Effect of the Orientation of an α-Substituent on Vicinal ¹³C–¹H Spin–Spin Coupling Constants

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The magnitude of the NMR spin-spin coupling constant, ${}^{3}J(CH)$, between a vicinal ${}^{13}C-1H$ pair depends, *inter alia*, on the value of the torsion angle $\Phi_{CH}({}^{13}C-C-C-H)$ and is influenced by the presence of an electronegative substituent located on the coupling ${}^{13}C$ nucleus. The form and magnitude of the effect of the orientation Ψ_{XC} of such an α -substituent were examined. The coupling constant between C-1 and a hydrogen atom located on C-3 in a series of α -substituted propanes were studied by means of the semi-empirical INDO method. In the calculations both Φ and $\Psi(X-{}^{13}C-C-C)$ were systematically varied in steps of 30°. These calculations reveal that the variation of Ψ at a constant Φ has a pronounced effect on the calculated coupling constant J_{calc} . The magnitude of this effect is shown to be strongly dependent on the electronegativity χ of the α -substituent. Thus, it is shown that J_{calc} depends on Φ and Ψ , in addition to χ . The resulting set of two-dimensional Karplus-type surfaces can be described by an equation that contains only nine adjustable parameters. Measurement of ${}^{3}J(CH)$ in *cis*- and *trans*-2,2,6,6-tetradeuterio-4-*tert*-butylcyclohexanol confirmed some of the theoretical predictions. In the *cis* compound ($\Phi_{CH} = 180^{\circ}$, $\Psi_{OC} = 60^{\circ}$) ${}^{3}J(C-1,H-3eq)$ is 7.1 Hz, whereas in the *trans* compound ($\Phi_{CH} = 180^{\circ}$, $\Psi_{OC} = 180^{\circ}$)

KEY WORDS Theoretical calculation of ¹³C-¹H spin-spin couplings Propanes Calculated ¹³C-¹H coupling constants

INTRODUCTION

Since the discovery by Karplus¹ that the magnitude of the three-bond spin-spin coupling constant, ${}^{3}J(HH)$, in ethane depends on the torsion angle Φ_{HH} between the coupling nuclei, numerous investigations have exploited the so-called Karplus equation [Eqn (1)] or variants thereof.

$${}^{3}J(\mathrm{HH})(\Phi) = A + B\cos(\Phi) + C\cos(2\Phi)$$
(1)

In order to obtain qualitative or quantitative insights into the structure and conformation of molecules in solution, various sets of theoretical and/or experimental parameters for use in Eqn (1) have been proposed. Studies by Glick and Bothner-By² revealed that ${}^{3}J(HH)$ depends not only on Φ , but also on the electronegativity, χ , of substituents attached to the H-C-C-H fragment. They assumed a linear decrease of ${}^{3}J(HH)$ with increasing χ . However, subsequent investigations by Booth³ showed that the magnitude of this decrease depends, in addition, on the orientation of the substituent(s) with respect to the coupling proton pair. Further studies by Abraham and Gatti⁴ indicated that, for certain orientations of the substituents in 1,2-disubstituted ethanes, ${}^{3}J(HH)$ even increases with increasing electronegativity. Subsequent extended Hückel theory MO calculations^{5,6} resulted in a clear prediction of the manner in which ${}^{3}J(HH)$ should depend on Φ and χ and on the orientation of attached substituents in monosubstituted ethanes. With this knowledge, it was

0749-1581/90/010068-07 \$05.00 © 1990 by John Wiley & Sons, Ltd. found possible to extend Eqn (1) with correction terms that account for all of the aforementioned effects.

For example, a Fourier series was proposed^{5,6} [Eqn (2a)], the coefficients of which were assumed to be linearly dependent on the electronegativity difference $\Delta \chi = \chi_{subst} - \chi_{hydrogen}$; the sine terms account for the asymmetry of the Karplus curve introduced by the substituent. A slightly different formalism, requiring fewer adjustable parameters, was introduced by Haasnoot *et al.*⁷ [Eqn (2b)].

$${}^{3}J(\text{HH}) = A + B\cos(\Phi) + C\cos(2\Phi) + D\sin(\Phi) + E\sin(2\Phi)$$
(2a)
$${}^{3}J(\text{HH}) = P_{1}\cos^{2}(\Phi) + P_{2}\cos(\Phi) + P_{3} + \sum_{i} \Delta \chi_{i}[P_{4} + P_{5}\cos^{2}(\xi_{i}\Phi + P_{6}|\Delta \chi_{i}|)]$$
(2b)

The experimental parameterization of Eqn (2b) produced a substantial increase in the accuracy with which geometrical parameters can be deduced from experimental coupling constants (for some recent examples, see Ref. 8).

The successful application of ${}^{3}J(HH)$ in conformational analysis, together with the advance of modern Fourier transform (FT) ${}^{13}C$ NMR spectrometers which made it possible to obtain coupling constants from natural abundance ${}^{13}C$ spectra, led to investigations in the early 1970s into the question of whether or not vicinal ${}^{13}C{}^{-1}H$ couplings, ${}^{3}J(CH)$, could be described by a Karplus-type equation. Theoretical work on substituted propanes^{9,10} predicted that this indeed should be possible. Moreover, calculations indicated that the influence exerted by electronegative substituents on ${}^{3}J(CH)$ is similar in magnitude to the influence on

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Figure 1. Torsion angles and atomic numbering in 1-substituted propanes. The coupling atoms are marked with an asterisk. The J(180,180) situation is shown.

 ${}^{3}J$ (HH), at least when these substituents are placed in the β or γ position with respect to the coupling (α -) ${}^{13}C$ nucleus (Fig. 1). Although a lack of accurate experimental data so far has prevented the development of a generalized Karplus equation such as Eqns (2a) and (2b), some parameterizations of Eqn (1) have appeared in the literature: for peptides see Refs. 11 and 12, for nucleotides see Ref. 13 and for hydrocarbons see Ref. 14.

The analogy between ${}^{3}J(\text{HH})$ and ${}^{3}J(\text{CH})$ may be expected to break down in cases where the coupling ${}^{13}\text{C}$ nucleus itself carries a substituent. Indeed, the fact that the electronegativity of this α -substituent has a profound influence on the magnitude of ${}^{3}J(\text{CH})$ has long been known, both from theoretical calculations¹⁰ and from experimental data.^{15–17} The influence of the relative orientation of such α -substituents is less well established. Wasylishen and Schaefer¹⁰ calculated ${}^{3}J(\text{CH})$ in 1-fluoropropane for two orientations of the fluorine atom, and found that the calculated values for ${}^{3}J(\text{CH})$ are substantially larger when the torsion angle $\Psi(\text{F}-{}^{13}\text{C}-{}^{-}\text{C}-{}^{-}\text{C})$ is set at 180° (antiperiplanar) than when it is set at 60° (gauche) (Fig. 1, X = F).

The magnitude of this effect was predicted to be as large as 3 Hz for the situation where $\Phi(^{13}C-C-C-H)$ equals 180°. Similar calculations were performed by Marshall et al.¹⁸ for ¹³C-¹³C vicinal coupling constants in butan-1-ol, where Φ was varied between 0° and 180° in 30° steps and Ψ was kept fixed at 60°, 120° or 180°. A marked influence of the orientation of the α -OH substituent was predicted, especially when $\Phi_{CC} = 0^{\circ}$ (eclipsed coupling carbon nuclei). In view of the possible importance of ${}^{3}J(CH)$ in stereochemistry and conformational analysis, it is surprising that no experimental verification of the predicted influence of α -substituent orientation appears to have been published. In contrast, some experimental evidence is available for ${}^{3}J(CP)$.¹⁹⁻²¹ Scheme 1 depicts some examples of compounds containing a ³¹P nucleus which couples with a ¹³C nucleus in antiparallel position, i.e. the torsion angle Φ_{CP} is approximately 180°.

Although the torsion angle Φ_{CP} between the coupling nuclei remains close to 180° in all cases, it is seen that when the phosphorus carries an axial substituent



Scheme 1. ${}^{3}J(CP)$ as a function of substituent orientation in some heterocyclic compounds. Z = O, S, NCH₃ (Ref. 20); Z = C=O (Ref. 21).

 ${}^{3}J(CP) \approx 0$, whereas with an equatorial substituent ${}^{3}J(CP)$ is large and ranges from 10.1 to 11.8 Hz, depending on the nature of Z (Scheme 1).

It seems clear that the possible existence of such an orientation effect of α -substituents on ${}^{3}J(CH)$ would place severe limits on the prospects of a general application of a simple Karplus-type ${}^{3}J(CH)$ equation to stereochemical problems. It was therefore thought advisable to gain more insight into the form and magnitude of this effect before an attempt was made to develop ${}^{3}J(CH)$ as a tool in conformational problems. With this purpose in mind, ${}^{3}J(CH)$ was calculated for a series of α -substituted propanes. In these calculations all three factors that are expected to have a substantial influence on ${}^{3}J(CH)$ were varied over their full range. The resulting two-dimensional Karplus-type surfaces were analysed by means of Fourier methods.

In order to put the predictions to the test, two specifically deuteriated cyclohexane derivatives were synthesized and the relevant couplings determined.

METHODS

Calculations of coupling constants are based on the formulation of finite perturbation theory (FPT) in the intermediate neglect of differential overlap (INDO) approximation of self-consistent field (SCF) molecular orbital (MO) theory. The CNINDO program of Dobosh and Ostlund²² was used without further modification.

For the propanes studied, standard bond lengths and bond angles²³ were maintained throughout. Both Φ and Ψ were varied from 0° to 360° in 30° steps, and the influence of substituent electronegativity was investigated by applying all calculations to propane, butane, 1-aminopropane, propan-1-ol and 1-fluoropropane (Fig. 1, X = H, CH₃, NH₂, OH and F, respectively). The electronegativity scale used is that developed by Huggins.²⁴ The $\Delta\chi$ values used in this paper are C = 0.4, N = 0.85, O = 1.3 and F = 1.7. The signs and magnitudes of torsion angles follow the usual IUPAC rules.²⁵

RESULTS AND DISCUSSION

The results for 1-fluoropropane will be discussed first, as the magnitude of the effect of orientation of an α -substituent on ${}^{3}J(CH)$ is expected to be at a maximum in this compound, resulting in a clear picture of the general form which the effect assumes.

Second, the results obtained for the other molecules will be taken into consideration, and a more general relationship between substituent electronegativity and the magnitude of the orientation effect is proposed.

1-Fluoropropane

The value of ${}^{3}J(CH)$ in 1-fluoropropane was calculated in 84 configurations: the torsion angles Φ and Ψ were

Table 1. ³J(CH) (Hz) in 1-fluoropropane as a function of Φ_{CH} and Ψ_{eC}

				Ψ (°)			
Φ (°)	0	30	60	90	120	150	180
0	6.43	6.45	6.93	8.09	8.95	8.61	8.17
30	4.83	4.93	5.39	6.23	6.74	6.31	6.11
60	1.89	1.99	2.21	2.52	2.50	2.18	2.21
90	0.70	0.71	0.70	0.69	0.73	0.80	0.76
120	2.71	2.68	2.75	3.19	4.01	4.30	3.93
150	6.25	6.32	6.7 9	8.03	9.43	9.66	9.21
180	7.97	8.15	8.88	10.41	11.82	11.98	11.74
210	6.25	6.46	7.11	8.33	9.27	9.24	9.21
240	2.71	2.82	3.14	3.67	3.86	3.73	3.93
270	0.70	0.67	0.67	0.70	0.72	0.73	0.76
300	1.89	1.83	1.82	2.11	2.61	2.59	2.21
330	4.83	4.84	5.07	5.96	6.87	6.65	6.11

both varied successively in 30° steps, Φ between 0° and 330° and Ψ between 0° and 180°. Because of symmetry, the following relationship holds for $J(\Phi_{CH}, \Psi_{FC})$: $J(180 - \Phi, 180 - \Psi) = J(180 + \Phi, 180 + \Psi)$. For example, J(60,210) equals J(300,150). It therefore suffices to vary Ψ between 0° and 180°. The 84 coupling constants so obtained are collected in Table 1. In addition to the symmetry mentioned above, the columns Ψ_{xc} = 0° and 180° display additional symmetry around $\Phi_{CH} =$ 180°. Therefore, there are 74 independent values, and our statistical analyses (see below) are based on these independent couplings only. Inspection of the calculated coupling constants reveals the existence of a considerable influence of the orientation of the fluorine substituent (i.e. the value of torsion angle Ψ) on ³J(CH). When the torsion angle Φ_{CH} between the coupling nuclei is kept constant at 180°, the calculated value of ${}^{3}J(CH)$ changes by as much as 4.01 Hz, or more than 50%, when $\Psi_{\rm FC}$ is varied from 0° (J = 7.97 Hz) to 150° (J = 11.98 Hz). Variations of similar relative magnitude are also noted for other values of Φ_{CH} . We conclude that, in cases where the coupling carbon nucleus is not part of a simple methyl group, ${}^{3}J(CH)$ should be



Figure 2. Three-dimensional representation of ${}^{3}J(CH)$ as a function of the two torsion angles $\Phi({}^{13}C-C-C-H)$ and $\Psi(F-{}^{13}C-C-C-H)$ and $\Psi(F-{}^{13}C-C-C-H)$ in 1-fluoropropane.

described as a function of at least two variables, Φ_{CH} and Ψ_{FC} . Such a description necessitates the analysis of a three-dimensional 'Karplus surface', as shown in Fig. 2.

When cross-sections of this surface parallel to the Φ_{CH} axis are taken, one obtains two-dimensional curves that display the familiar form of the Karplus curve (not shown, see Ref. 10). The amplitudes of these curves depend heavily on the value of Ψ_{FC} at which the cross-section is taken. Cross-sections taken parallel to the Ψ_{FC} axis reveal the functional form of the influence exerted by the value of this torsion angle, i.e. the effect that the orientation of the fluorine atom has on the value of J. Two of these cross-sections (at Φ_{CH} 120° and 180°, respectively) are shown in Fig. 3.

A Fourier series appears to be the logical choice for a mathematical description of these curves. A description of the entire surface (Fig. 2) clearly necessitates the introduction of a double Fourier series:

$${}^{3}J(CH) = \sum_{i=0}^{n} \sum_{j=0}^{n} C_{i,j} \cos(i\Phi)\cos(j\Psi)$$

+
$$\sum_{i=1}^{n} \sum_{j=1}^{n} S_{i,j} \sin(i\Phi)\sin(j\Psi)$$

+
$$\sum_{i=0}^{n} \sum_{j=1}^{n} T_{i,j} \cos(i\Phi)\sin(j\Psi)$$

+
$$\sum_{i=1}^{n} \sum_{j=0}^{n} U_{i,j} \sin(i\Phi)\cos(j\Psi)$$
(3)

As the surface to be described is point-symmetrical around $(\Phi, \Psi = (180, 180))$, the coefficients of the terms in Eqn (3) that do not fulfil the symmetry condition are necessarily equal to zero. This applies to both $\sin(i\Phi)\cos(j\Psi)$ and $\cos(i\Phi)\sin(j\Psi)$, because these terms are antisymmetrical with respect to (180,180). Equation (3) can now be simplified to yield

$${}^{3}J(CH) = \sum_{i=0}^{n} \sum_{j=0}^{n} C_{i,j} \cos(i\Phi) \cos(j\Psi) + \sum_{i=1}^{n} \sum_{j=1}^{n} S_{i,j} \sin(i\Phi) \sin(j\Psi)$$
(4)

The coefficients $C_{i,j}$ and $S_{i,j}$ in Eqn (4) were determined by means of linear regression analysis of the coupling constants shown in Table 1. For *n* a value of 3 proved to be sufficient, i.e. it was not found necessary to take into account terms of higher order than 3Φ and 3Ψ . The 25 parameters thus obtained are collected in Table 2. The surface of Fig. 2 can be described by these 25

Table 2. Coefficients $C_{i, j}$ and $S_{i, j}$ (Hz) of Eqn (4) for 1-fluoropropane							
			i				
Parameter i	0	1	2	3			
<i>C</i> 0	4.851	-0.917	-0.178	0.207			
1	-1.237	0.480	-0.060	0.007			
2	4.116	-0.850	-0.183	0.182			
3	-0.011	0.012	0.009	0.006			
<i>S</i> 1		0.008	-0.010	0.021			
2		0.078	0.179	-0.131			
3		-0.002	-0.006	-0.003			



Figure 3. ³*J*(CH) as a function of the torsion angle Ψ_{FC} at a constant Φ_{CH} . (A) Φ_{CH} 120°; (B) Φ_{CH} 180°. The dashed curves show the least-squares approximation by a cosine function to the indicated points.

parameters with a root-mean-square (rms) error of only 0.04 Hz.

Inspection of Table 2 shows that many of the coefficients are small (13 terms display a magnitude of less than 0.1 Hz). Of the remaining 12 coefficients, 6 clearly stand out, and it was thought of interest to investigate the possible further reduction of Eqn (4) to Eqn (5). (A comma signifies the separation of indices over two different angles. This convention was introduced in order to avoid confusion with the notation introduced by Diez and co-workers.^{26,27})

$${}^{3}J(CH)(\Phi,\Psi) = C_{0,0} + C_{1,0}\cos(\Phi) + C_{2,0}\cos(2\Phi) + [C_{0,1} + C_{1,1}\cos(\Phi) + C_{2,1}\cos(2\Phi)]\cos(\Psi)$$
(5)

This equation consists of two parts. The first three terms give the well known Karplus relationship,¹ which can be seen as a mean function of $J(\Phi)$ as the influence of the rotation of the CH₂F group is averaged out. The second set of three terms describe the correction that is necessary as a consequence of the dependence of J on the torsion angle Ψ_{FC} . This again takes the form of a Karplus-type equation, now multiplied by $\cos(\Psi)$. The above formalism corresponds to the description of the Ψ -dependence of ³J(CH) by

$${}^{3}J(CH)(\Psi) = P(\Phi) + P'(\Phi)\cos(\Psi)$$
(6)

Figure 3 indeed shows that the curves can be approximated well with a simple cosine description (dashed curves). In addition, the two main deviations resulting from the approximate nature of Eqns (5) and (6) become clear. First, the dip in the curves at $\Psi = 180^{\circ}$ cannot be reproduced by Eqn (5). This is caused by the neglect of terms of higher order than $\cos(\Psi_{\rm XC})$. Second, the asymmetry with respect to $\Psi = 180^{\circ}$, which appears for values of $\Phi_{\rm CH}$ different from 0° and 180°, is smoothed out owing to the absence of sine terms in Eqns (5) and (6).

Opposed to these more or less crude defects stands the advantage of a compact formulation. When the parameters $C_{0,0}-C_{2,1}$ are determined from the ³J(CH) values in Table 1 with the aid of a least-squares minimization (Table 5), the acceptability of the aforementioned approximations becomes apparent: the rms error amounts to only 0.27 Hz [maximum deviation 0.75 Hz at (0, 180)], i.e. Eqn (5) reproduces the 74 calculated coupling constants, with values ranging from 0.7 to 12.0 Hz, with an accuracy of approximately 0.3 Hz. It can therefore be concluded that the way in which ${}^{3}J(CH)$ depends on the angles Φ_{CH} and Ψ_{XC} can be described with satisfactory accuracy by means of only six parameters.

Other α -substituted propanes

The calculations on the remaining propanes (Fig. 1, X = OH, NH_2 , CH_3 , H) were carried out in an analogous fashion to 1-fluoropropane. As the hydrogen atoms in the OH and NH_2 groups have an additional degree of orientational freedom, the calculations for propan-1-ol and 1-aminopropane were conducted in triplicate, with values for the torsion H—X—C-1—C-2 held at 60°, 180° and 300°, respectively. The calculated couplings were averaged, and these averages are presented here as the set of calculated values for ³J(CH) in propan-1-ol and 1-aminopropane.

In order to give an impression of the way in which the nature of the substituent and its orientation affect ${}^{3}J(CH)$, some of the calculated values are collected in Tables 3 and 4. The values in Table 3 were obtained by keeping Φ_{CH} fixed at 180° while Ψ_{XC} was varied between 0° and 180° in 30° steps. Because of symmetry in the molecules, the following relationship holds for all compounds: ${}^{3}J(180 - \Psi) = {}^{3}J(180 + \Psi)$. Table 4 gives the values of ${}^{3}J(CH)$ in the staggered conformations of the substituted propanes. Again, the value of ${}^{3}J(CH)$ in the

Table	3. ³ J(C	CH)(180	, Ψ) (H	z) for five	e differen	t X subst	ituents
				Ψ _{xc} (°)	•		
х	0	30	60	90	120	150	180
Н	9.60	9.20	8.81	9.20	9.60	9.20	8.81
CH₃	9.19	8.98	8.77	9.11	9.48	9.13	8.77
NH ₂	8.20	8.24	8.53	9.36	10.09	9.90	9.58
он	8.00	8.13	8.68	9.82	10.81	10.72	10.41
F	7.97	8.15	8.88	10.41	11.82	11.98	11.74

Х (60 60)				
	00, 00)	(60, 180)	(60, 300)	(180, 60)	(180, 180)
н	2.01	2.01	2.01	8.81	8.81
CH ₃	1.99	1.97	1.80	8.77	8.77
NH ₂	2.05	2.05	1.76	8.53	9.58
он	2.13	2.14	1.83	8.68	10.41
F	2.21	2.21	1.82	8.88	11.74

Table 4. ³J(CH) (Hz) for the staggered conformations of some 1-X-propanes

other staggered conformations can be obtained by applying the symmetry relationship $J(180 - \Phi, 180 - \Psi) = J(180 + \Phi, 180 + \Psi)$.

Inspection of the values in Table 3 reveals the following facts:

- i. Rotation of the methyl group that contains ${}^{13}C$ in propane is predicted to cause some variation in J (0.8 Hz), but this finding is obviously of little practical interest.
- ii. The influence of α -methyl substitution (butane) on ${}^{3}J(CH)$ is small: the largest difference with respect to propane itself amounts to about 0.4 Hz. More important, at or near conformationally interesting regions ($\Psi_{\rm XC} \pm 60^{\circ}$, 180°), an α -carbon substituent is predicted to behave as if it were a hydrogen. This finding, if substantiated by experiment, will help to simplify future experimental parameterizations of ${}^{3}J(CH)$ Karplus-like equations.
- iii. For $\Psi < 60^{\circ}$, J decreases with increasing electronegativity. At $\Psi = 60^{\circ}$, substituent effects are negligibly small. This means that in sufficiently rigid compounds, where Φ_{CH} and Ψ_{XC} are constrained to assume values of approximately 180° and 60°, respectively, ${}^{3}J(CH)$ is predicted to be virtually independent of substituent electronegativity. When $\Psi > 60^\circ$, ${}^3J(CH)$ increases with increasing electronegativity, χ . This increase in J with increasing χ of the α -substituent is in accordance with experimental data for 1-substituted propanes.^{15,16} In such an experiment, C-1 will couple with the three hydrogen atoms located on C-3 over torsion angles Φ_{CH} of 60°, 180° and 300°. At room temperature both gauche ($\Psi_{\rm XC}$ 60°, 300°) and trans ($\Psi_{\rm XC}$ 180°) rotamers will occur in solution,²⁸ the relative population depending on the nature of the substituent X. In an NMR experiment the coupling measured will be a weighted average of the values of ${}^{3}J(CH)$ for each of the individual rotamers present. The experimental values^{15,16} range from 5.3 Hz for butane $(X = CH_3)$ to 6.2 Hz for 1-fluoropropane. Note that the values in Table 4 seem to indicate that this increase is almost completely caused by the large electronegativity dependence of ${}^{3}J(CH)$ in the conformer with $\Phi_{CH} = \Psi_{XC} = 180^{\circ}$. For other combinations of Φ_{CH} and Ψ_{XC} ³J(CH) is virtually independent of the nature of the attached substituent.
- iv. The amplitude of the orientation effect increases with increasing χ . As a quantitative measure of this effect one could choose to take the difference between ${}^{3}J(180, 120)$, where the curves of ${}^{3}J(CH)$ as

Table 5.	Parameters	$C_{0,0} - C_{2,1}$	(Hz)	in	Eqn	(5)	for	some	1-
	X-propanes	-,,-							

x	С _{о. о}	C _{1.0}	C _{2.0}	C _{0.1}	<i>C</i> _{1.1}	C _{2.1}	Rms
н	4.49	-1.00	3.75	0	0	0	0.22
CH ₃	4.38	-1.04	3.70	-0.05	-0.07	-0.02	0.20
NH ₂	4.42	-1.07	3.69	-0.42	0.13	-0.37	0.22
он	4.60	-1.12	3.83	-0.63	0.27	-0.57	0.25
F	4.84	-1.24	4.10	-0.90	0.48	-0.81	0.27
Xª	4.55	-1.10	3.83	-0.41	0.16	-0.38	0.45
ª Data	for all s	ubstituen	ts taken	together.			

a function of $\Psi_{\rm XC}$ reach their maximum, and ${}^{3}J(180, 0)$, at the minimum of these curves. This difference amounts to 50% for F, 35% for OH, 22% for NH₂, 8% for CH₃ and 0% for H.

In the case of 1-fluoropropane, the calculated J values could be reproduced well with the aid of Eqn (5) (see above). Therefore, a similar calculation was carried out on the theoretical data collected for the remaining propanes. The parameters $C_{0,0}-C_{2,1}$ deduced for each of the molecules investigated are collected in Table 5, together with the rms error of the fit. It is gratifying to find that this error has the same order of magnitude for all molecules (0.20–0.27 Hz). Thus we conclude that Eqn (5) gives a satisfactory description of the way in which ${}^{3}J(CH)$ depends on Φ_{CH} and Ψ_{XC} . Further scrutiny of the parameter values in Table 5

Further scrutiny of the parameter values in Table 5 shows a clear substituent dependence of these parameters: $C_{0,0}$, $C_{2,0}$ and $C_{1,1}$ tend to increase with increasing substituent electronegativity $\Delta \chi$, whereas $C_{1,0}$, $C_{0,1}$ and $C_{2,1}$ tend to decrease. The fact that this $\Delta \chi$ dependence cannot be neglected becomes evident when one attempts to fit all 340 calculated coupling constants to Eqn (5). The rms error now rises to 0.45 Hz. In addition, the maximum deviation between ${}^{3}J(CH)$ calculated by INDO and ${}^{3}J(CH)$ calculated by means of Eqn (5) rises sharply to 1.91 Hz in fluoropropane at (Φ_{CH} 180°, Ψ_{XC} 120°).

A plot of the parameters $C_{0,0}-C_{2,1}$ versus $\Delta \chi$ reveals an approximately linear relationship between $\Delta \chi$ and $C_{i,j}$ (Fig. 4). Thus, the parameters $C_{i,j}$ of Eqn (5) can be substituted by terms of the form $C_{i0,j} + C_{i1,j}\Delta \chi$.

Because of the threefold symmetry present in propane, the parameters $C_{0,1}$, $C_{1,1}$ and $C_{2,1}$ which describe a cosine effect with only two-fold symmetry, are necessarily zero. Therefore, when $\Delta \chi$ equals zero, $C_{i0,1} + C_{i1,1}\Delta \chi$ (i = 0, 1, 2) must be equal to zero, which in turn forces $C_{00,1}$, $C_{10,1}$ and $C_{20,1}$ to be zero. These considerations lead to a nine-parameter expression, which describes ${}^{3}J(CH)$ as a function of Φ , Ψ and $\Delta \chi$:

$${}^{3}J(CH) = (C_{00,0} + C_{01,0}\Delta\chi) + (C_{10,0} + C_{11,0}\Delta\chi)\cos(\Phi) + (C_{20,0} + C_{21,0}\Delta\chi)\cos(2\Phi) + \Delta\chi\cos(\Psi) \times [C_{01,1} + C_{11,1}\cos(\Phi) + C_{21,1}\cos(2\Phi)]$$
(7)

A least-squares fit of the set of 340 calculated coupling constants to Eqn (7) yields the values displayed in



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Figure 4. Parameters $C_{0,0}$ - $C_{2,1}$ of Eqn (5) as a function of the electronegativity²⁴ difference, $\Delta \chi$, between the substituent and hydrogen. The straight lines are least-squares fits to the data points. For reasons of symmetry the fits for $C_{0,1}$, $C_{1,1}$ and $C_{2,1}$ are constrained to go through the origin (see text).

Table 6 for $C_{00,0}$ - $C_{21,1}$. The overall rms error now amounts to 0.267 Hz, i.e. of comparable magnitude to the rms errors obtained when the data for each of the compounds were fitted separately to Eqn (5). We conclude that Eqn (7) represents a reasonably accurate formalism for the description of ${}^{3}J(CH)$ in α -substituted propanes.

Experimental verification

In order to investigate whether or not the predicted changes in ${}^{3}J(CH)$ on changing the orientation of an α -substituent are real, measurements should be performed on a series of suitable model compounds. These compounds will have to fulfil several demands. First, the chosen molecules should be sufficiently rigid to

Table 6. Least-squares-fit parameters forEqn (7)

Parameter	Value (Hz)	Parameter	Value (Hz)
$C_{00,0}$	4.36	C _{21.0}	0.19
$C_{10,0}$	-0.98	$C_{01,1}$	-0.50
C20.0	3.65	C _{11,1}	0.23
C_{01}	0.22	C21 1	-0.45
C _{11,0}	-0.13		

ensure that the torsion angles Φ_{CH} and Ψ_{XC} are well determined. Further, it is desirable that Φ_{XC} is the only angle that takes different values, whereas all other geometrical parameters remain the same, in order not to obscure the effects induced by the variation of Ψ_{XC} . As the sought effect was predicted to assume a cosine form, with extremes at 0° and 180°, the respective values of Φ_{CH} should lie in the neighbourhood of these values. The torsion angle Φ_{CH} is preferred to be approximately 180°, as in this case the coupling constant ³J(CH) is expected to be at a maximum.

The above demands are fulfilled almost perfectly by cis- and trans-4-tert-butylcyclohexanol (Fig. 5). The tertbutyl group ensures rigidity of the compounds, $\Phi_{CH}(C-1-C-2-C-3-H-3,eq)$ is constant at approx-imately 180°, while $\Psi_{OC}(HO-C-1-C-2-C-3)$ is approximately 60° in the cis compound and 180° in the trans compound. These situations are expected to result in an effect on J of ca. 1.8 Hz (Table 3). This difference should therefore be large enough to give an irrefutable experimental answer. In order to avoid possible problems in the assignment of the different splittings of the C-1 signal, the 2,2,6,6-tetradeuteriated derivatives 1 and 2 were synthesized. These compounds are expected to exhibit a particularly simple C-1 signal, viz. a triplet of triplets, originating from a large coupling with the equivalent protons H-3,eq and H-5,eq and a smaller coupling with the H-3,ax-H-5,ax pair. Figure 6 shows the high field regions of the C-1 signal of 1 and 2 in the proton-coupled ¹³C NMR spectrum. It is seen that the small coupling ${}^{3}J(C-1,Hax)$ remains unresolved, owing to line broadening caused by small couplings with the deuterium substituents. The large coupling ${}^{3}J(C-1,Heq)$, however, can be measured without difficulty: ${}^{3}J(CH) = 7.1$ Hz for 1 and ${}^{3}J(CH) = 10.4$ Hz for 2. The observed effect is even larger than predicted and amounts to 3.3 Hz or 47% when going from $\Psi_{\rm OC} = 60^{\circ}$ to 180°.



Figure 5. cis-(1)- and trans-(2)-2,2,6,6-tetradeuterio-4-tert-butylcyclohexanol. The vicinal coupling pathway between C-1 and H-3eq is indicated.



Figure 6. High-field regions of the C-1 signal in the protoncoupled ¹³C NMR spectra of compounds 1 (left) and 2 (right). The low-field regions, arising from the large ¹J(C-1,H-1) coupling, are virtually indistinguishable from the spectra shown.

CONCLUSIONS

INDO calculations on α -substituted propanes indicate that ${}^{3}J(CH)$ depends on the values of the torsion angles Φ_{CH} and Ψ_{XC} and on the substituent electronegativity χ .

All three effects can be reproduced with satisfactory accuracy by a nine-parameter equation [Eqn (7)].

Experimental verification of the predicted effect of $\Psi_{\rm XC}$ could be provided by measuring ³J(CH) in two tailor-made compounds 1 and 2. It was seen that the measured effect was even larger than that predicted, and therefore cannot be ignored when one wishes to extract accurate geometrical parameters from vicinal carbon proton coupling constants.

It should be emphasized that the predictions of ${}^{3}J(CH)$ values laid down here appear to be valid for the molecular fragments indicated X— ${}^{13}C$ — CH_{2} — CH₂—H, i.e. the influence of substituents located on the carbons in the coupling pathway should be taken into account in some way or another. Calculations to establish these influences are currently being undertaken.

EXPERIMENTAL

Compounds 1 and 2 were synthesized by two-fold lyophilization of commercially available (Aldrich) 4-*tert*butylcyclohexanone with 0.1 M NaOD in D₂O solution. The resulting 2,2,6,6-tetradeuteriated ketone was reduced, under kinetic control, with LiALH₄-AlCl₃^{29,30} and the resulting mixture of 1 and 2 was separated by means of preparative gas chromatography [Carbowax 20 MTPA (20%), temperature 180 °C].

¹³C NMR spectra were recorded at 75.4 MHz on a Bruker WM 300 spectrometer. The sample concentration was ca 1 M in CDCl₃. Proton-coupled ¹³C NMR spectra were recorded by means of the gated-decoupling technique, which preserves the nuclear Overhauser enhancement, leading to better signal-to-noise ratios. Unfortunately, it proved impossible to apply deuterium decoupling, as the deuterium signal was used to lock the spectrometer field.

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