)-th substituent, \( \xi \) amounts 1 or -1 depending on the orientation of \( i \)-th substituent, and \( A-F \) are adjustable parameters.

The standard deviation for the 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.

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

Methodology

In our investigations, the interactive molecular mechanics program PC MODEL, version 4.0 [13],...
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 rota-
mers 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 con-
stants 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 con-
stants. 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].

\[
J = Ar + B \cos \omega + E , \quad (4)
\]

\[
J = Ar + B \cos \omega + C \sum \Delta E_i^n + E , \quad (5)
\]

\[
J = Ar + B \cos \omega + C \sum \Delta E_i^n + Dn + E , \quad (6)
\]

\[
J = Ar + B \cos \omega + C \sum \Delta E_i^n + Dn . \quad (7)
\]

In the equations above, \(r\) and \(\omega\) represent the
distance and the dihedral angle, respectively, between
coupling protons, \(\Sigma \Delta E_i^n\) stands for Mullaly's sum of
electronegativities [17], whereas \(n\) represents the num-
ber of substituents that are bonded to \(\alpha\)-C atoms,
other than hydrogen. Here, as before, \(A – E\) stand for
adjustable parameters. These constants were deter-
mined 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 sug-
gested, (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 neces-
sary.

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 interpola-
tion. 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. Accord-
ing 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>
<thead>
<tr>
<th>Eq.</th>
<th>(A)</th>
<th>(B)</th>
<th>(C)</th>
<th>(D)</th>
<th>(E)</th>
<th>RMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>(-2.4673)</td>
<td>(6.0845)</td>
<td>(14.7046)</td>
<td>(-5.4947)</td>
<td>(7.3613)</td>
<td>0.758</td>
</tr>
<tr>
<td>(2)</td>
<td>(9.7991)</td>
<td>(7.1685)</td>
<td>(-13.6713)</td>
<td>(-6.2269)</td>
<td>(0.753)</td>
<td>0.708</td>
</tr>
<tr>
<td>(3)</td>
<td>(4.7334)</td>
<td>(9.8426)</td>
<td>(-0.9229)</td>
<td>(-13.4208)</td>
<td>(0.704)</td>
<td>0.722</td>
</tr>
<tr>
<td>(4)</td>
<td>(4.8986)</td>
<td>(9.6926)</td>
<td>(-0.4529)</td>
<td>(-335.9282)</td>
<td>(-343.7747)</td>
<td>0.627</td>
</tr>
<tr>
<td>(5)</td>
<td>(4.7412)</td>
<td>(9.9970)</td>
<td>(-0.4529)</td>
<td>(-12.1534)</td>
<td>(-11.5582)</td>
<td>0.628</td>
</tr>
<tr>
<td>(6)</td>
<td>(4.7412)</td>
<td>(9.9970)</td>
<td>(-0.4529)</td>
<td>(-10.1325)</td>
<td>(-10.1723)</td>
<td>0.627</td>
</tr>
</tbody>
</table>

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.
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 $\alpha$-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.