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Spin-Spin Coupling between Geminal and Vicinal Protons

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The geminal (HCH) and vicinal (HCCH) proton spin-spin coupling constants are of fundamental importance in the applications of nuclear magnetic resonance (NMR) spectroscopy in structural and conformational analysis, since they are extremely sensitive to fine details of steric and electronic molecular structure. The nature of the dependence of the constants on individual structural factors (bond length, valence and dihedral angles, electronic structure of the substituents and their orientation, etc.) has been examined in detail. At present *a priori* theoretical calculations do not allow an exact description of these relations and therefore a semiempirical approach, based on general qualitative relations found by quantum-mechanical calculations, is very promising.
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I. INTRODUCTION

Spin–spin coupling between protons observed in the NMR spectra of liquids and gases has been attracting attention for many reasons. From the theoretical standpoint, this is one of the simplest cases of the transfer of nuclear spin polarisation via the electron cloud, which depends in the most critical way on the electronic structure of the molecule. From the practical standpoint, the H–H constants in fact constitute the basis of the study of molecular structure, conformation, and configuration—one of the most important applications of NMR spectroscopy in chemistry. Moreover, H–H constants (J_{HH}) are important for structural analysis and the study of the electronic structure of molecules and kinetic processes, such as internal rotation, inversion transitions, and hydrogen exchange[1].

In the present review attention has been concentrated on the relation between the H–H constants and the steric and electronic structures of molecules. On the basis of the extensive data which have accumulated, a number of correlations have been obtained, in particular with the relative steric positions of hydrogen atoms. Some of these relations have found wide application in the solution of chemical structural problems, while others are not so well known. Many of the correlations have a firm theoretical basis. In order to employ such correlations, it is important to bear in mind the limits of their applicability and also the deviations caused by certain structural factors. One must also emphasise that the ranges of the possible values of the H–H constants for the fundamental structural fragments overlap significantly:

		+280 Hz
^1J	H—H	(Carr and Purcell) (Ref.2)*
^2J	H—C—H	from −22 to +40 Hz
^3J	H—C—C—H	from 0 to +19 Hz
^4J	H—C—C—C—H	from −2 to +18 Hz

* The sign of the constant was established for HD molecules by the molecular beam method[3].

This makes it necessary to analyse thoroughly the causes of the variation of the constants by both theoretical and empirical procedures.

Spin–spin coupling in molecules with saturated valences is due to slight unpairing of the electron pair spins (i.e. a contribution by excited electronic structures), induced by the magnetic moment of the nucleus. It has been reliably established[4-6] that the principal mechanism (which can actually be said to be dominant) of the transfer of interaction between protons is Fermi contact interaction. The extent of this interaction is proportional, to a first approximation, to the probability $S(0)$ that the orbital electrons are located at the sites of the protons A and B (Fig. 1):

$$J \propto S_A^2(0) S_B^2(0).$$

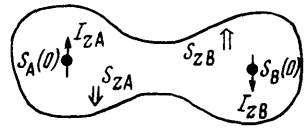


Figure 1. Schematic representation of the electronic properties of the spin–spin contact interaction between protons. I_{zA} and I_{zB} are the spin moments of electrons.

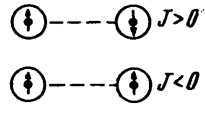


Figure 2. Illustration of the physical significance of the sign of the spin–spin coupling constant.

The sign of the coupling constant, which characterises the relative distribution of the spin energy levels of the nuclear system, is a characteristic no less important than J itself. If the lowest level corresponds to a state with an antiparallel arrangement of nuclear spins (Fig. 2*a*), a positive sign is attributed to the constant, a negative sign corresponding to a parallel arrangement (Fig. 2*b*).

The signs of the coupling constants are established by special methods. The absolute signs are determined from spectra in nematic solvents [7,8], from the changes in splitting in a strong electrostatic field [8], and from the relaxation parameters of multispin systems [9]. The relative signs of the constants are determined by double resonance methods [10], by analysing spectra with strong interaction [11], and from the positions of the signals due to two-quantum transitions [12].

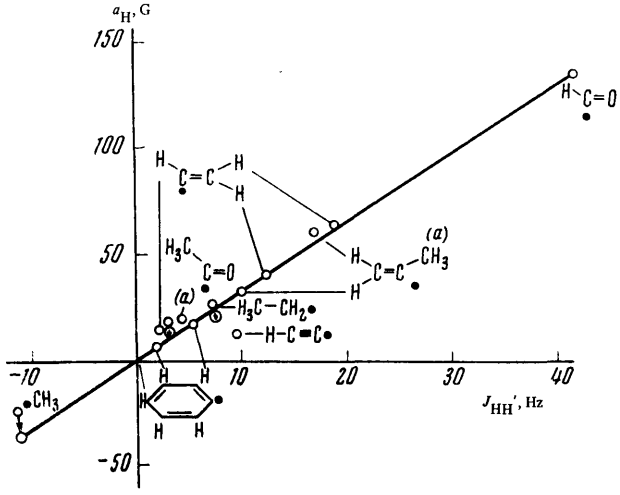
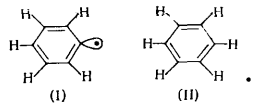


Figure 3. Relation between the spin–spin proton coupling constant $J_{HH'}$ (NMR) and hyperfine coupling constant a_H (ESR). The values of a_H for the radicals $\dot{C}H_3$, $\dot{C}H_2CH_3$, and $\dot{C}OCH_3$ have been corrected for the structure factor; the corrected values are designated by an arrow [15].

The problem of the relations governing the transfer of unpaired-electron density is of considerable interest for theoretical chemistry. Together with the widely familiar delocalisation over a system of conjugated bonds, the methods of magnetic microwave spectroscopy made it possible to investigate finer details of the perturbing influence of the unpaired electron, largely localised at a single atom. The delocalisation of spin density caused by such perturbation may be reflected in various molecular parameters—such as the spin–spin coupling constant J in molecules with saturated valences and the contact chemical shift in the NMR spectra of paramagnetic complexes as well as the isotropic hyperfine coupling constant (a) in electron spin resonance spectra. The most typical example demonstrating the general properties of delocalisation is provided by a comparison of the constants a for free radicals with a localised valence [for example the phenyl radical (I)] and the constants J_{HH} of the corresponding molecules [benzene (II)] in which the free valence is saturated by a hydrogen atom (H) [13–17].



(I) (II)

The linear relation obtained (Fig. 3) [15],

$$J_{HH'} \simeq 0{,}3\,a_H,$$

where J_{HH} and a_H are expressed in Hertz and Oersted units respectively, shows that the non-compensated electron density at the σ orbital of the carbon atom, induced by the magnetic moment of the H′ proton, plays a fundamental role in the spin–spin interaction. Therefore the perturbing effects in the molecule and the free radical obey the same relation. Recent theoretical calculations [17] by the valence bond method confirmed the existence of a linear relation:

$$J_{HH'} = 4.1\,a_H/\Delta E,$$

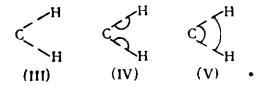
where ΔE is the average energy of the perturbed state in electron-volts. With the usually adopted value $\Delta E =$ 10 eV, the proportionality coefficient (0.41) agrees satisfactorily with the empirical value. A linear relation has also been found between the J_{HH} constants and contact chemical shifts [15]. Thus the data obtained by different methods for similar systems with identical structures can significantly complement one another. For example, the sign of a_H may be established from that of J_{HH} or from the sign of the contact chemical shift.

We shall now pass to a discussion of the dependence of the H–H interaction constants for HCH and HCCH structural fragments in organic compounds on various factors associated with steric and electronic structures.

II. THE GEMINAL CONSTANT $^2J_{HH}$

The simplest fragment (apart from the hydrogen molecule) is H–C–H, where the hydrogen atoms occupy *gem*-positions (with the geminal constant $^2J_{HH}$). As already mentioned, the values of ^2J are in the range between −22 and +40 Hz, i.e. not only their magnitude but also their sign can vary.

In the calculation of ^2J by the valence bond method, the geminal fragment is regarded as a four-electron system (III), consisting of two 1s orbitals of the hydrogen atoms and two hybridised sp orbitals of carbon [18,19]. The ground electronic state (IV) corresponds to complete pairing of bond electrons. Since there is then no interaction between the electron pairs, no spin–spin coupling between protons is shown. For H–H interactions to occur, it is necessary to mix the ground state (IV) with an excited state (V).



(III) (IV) (V)

The degree of such mixing is determined by the energy difference between the ground and excited states, which is as a rule estimated very approximately. In terms of the mean excitation energy approximation, it has been found [18,19] that

$$^2J \propto \frac{K(\mathrm{HH'}) + K(\sigma\sigma') - 2K(\sigma\mathrm{H'})}{K(\sigma\mathrm{H})}, \qquad (1)$$

where K are exchange integrals between the corresponding atomic orbitals (Fig. 4). The values of these integrals are difficult to estimate quantitatively. One can only assume with a degree of certainty [20] that $K(\sigma\mathrm{H}) < 0$, $K(\mathrm{HH''}) < 0$, and $K(\sigma\sigma') > 0$. It then follows from Eqn. (1) that the contribution by the $K(\mathrm{HH'})$ integral to ^2J is positive and that of $K(\sigma\sigma')$ is negative. However, calculations show that the absolute values of $K(\mathrm{HH'})$ and $K(\sigma\sigma')$ are approximately the same and cancel out. $K(\sigma\mathrm{H'})$ is even more

difficult to calculate. Its sign may be both positive or negative. In the first case $^2J < 0$ and in the second $^2J > 0$. The error in the estimation of the integrals (about ±10%) can lead to discrepancies between the values of $^2J_{HH}$ up to ±6 Hz.[6]

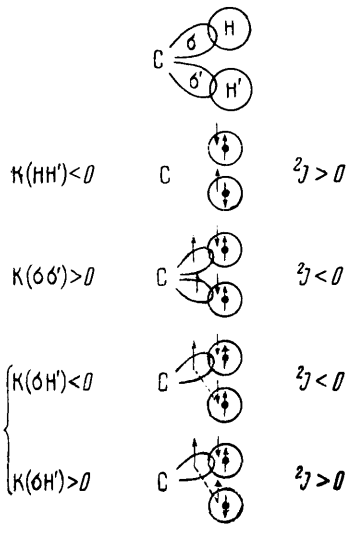


Figure 4. The H–H geminal constant within the framework of the valence bond method and a schematic representation of exchange integrals. In this and other figures the arrows denote energetically favourable relative orientations of the spin moments of protons and orbital electrons.

Numerical calculations by both the valence bond method[20-23] and by the molecular orbital method[24-36] in different modifications show significant discrepancies with experimental data (Table 1)†. This applies not only to the absolute values but even to the sign. Therefore analysis of the empirical relations becomes important. The theoretical justification and prediction of the relation between ^2J and molecular structure probably should not be based on the calculation of the overall values of the constants but should consist in isolating the additional contributions due to specific structural factors.

Significant advances on these lines have been achieved by the molecular orbital method taking into account the excitation energies of the triplet states[20,36,39,40]. For a qualitative examination[39] of an isolated four-electron CH_2 fragment, one may restrict the treatment to four molecular orbitals ψ_i (Fig. 5) constructed by a linear combination of the atomic orbitals φ_k:

$$\psi_i = \sum_k c_{ik}\varphi_k.$$

Table 1. Theoretical calculations of the $^2J_{HH}$ geminal constant (Hz) by the valence bond method (VB), the molecular orbital method without allowance for overlapping (MO), with allowance for overlapping (MO–O), with allowance for delocalisation (MO–D), by the self-consistent field method with complete and partial neglect of differential overlapping (CNDO and INDO), and the complete self-consistent field method (SCF).

Compound	Experiment	VB (Ref.20)	MO (Ref.25)	MO–O (Ref.26)	MO–D (Ref.27)	CNDO (Ref.27)	INDO (Refs.28 & 36)	SCF (Ref.32)
CH_4	−12.4[37]	+12.5	+20.7	−16.5	−2.1	+1.17	−6.13	−7.0
$CH_2{=}CH_2$	+2.5[38]	+3.05	+32.5	−15.2	+1.5	+8.48	+3.24	+9.6

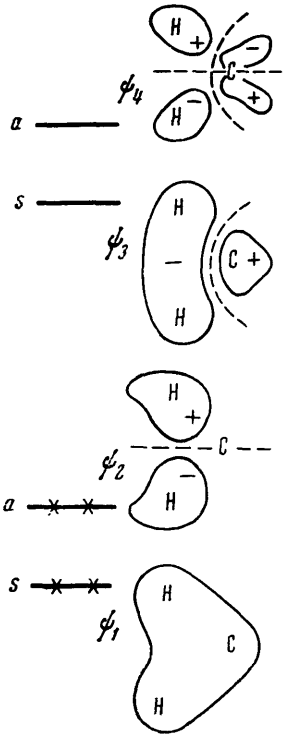


Figure 5. Molecular orbitals of the CH_2 fragment.

Two of the molecular orbitals are bonding and populated (ψ_1 and ψ_2) and two are non-bonding and unpopulated (ψ_3 and ψ_4). These orbitals are delocalised over both C–H bonds and can be divided into symmetrical (s) and antisymmetric (a) orbitals in relation to the plane bisecting

†The geminal constant $^2J_{HH}$ for the magnetically equivalent CH_3 protons is found from the $^2J_{HD}$ constant for the CHD fragment in the spectra of the corresponding deuterated compounds[37]: $^2J_{HH} = (\gamma_H/\gamma_D)\ ^2J_{HD} = 6.5144\ ^2J_{HD}$, where γ_H and γ_D are the gyromagnetic ratios for the proton and deuteron respectively. $^2J_{HH}$ for CH_2CH fragments with magnetically equivalent CH_2 protons may be determined from the satellite spectra due to ^{13}C.[38]

the H–C–H angle. The symmetrical bonding orbital ψ_1 includes the 2*s* orbital of the carbon atom and therefore has a lower energy than ψ_2 which includes the 2*p* carbon orbital. The proton spin–spin interaction constant is expressed as follows in perturbation theory:

$$^2J_{HH'} \propto S_H^2(0)\, S_{H'}^2(0)\, \pi_{HH'}, \quad (2)$$

$$\pi_{HH'} = -4 \sum_k \sum_l (E_l - E_k)^{-1} c_{kH} c_{kH'} c_{lH} c_{lH'}, \quad (3)$$

where $S_H(0)$ and $S'_H(0)$ are the densities of the 1*s* atomic orbitals at the H and H′ protons, $\pi_{HH'}$ is the mutual polarisibility coefficient of the hydrogen 1*s* orbitals of H and H′, the index *k* corresponds to populated states and *l* to unpopulated states.

Table 2.

Transition	Sign of contribution to $^2J_{HH}$
$\psi_1 \rightarrow \psi$	–
$\psi_1 \rightarrow \psi$	+
$\psi_2 \rightarrow \psi_3$	+
$\psi_2 \rightarrow \psi_4$	–

The $\psi_k \rightarrow \psi_l$ electronic transitions make contributions of different signs (Table 2), which are determined by the coefficients c_{kH}, $c_{kH'}$, c_{lH}, and $c_{lH'}$. The effect of different factors on $^2J_{HH}$ is treated as a change in the relative contribution caused by a given electronic transition, taking into account the energy difference of the transition $(E_l - E_k)^{-1}$. A number of qualitative conclusions based on this theory[39] and the results of calculations by the INDO method[36] will be discussed below.

One can regard it as established that the H–H geminal constant for the H_2C–X–Y system depends on the following fundamental factors[6,41–45]: (1) hybridisation of the carbon atom; (2) electronegativity of the substituent X; (3) the presence of a π-electron system at the atom X; (4) the presence of a lone electron pair at the atom X; (5) the nature of the β-substituent Y; (6) the nature of the solvent‡. These factors will be considered separately.

1. Hybridisation of the Carbon Atom

Experimental data for hydrocarbons show that, as the contribution by the *p* orbital of the carbon atom diminishes, $^2J_{HH}$ increases (Table 3).

A more detailed relation can be more conveniently derived[43] on the basis of the valence angle α as the parameter determining the hybridisation of carbon (Fig. 6). The relation is of course significant only for systems where the effect of the other factors mentioned above is fairly weak§. However, as a rule such "pure" systems are encountered rarely and therefore in the general case the determination of valence angles from the constant $^2J_{HH}$ is invalid. It is remarkable that the first calculation of $^2J_{HH}$ by the valence bond method[18,19] predicted an approximately the same relation but with the opposite sign of the constant (Table 1). Recent calculations by the molecular orbital method[26,36] yielded the correct sign of $^2J_{HH}$ and the correct overall relation with the valence angle, but for specific molecules (ethylene, cyclopropane, cyclohexane, and methane) there was no agreement with experiment (Table 1).

Table 3.

Molecule	CH_4		$H_2C{=}CH_2$
Hybridisation	sp^3	$sp^{2,3}$	sp^2
HCH angle	109°	116°	120°
^2J, Hz	–12.4[37]	–4.31[55]	+2.5[38]

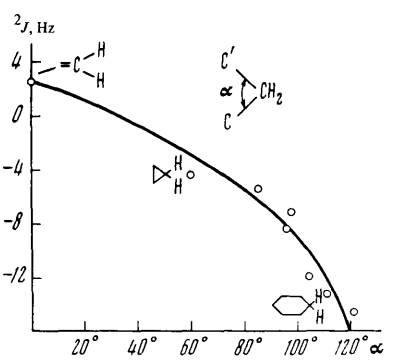
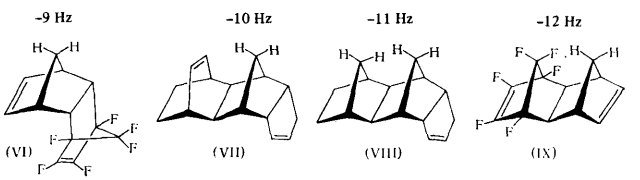


Figure 6. Variation of the H–H geminal constants with the C–CH_2–C valence angle for hydrocarbons[43].

One of the features of the relation between $^2J_{HH}$ and the H–C–H angle is the effect of the steric factor. For example, the constant for the bridge protons in the bicyclo[2,2,1]heptane system decreases with increasing degree of steric hindrance in the series (VI)–(IX).[57–59] We may suppose that the H–C–H angle decreases in the same series.



‡A change in temperature is reflected in a redistribution of the populations of the torsional vibrational levels of the HCH fragment, which should lead to a change of the H–H geminal constant. Experimental data[46–54] and theoretical calculations[46,47,49,50] show that, with increase of temperature, the absolute value of $^2J_{HH}$ increases only slightly (the relative change is about 3×10^{-4} per degree).

§The lack of the $^2J_{HH}$ constants for cyclobutane makes it difficult to decide whether four-membered rings obey this relation. For cyclobutane derivatives, values of ^2J ranging from –11.0 to –14.0 Hz have been observed[43,45,56].

2. Effect of the α-Substituent

In the presence of a substituent X at the carbon atom ($X-CH_2$), one can postulate intuitively that, since the electron-accepting inductive effect of X leads to a decrease of electron density at H atoms, the absolute value of $^2J_{HH}$ should diminish. Such a relation is in fact observed experimentally (Table 4).

Table 4. Variation of $^2J_{HH}$ with the electronegativity of the α-substituent.

Compound	$^2J_{HH}$, Hz	X	$^2J_{HH}$, Hz
$(CH_3)_4C$	−14.1[60]	CH_2	−4.31[55]
CH_4	−12.4[37]	S	−1.4[62]
$(CH_3)_3N$	−11.7[44]	NCH_3	+1.0[63, 64]
CH_3OH	−10.8[61]	O	+5.4[65]
CH_3F	−9.6[61]	N+<	+5[66]

A qualitative explanation of the effects of electronegative α-substituents on $^2J_{HH}$, based on the molecular orbital method[39], involves an inductive withdrawal of electrons from the symmetrical orbital ψ_1 (Fig. 5). As a result, the orbital becomes less "hydrogen-like" and the coefficients c_{1H} and $c_{1H'}$ in Eqn. (3) diminish. Since the molecular orbitals are made up of a complete orthogonal set of atomic orbitals, the other symmetrical orbital ψ_3 becomes more "hydrogen-like" and the coefficients c_{3H} and $c_{3H'}$ increase. In view of the fact that the antisymmetric orbitals do not change under the influence of the inductive effect of the substituent, the product of the coefficients in Eqn. (3) for the $\psi_1 \rightarrow \psi_4$ transition will be more negative and for the $\psi_2 \rightarrow \psi_3$ transition less negative. Since a lower excitation energy $E_3 - E_2$ corresponds to the latter transition than to the $\psi_1 \rightarrow \psi_4$ transition (Fig. 5), the overall contribution to the change in $^2J_{HH}$ is positive. Thus theoretical considerations are consistent with experimental data (Table 4): electronegative substituents (for example F) in the CH_3X series leads to an increase of $^2J_{HH}$ and electropositive substituents (for example Si) lead to a decrease of the geminal constant relative to methane. Theoretical calculation by the MO–INDO method[36] indicated an increase of $^2J_{HH}$ for CH_3F by 4.28 Hz compared with methane (Table 1).

In the valence bond method, the inductive effect of the substituent on $^2J_{HH}$ is taken into account by including polar structures reflecting the ionic character of the C–X bond[21,22]. These calculations yield an incorrect sign of the geminal H–H constant, but correctly predict a decrease of $|^2J_{HH}|$ with increasing amount of ionic character of the C–X bond.

However, the electronic properties of the substituent X are not restricted to electronegativity. For example, a relation has been derived between $^2J_{HH}$ for compounds of the type $(CH_3)nX$ and the number of the Period of the atom X (Fig. 7), which makes it possible to predict the constant for compounds not hitherto investigated[67].

3. Effect of the π-Electron System of the Substituent X

If the electronic system of X includes a π orbital, an additional contribution to the constant $^2J_{HH}$ for the $X-CH_2$ fragment is generated. In the valence bond method this contribution is proportional to the product of the overlap integrals of the C–H orbitals and the π orbital of the atom X:[19,68]

$$\Delta^2 J^{\pi} \sim -K(\sigma\pi)\, K(\sigma'\pi).$$

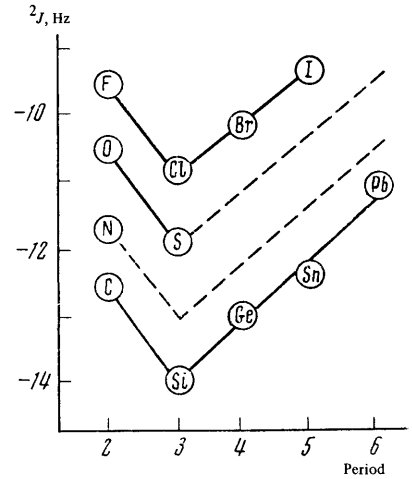
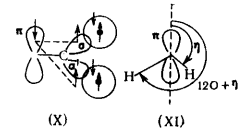


Figure 7. Variation of the H–H geminal constants for compounds of the type $(CH_3)_nX$ with the number of the Period of the atom X.[67]

Its negative sign is due to the preferential antiparallel orientation of proton spins when the interaction is transmitted via the π orbital of the atom X (X). Indeed the $^2J_{HH}$ constant for the methyl group decreases in the series CH_4 (−12.4 Hz)[37] > CH_3Ph (−14.6 Hz)[19] > $CH_3C{\equiv}N$ (−16.9 Hz)[19]. In acetonitrile the first atom of the substituent has two π orbitals, which results in a doubling of the contribution $\Delta^2 J^{\pi}$.



Since the integral $K(\sigma\pi)$ is proportional to $\cos^2\eta$, where η is the dihedral angle between the C–H bond at the direction of the π orbital (XI), it follows that, for molecules with fixed positions of the C–H bonds, the contribution by the π-electron system depends on the angle η:[68]

$$\Delta^2 J^{\pi} \propto \cos^2\eta \cos^2(120 + \eta).$$

This theoretical relation (Fig. 8) is satisfactorily confirmed by experiment[43,68] (almost quantitatively), which makes it possible to employ it for the determination of molecular structures and conformations.

Qualitative[39] and quantitative[36] treatment by the molecular orbital method leads to similar conclusions concerning the sign of the contribution of the π orbital or the α-substituent to the geminal H–H constant and its dependence on

stereochemical factors. The effect of the π orbital is treated as involving a withdrawal of electron density from the antisymmetric populated orbital ψ_2 of the CH_2 fragment (Fig. 5).

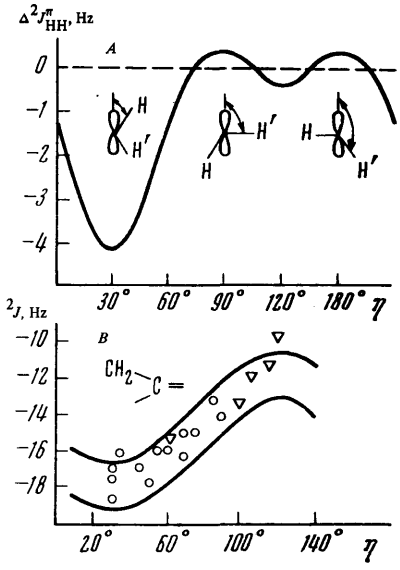
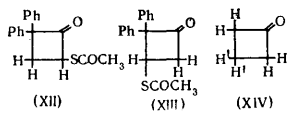
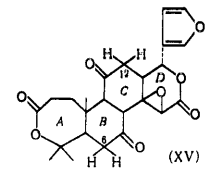


Figure 8. Theoretical [68] (*A*) and experimental (*B*) [43] dependence of the contribution by the π-electron system to the constant $^2J_{HH}$ on the projection angle η.

As an example of structural studies, one may quote the determination of the position of the acetylthio-group in a derivative of cyclobutane [69]. For structure (XII), $^2J_{HH}$ should not differ markedly from the usual value for cyclobutanes, i.e. -(12-15) Hz. [42,56] On the basis of the theoretical relation (Fig. 8), -4.2 Hz ($\eta \simeq 30°$) should be added for structure (XIII) because of the neighbouring π-electron system of the carbonyl carbon atom: $^2J \simeq -(16-19)$ Hz. Experiment yielded -18.4 Hz, which proved structure (XIII). For unsubstituted cyclobutanone (XIV), it has been found that $^2J_{HH} = -17.5$ Hz and $^2J_{H'H'} = 11.1$ Hz. [70]

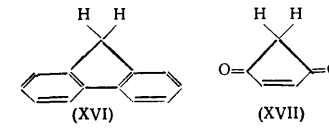


The angular variation of the contribution by the π orbital may be used, for example, to determine the conformation of the cyclohexane ring. In the chain conformation ($\eta \simeq 86°$) the geminal constant has the normal value for cyclohexanones (-13 Hz). In the boat conformation ($\eta \simeq 30°$), a decrease of the constant by 4-5 Hz is to be expected. For zapoternone (XV) [71], $^2J_{HH} = -13$ Hz for the $C_{(6)}H_2$ methylene group, which indicates a chair conformation of the *B* ring, while -19 Hz was found for the $C_{(12)}H_2$ group, which corresponds to a boat conformation of the *D* ring:



(XV)

The effect of the π-electron system leads to values of $^2J_{HH}$ which constitute the lower limit of the known geminal constants. For fluorene (XVI) [72] and cyclopenta-3,5-dione (XVII) [68], in the molecules of which the methylene group is linked to two carbon atoms involved in a double bond, $^2J_{HH} = -22.3$ and -21.5 Hz were found respectively.



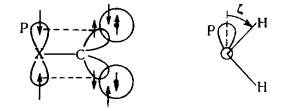
(XVI) (XVII)

These values agree well with $^2J_{HH} \simeq -12.5-4.2-4.2 = -20.9$ Hz calculated for $\eta = 30°$.

The lower value of $^2J_{HH}$ for 1,1-dimethylallene (-9.0 Hz) [73] compared with ethylene (+2.5 Hz) [38] can also be attributed to the effect of the additional π orbital of the atom X. For keten $H_2C=C=O$ ($^2J_{HH} = -15.8$ Hz) [73], the effect of the electronegativity of the β-substituent is also important (see Section II, 5).

Effect of the Lane Electron Pair of the Substituent

According to theoretical considerations based on the valence bond [6] and molecular orbital [36,39] methods, the contribution by the lone pair to the geminal constant should be positive [formula (XVIII)] and should depend on the dihedral angle ζ [formula (XIX)] between the C-H bond and the axis of the lone pair. In the qualitative molecular orbital theory [39], this effect is regarded as due to the supply of electron density to the antisymmetric populated orbital ψ_2 (Fig. 5). The effect is opposite in sign to that of the π orbital of the α-substituent.

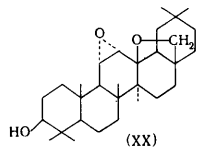


(XVIII) (XIX)

A confirmation of the effect of the lone pair can be found by comparing the $^2J_{HH}$ constants in the series of six- and five-membered heterocyclic compounds (Table 5). Two factors are noteworthy. Firstly, the monotonic increase of $^2J_{HH}$ with increasing electronegativity breaks down at the piperidinium and pyrrolidinium cations. Although the electronegativity of N^+ is higher than that of N, the latter has a lone electron pair, the positive contribution $\Delta^2 J^P$ of which increases $^2J_{HH}$, which leads to the breakdown of the sequence. Secondly, the introduction of the heteroatom has a much greater effect on $^2J_{HH}$ in five-membered rings than in six-membered rings. One must assume that this is due to the difference between the angles ζ in the two types of rings.

Theoretical calculation by the MO-INDO method showed [36] that the geminal constant for methanol depends on the orientation of the O-H bond. However, the numerical result, in particular -2.12 Hz for the average value of

$^2J_{HH}$, differs significantly from the experimental constant (Table 4). The actual variation of the geminal constant for the CH_2 group with the orientation of the lone pairs of α-oxygen can be found from the experimental data taking into account the form of the theoretical curve. Tetrahydropyran ($\zeta \simeq 180°$ and 300°), tetrahydrofuran ($\zeta \simeq 210°$ and 270°), oxetane (−6.02 Hz, [182] $\zeta \simeq 240°$) and a steroid (XX) [45] (−6.0 Hz, [83] $\zeta \simeq 240°$) were chosen (Table 5) as the reference points in the above relation (Fig. 9).



(XX)

Table 5. Values of $^2J_{HH}$ (Hz) for five- and six-membered heterocyclic compounds [43,44,74,75].

X	Y		
CH_2	CH_2	−13.05 [76]	−13
S	CH_2	−13	−10
S+	CH_2	−15 [77]	—
N	CH_2	−12.0 [78]	−9.5
N+	CH_2	−13	−13
O	CH_2	−11.5	−8
S	S	−14	−9.7
N	S	—	−9.4
N	N	−8.5	−3.5
O	N	−8	−2.5
O	S	−11.1	−5.2
O	O	−6.18 [79,80]	+0.8 [81]

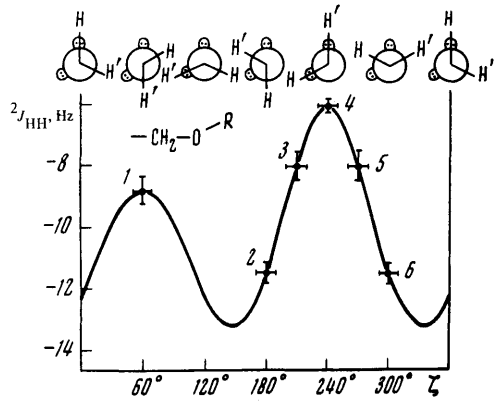


Figure 9. Variation of the H_2C-O geminal constant with the orientation of the orbitals of the lone electron pairs of oxygen: 1) calculated from the average $^2J_{HH}$ for $(CH_3)_2O$ (see text); 2) and 6) tetrahydropyran; 3) and 5) tetrahydrofuran; 4) steroid (XX) and oxetane.

The value for $\zeta \simeq 60°$ was calculated from $^2J_{HH} = -10.6$ Hz for $(CH_3)_2O$, [44] assuming rotational averaging:

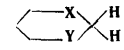
$$\langle {}^2J_{HH}\rangle = \frac{1}{3}(J_{60°} + J_{180°} + J_{300°}),$$

where $J_{180°} = J_{300°} = -11.5$ Hz, as for tetrahydropyran.

Fig. 9 shows that the maximum contribution by the lone pair orbitals of α-oxygen is +7.8 Hz when both C−H bonds are eclipsed¶. The minimum value in Fig. 9 (−13.3 Hz) is confirmed indirectly by the minimum recorded value $^2J_{HH} = -14$ Hz for the CH_2-O fragment [45,84].

An empirical analysis of the effect of the orientation of the lone pair on the geminal constant has been carried out for nitrogen-containing cyclic compounds with a fixed conformation [86]. Table 6 lists the values of $^2J_{HH}$ for six-membered rings. Comparison of the geminal constants for five- and six-membered nitrogen-containing rings with known steric structures made it possible to derive a relation between $^2J_{HH}$ and the dihedral angle ζ (Fig. 10).

Table 6. Effect of the orientation of the lone electron pair of nitrogen (indicated in brackets) on the geminal constants of the six-membered rings [86]



X	Y	$^2J_{HH}$, Hz	Refs.
N (e)	CH_2	−13.6	87
N (a)	CH_2	−11.5	88
N (e)	O	−10.5	88
N (a)	O	−7.5	89
N (e)	N (e)	−13.0	90
N (e)	N (a)	−11.3	86
N (a)	N (a)	−8.5	91

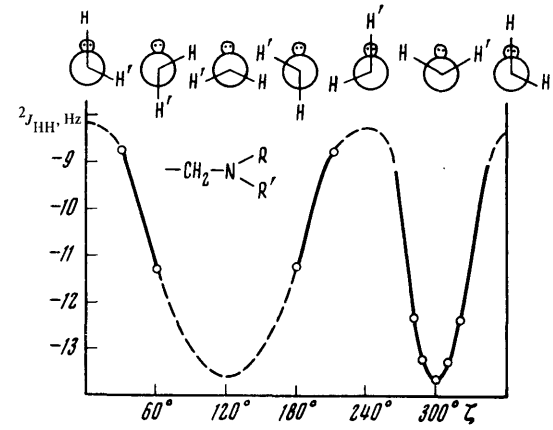
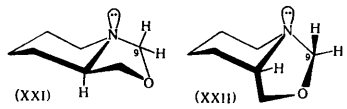


Figure 10. Variation of the H_2C-N geminal constant with the orientation of the lone electron pair of nitrogen in cyclic systems with a fixed conformation [86].

¶Empirical analysis of data for oxygen-containing ring systems showed [84,85] that, when one of the C−H bonds is eclipsed by the lone pair of the α-substituent X, the geminal constant for the H_2C-X fragment increases by 1.8 Hz. Theoretical calculation [40] by the molecular orbital method gave a maximum contribution of +12.6 Hz by the p^π orbital of the lone pair, +5.3 Hz by the sp^2 orbital, and a negative contribution by the σ orbital.

As an example of the use of the lone pair effect in conformational analysis, one may quote the determination of the configuration of the isomers of 1-aza-8-oxabicyclo-[4,3,0]nonane with *trans*- (XXI) and *cis*-junctions (XXII) between the six- and five-membered rings [92]. In the *trans*-isomer the C_9–H bond is virtually eclipsed by the lone pair of electrons of nitrogen ($\zeta \simeq 210°$) and oxygen, while in the *cis*-isomer the projection of the axis of the nitrogen lone pair bisects the H–C_9–H′ angle ($\zeta \simeq 300°$). In the first case there is a possibility of a considerable positive contribution to the H–C_9–H′ geminal constant (Fig. 10). In fact the constant for isomer (XXI) is less negative (−0.8 Hz) than for isomer (XXII): −5.0 Hz.



The effect of the lone pair together with that of the electronegativity of the α-atom explains [36,39] the very high positive values of the H–H geminal constants for formaldehyde O=CH_2 (+42.4 Hz) [93] and *N*-alkylmethyleneimines RN=CH_2 [up to +16.5 Hz, R=$C(CH_3)_3$]. [94,95] The formaldehyde value is the upper limit of the known range of $^2J_{HH}$ constants.

A non-linear relation between $^2J_{HH}$ and the electronegativities of the substituents (E_X and E_Y) was found [103] for compounds of the type H_2C=CXY:

$$^2J_{HH} = \frac{61.6}{E_X + E_Y} - 12.9 . \quad (4)$$

The form of this relation differs significantly from the linear relation proposed previously [99] on the basis of limited data:

$$^2J_{HH} = 8.7 - 2.9(E_X + E_Y). \quad (5)$$

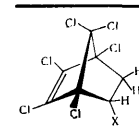
In order to refine the relation between $^2J_{HH}$ and electronegativity, theoretical calculations are probably necessary. Nevertheless, the available data [39,43,44,99,103,104] make it possible to employ the value of $^2J_{HH}$ in order to obtain information about the structure of olefins.

The effect of the β-substituent in saturated fragments depends on its orientation relative to the geminal protons. Theoretical considerations [39] lead to the qualitative conclusion that, when the β-substituent X is within the H–C–H′ geminal angle on the Newman projection (XXIII), the contribution to the $^2J_{HH'}$ constant is positive, but, if the β-substituent is outside this angle, the contribution is negative, i.e. $^2J_{HH'} > {}^2J_{H'H''}$. In contrast to ethylenes, the H–H geminal constants for *endo*-substituted hexachlorobicyclo[2,2,1]heptenes are seen to decrease (Table 8).

Table 7. Effect of the β-substituent on the geminal constant.

H_2C=CHY	$^2J_{HH'}$, Hz	Refs.	H_2C=CHY	$^2J_{HH'}$, Hz	Refs.
Li	+7.1	96	I	−1.5	53
$Si(CH_3)_3$	+3.6	97	Cl	−1.5	53
H	+2.5	38	Br	−1.7	53
CH_3	+2.1	98	OCH_3	−2.0	100
$N(CH_3)_2$	0.0	99	F	−3.2	53
SCH_3	−0.3	100, 101	$N^+(CH_3)_3$	−4.1	102

Table 8.

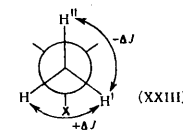
	$^2J_{HH'}$, Hz	Refs.
H	−12.62	105
SCH_3	−13.00	106
$SCOCH_3$	−13.10	10
Br	−13.30	107,108
Cl	−13.32	109
$OCOCH_3$	−13.3	109
F	−13.53	110

5. Effect of the β-Substituent

The H–H geminal constant is influenced not only by the α-substituent but also by the more remote β-substituent. The general tendency, observed for substituted ethylenes, indicates a decrease of $^2J_{HH}$ with increasing electronegativity of the β-substituent (Table 7). The tendency is opposed to that observed for the effect of the α-substituent, which is consistent with the intuitive hypothesis concerning the influence of the inductive effect. This example clearly illustrates the limitations of such intuitive considerations concerning the influence of the inductive effect in NMR.

In the molecular orbital method [39] the effect of the electronegative β-substituent is treated as a result of the withdrawal of electron density from the antisymmetric bonding orbital ψ_2 of the CH_2 fragment (Fig. 5). In contrast to the effect of the α-substituent, in this case theory predicts a negative contribution to $^2J_{HH}$ with increasing electronegativity.

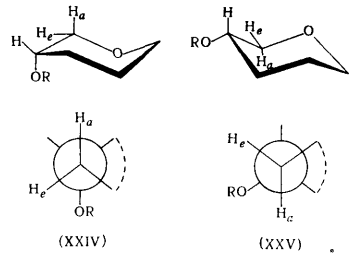
In this case the substituent is at the limit of the H–C–H geminal angle.



(XXIII)

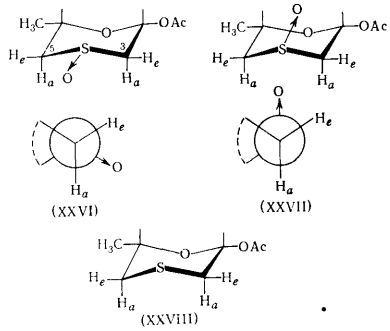
The geminal H–H constants for the inversion conformations of a number of heterocyclic compounds provide an experimental confirmation of the theoretically predicted orientation effect of the substituent. For example, among pentopyranose derivatives [111,112] a lower constant $^2J_{5e,5a}$ = −13.3 Hz is observed for the axial orientation of the substituent C_4OR (XXIV) (the electronegative β-oxygen atom is outside the $H_eC_5H_a$ geminal angle) than for the equatorial orientation (XXV): $^2J_{5e,5a}$ = −11.2 Hz (the oxygen atom is

within the $H_eC_5H_a$ angle). Similarly among 2-deoxy-D-arabohexapyranose derivatives[112], $^2J_{2e,2a} = -13.8$ Hz for the axial C_1–OR orientation is lower than for the equatorial orientation: $^2J_{2e,2a} = -12.4$ Hz.



(XXIV) (XXV)

The orientation effect of the β-atom has been used in the determination of the absolute configuration of the sulphoxide group in derivatives of 1,4-oxathian *s*-oxide[113]. For the equatorial orientation of the oxygen atom in the S → O group (XXVI), the $^2J_{5e,5a}$ and $^2J_{3e,3a}$ constants should be higher than for the axial orientation (XXVII), since in the first case the β-atom is within the H_eCH_a geminal angle. Therefore the isomer with constants of −12.0 and −11.3 Hz can be regarded as having an equatorial S → O bond, while the isomer with constants of −14.2 and −13.8 Hz should have an axial S → O bond. For comparison, we may point out that the corresponding sulphide (XXVIII) has $^2J_{5e,5a} = -13.1$ Hz and $^2J_{3e,3a} = -13.5$ Hz.



(XXVI) (XXVII)

(XXVIII)

After a suitable detailed development, the orientation effect of the β-substituent may find large-scale application in conformational analysis.

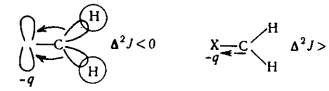
The γ-substituent (the substituent in the 4-position) has been found to influence the coupling constant of the O–CH_2–O *gem*-protons in 1,3-dioxans, the effect depending on the electronic nature and orientation of the substituent[114].

6. Effect of the Medium

Careful investigations[50,51,81,93–95,115–122] showed that the H–H geminal constant clearly depends on the dielectric constant of the medium ϵ (Fig. 11). With increase of the polarity of the medium, the negative contribution to $^2J_{HH}$ also increases, the direction of the effect having an equal influence on positive (formaldehyde[93]) and negative (phenylthi-iran[81]) H–H constants (Fig. 11). The experimental data show that the effect may be used to determine the sign of ^2J: if $^2J > 0$, an increase of ϵ should entail a decrease of the absolute value of the H–H constant; if $^2J < 0$, the constant should increase.

The reason for the variation of $^2J_{HH}$ under the influence of the medium is the effect of the reaction field, induced by the solvent molecules, on the molecular dipole of the test compound[81]. Under the influence of this field, the local dipole moment of the molecule increases in two possible ways.

a. By pseudoconjugation [formula (XXIX)] in which the effect of the lone electron pair of the α-atom diminishes (see Section II, 4), resulting in a positive contribution to $^2J_{HH}$. Consequently when this effect is weakened under the influence of the medium, $^2J_{HH}$ decreases owing to the withdrawal of electrons from the antisymmetric orbital ψ_2 (Fig. 5).



(XXIX) (XXX)

b. By an inductive effect [formula (XXX)] involving the C–X σ bond, which is equivalent to an increase of the electronegativity of X. This should entail a positive contribution to $^2J_{HH}$ in consequence of the withdrawal of electrons from the symmetrical orbital ψ_1 (Fig. 5).

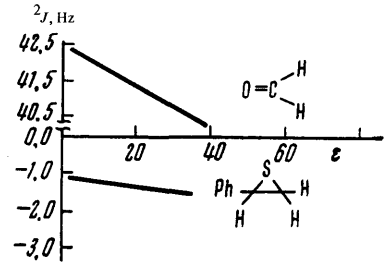


Figure 11. Effects of the polarity of the medium on the H–H geminal constants of formaldehyde[93] and phenylthi-iran[81].

Experimental data have shown that the main contribution comes from pseudoconjugation. Evidently the higher the dipole moment of the molecule, the greater the influence of the solvent. This has been confirmed experimentally: the slope of the plot of $^2J_{HH}$ against ϵ is higher for formaldehyde than for phenylthi-iran (Fig. 11).

7. H–X–H Heteroatomic Fragments

H–H geminal coupling is transmitted not only via the carbon atom but also via any other atom X of the H–X–H fragment (Table 9).

Certain evident analogies with the $^2J_{HCH}$ constant (for example the identity of the sign and the similarity of the magnitudes of the $^2J_{HH}$ constants for CH_4, NH_3, N^+H_4, PH_3, $RCONH_2$, and $CH_2{=}CH_2$) suggest that many relations found for the H–C–H fragment are valid also for H–X–H. The increase of $^2J_{HH}$ in the series of $CH_4 < SiH_4 < GeH_4 < SnH_4$ can be explained qualitatively by an increase in the difference between the energies of the bonding and antibonding orbitals of the H–X–H fragment (Fig. 5), as a result of which the positive contribution by the $\psi_2 \rightarrow \psi_3$ transition becomes dominant[134]. The relatively high value of $^3J_{HH}$ for interaction between the bridge and "window" hydrogen

atoms in diborane indicates the presence of a stable three-electron bond[134]. Unfortunately the sign of this constant has not been determined, which makes comparison with theoretical calculations difficult[33].

Table 9. Geminal interactions between the protons of the H–X–H heteroatomic fragments.

Fragment	Compound	$^2J_{HH'}$, Hz	Refs.
H–B–H	B^-H_4	10.7	123
H···B–H	B_2H_6	7.0	124
H–C–H	CH_4	−12.4	37
H–N–H	NH_3	−10.35	125
	N^+H_4	−11.6	126
H–O–H	H_2O	7.2	127
H–P–H	PH_3	−13.2	128,129
H–S–H	H_2S	13.7	130
H–Si–H	SiH_4	+2.75	131,132
H–Ge–H	GeH_4	+7.69	133
H–Sn–H	SnH_4	+15.3	134
H–C–H ‖ H–N–H	$CH_2=CH_2$ $RCONH_2$	+2.5 +2.8	38 135

There is no doubt that more extensive studies and theoretical calculations of $^2J_{HXH}$ are of considerable importance for the understanding of the nature of geminal coupling.

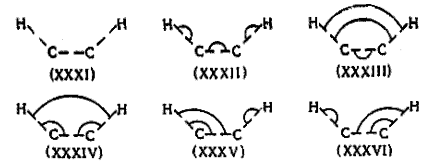
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In conclusion of the discussion of the H–H geminal constant, we may note that the constant contains information not only about the electronic structure of the molecule but also about the conformation of adjacent atomic fragments. Although the use of $^2J_{HH}$ for conformational analysis is at present limited by the inadequate knowledge of the orientation effect and the insufficiently clear separation of the contributions by different factors, one can reasonably suppose that these limitations will be overcome by systematic accumulation of experimental data and theoretical calculations. Then NMR spectroscopy will acquire a new parameter for the conformational analysis of molecules.

III. THE VICINAL CONSTANT $^3J_{HH}$

One can claim without exaggeration that spin–spin interaction between the vicinal protons of the H–C–C–H fragment deservedly attracted most attention. The $^3J_{HH}$ constants are widely and very successfully employed in structural analysis (in the determination of the number of adjacent protons and the nature of substitution in molecules), in the study of exchange processes (based on the "obliteration" of the multiplet structure of the spectra), and particularly in configurational and conformational analysis.

Calculation by the valence bond method of the constant for the interaction between vicinal protons in the six-electron system (XXXI) takes into account the mixing with the ground state (XXXII), in which electron pairing is complete, of the four excited states (XXXIII)–(XXXVI).

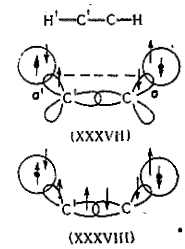


(XXXI) (XXXII) (XXXIII) (XXXIV) (XXXV) (XXXVI)

The electronic mechanism of the vicinal interaction is determined mainly by the polarisation of the "quasi-π" orbitals of the C–H and C–H bonds [(XXXIII) and (XXXVII)], which makes a positive contribution[136]:

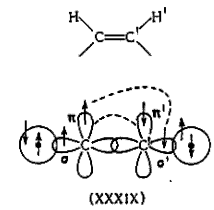
$$^3J \propto 3K(\sigma\sigma')/K(\sigma H)\,, \qquad (6)$$

where $K(\sigma H)$ is an integral with a constant value and $K(\sigma\sigma')$ depends on the relative positions of the σ and σ' orbitals. The mechanism of the consecutive transmission of spin–spin polarisation via the chain of atoms—Hund's mechanism[137] [formula (XXXVIII)]—also makes a positive, but probably very small, contribution.



(XXXVII) (XXXVIII)

Therefore, in contrast to the geminal constant, in the case of the H–H vicinal constant there is no competition between mechanisms with different signs. All the experimental $^3J_{HH}$ values available are positive.



(XXXIX)

If the carbon atoms of the vicinal fragments are separated by a double (or triple) π bond, additional contributions[138] [formula (XXXIX)] to the $^3J_{HH}$ constant are produced and are transmitted via a σ–π interaction mechanism—from the hydrogen atom to the carbon π orbital:

$$\Delta^3J(\sigma\pi) \propto K(\sigma\pi')K(\sigma'\pi)[K(\sigma H) + K(\pi\pi')]\,.$$

This contribution depends on the relative orientations of the C–H bond and the π orbital and is independent of the configurational orientation of the C–H bonds (*cis*- or *trans*-). Comparison of the theoretical relations for the contribution by the σ–π interaction to the vicinal coupling constant and for the hyperfine structure constant in the ESR spectra shows that the contribution by π electrons may be expressed in terms of experimental parameters[138]:

$$\Delta^3J_{HH'}(\sigma\pi) = h a_H(T) a_{H'}(T)/2\Delta E\,,$$

where $a_H(T)$ and $a_{H'}(T)$ are hyperfine coupling constants for the radical fragment H–Ċ=C and ΔE is the average singlet–triplet excitation energy. With $a_H(H-C_{sp^2}) = -65 \times 10^6$ Hz and $\Delta E = 6$ eV, +1.5 Hz was found for ethylene, and with $a_H(H-C_{sp}) = 95 \times 10^6$ Hz and $\Delta E = 8$ eV, +4.6 Hz was found for acetylene[138].

1. Dependence of $^3J_{HH}$ on the Stereochemical Factor

The $K(\sigma\sigma')$ exchange integral in Eqn. (6) depends on the dihedral angle θ between the H–C–C and C–C–H planes [139]. Hence follows the familiar Karplus relation [136] (Fig. 12), which constitutes the basis of the configurational and conformational analysis in NMR spectroscopy. Since the function $K(\sigma\sigma') = f(\theta)$ does not have an [exact] analytical expression, several versions of an analytical equation have been proposed to describe the variation of $^3J_{HH}$ with the stereochemical factor:

$$^3J_{HH} = k_i \cos^2\theta + C \begin{cases} k_1 & \text{for } 0° < \theta < 90° \\ k_2 & \text{for } 90° < \theta < 180°; \end{cases} \quad (7)\ [136]$$

$$^3J_{HH} = A\cos^2\theta - B\cos\theta + C; \quad (8)\ [6]$$

$$^3J_{HH} = \alpha\cos 2\theta - \beta\cos\theta + \gamma\ . \quad (9)\ [141]$$

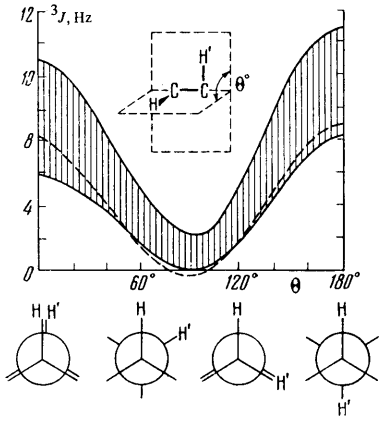


Figure 12. Variation of the vicinal constant $^3J_{HH}$ with the dihedral angle θ for the HC–CH saturated fragment. The dashed curve represents Karplus's theoretical calculation [138,141]. The shaded band corresponds to the most probable values of $^3J_{HH}$. Its upper limit is the curve for ethane [140].

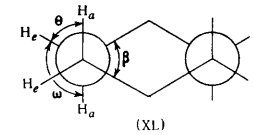
With appropriate values of the constant coefficients (all positive), these equations yield virtually coincident curves, so there is no fundamental difference between them. The choice of the equation is dictated by the suitability of its formulation. Eqns. (7) and (8) are usually employed.

The coefficients of Eqns. (6)–(8) have been evaluated theoretically [6,136,141], but these differ significantly from the experimental values (see Section III, 4). Therefore in the analysis of the conformational states of a particular series of compounds, it is recommended that these coefficients be determined empirically on the basis of models for the given series.

As an example, one may quote the determination of the HCCH dihedral angle in cyclohexane. At –100°C the rate of the "chair–chair" inversion is retarded so much that the individual signals due to the axial and equatorial protons are observed in the NMR spectrum of cyclohexane (5% solution in CS_2). The vicinal constants of these protons have been measured for 1,1′,2,2′,3,3′,4,4′-octadeutero-cyclohexane: $^3J_{aa}$ = 13.12 Hz, $^3J_{ae}$ = 3.65 Hz, and $^3J_{ee}$ = 2.96 Hz [formula (XL)]. [76] These data made it possible to determine by Eqn. (8) with $C = 0$ the $H_aC–CH_e$ dihedral angle ($\theta = 57°$) for $\omega = 118°$. The stereochemical relation for cyclohexane then becomes:

$$^3J_{HH} = 12.95\cos^2\theta - 0{,}26\cos\theta\ .$$

The value of θ obtained agrees extremely well with electron diffraction data for cyclohexane in the gas phase (CC–CC dihedral angle $\beta = 55.9°$). [142]

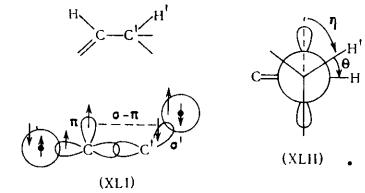


(XL)

When the values of $^3J_{HH}$ and the corresponding angles θ are plotted for compounds of different classes, a fairly broad band is obtained (Fig. 12). The scatter is due to the effect of a number of electronic and geometrical structural properties of the molecules, which are discussed below.

When vicinal protons interact in a system with an allylic double bond =CH–CH, an additional contribution by the interaction of the σ and π orbitals appears together with the interaction between σ orbitals (which depends on the orientation of the C–H bonds) [138,143,144] [formula (XLI)]:

$$\Delta^3J^{\sigma\pi}_{HH} \sim K(\sigma'\pi),$$



(XLI) (XLII)

The contribution is positive and depends on the projection angle η between the direction of the π orbital and the C–H bond [formula (XLII)]:

$$\Delta^3J^{\sigma\pi}_{HH} \propto \cos^2\eta \equiv \sin^2\theta\ .$$

The overall stereochemical relation for the vicinal interaction constant $^3J_{HH}$ for the =CH–CH fragment is (Fig. 13)

$$^3J_{HH} = {}^3J^{\sigma\sigma}_{HH} + {}^3J^{\sigma\pi}_{HH} = A\cos^2\theta - B\cos\theta + D\sin^2\theta\ . \quad (10)$$

The coefficients were determined empirically from data for a set of compounds with a fixed geometry: A = 9.1 Hz, B = 2.5 Hz, and D = 2.6 Hz. [145] D = 3.4 Hz was calculated theoretically [138]. Owing to the contribution by $^3J^{\sigma\pi}_{HH}$, the above stereochemical relation is smoother than the analogous relation for the saturated HC–CH fragment.

The coefficients in the stereochemical relations [Eqns. (7)–(9) and (10)] depend significantly on the nature of the compound containing the given CH–CH fragment. The most important factors are the geometry of the fragment (the H–C–C valence angle and the C–C bond length and also the nature and orientation of the X–CH–CH substituent.

2. Effects of the H–C–C Valence Angle and the C–C Bond Length

An increase of $^3J_{HH}$ for the CH=CH fragment of cycloolefins with increasing ring size has been observed experimentally [148,149] (Table 10). The H–C–C valence angle decreases in the same sequence, from about 150° for cyclopropene and about 135° for cyclobutene to the

normal value of about 120°. A similar tendency has been noted for $^3J_{HH}$ in aromatic systems. For example, the constant is ≤ 0.25 Hz for the three-membered cyclopropenium ring[152], 4.0 Hz for the five-membered azulene ring[153], 7.54 Hz for benzene[154], and 9.5 and 10.3 for the seven-membered azulene ring[153]. Possibly the reason for the variation of the vicinal constant with ring size arises from a number of factors, including the hybridisation of the carbon atoms, the degree of strain in the ring, and geometrical parameters of the CH=CH fragment. The above tendency may be represented[155] by a relation between $^3J_{HH}$ and the C–CH=CH valence angle (Fig. 14), which has been determined for many compounds by X-ray diffraction analysis.

Table 10. The $^3J_{HH}$ constants in the series of cycloolefins



n	1	2	3	4	5	6	7	8	9
$^3J_{HH}$, Hz	1.3 [149]	2.87 [150]	5.57 [151]	10.11 [151]	10.8 [146]	10.3 [146]	10.7 [146]	10.8 [146]	10.7 [146]

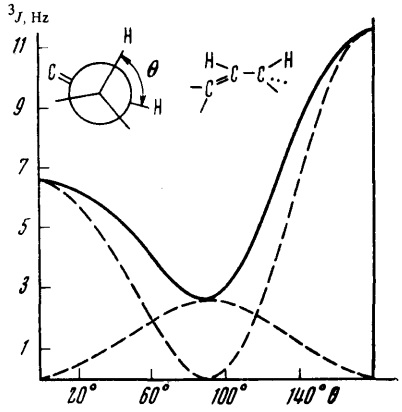


Figure 13. Variation of $^3J_{HH}$ for a vicinal fragment having an allylic double bond with the stereochemical factor[145]. The dashed curves represent the contributions by $^3J(\sigma\sigma)$ and $^3J(\sigma\pi)$.

The observed variation of $^3J_{HH}$ with the valence angle has been given a theoretical basis[27,141,161]. With increasing ring size, the distance between the hydrogen atoms diminishes and consequently the contribution by the canonical structures (XXXIII) and (XXXIV) increases, which leads to a higher vicinal constant. However, the theoretical values[141], 2.1 Hz for an H–C–C angle of 130°, 6.1 Hz for 120°, and 16.0 Hz for 110°, agree with the experimental data only qualitatively. The molecular orbital method gives a less critical sequence, namely 2.4, 5.7, and 10.1 Hz respectively[27] (see the dashed curves in Fig. 14).

It has also been shown theoretically[141] that the vicinal constant for the ethylene fragment *cis*-CH=CH decreases with the length R (Å) of the C=C bond:

$$^3J_{cisHH} = J_0[1 - 2.9(R - 1.35)], \quad (11)$$

where J_0 is the interaction constant for R = 1.35 Å.

The experimental data for carbocyclic compounds (cyclohexene, cyclohexa-1,3-diene, 1,2-dihydronaphthalene, benzene, and condensed aromatic compounds) also yield a linear relation[151]:

$$^3J_{cis} = -36.40R + 58.46,$$

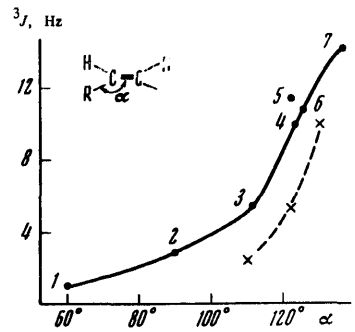


Figure 14, Variation of the vicinal constant $^3J_{cis}$ for an olefinic fragment with the valence angle α.[155] Experimental points: 1) cyclopropene[149]; 2) cyclobutene[150]; 3) cyclopentene[151]; 4) cyclohexene[151]; 5) ethylene[19]; 6) *cis*-but-2-ene[156]; 7) *cis*-di-t-butylethylene[155]. The X-ray diffraction data for compounds *3–7* were taken from Refs. 157–160. The dashed curve represents the theoretical calculation[27].

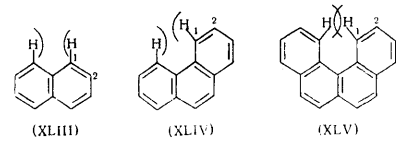
which agrees fairly well with the theoretical Eqn. (11): the ratio of the constants for bond lengths of 1.35 and 1.45 Å is 1.63, whereas Eqn. (11) predicts 1.41. For compounds of the type $R(CH{=}CH)_nCH{=}R'$ with a *trans*-configuration of the double bonds, it has been found that[162]

$$^3J_{transHH} = -81.85R + 127.86,$$

which yields the ratio $^3J_{1.35Å}/^3J_{1.45Å} = 18.4$, also in satisfactory agreement with theory.

It is noteworthy that the constants $^3J_{HH}$ for the above series of compounds[151,161] and also for a series of aromatic compounds[163,164], including charged five-membered rings[165], are linearly correlated with the C=C bond order calculated by the simple Hückel method.

When the vicinal protons come closer together in space in a series of condensed aromatic molecules, $^3J_{HH}$ deviates from the linear relation with the length and order of the bond[151].



(XLIII) (XLIV) (XLV)

The steric contraction effect leads to an increase of the $^3J_{1,2}$ constants by 0.08 Hz for naphthalene (XLIII), 0.30 Hz for phenanthrene (XLIV), and 0.50 Hz for benzo[*c*]phenanthrene (XLV). It has been suggested that the reason for the deviations is distortion of molecular geometry, and in the first place a decrease of the $H-C_1=C_2$ valence angle [151].

3. Effect of the Electronegativity of the Substituents

Many experimental data show that the constant $^2J_{HH}$ for the X–CH=CH fragment as a rule decreases with increasing electronegativity of the substituent X (Tables 11 and 12).

Table 11. Effect of the α-substituent X on the vicinal constant $^3J_{HH}$ (Hz).

X	CH_3CH_2X	refs.	CH_2=CHX			
			trans-H–H	refs.	*cis*-H–H	refs.
Li	8.90	167	23.9	96	19.3	96
$Si(CH_3)_3$	8.0	168	20.2	97	14.6	97
$H(^3J_0)$	8.0	38	19.1	38	11.5	38
CH_2R	7.53*	169	16.8**	98	10.0**	98
SCH_3	7.42	170	16.4	100,101	10.3	100,101
I	7.45	169	15.9	53	8.0	53
Br	7.33	169	15.0	53	7.2	53
$N(C_2H_5)_2$	7.13	169	16.1	99	9.4	99
Cl	7.23	169	14.8	53	6.9	53
OC_2H_5	6.97	169	14.5	100	7.0	100
F	6.9	171	12.6	53	4.6	53
$C^+(CH_3)_2$	5.2	172	—		—	
$N^+(CH_2R)_3$	7.4**	173	15.0*	102	8.5*	102
$O^+(C_2H_5)_2$	4.7	174	—		—	
k experiment	−0.09	41	−0.17	41,99	−0.34	41,99
k calculation (Ref.141)	−0.07		−0.25		−0.60	

*R=CH_3;
**R=H.

It has been established [41,42,99,166] that the relation is as a rule described by the additive equation

$$^3J_{HH} = {}^3J_0\left(1 + k\sum_i \Delta E_{X_i}\right), \qquad (12)$$

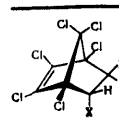
where $^3J_0$ is the interaction constant for the unsubstituted fragment (X=H), k a coefficient which depends on the class of compound (usually $k < 0$), and $E_X = E_X - E_H$ the difference between the electronegativities of the first atom of the substituent and hydrogen. The coefficients k found experimentally for substituted ethanes and ethylenes† (Table 11) agree satisfactorily with the values calculated theoretically [141] by the valence bond method taking into account ionic structures [175,176]. The dependence of $^3J_{HH}$ on the substituent is used to determine the mutual influence of the electronegativities of the groups of disubstituted ethylenes [177].

†On the basis of a set of disubstituted ethylenes XCH=CHY with a wider range of electronegativities of the substituents, non-linear relations of the type of Eqn. (4) have been found [71]:

$$^3J_{cis} = 91.2/(E_X+E_Y)-9.7,$$
$$^3J_{trans} = 75.0/(E_X+E_Y)+0.3.$$

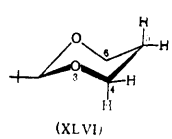
It is striking that the electronegativity of the substituent in the ethylene fragment affects the constant $^3J_{HH}$ for *cis*-protons much more than for *trans*-protons. The influence of the orientation of the substituent X must also be taken into account for the saturated fragments X–CH–CH, [178] otherwise erroneous conclusions concerning the conformation of the compound may be arrived at.

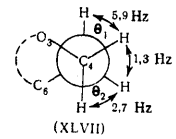
Table 12.

	Refs.	$^3J_{cis}$	$^3J_{trans}$
H	105	9.63*	3.67
C_6H_5	121	9.16	4.27
$SCOCH_3$	10	8.85	3.88
Br	107,108	8.4	3.5
Cl	121	8.20	3.16
OH	121	7.70	2.51
$OCOCH_3$	121	7.58	2.47
F	110	7.19	1.81
k	109	−0.14	−0.33

*$^3J_{endo\text{-}endo}$ = 9.17 Hz. [105]

We shall now consider an example of such influence. For 2-t-butyl-1,3-dioxan (XLVI), the dihedral angles θ_1 and θ_2 in the C_5–C_6 fragments (XLVII) should be identical (regardless of the distortion of the ring conformation) in consequence of their symmetrical disposition relative to the symmetry plane of the ring. The different values of $^3J_{HH}$ corresponding to these dihedral angles (5.9 and 2.7 Hz) [85] are due to the orienting influence of the electronegativities of the O_3 and C_6 atoms. Protons with θ_1 and $^3J_{HH}$ = 5.9 Hz have hydrogen and carbon atoms in the *trans*-position (the oxygen atom is in the *gauche*-position), while protons with θ_2 and $^3J_{HH}$ = 2.7 Hz have a hydrogen atom and an oxygen atom (which is more electronegative than the carbon atom) in the *trans*-position (the carbon atom is in the *gauche*-position). An even lower value $^3J_{HH}$ = 1.3 Hz corresponds to protons with carbon and oxygen atoms in the *trans*-position.

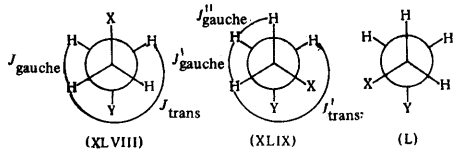

(XLVI)



(XLVII)

A systematic study of the orienting effect of substituents on the vicinal constants has been made for 1,2-disubstituted ethanes XCH_2CH_2Y. [179–186] A special technique for the interpretation of the variation of the observed constants, which have been averaged over the rotational states [formula (XLVIII)–(L)], with the polarity of the medium makes it possible to determine the constants J_{trans} and J_{gauche} for the *trans*-isomer (XLVIII) and the

constants J'_{gauche} and J''_{gauche} + J'_{trans} for the *gauche*-isomers (XLIX) and (L).[181,185]



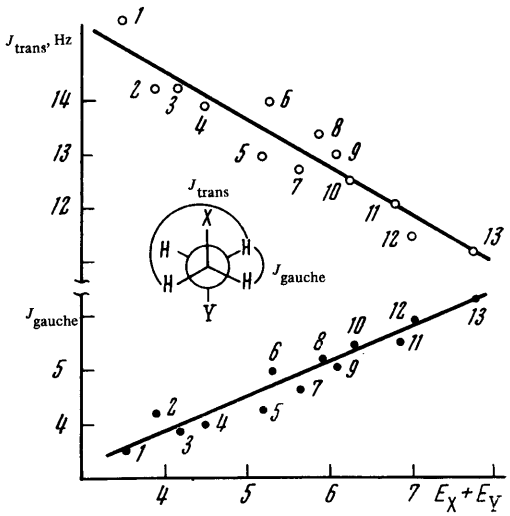


Figure 15. Variation of the vicinal constants for the *trans*-isomers of 1,2-disubstituted ethanes with the electronegativity of the substituents[185]. Substituents X and Y: 1) $C(CH_3)_3$, Li; 2) $C(CH_3)_3$, MgR_2; 3) $C(CH_3)_3$, AlR_3; 4) $C(CH_3)_3$, $Si(CH_3)_3$, 5) $C(CH_3)_3$, $C(CH_3)_3$; 6) I, I; 7) $C(CH_3)_3$, $N^+(CH_3)_3$; 8) Br, Br; 9) Cl, Br; 10) Cl, Cl; 11) F, Br; 12) F, Cl; 13) F, F. The data were taken from Ref. 1.79 for points *1*, *3*, and *4*, from Ref. 180 for point *2*, and from Ref. 185 for points *5–13*.

Fig. 15 shows the variation of J_{trans} and J_{gauche} for the *trans*-isomers with the sum of the electronegativities of the substituents X and Y. In agreement with the theoretical calculations[141], the J_{trans} constant decreases with increasing E_X and E_Y:[185]

$$J_{trans} = 14.28\,[1 - 0.062\,(\Delta E_X + \Delta E_Y)]\,. \qquad (13)$$

However, J_{gauche} increases with the electronegativity ($k > 0$):

$$J_{gauche} = 3.99\,[1 + 0.16\,(\Delta E_X + \Delta E_Y)], \qquad (14)$$

which is inconsistent with the theoretical prediction. The constant J_{ee} for *trans*-1,2-disubstituted 4-t-butylcyclohexanes[187], which corresponds to the same orientation relative to the substituents as J_{gauche} in 1,2-disubstituted ethanes, behaves in the same manner.

The coefficients J_0 in Eqns. (13) and (14) may be assumed to be identical with J_{trans} and J_{gauche} for unsubstituted ethane, if one postulates that in the *trans*-isomer the H–C–C–H dihedral angles are not distorted by substituents. In agreement with theory, the constants for the *gauche*-isomers are found to decrease as $E_X + E_Y$ increases[185]:

$$J'_{gauche} = 4.99\,[1 - 0.24\,(\Delta E_X + \Delta E_Y)], \qquad (15)$$

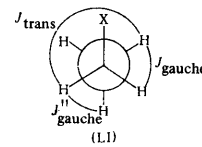
$$J''_{gauche} = 4.45\,[1 - 0.32\,(\Delta E_X + \Delta E_Y)], \qquad (16)$$

$$J'_{trans} = 13.95\,[1 - 0.043\,(\Delta E_X + \Delta E_Y)]. \qquad (17)$$

It is quite likely that the inconsistency between the coefficients J_0 for the *trans*- and *gauche*-oriented protons in the relations for the *trans*- and *gauche*-isomers [Eqns. (13)–(17)] indicates different dihedral angles, which may be due, in particular, to steric and electrostatic interactions between the substituents in the *gauche*-isomer. Moreover, the changes in the C–H and C–C bond lengths and in the H–C–C valence angles under the influence of substituents may play a definite role.

Nevertheless the coefficients $J_0 = 7.9$ Hz and $k = -0.074$ for the averaged vicinal constant $\langle J \rangle$ for monosubstituted ethanes (LI), calculated by the equation

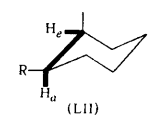
$$\langle J \rangle = (1/3)(J_{trans} + J_{gauche} + J''_{gauche}),$$



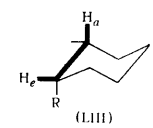
(LI)

and Eqns. (13), (14), and (16), agree satisfactorily with the experimental data (Table 11).

One must assume that the orienting effect of the substituent is in fact responsible for the observed inequality $^3J_{ae} > {}^3J_{ea}$ of the vicinal constants for six-membered rings (cyclohexanes[178,187], steroids[188]), while the dihedral angle is the same ($\theta \simeq 60°$). For example, in the series of 5β-steroids with a 3α-hydroxy- or acetate group (occupying an equatorial position), $J_{ae} \simeq 5.5$ Hz is observed [compound (LII)] and in the series of 5α-steroids with 3β-substituents (in the axial position), $J_{ae} \simeq 2.5$–3.2 Hz has been found [compound (LIII)].[189] In the first case the electronegative substituent has the *gauche*-orientation relative to the vicinal proton H_e and has virtually no effect on $^3J_{HH}$. In the second case the substituent occupies the *trans*-position relative to the proton H_a and therefore a significant effect of its electronegativity appears.



(LII)



(LIII)

The angular variation of $^3J_{HH}$ with the orientation of the substituent can be conveniently represented by a schematic relation between the coefficient k in Eqn. (12) and the dihedral angle ξ between the substituent X and one of the protons (Fig. 16). The greatest effect of the substituent is to be expected with the C–X and C–H bonds in the eclipsed and *trans*-positions.

Another type of orientation relation has been proposed[193] on the basis of an empirical treatment of a large number of experimental data for fragments of the type X_1X_2CH–CHX_3X_4:

$$^3J_{HH} = 11.3\cos^2\theta - 2.5\cos\theta + 1.8 - \left(0.4 + 1.2\cos^2\frac{3}{2}\theta\right) \cdot \sum_{i=1}^{4} \frac{1}{i}\,\Delta E_{X_i}.$$

Appropriate recalculation shows that this equation yields a result which differs significantly from the $k-\xi$ plot in Fig. 16. There is no doubt that the orientation effect of the substituent on the H–H vicinal constant requires further detailed experimental and theoretical study.

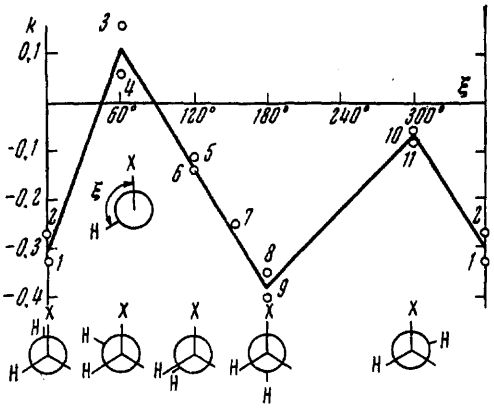
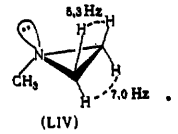


Figure 16. Variation of the effect of the electronegativity (k) of the substituent X on the $^3J_{HH}$ constant with the orientation of X relative to the interacting protons of the X–CH–CH fragment: 1) and 6) hexachlorobicyclo[2,2,1]-heptenes[109] ($\theta \simeq 120°$ and 0°); 2) and 7) cyclopropanes[190] ($\theta \simeq 147°$ and 0°); 3) and 10) *trans*-isomers of 1,2-disubstituted ethanes[185] ($\theta \simeq 60°$ and 180°); 4) and 8) *trans*- and *cis*-isomers of 1,2-disubstituted 4-t-butylcyclohexanes[187] ($\theta \simeq 60°$ and 180°); 5) bicyclo[2,2,1]heptenes[191] ($\theta \simeq 120°$); 9) and 11) 6β- and 6α-substituted 5α-cholestan-7-ones[192] ($\theta \simeq 60°$ and 180°).

An additional complication in the analysis of the effect of the electronegativity of the substituent on the vicinal constant arises from the fact that substituents do not have axial symmetry as a rule. The orientation of the C–X bond is especially significant for substituents having a lone electron pair. In particular, $^3J_{HH}$ in the series of five-membered heterocycles with X = S and O and also $^3J_{trans}$ in the series of four-membered ring compounds have high values, contrary to the expected low values (Table 13), while for three-membered heterocycles the usual tendency towards a decrease of $^3J_{HH}$ with increasing electronegativity of the atom X is observed. It has been suggested[86,198] that the lone electron pair of the heteroatom makes a positive contribution to the constant $^3J_{HH}$, which reaches 2.3 Hz[88] for the transoid orientation of the C–H bond relative to the axis of the lone pair atomic orbital. The higher value of the constant $^3J_{cis}$ for protons with *cis*-orientation relative to the substituent in *N*-methylaziridine (LIV) compared with $^3J_{cis}$ for protons with *trans*-orientation relative to N–CH_3 serves as a clear illustration[94]. In the first case the lone electron pair of the nitrogen atom occupies the transoid position relative to the C–H bonds of the interacting protons.



(LIV)

The orientation effect of the substituent gives rise to significant difficulties in the employment of H–H vicinal constants for the investigation of conformational equilibrium processes[200]‡. Even when a Karplus curve is plotted for the given class of compounds, the required accuracy in the determination of the statistical weight of the conformers from the average constant ^3J is not secured under conditions of a rapidly attained equilibrium[204].

Table 13.

X		CH_2	References	C=O	References	S	References	NH	References	O	References
	J_{cis}	8.98	55	—		7.15	63	6.3	63	4.45	63
	J_{trans}	5.57	55	—		5.65	63	3.8	63	3.08	63
	J_{cis}	10.4	194	10.4	70	8.93	195	—		8.65	196
	J_{trans}	4.9	194	6.4	70	6.27	195	—		6.87	196
	J_{cis}	7.4	197,198	7.2	197,198	10.0	199	8.83	199	10.7	197,198
	J_{trans}	4.6	197,198	2.2	197,198	7.5	199	8.85	199	8.3	197,198

There are certain data showing that the sign of the effect of electronegativity alternates with increase of the number of chemical bonds between the substituent and the fragment with vicinal protons[205]. The $^3J_{12}$ vicinal constant for the $XC_1H-C_2H-C_3H-C_4H$ chain decreases with the electronegativity of the substituent X ($k < 0$, see above), the constant $^3J_{23}$ increases ($k > 0$), and $^3J_{34}$ again decreases. A number of examples are presented in Table 14. It is noteworthy that the magnitude of the effect decays rapidly as the substituent becomes more remote. For example, the following formula has been found to represent the constant for the interaction of *ortho*-protons of monosubstituted benzenes[212]:

$$^3J_{23} \equiv {}^3J_{ortho} = 7.56(1+0.065\ \Delta E_X),$$

where k is smaller by a factor of 5 than for the *cis*-protons of monosubstituted ethylenes (Table 11). In order to observe the expected changes in $^3J_{34}$, a very high experimental accuracy is required.

4. Theroetical Calculations of $^3J_{HH}$

A complete *a priori* calculation[6] of vicinal constants has been made both by the valence bond[136,138,141,175,176,218] and molecular orbital[25–27,29–33,35,219,220] methods. However, the calculated values agree with experiment only qualitatively (Table 15). The difficulties encountered in the calculations apply generally to the quantum-chemical theory of complex chemical compounds. This is primarily

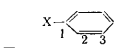
‡In the absence of conformational transitions or when the energy parameters of the conformations with respect to which $^3J_{HH}$ is averaged are equal, temperature has a very weak effect on the vicinal constant[46,48,52–54]. The solvent may be responsible for changes in $^3J_{HH}$ for polar molecules[201–203], but as a rule this effect is much weaker than the effect on the H–H geminal constant[121].

due to the approximate nature of the mathematical expressions for the physical quantities and the low accuracy of the estimates of the parameters entering into the equations.

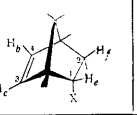
Table 14. Effect of substituents on the vicinal constants in the $XC_1H-C_2H-C_3H$ chain.

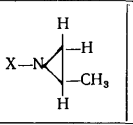
$XC_{(1)}H=C_{(2)}-C_{(3)}H_3$		J_{12}^{trans}	J_{23}
Li	206	22.2	4.2
$Ge(CH_3)_3$	207	19.2	4.8
$Si(CH_3)_3$	207	18.6	5.4
H	98	16.81	6.4
Br	208	13.5	6.8
Cl	208	13.2	6.9
F	208	11.1	7.0

$XC_{(1)}H_2C_{(2)}H_2C_{(3)}H_3$		J_{12}	J_{23}
H	209	7.35	7.35
Cl	210	6.3	7.4
NO_2	210	6.8	7.5
NO_3	210	6.5	7.6

		J_{23}	J_{34}
H	154	7.54	7.54
CH_3	211	7.68	7.48
Cl	212	8.05	7.46
Br	212	8.01	7.42
OCH_3	212	8.33	7.37

$XC_{(1)}H_2C_{(2)}H=C_{(3)}H_2$		J_{12}	J_{23}^{cis}	J_{23}^{trans}
H	98	6.4	10.02	16.81
CH_3	98	6.22	10.32	17.23
Cl	213	6.46	10.11	16.92
F	214	5.31	10.64	17.21

		$J_{12(ef)}$	$J_{34(bc)}$
H	191	(9.2)	5.8
COOH	191	8.5	5.7
Cl	191	8.2	5.6
$OCOCH_3$	191	7.9	5.4

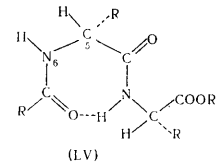
		$J_{22'}^{cis}$	$J_{22'}^{trans}$	J_{33}
$Si(C_2H_5)_3$	215	4.2	2.2	5.0
H	216	5.6	3.2	5.2
$SO_2C_6H_5$	217	7.2	4.5	5.5
Br	215	7.4	5.5	6.0

Therefore a semiempirical approach is promising. When an equation giving a correct description of the qualitative aspect of the spin–spin interaction (for example, the stereochemical relation) is available, it is possible to determine from the experimental data a number of parameters (for example, the overlap integrals, the exchange integrals, and the average excitation energies) of the theoretical equations. The values may be used to calculate other interaction constants or may be employed in other types of quantum-chemical calculations. In particular, the spin–spin interaction constants may serve as a basis for the calculation of the contribution by the spin-polarisation mechanism to the hyperfine structure constant of ESR spectra [13–17] and also the reactivities of compounds in scission [221] and bimolecular nucleophilic [222] reactions.

5. Vicinal Interaction in Heteroatomic Fragments

Experimental data show that, when the vicinal interaction is transmitted via the heteroatom (H–X–C–H), the sign of the $^3J_{HH}$ constant persists (Tables 16 and 17). It is quite likely that the properties of the vicinal interaction examined above for the HC–CH fragment hold also (at least qualitatively) for the HX–CH heteroatomic fragment. In particular, the higher value for the H–H *trans*-configuration relative to the *cis*-configuration is maintained (Table 16).

The variation of the HX–CH vicinal constant with the dihedral angle is particularly important for conformational analysis. For the CONH–C$^{\alpha}$HRR′ peptide fragment, a relation of this kind has been derived by analysing data for dipeptides with *trans*-amide bonds [240–244]. Since the N–CO bond has partial double bond character, a contribution to $^3J_{NHCH}$ by the π orbital of the nitrogen atom should be expected. Therefore the analysis was based on Eqn. (10). Positive values of its coefficients were chosen, since it is known that $^3J_{NHCH}$ for amide fragments is positive [135]. Since it has been pointed out that $^3J_{NHCH}$ for substituted N-methylanilines decreases with the electronegativity of the ring substituent [245], the effect of the substituent at C$^{\alpha}$ was taken into account by means of Eqn. (12). The coefficient $k = -0.1$ was chosen on the basis of experimental data for ethanes (Table 11 and Ref. 246).



(LV)

Table 15. Comparison of the experimental constants $^3J_{HH}$ (Hz) for the interaction of vicinal protons and the values calculated by the valence bond method (VB), the molecular orbital method without allowing for overlapping (MO) with allowance for overlapping (MO–O), with allowance for delocalisation (MO–D), and by the self-consistent field method with complete and partial neglect of differential overlapping (CNDO and INDO).

Compound	$^3J_{HH}$	Experiment	VB[136, 141]	MO[25]	MO–O[128]	MO–D[17]	CNDO[28]	INDO[28]
Ethane	$\langle J \rangle$	8.0±0.2[38]	4.3	5.5	5.2	5.8	6.76	8.38
	$J_{180°}/J_{60°}$	3.3	5.4	2.9	6.6	6.0	6.35	5.73
	$J_{cis\ 0°}$	13.0[a]	8.2	11.7	7.8	10.3	11.61	14.89
	$J_{trans\ 180°}$	15.0[a]	9.2	9.8	11.9	13.1	15.43	18.63
	$J_{gauche\ 60°}$	4.5[a]	1.7	3.4	1.8	2.2	2.43	3.25
	A[b]	12.0	9.0	10.8	9.6	11.7	13.52	16.76
	B[b]	1.0	0.5	−1.0	2.1	1.4	1.91	1.87
	C[b]	2.0	−0.3	~0.0	0.2	0.0	~0.0	~0.0[d]
Ethylene	J_{cis}	11.6±0.1[38]	7.6[c]	8.2[c]	7.4[c]	7.2[c]	8.04	9.31[d]
	J_{trans}	19.1±0.1[38]	13.4[c]	11.8[c]	18.3[c]	17.9[c]	19.50	25.15[d]
	J_{trans}/J_{cis}	1.65±0.02	1.77	1.44	2.48	2.49	2.40	2.70
Acetylene	$^3J_{HH}$	9.5±0.1[38]	11.6	6.5[c]	13.1[c]	8.9[c]	6.55	10.99
Benzene	$^3J_{HH}$	7.54±0.04[154]	—	—	7.24	7.6	7.55	8.15

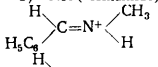
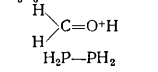
a. Found for 1,2-disubstituted ethanes taking into account the effect of electronegativity of the substituents [140].
b. The coefficients in Eqn. (8).
c. Taking into account the contributions of the π-electron systems for ethane (1.5 Hz) and acetylene (4.6 Hz) [138].
d. Application of the complete self-consistent field method showed that $J_{cis} = 9.6$ Hz and $J_{trans} = 20.1$ Hz. [32]

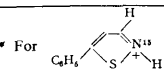
In view of the planarity of the group $\diagdown N-C\overset{O}{\diagup}$, there is no reason to expect in this case an orientation effect of the substituents R and R′ (see Section III, 3). Infrared spectroscopic data show that in a non-polar medium dipeptide molecules exist predominantly in the coiled form (LV) [246, 248], which limits significantly the range of permissible dihedral angles for the N_6H-C_5H fragment. The rotational states of this bond have been examined for two models

using the constants averaged with respect to the dihedral angles (*N*-methylformamide, Table 17). The model with the discrete angles $\theta = 0°$, 60°, 120°, 240°, and 300° led to the following ranges of allowed values (in Hz) of the coefficients of Eqn. (8):

$$8.0 \leqslant A \leqslant 9.8;\ 0.0 \leqslant B \leqslant (A - 8.0) \text{ and } C = 9.8 - A.$$

Table 16. The vicinal constants $^3J_{HH}$ for the *trans*- and *cis*-configurations in heteroatomic fragments.

Fragment	References	$^3J_{trans}$	$^3J_{cis}$
HC=CH (ethylene)	38	+19.1	+11.5
HC(=O)—NH (formamide)	135	+13.4	+1.7
	223	17.4	(4.2)*
	224	19.0	9.0
$H_2P—PH_2$	128, 129	+10.5	+6.8

* For  см. see Ref. 225

These data yield the region corresponding to the stereochemical relation between $^3J_{NHCH}$ and the angle θ bounded by the extreme curves in Fig. 17. The average values for this region may be fitted by the equation [240,241]

$$^3J_{NHCH} = 9.4\cos^2\theta - 0.5\cos\theta + 0.9\sin^2\theta. \quad (18)$$

Table 17. The vicinal constants $^3J_{HH}$ averaged over the rotational states for heteroatomic fragments with an X–Y single bond.

Fragment	Compound	⟨J⟩	Refs.	Fragment	Compound	⟨J⟩	Refs.
H—C—C—H	CH_3CH_3	+8.0	38	H—Si—P—H	H_3SiPH_2	5.1	236
H—C—P—H	CH_3PH_2	+8.2	226, 227	H—Si—As—H	H_3SiAsH_2	5.1	236
H—C—S—H	CH_3SH	+7.45	170	H—Ge—P—H	H_3GePH_2	4.8	236
H—C—P⁺—H	$(CH_3)_3P^+H$	5.48	228	H—Ge—As—H	H_3GeAsH_3	4.8	236
H—C—N⁺—H	$(CH_3)_3N^+H$	5.15	229	H—Ge—Ge—H	$H_3GeGeH_2(CH_3)$	3.9	237
H—C—O—H	CH_3OH	+5.08	230	H—Si—Si—H	H_3SiSiH_3	4.0	238
H—C—O⁺—H	$CH_3O^+H_2$	3.6	231	H—C—CH=C	$CH_3CH{=}CH_2$	+6.40	98
H—C—Ge—H	CH_3GeH_3	+4.22	133	H—C—CH=O	CH_3CHO	+2.83	48
H—C—Si—H	CH_3SiH_3	+4.68	232, 233	H—C—CH=O⁺	$CH_3CH{=}O^+H$	3.5	239
H—C—Sn—H	CH_3SnH_3	+2.7	233, 234	H—C—NH⋯	$CH_3NHCH(=O)$	+4.9	135
H—C—Pb—H	$(CH_3)_3PbH$	+1.47	234	H—C—N⁺H=	$CH_3N^+H{=}C(CH_3)_2$	5.0	223
H—B . . . P—H	$H_3B \ldots PH_3$	8.0	235				

The free rotation model with allowance for the maximum values of the constants $^3J_{NHCH}$ for the angle $0° \leqslant \theta < 90°$ (8.9 Hz for 5,6-dihydrouracils [254] and 8.0 Hz for valinomycin [250]) yielded narrower ranges of the coefficients:

$$8.9 \leqslant A \leqslant 9.8,\ 0 \leqslant B \leqslant (A - 8.9), \text{ and } C = 9.8 - A,$$

represented by the shaded region in Fig. 17. The equation corresponding to the average values for this region is of the form [242]:

$$^3J_{NHCH} = 9.6\cos^2\theta - 0.3\cos\theta + 0.5\sin^2\theta. \quad (19)$$

Comparison of Eqns. (18) and (19) shows that the result is almost independent of the choice of model for rotation relative to the N–C$^\alpha$ peptide bond.

The $^3J_{NHCH}(\theta)$ stereochemical relation has served as a basis of the conformational analysis of peptides and depsipeptides [240–244,255–258]. The dihedral angle θ determines the rotational state of the N–C$^\alpha$ bond, one of the two single bonds in the peptide fragment –CON–C$^\alpha$–CO.

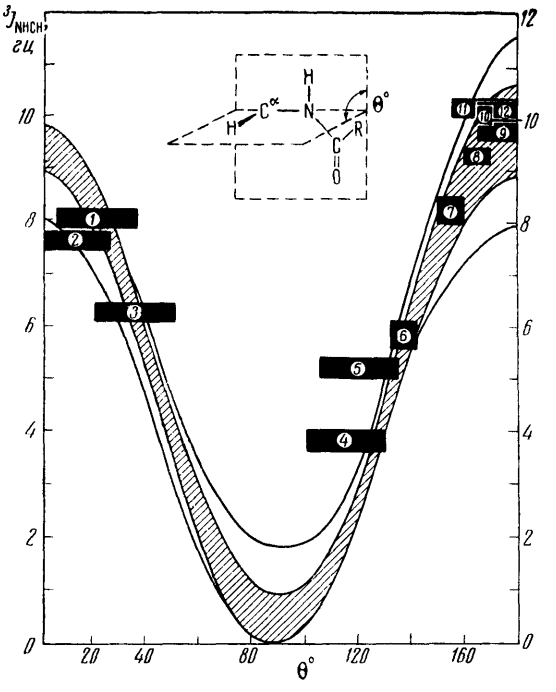


Figure 17. Stereochemical relation between the vicinal constant for the NH–CH peptide fragment and the dihedral angle θ. [240–244] The extreme curves bound the region calculated for the discrete-rotation model. The shaded region corresponds to the free-rotation model. The filled rectangles denote the experimental data for aminoacid residues: 1) D-valine of valinomycin in a non-polar medium [249]; 2) L-valine of valinomycin in a polar medium [249,250]; 3) L-valine of valinomycin in a non-polar medium [249]; 4) D-phenylalanine of gramicidin S in a polar medium [251]; 5) L- and D-valine of lincomycin in a complex with K^+ ion [249,250]; 6)–8) L-ornithine (1, 2, and 3) of alumichrome A in water [252] (X-ray diffraction analysis of ferrichrome-A) [253]; 9) L-ornithine of gramicidin S in a polar medium [251]; 10) D-valine of valinomycin in a polar medium [249,250]; 11) and 12) L-valine and L-leucine of gramicidin S in a polar medium [251].

The angle θ may be converted into the conventional angle [259] φ for the N–C$^\alpha$ bond by means of the following relations:

for L-aminoacid residues, $\varphi = 240 \pm \theta$.
for D-aminoacid residues, $\varphi = 120 \pm \theta$.

The preferred rotational states found from the $^3J_{NHCH}(\theta)$ relation have served as a basis for the determination of the conformations in solution of important biologically

active peptides and depsipeptides such as valinomycin [249,250,258], enniatin B [258,260], gramicidin S [251,258], antamanide [258,261], actinomycin D [262], oxytocin [263], alumichrome A [252], α-chymotrypsin substrates [264], and complexes of valinomycin and enniatin B with alkali metal cations. The data for valinomycin, gramicidin S, and alumichrome A, which have been reliably confirmed by data obtained by other methods, in particular by theoretical conformational and X-ray diffraction analysis, are plotted in Fig. 17.

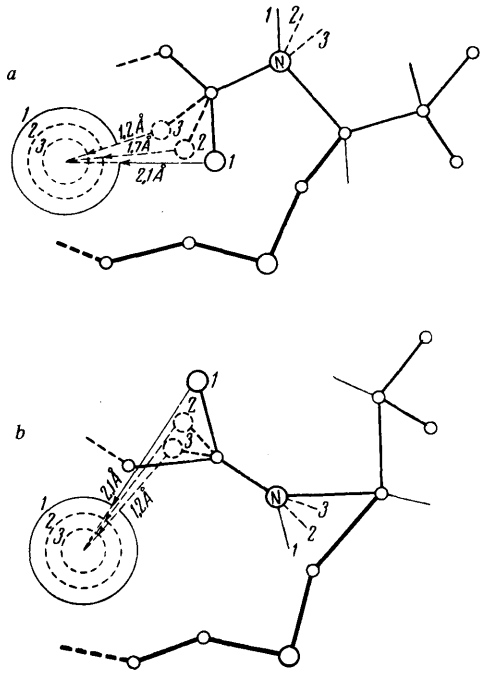
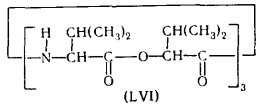


Figure 18. Effect of the dimensions of the complex cation on the orientation of the amide group of (tri-*N*-desmethyl)enniatin B in conformations P_1 (*a*) and P_2 (*b*).

As an example of studies on the conformations of cyclic antibiotics, one may quote the determination of the conformation of an analogue of enniatin B—(tri-*N*-desmethyl)-enniatin B (LVI)—in the formation of complexes with alkali metal cations [260].



(LVI)

Examination of molecular models showed that complexes may be formed when the cation enters the cavities in two conformations P_1 and P_2. With increasing diameter of the cation, an increase of the size of the inner cavity, formed by the carbonyl groups involved in ion–dipole interaction with the cations, may be expected (Fig. 18). Evidently the effective size of the cavity for a given ring size is determined by the orientation of the carbonyl groups. In a complex with a cation having a smaller diameter, the carbonyl oxygen should be closer to the centre of the molecule than in a complex with a larger cation. The change in the conformation of the complex with increasing size of the cation may be compared with the opening of a flower bud. Fig. 18 shows that such a change in the orientation of the carbonyl groups inevitably leads to the rotation of the CONH plane, which causes a change in the orientation of the N–H and C^{α}–H bonds, i.e. in the angle θ.

Table 18. The dihedral angles and the constants $^3J_{NHCH}$ for the complexes of (tri-*N*-desmethyl)enniatin B with univalent cations [260].

Calculation					Experiment		
	P_1		P_2				
diameter of cavity, A	θ,°	J, Hz	θ,°	J, Hz	cation	diameter of cation, A	$^3J_{NHCH}$, Hz
1.7	120	2.9	0	8.9	Li^+	1.40	4.9
2.7	130	4.6	10	8.6	Na^+	1.96	6.4
3.2	140	6.2	20	7.8	K^+	2.66	7.9
3.7	150	7.4	30	6.6	Rb^+	2.98	7.9
4.2	165	9.0	45	4.3	Cs^+	3.30	8.5

Analysis of molecular models shows that, with increase of the size of the inner cavity, the angle θ increases in the range 120–170° for conformation P_1 and in the range 0–60° for conformation P_2 (Table 18). It follows from the stereochemical relation for $^3J_{NHCH}$ that, with increase of the diameter of the cation, the constant should increase in the first case and decrease in the second. The experimental data for the complexes (LVI) with Li^+, Na^+, K^+, Rb^+, and Cs^+ demonstrate reliably that conformation P_1 obtains (Fig. 19). The knowledge of the steric structure of biologically active substances permits a more profound study of the mechanism of the action of these compounds, in particular the mechanism of the selective transport of cations across cell membranes.

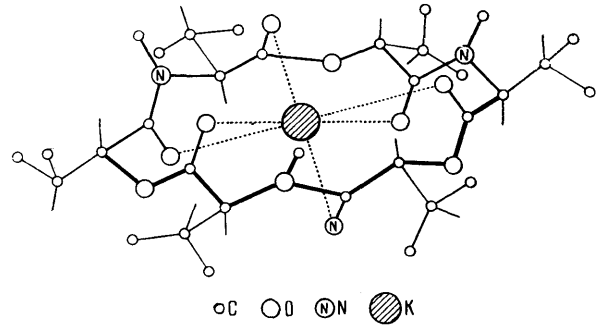


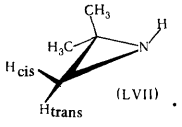
Figure 19. Conformation of the complex of enniatin B with the potassium ion.

The following relation has been found for six- and five-membered rings with a *cis*-amide bond (in contrast to compounds with a *trans*-amide bond) [265]:

$$^3J_{NHCH} = 9.3\cos^2\theta - 3.5\cos\theta + 0.3\sin^2\theta\ .$$

It differs appreciably from Eqns. (18) and (19), particularly in the range $0° < \theta < 60°$. Possibly the difference can be accounted for by the specificity of the electronic structure of the nitrogen atom, which is reflected in the value of the overlap integral $K(\sigma\sigma')$ for an electronic structure of type (XXXIII), in the *trans*-amide bond and in relatively strained systems with a *cis*-amide bond.

The measurement of the ^3J(NH–CH) constants for amines is very difficult owing to the high mobility of the NH proton and requires careful elimination of catalytic acid and basic impurities. The data for 2,2-dimethylaziridine (LVII), $^3J_{cis} = 7.5$ Hz and $^3J_{trans} = 10.2$ Hz,[266] which indicate a dependence of the constant on the dihedral angle, are noteworthy. In ammonium salts the proton exchange involving the N⁺H group is significantly retarded, which facilitates the measurements of the constants for the coupling of the N⁺H–CH protons particularly in highly acidic media.



(LVII).

A definite indication of the dependence of this constant on the stereochemical factor has been obtained[267] for protonated benzylamines $C_6H_5CH_2N^+HRR'$. Approximate analysis showed that, for the CH–N⁺H fragment, the constant $^3J_{trans,\ 180°} > 9.45$ Hz and $^3J_{gauche,\ 60°} < 3.15$ Hz.[267]

The constant for the HO–CH fragment in alcohols was found to depend on the stereochemical factor[268]:

$$^3J_{HCOH} = 10.4\cos^2\theta - 1.5\cos\theta + 0.2\ .$$

Owing to conformational factors, $^3J_{HCOH}$ for the equatorial OH group in cyclohexanols is higher by 1.0–1.5 Hz than for the axial group[230,269].

Incomplete data indicate the existence of a similar relation for the HS–CH fragment with $^3J_{gauche} < 4.03$ Hz and $^3J_{trans} > 14.9$ Hz.[270,271]

Valence bond theory predicts[17], on the basis of hyperfine structure constants of ESR spectra, the following relations for the HN–CH and HO–CH fragments:

$$^3J_{HNCH} = 12\cos^2\theta + 0.2, \qquad (20)$$

$$^3J_{HOCH} = 10\cos^2\theta - 1.0. \qquad (21)$$

The agreement with experiment for the HN–CH fragment is fairly satisfactory except that Eqn. (20) does not reflect the difference for dihedral angles of 0° and 180°. An additional discrepancy for the HO–CH fragment is that the predicted negative sign of $^3J_{HOCH}$ for $\theta = 90°$C is not confirmed by experiment.

Deviating somewhat from the subject of the review, we may mention that stereochemical relations, described by equations of type (7)–(9), have been established for the interaction of the vicinal H and ^{19}F(HC–CF) nuclei[110,272,273]:

$$^3J_{HF} \simeq 37.5\cos^2\theta - 6.5\cos\theta,$$

and H and ^{31}P(HC–CP) nuclei[274–279]:

$$^3J_{HP} \simeq 25\cos^2\theta - 9\cos\theta.$$

There are also important grounds for the expectation that analogous relations should hold for the (^{31}P–O–C–H),[277–282] (^{14,15}N–C–C–H),[276,283–285] (^{13}C–C–C–H),[286] and (^{199}Hg–C–C–H)[287] vicinal constants. Special emphasis must be laid on the importance of a future determination of the stereochemical characteristic of the constant $^3J_{^{15}NCCH}$ for the HC$^{\alpha}$–CO–^{15}N peptide fragment, which would make it possible to determine the rotational conformation of the peptide chain at the C$^{\alpha}$–C(O) bond (angle ψ). NMR spectroscopy would then make it possible to establish completely the conformation of peptides, since the rotational state of the NH–C$^{\alpha}$H bond (angle φ) may be determined from the constant $^3J_{HNCH}$ (see above).

It has been shown theoretically for the H–C–C–X fragments, where X = B, C, N, O, or F, that the $^3J_{HX}$ interaction constants are positive because the contribution by orbitals not involved in valence bonds is decisive.

Without exaggeration, one may claim that the stereochemical relations for vicinal fragments are of the greatest importance for conformational analysis by the NMR method. The determination of the relations for new fragments leads to many possible applications of a physicochemical method as powerful as NMR spectroscopy in the study of conformational states of a wide variety of compounds.

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Summarising the present state of the theoretical and empirical relations, one may conclude that the geminal and vicinal H–H spin–spin coupling constants are extremely sensitive to fine details of the electronic and steric structures of molecules§. In a comprehensive approach, the H–H constant constitutes an effective research tool, but this NMR spectroscopic parameter must be employed with caution, bearing in mind the complete set of effective factors involved. Probably at present the empirical approach to relations governing the interaction constants is more promising than direct theoretical calculations, which necessarily involve serious approximations. However, the theoretical approach makes it possible to find the "guide lines" for a systematic arrangement of experimental data.

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§As the NMR spectroscopic technique is improved, more distant spin–spin interactions, via four and more chemical bonds, are acquiring increasing importance for structural and conformational analysis. A number of interesting reviews have been devoted to such interactions[44,289,290]. The dependence of $^4J_{HH}$ on the steric structure of the H–C–C–H fragment, determined on the basis of experimental data[10,291] significantly complements the vicinal constant $^3J_{HH}$ in conformational analysis by the NMR method[107,108,292,293].

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