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THE RELATIONSHIP BETWEEN PROTON–PROTON NMR COUPLING CONSTANTS AND SUBSTITUENT ELECTRONEGATIVITIES—I

AN EMPIRICAL GENERALIZATION OF THE KARPLUS EQUATION†

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Abstract—A new coupling constant–torsion angle relation for the three-bond ^1H–^1H spin spin coupling constant is formulated. The relation includes a correction for the electronegativity of substituents. The correction term is written as a function of the electronegativity, the H–C–C–H torsion angle, and the orientation of each substituent relative to the coupled protons. A dataset consisting of 315 experimental coupling constants was used to derive six empirical parameters by means of an iterative least-squares minimization procedure. The precision of the proposed equation, expressed as the root-mean-square deviation (0.48 Hz), is superior to any hitherto reported. It is shown that separate treatment of CH_2CH_2, CH_2CH and CHCH fragments even improves this precision. An application in the field of monosubstituted cyclohexanes is given.

One of the prime reasons for the success of NMR-spectroscopy as a structural tool has been the widespread application of vicinal proton-proton coupling constants to stereochemistry. However, the well-known Karplus-equation,[1] which relates the vicinal coupling constants to the torsion angle between the coupling protons and originally derived from Valence Bond calculations for the unperturbed ethane molecule, was shown[2] to depend also on a variety of other molecular parameters, such as substitution, bond-angles, bond-lengths etc. Changes with bond-lengths and bond-angles however appeared to be minor,[2] just as the effect of molecular vibrations is small[3] compared to the effect of electronegativity and relative position of substituents attached to the H–C C–H fragment. In fact, ample experimental proof is now available to demonstrate that the latter effect is the second important factor, next to the dihedral angle dependence, in determining the magnitude of vicinal coupling constants.[4]

In order to account for this influence of substituents, several approximating approaches have been advocated in the past. The most disseminated method is the parametrization of the Karplus-equation to the H–C–C–H fragment to be studied, thus yielding Karplus-type relations for highly specific compounds such as nucleotides,[5,6] peptides[7] and so forth. The drawback of this method is, among others *vide infra*, the need of more or less rigid model compounds for the H–C–C–H fragment under study, in order to provide for the necessary Karplus parameters.

A second approach is the "generalization" of the Karplus-relation by superimposing upon the angle dependency of the vicinal coupling constant a linear dependency on the electronegativity of the substituents attached to the H–C–C–H fragment under study. This method is based upon the well-documented linear decrease of the averaged coupling constants in substituted ethanes. A general relation for this type of molecules was formulated by Abraham and Pachler:[8]

$$^3J_{av} = 8.0 - 1.0 \times \Sigma\Delta\chi_i \qquad (1)$$

where $\Sigma\Delta\chi_i$ is the sum of the electronegativity differences between the substituents attached to the ethane fragment and hydrogen. Durette and Horton[9] e.g. combined this dependency on electronegative substituents with the Karplus-equation and parametrized the formula thus found by means of coupling constants found in carbohydrate compounds, yielding:

$$^3J_{HH} = (7.8 - 1.0\cos\phi + 5.6\cos2\phi)(1 - 0.1\Sigma\Delta\chi_i) \qquad (2)$$

in which ϕ is the proton-proton torsion angle.

The third method to be mentioned is the elimination of electronegative substituent effects by using ratio methods, such as the R-value method[10,11] or the "Dihedral Angle Estimation by the Ratio Method (DAERM)".[12] The application of these methods, however, is restricted to alicyclic compounds.

A common feature of the forementioned methods is the implicit or explicit decrease of the coupling constant with increasing electronegativity of substituents. However, it is now well established that certain orientations of electronegative substituents relative to the coupled protons cause an increase of the coupling constant with increasing electronegativity.[13,14] The latter phenomenon was extensively studied by means of theoretical MO calculations.[15-17] In a study onto the influence of electronegative substituents upon the vicinal coupling constants in ethylderivatives, Pachler used a modification of the LCAO-MO theory of coupling constants formulated by Pople and Santry.[18] It was found that the calculated coupling constants for all compounds investigated were well represented by a trigonometric function of the form:

$$^3J = A + B\cos\phi + C\cos2\phi + D\sin\phi + E\sin2\phi \qquad (3)$$

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† This paper is dedicated to the 70th birthday of Prof. Dr. E. Havinga.

in which the sine terms were added to the original Karplus-equation in order to account for the asymmetry of the calculated coupling constant curves with respect to $\phi = 0°$ upon substitution of a hydrogen atom. Pachler[16, 19] correlated the constants in eqn (3) to the Huggins electronegativity[20] of the substituents and empirically parametrized this relation by means of a number of experimental coupling constants. In this paper we intend to put formula (3), and some closely related ones, empirically to the test in order to find a generalized Karplus-type relation for vicinal proton–proton coupling constants and, moreover, to find its limitation in application.

METHODS

In order to determine empirically the parameters in a Karplus-type relation a large dataset consisting of vicinal proton–proton coupling constants with corresponding proton–proton torsion angles is called for. Therefore, a large number of experimental values of vicinal proton couplings were selected from the literature. Care has been taken to choose only those coupling constants that were obtained from a proper analysis of the ^{1}H-NMR spectrum. The dataset was restricted to conformationally rigid structures, largely 6-membered rings with holding groups, that can be assumed to exist in a single conformation. Norbornane- and norbornene-derivatives were excluded from the dataset for two reasons:

(1) The geometry of this type of molecules is less well known. It was shown from X-ray diffraction and Valence Force Field calculations that on substitution considerable twist (up to 14°) in the norbornane skeleton may occur.[21]

(2) Marshall *et al.*[22] demonstrated that the non-equivalence of exo–exo and endo–endo vicinal H–H coupling constants in norbornane is due to the interaction of the C7 methylene bridge with the bonds of the C2–C3 fragment. The existence of such an extra coupling pathway in this type of molecules clearly prohibits the use of these coupling constants in a parametrization of a Karplus-type relation.

Next to the coupling constant, the appropriate proton–proton torsion angle is a prerequisite molecular parameter. Several methods that have been used in the past to determine this parameter were discarded on various grounds:

(a) All approaches using NMR, such as the R-value method etc., were relinquished in order to preclude a circular reasoning, for all these methods are to some extent based upon Karplus-relations.

(b) The classical approach, estimating the proton–proton torsion angles from Dreiding or other models, was discarded for its obvious crudeness, yielding large errors (up to 10°) in the extracted torsion angles.

(c) The use of X-ray crystallographic data was taken into consideration but abandoned for the following reasons:

(1) Not every compound for which accurate coupling constants are available has been studied by X-ray diffraction techniques. In this way a severe restriction would be imposed upon the dataset.

(2) Individual molecules may show to some extent a typical behaviour due to special crystal packing effects and/or H-bonding. From a statistical analysis of about 50 crystallographic studies of the α-D-glucopyranose moiety e.g. it was found[23] that an individual endocyclic pyranose torsion angle may vary over more than ten degrees due to these effects. Of course, a solution for this problem may be found in statistical procedures (i.e. averaging of similar structures), but this would restrict the dataset even further (see point 1), probably beyond practicability.

(3) Not all X-ray crystallographic studies comprise the determination of the H coordinates, but in those which do the error in the H atom positions is fairly large (see e.g. Ref. 5). Little resource can be had to neutron diffraction studies (which are able to give accurate H atomic coordinates) due to the paucity (relative to X-ray data) of this kind of studies.

In order to circumvent all forementioned difficulties we finally settled upon the determination of the necessary torsion angles via General Valence Force Field methods, using the energy minimization procedure incorporated in the computer program UTAH5.[24] The force field currently employed was taken from Allinger[25] (MM1). We found[23] that this field reproduces the heavy atom skeleton of carbohydrates and other heterocyclic compounds in a satisfactory way. Comparison of the calculated hydrogen positions with the experimental proton positions from the (scarce) neutron diffraction data however showed substantial differences. This situation was remedied[23] by fixing the protons onto the calculated heavy atom skeleton, using the following guide-lines:

(a) methylene groups retain C_{2v}-symmetry (H–C–H bond angle = 107.6°),

(b) methine protons have equal bond-angles to the heavy atoms.

The overall agreement of calculated geometries with neutron diffraction data was satisfactory.†

In this way our dataset, consisting of 315 coupling constants from 109 compounds with the proton–proton torsion angles to match, was created. A few remarks towards the design of this dataset is now in order. Inherent to our choice of using conformationally "rigid" structures, i.e. principally six-membered rings, the dataset is necessarily biased towards torsion angles about *ca* 60° and 180°. Owing to the same limits, most coupling constants occur in the ranges 0–5.5 Hz and 7.5–13 Hz. Another partiality is found in the nature of the primary substituents attached to the H–C–C–H fragments: the most frequently occurring ones are C and O; with smaller numbers of N, S, Halogens, Si and Se. Be this as it may, in our opinion the dataset is the best obtainable at this moment. However, it is clear that the use of this dataset implies a thorough recheck afterwards, in which special attention has to be given to those couplings which lie outside the forementioned biases present in this dataset. It is required that the latter couplings, statistically speaking, give the same result as the complete dataset does.

Several Karplus-type relations were tested (*vide infra*) using the dataset as an inputfile. Optimum values

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†It is difficult to judge the accuracy of our calculated geometries. The torsion angles involving non-hydrogen atoms appear to be correct within one to two degrees;[23] the calculated torsions involving hydrogens cannot be subjected to a statistical comparison with experiment but we are convinced that the error in the latter torsions is less than three degrees.

for the parameters in such a Karplus-type relation were obtained via a standard Newton–Raphson iterative minimization procedure.[26]

RESULTS

Pachler[16] calculated the angular dependence of the coupling constants in a number of monosubstituted ethanes by means of the Pople–Santry MO theory of coupling constants.[18] It was found that the resulting coupling constant curves could be adequately described by a trigonometric function as in (3). As a matter of fact, this equation corresponds to a truncated Fourier series comprising the fundamental frequency and one overtone. The calculated constants in eqn (3) were assumed to be linearly related to the electronegativity of the substituent. In a subsequent paper[19] Pachler introduced a closely related formula:

$$\begin{aligned}{}^{3}J_{HH} = {} & (A - a\Sigma\Delta\chi_i) + \\ & (B - b\Sigma\Delta\chi_i)\cos(\phi - \varepsilon\Sigma'\Delta\chi_i) + \\ & (C - c\Sigma\Delta\chi_i)\cos 2(\phi - \varepsilon\Sigma'\Delta\chi_i) \end{aligned} \qquad (4)$$

In this relation ϕ is the proton–proton torsion angle, $\Sigma\Delta\chi_i$ is the sum of the differences in electronegativity between the substituents of the H–C–C–H fragment under study and hydrogen, and $\Sigma'\Delta\chi_i$ is the "signed" sum of these differences. The latter factor is important in that it introduces the asymmetry in the coupling constant curve with respect to $\phi = 0°$ in asymmetrically substituted H–C–C–H fragments. For this purpose a sign (plus or minus) is allotted to a substituent in accordance with its orientation with respect to the coupled protons. Using the notation and sign-convention of Pachler[19] we utilized our coupling constant dataset to determine the optimum parameters for eqn (4). The results are given in the last entry of Table 1. For purposes of comparison we also calculated optimized parameters for the standard Karplus-equation:

$${}^{3}J_{HH} = A\cos^{2}\phi + B\cos\phi + C \qquad (5)$$

without any electronegativity correction (Table 1, first column) and also determined the statistics for our dataset using the original parameters published by Pachler[19] (Table 1, column 2). Table 1 clearly shows a progressive improvement of the fit of the data upon the parametrization used. However, even with the seven optimized parameters a root-mean-square (rms) deviation of 0.53 Hz remains. Moreover several of the optimized parameters showed a strong correlation. In order to improve the result we wished to devise an alternative relation and explored the following strategy:

As was noted in the Introduction, vicinal proton–proton coupling constants depend on a number of factors. In principle it should be possible to write this dependency in a Taylor-like expansion, i.e. a formalism like:

$$\begin{aligned}{}^{3}J_{HH} = {} & f(\phi) + \Sigma f'(\phi, \Delta\chi_i) + \Sigma\Sigma f''(\phi, \Delta\chi_i, \Delta\chi_j) \\ & + f'''(\text{other}) \end{aligned} \qquad (6)$$

The first term describes the dependency of the coupling constant on the proton–proton torsion angle ϕ. The second term should account for the dependency on an electronegative substituent and (as the orientation of the substituent relative to the coupled protons plays an important role in this effect) this function will also be dependent on ϕ. Of course this term should be applied to all non-hydrogen substituents, which is symbolized by the summation sign. The use of an electronegativity scale relative to hydrogen (i.e. $\Delta\chi_i = \chi_{subst} - \chi_H$) eliminates the application of this term for each hydrogen substituent. The third term in (6) may be interpreted as the influence of the electronegative substituents upon each other, i.e. a correction term for the implicitly assumed additivity of the effect of electronegative substituents in the second term. The MO-calculations performed by Pachler[19] point to the necessity of this term as the calculated 1,1-difluoroethane couplings (having one "positive" and

Table 1. Empirical parameters and statistics for eqns (4) and (5)

Parameter	Karplus equation(5) (this work)	Pachler equation(4) (see ref.19)	Pachler equation(4) (this work)
A	7.76	7.49	7.19
a	--	0.76	0.69
B	-1.10	-1.62	-1.65
b	--	0.05	-0.24
C	1.40	4.84	5.12
c	--	0.30	0.27
ε	--	5.0°	6.3°
Statistics[†]			
rms-deviation	1.201	0.751	0.526
slope	0.902	1.050	0.982
intercept	0.607	-0.389	0.104
correlation coefficient	0.947	0.985	0.990

[†] Statistics for a least-squares straight line regression analysis of calculated *vs.* experimental coupling constants.

one "negative" substituent) deviate from the corresponding calculated 1,2-difluoroethane couplings, thus suggesting a difference between vicinal and geminal substitution. The last term in eqn (6) ought to describe all other molecular parameters such as deviations in bond-lengths, bond-angles etc.

Following this line of thought the classical Karplus relation was taken to describe the angular dependence of the coupling constant, i.e. the first term in eqn (6). In order to account for the influence of electronegative substituents (second function in eqn (6)), we started from the results of the MO-calculations of coupling constants in monosubstituted ethanes performed by Pachler.[16] The correction term sought should describe the difference curves between the calculated coupling constants in ethane and those in ethylderivatives as a function of ϕ and $\Delta\chi$. Calculated difference curves for chloro- and fluoroethane vs ethane are shown in Fig. 1. Such curves may be approximated by a $\cos^2$-function which is phase-shifted with respect to the Karplus $\cos^2$-function. The magnitude of this phase-shift was assumed to be linearly related to the electronegativity of the substituent. Besides the parameter describing the phase-shift, two more are required: one parameter to

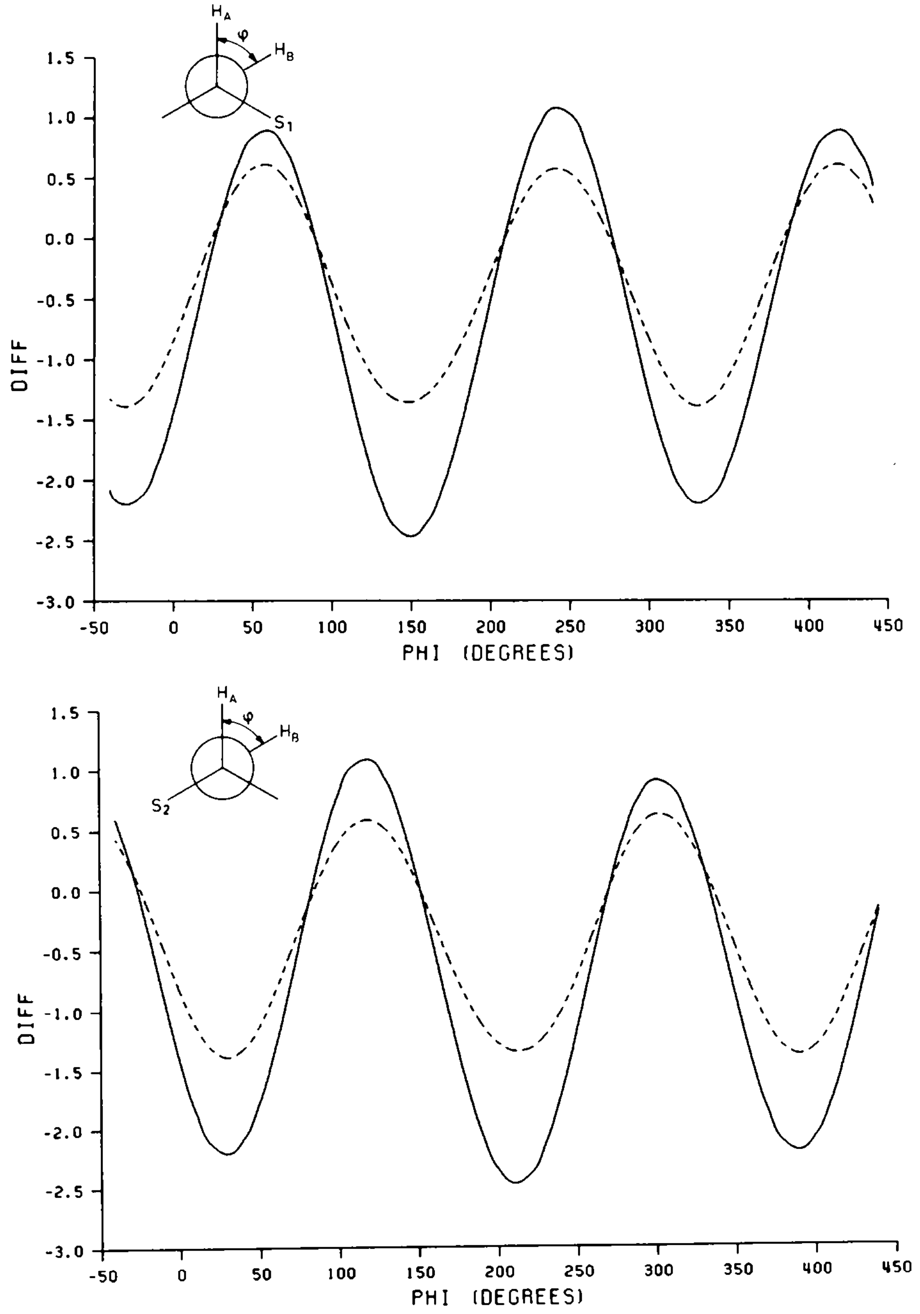

Fig. 1. The calculated difference $\Delta J = J_{CH_3CH_2X} - J_{CH_3CH_3}$ (solid line X = F, dashed line X = Cl) for the two orientations of X relative to the coupled protons H_A and H_B. The calculations were carried out at intervals of 10 in ϕ_{HH} by means of a modified Extended Hückel method (C. A. G. Haasnoot and C. Altona—to be published).

ascertain the amplitude of the correction term and another to determine the shift along the ordinate axis (defining the zero-points of the function). As the size of the influence of a substituent i is linearly correlated with its electronegativity, the term is multiplied by the difference in electronegativity between the substituent and hydrogen, thus yielding:

$$f(\phi,\Delta\chi_i) = \Delta\chi_i\{P_4 + P_5\cos^2(\xi_i\cdot\phi + P_6\cdot|\Delta\chi_i|)\} \tag{7}$$

Figure 1 shows that a change of the position of a substituent S with respect to its geminal proton (for example from position S_1 to position S_2 with respect to H_A) causes in fact a change of direction of the ϕ_{HH} axis, i.e. $+\phi$ becomes $-\phi$. This change is incorporated into the correction term (7) by means of ξ_i, which stands for +1 or −1 according to the orientation of the substituent (Fig. 2).

The proton–proton torsion angle is defined the usual way, i.e. $-180° < \phi \leqq 180°$ or $0° \leqq \phi < 360°$. Projecting the H_A–C_1–C_2–H_B fragment along the vector C_1C_2 (Fig. 2(b)) we define the orientation of a substituent S on C_1 as being positive when the projected valency angle between H_A and S amounts to approximately +120°, counting clockwise from H_A (S_1 in Fig. 2; analogously S_3 is defined as being positive). The orientation of a substituent is negative when the angle amounts to 240° (S_2 and S_4 in Fig. 2). This definition determines the sign of each substituent independent of the instant value of ϕ.†

Summation of the corrections due to the individual substituents calculated by means of eqn (7) for every substituent of the H–C–C–H fragment yields the effect of the electronegative substituents upon the coupling constant under study. Neglecting for the moment the remaining terms in eqn (6), i.e assuming a strict additivity of the influence of substituents upon the coupling constant, we then may write:

$$^3J_{HH} = P_1\cos^2\phi + P_2\cos\phi + P_3 + \Sigma\Delta\chi_i\{P_4 + P_5\cos^2(\xi_i\cdot\phi + P_6\cdot|\Delta\chi_i|)\}. \tag{8}$$

The parameters P_1–P_6 in this equation were empirically determined with the aid of the complete coupling constant dataset (315 couplings). It turned out, however, that a strong correlation exists between P_1 and the torsion angle-independent parameter P_3. In view of the apparent impossibility to obtain unambiguous values for both parameters simultaneously, P_3 was arbitrarily set equal to zero. The results of the least-squares treatment are summarized in the first column of Table 2, (parameter set A). Comparison of the statistics of this minimization with that of the Pachler-equation (4) (last entry Table 1) shows that the rms-deviation of the calculated coupling constants with respect to the experimental coupling constants drops to 0.511 Hz, in spite of the fact that only 5 parameters are used in eqn (8) against 7 parameters in eqn (4). Furthermore, slope and intercept of the least-squares regression line are considerably improved. We thus conclude that equation (8) reproduces the experimental coupling constants in our dataset significantly better than does eqn (4) and therefore will focus our attention on eqn (8) in the remainder of this paper.‡

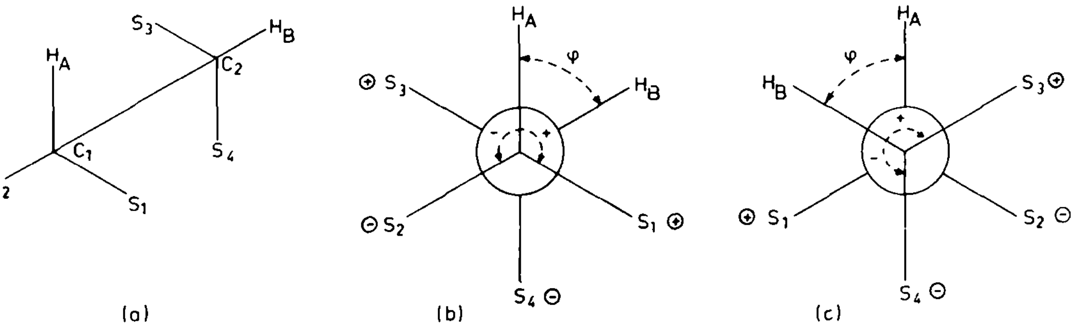

Fig. 2. Definition of "positive" and "negative" substituents (see text).

Up till here we have only taken into account the effect of the primary substituents upon the vicinal coupling constants. Although this effect is by large the most important one, Schrumpf and Klein[27] unambigously demonstrated that β-substitution also influences the vicinal proton–proton coupling. In a series of primary n-pentyl derivatives they found that the observed values of vicinal coupling constants increased with increasing β-substituent electronegativity. Perusal of the relevant literature showed that this trend is also detectable in the older coupling constant data as for instance compiled by Abraham and Pachler.[8] Moreover, preliminary EHT–MO calculations of vicinal coupling constants (C. A. G. Haasnoot, F. A. A. M. de Leeuw and C.

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†The term "positive" or "negative" substituent is not free from ambiguity. In the remainder of this paper we will refer to a "positive" substituent in the sense defined in Fig. 2 (S_1 and S_3) and similarly to a "negative" substituent (S_2 and S_4), hence the sign referred to is solely determined by the orientation of the substituent. It should be stressed that the actual value of $\Delta\chi_i$ (including sign) is given by $\Delta\chi_i = \chi_{subst} - \chi_H$. The use of the absolute value of $\Delta\chi_i$ in the cosine square term of eqn (7) ensures symmetry of the correction term about $\Delta\chi_i = 0$.

Note that our sign-definition of substituents differs from the one proposed by Pachler.[19] as the latter has two serious drawbacks:

(a) The Pachler definition of the proton–proton torsion angle ($0° \leqq \phi \leqq 180°$, always taken positive independent of its sense of rotation) is at variance with the IUPAC rules.

(b) The signs of the substituents are undefined for proton–proton torsion angles of 0° and 180°

‡It should be noted that an rms-deviation in itself gives no indication about the nature of the differences between calculated and experimental couplings. In order to check for any effects of a systematic nature chi-square tests[26] on the distribution of these differences (significance level 0.05) were performed on all results presented in Table 2. Gaussian distributions about zero were confirmed, i.e. the differences are of a random nature.

Table 2. Empirical parameters and statistics for eqn (8)

Set Parameter	A equation(8)	B equation(8) including β-effect	C equation(8) 2 substituents	D equation(8) 3 substituents	E equation(8) 4 substituents
P_1	13.86	13.70	13.89	13.22	13.24
P_2	-0.81	-0.73	-0.98	-0.99	-0.91
P_3	0^*	0^*	0^*	0^*	0^*
P_4	0.56	0.56	1.02	0.87	0.53
P_5	-2.32	-2.47	-3.40	-2.46	-2.41
P_6	17.9°	16.9°	14.9°	19.9°	15.5°
P_7	--	0.14	0.24	0	0.19
Statistics[†]					
rms-deviation	0.511	0.479	0.367	0.485	0.359
slope	0.997	1.001	1.000	0.996	0.991
intercept	0.023	-0.053	-0.029	-0.007	0.049
correlation coefficient	0.991	0.992	0.995	0.993	0.995
# couplings	315	315	45	100	170

[*] Constrained value, see text.

[†] Statistics for a least-squares straight line regression analysis of calculated *vs.* experimental coupling constants.

Altona—unpublished results) point into the same direction. The latter calculations showed that the influence of β-substituents upon vicinal couplings is, apart from electronegativity, also dependent on the orientation of this β-substituent with respect to the coupled protons. However, further work is necessary to elucidate this orientation dependency, therefore we restrict ourselves for the time being to take into account only the direct electronegativity effect. As electronegative β-substituents demonstrate an opposite behaviour compared to that of α-substituents, we may consider the influence of a β-substituent as moderating the electronegativity effect of an α-substituent. This may be expressed in a formalism in which the electronegativity of an α-substituent is defined using eqn (9):

$$\Delta\chi^{\text{group}} = \Delta\chi^{\alpha\text{-substituent}} - P_7 \cdot \Sigma\Delta\chi_i^{\beta\text{-substituent}} \qquad (9)$$

where the summation is over all the substituents attached to the α-substituent. Using this eqn (9) to calculate $\Delta\chi_i$ in eqn (8) for every substituent of a H–C–C–H fragment, we are able to introduce a first order correction for the influence of β-substituents upon vicinal coupling constants. The optimum values of P_1–P_7 for our coupling constant dataset were determined using an iterative least-squares procedure, the results of which are tabulated in the second entry of Table 2, (parameter set B). In Fig. 3 the experimental couplings are compared with the values calculated with eqn (8) in combination with eqn (9) using the forementioned parameters. It is encouraging to note that even our crude description of this "β-effect" is reflected in a significant lowering of the overall rms-deviation (from 0.511 Hz to 0.479 Hz).

DISCUSSION

In the derivation of eqns (8) and (9) several simplifying assumptions were made. Most important, it was explicitly stated that a strict additivity of the influence of substituents upon the coupling constants is assumed, i.e. the third and fourth term in eqn (6) are neglected. However, as this simplification does not seem to be supported by the MO-calculation data of Pachler[19] and may be contraindicated by experiment,[14b] we will now explore the significance of this presumption.

In the preceding section we showed that eqn (8) used in conjunction with eqn (9) satisfactorily describes the experimental coupling constants of our dataset. Therefore, one may ask whether or not the forementioned neglected correction terms in eqn (6) are very small or are to some extent correlated with the first two terms in eqn (6) and will thus be more or less assimilated in the parameters determining the first two terms.

In order to investigate this query we have split our dataset into three parts: H–C–C–H fragments having respectively two, three and four non-hydrogen substituents. For each of the three parts an optimized set of parameters P_1–P_7 for eqns (8) and (9) was determined. The results of these minimization procedures are tabulated in respectively the third, fourth and fifth entry of Table 2 (parameter sets C, D and E).

In case that the neglected terms in eqn (6) really are dispensable, the parameters P_1–P_7 would be independent of the dataset used for gauging. However, the three sets of parameters P_1–P_7 (Table 2) differ significantly (differences greater than the 90% confidence limit intervals) and show definite trends in going from two to four substituents. These findings

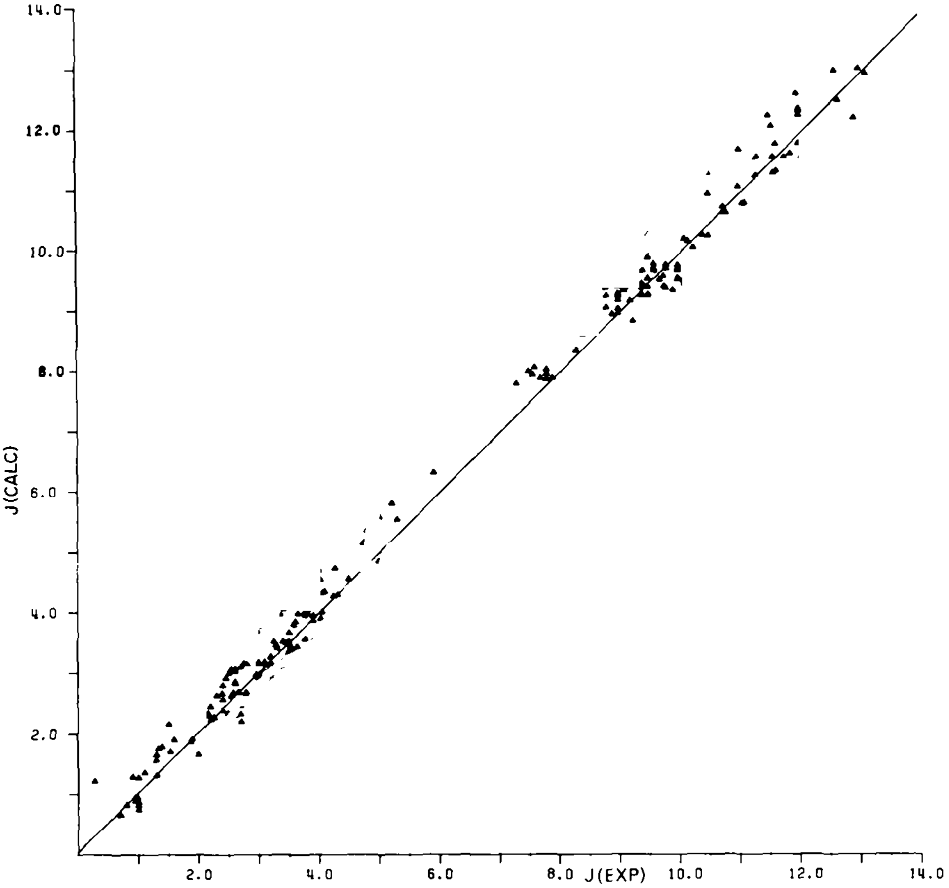

Fig. 3. Calculated *vs* observed vicinal proton proton coupling constants.

imply that the omitted terms in eqn (6) indeed are not negligible; but from the agreement between the experimental and calculated coupling constants it is concluded that the effect of the omission of these terms are small with respect to the effect of the second term (the first order electronegativity correction term) in eqn (6). This conclusion may be illustrated by comparing the rms-deviation of the minimization of the parameters for a standard Karplus-equation (Table 1, column 1) and the rms-deviation of the corresponding minimization for eqn (8) (Table 2, set B): the rms-deviation drops from about 1.2 Hz to about 0.5 Hz. As we estimate the experimental errors in the coupling constants of our dataset to account for a rms-deviation of about 0.2–0.3 Hz,† the neglected terms in eqn (6) may be held responsible for the remaining 0.2–0.3 Hz rms-deviation.‡

Inspection of the relevant data in Table 2 (parameter sets C, D and E) discloses that division of the dataset into three parts and subsequent independent optimization of the parameters yields a better agreement between the calculated and experimental coupling constants compared to the corresponding minimization using the complete dataset (Table 2, set B). Presumably, this observation is another direct consequence of the neglect in eqn (8) of the influence of substituents upon each other. We postulate that changes in the parameters P_1–P_7 may partly compensate for this omission when the substitution patterns (i.e. 2, 3 or 4 non-hydrogen substituents) of the couplings under study are alike. When the complete dataset is used in the determination of the parameters P_1–P_7, some weighted average of the different effects due to these substitution patterns will be calculated. It is seen from the rms-deviations in column 3, 4 and 5 of Table 2, that the coupling constants in H–C–C–H fragments having two or four non-hydrogen substituents are significantly better reproduced by eqns (8) and (9) than the couplings in fragments bearing three substituents. This may point to the effect of some internal cancellation in the neglected interaction of substituents, which will be absent in the coupling constants of tri-substituted fragments, as they always have 2 "positive" (or "negative") substituents versus 1 "negative" (or "positive") substituent. It is clear that these flaws should be removed by adding one or more extra correction terms to eqn (8). However, at this stage no formalism for such terms is envisaged.

Some observed phenomena are clearly not reproduced by eqn (8). The calculation of the averaged

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†We deliberately do not take into account the errors in the H–H torsion angles of our dataset as they will probably be of a systematic nature. For the sake of completeness however: a rough estimate of the effect of a one degree random error in the calculated H–H torsion angles yields an rms-error of about 0.1 Hz.

‡We are fully aware of the fact that this interpretation of rms-deviations is not based upon statistical grounds whatsoever. A full statistical treatment however lies outside the scope of this paper as it is only intended to give the reader an impression of the relative importance of the terms in eqn (6).

coupling constant in ethane for instance yields a value (*ca* 7 Hz) which is too low compared to the experimental value (*ca* 8 Hz). A similar trend is found for the averaged coupling constants in 1,1-disubstituted ethanes (using the parameters determined for 2 substituents).

It could be argued that the latter failure is to be ascribed to the fact that the parameters used for these calculations were determined for fragments having a 1,2-disubstitution pattern. The compensation for the neglected influences of substituents upon each other in these parameters used in eqn (8) may well be at fault for 1,1-disubstitution patterns. However, this may not be the only reason. In an attempt to reproduce the regression lines of the coupling constant dependencies upon electronegativity in 1,2-disubstituted ethanes as determined by Abraham and Gatti[14a] with the help of eqn (8), we found that the trends in these couplings could be engendered, but systematic differences occurred. The assumption of classical *gauche* (60°) and *trans* (180°) conformers in the 1,2-disubstituted ethanes, as was made by Abraham and Gatti,[14a] may in part be held responsible for these deviations, but that does not alter the fact that systematic divergencies remain. Interestingly, Phillips and Wray,[14b] in an alternative analysis of Abraham and Gatti's data,[14a] have indicated that the magnitude of the variation in *gauche* couplings with substituent change depends upon the other substituent present in the ethane fragment. For these reasons we conclude that eqn (8) should not be applied to 1,2-disubstituted ethanes.

Our present researches (unpublished) into the applicability of parameter sets C, D and E (Table 2) in solving various stereochemical problems tend to strengthen and extend this conclusion. Parameter sets D and E appear to yield quite reliable results in practice (keeping in mind the respective rms-deviations). However, parameter set C (two substituents) yields calculated values of coupling constants which are in some cases (including ring compounds) more at variance with experimental results than can be expected on the basis of the small rms value associated with this set. We note that coupling constants in CH_2CH_2-fragments, incorporated in an alicyclic ring, can be predicted with fair accuracy when parameter set B is used.

For the time being we propose to use eqns (8) and (9) with the appropriate parameter sets D and E for the calculation of $^3J_{HH}$ in H–C–C–H fragments that carry three or four non-hydrogen substituents, respectively. For 1,2-disubstituted alicyclic fragments we recommend the (cautious) use of parameter set B. It appears that further improvements on the present formalism will require a deeper insight into the effect of non-additivity of substituent electronegativities (third term in eqn (6)).

We propose to deal with specific applications of eqn (8) to stereochemical problems in following papers (proline ring, ribose ring in nucleosides and nucleotides, R-value). Presently we wish to illustrate the potential usefulness of our generalized Karplus eqn (8) by applying it to the case of monosubstituted cyclohexanes.

Before we do so, we introduce a shorthand notation to indicate the "positive" or "negative" orientation of substituents with respect to the two coupled protons in order to facilitate the discussion given below. From Fig. 2 it is seen that C_1 always carries a (+) and a (−) substituent, the same rule applies to C_2 (including H atoms as substituents). These substituents are written in the sequential order: $S_1S_2S_3S_4(\phi)$. In this notation ϕ denotes the torsion angle between the coupled protons. The sign sequence thus defined is (+, −, +, −). A slash may be used to separate a pair of geminal substituents from its neighbour pair, thus: S_1S_2/S_3S_4. This convention is exemplified by the case of equatorial and axial monosubstituted cyclohexanes (Fig. 4). Assuming in a first approximation a flattened cyclohexane chair (endocyclic torsion angle 56°) and an approximately trigonal projection symmetry (projected† H–C–H angle 118°) about each carbon–carbon bond one obtains:

Equatorial conformer

(1) $J_{ac} = J_{12} = J_{CX/HC(304°)}$ or its equivalent $J_{ac} = J_{12'} = J_{XC/CH(56°)}$

(2) $J_{aa} = J_{13} = J_{CX/CH(186°)}$ or its equivalent $J_{aa} = J_{13'} = J_{XC/HC(174°)}$

Axial conformer

(1) $J_{ea} = J_{12} = J_{CX/HC(56°)}$ or its equivalent $J_{ea} = J_{12'} = J_{XC/CH(304°)}$

(2) $J_{ee} = J_{13} = J_{CX/CH(298°)}$ or its equivalent $J_{ee} = J_{13'} = J_{XC/HC(62°)}$.

Of course, ring carbons are included as "substituents" on the $CHCH_2$ fragment in question. Obviously, ring inversion ($J_{ac} \rightleftarrows J_{ca}$, $J_{aa} \rightleftarrows J_{ee}$) does not change the sequence of substituents for a given pair of vicinal protons. However, J_{ac}(304°) reverses to J_{ea}(56°) and this reversal leads to an entirely different behaviour of the coupling constant with respect to substituent X. In accordance with Booth's rule,[4] J_{ea} decreases with increasing electronegativity of X, one of the coupling protons being antiperiplanar to the C–X bond. However, J_{ac} and J_{ee} are predicted to increase with increasing electronegativity of X. This situation should occur when X is a (+) substituent with ϕ_{HH} about 60° or when X is a (−) substituent with ϕ_{HH} about 300°. In practice, each J_{ae} and J_{ee} (in a six-membered ring) where one or more electronegative exocyclic *gauche* substituents are present should experience this positive effect: We propose to call this phenomenon the positive *gauche* effect on *gauche* coupling constants. It occurs twice for J_{12} in 1,2-diaxially substituted cyclohexanes, in which compounds the effect was first observed,[28] but not interpreted along these lines. A recent study of a series of monosubstituted cyclohexanes by Höfner *et al.*[29] allows us to compare some accurate experimental couplings with the ones calculated by means of eqns (8)

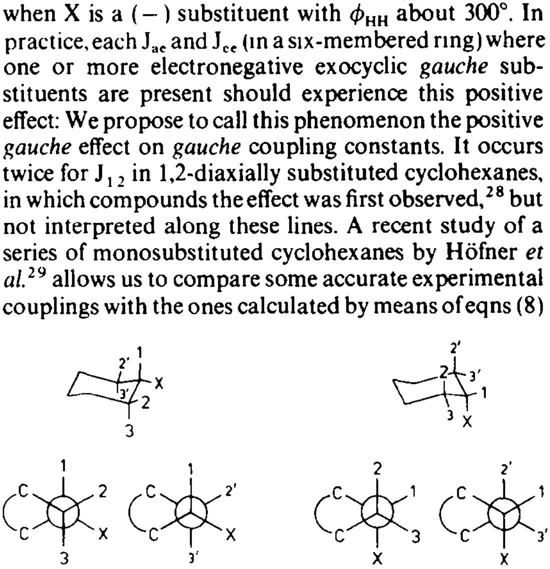

Fig. 4. Conformations of monosubstituted cyclohexane and labelling of the protons.

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†The H–C–H valency angle is well known to be 1–2° smaller than the tetrahedral value.

Table 2. Experimental[29] and calculated vicinal coupling constants (Hz) of some monosubstituted cyclohexanes

			Equatorial X						Axial X					
	$\Delta\chi_{subst}^{a}$		$J_{XC/CH(56^\circ)}$			$J_{XC/HC(174^\circ)}$			$J_{XC/CH(304^\circ)}$			$J_{XC/HC(62^\circ)}$		
X	set B	set C/D	J_{calc}^{b}	J_{calc}^{c}	J_{obs}	J_{calc}^{b}	J_{calc}^{c}	J_{obs}	J_{calc}^{b}	J_{calc}^{c}	J_{obs}	J_{calc}^{b}	J_{calc}^{c}	J_{obs}
H	0	0	3.72	3.76	3.61	13.03	13.33	12.85	3.72	3.76	3.61	2.54	2.62	2.92
CN	0.28	0.43	3.71	3.80	3.53	12.50	12.27	12.66	3.61	3.55	4.27	2.58	2.70	2.69
Br	0.75	0.75	3.90	4.10	4.05	11.63	11.75	12.21	3.16	3.25	3.03	2.83	3.02	3.04
Cl	0.95	0.95	4.03	4.31	4.08	11.29	11.51	11.88	2.88	2.99	2.97	2.97	3.23	3.03
OCD_3	1.24	1.30	4.26	4.71	4.05	10.86	11.21	11.11	2.36	2.39	2.48	3.19	3.59	3.29

[a] $\Delta\chi_{C}$(ring): set B=0.344, set C=0.304, set D=0.400; calculated from equation (9) and the P_7-values in Table II.

[b] Calculated using parameter set B, Table II.

[c] Calculated using parameter set C for cyclohexane (X=H) and set D for the remaining compounds, see Table II.

and (9), using various parameter sets of Table 2. The results are shown in Table 3.

The calculations appear to be quite satisfactory. Not only are the experimental trends well reproduced but also most of the differences between observed and calculated values appear within one standard deviation from the latter (*ca* 0.5 Hz). The nitrile behaves slightly out of line. One would expect a negligible difference to occur between J_{ae} and J_{ea} for X = CN due to its low $\Delta\chi_i$ value, but the experimental results indicate that $J_{ea} - J_{ae} = 0.74$ Hz, the calculated difference amounts from −0.10 up to −0.25 Hz. This surprising behaviour remains unexplained for the time being.

The calculated values for J_{aa} in chloro- and bromocyclohexane turn out to be on the low side. This situation cannot be remedied by assuming a different geometry (within reasonable limits) and may be taken as a warning. We insist that eqn (8) should not be used to extract an "accurate" value of a torsion angle from a single experimental coupling constant. Utmost care should be employed even when two or more couplings define a single torsion angle. However, trends in coupling constants now appear amenable to semi-quantitative analysis on a more accurate basis than was hitherto possible.

CONCLUSION

We have demonstrated that the behaviour of vicinal proton–proton coupling constants is satisfactorily described by the well-known Karplus equation extended with a correction term for electronegative substituents. It is acknowledged that the elegance of the Karplus equation, i.e. the straightforward relation between the proton–proton torsion angle and the coupling constant, has disappeared in the generalized Karplus eqn (8). However, with the rapid advent of powerful programmable pocket calculators this loss cannot be taken as a serious drawback. Using a computer the calculation of a coupling constant, starting from the proton–proton torsion angle and the geometry of the substituents attached to the H–C–C–H fragment follows a straightforward algorithm. The reverse case, i.e. calculating the proton–proton torsion angle starting from the coupling constant, is more difficult. Here we have to take recourse to a trial-and-error method or to a graphical determination. The latter method is facilitated by our computer program CAGPLUS, written in Fortran IV, which calculates and (optionally) plots the coupling constant of a given H–C–C–H fragment as a function of the proton–proton torsion angle.

The advantages of eqn (8) over the standard Karplus relation are obvious: it accounts for the increase of coupling constant values with increasing electronegativity of substituents in particular orientations, and furthermore eqn (8) is, without further parametrization, applicable to a wide variety of compounds.

We are aware of the fact that eqn (8) does not represent a closed analytical solution of the dependency of vicinal proton–proton couplings on all conformational factors involved, but for the moment it appears to be a useful approximation which may well serve existing stereochemical needs.

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