APPLICATION OF NMR SPECTROSCOPY FOR THE STUDY
OF THE THREE-DIMENSIONAL STRUCTURES
OF HYDROGENATED HETEROCYCLES (REVIEW)

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A review of the dependences of the direct, geminal, vicinal, and long-range spin–spin coupling constants on the valence, dihedral, and torsion angles, and on the electronegativities and orientations of the heteroatoms is given. The empirical and nonempirical dependences for the constants with participation of the nuclei of the ^1H, ^{13}C, ^{14}N, ^{15}N, ^{19}F, ^{31}P, ^{29}Si, ^{119}Sn, and ^{199}Hg isotopes are presented.

High-resolution NMR spectroscopy has currently become one of the widely used physical methods for the investigation of the chemical and three-dimensional structures of molecules of organic compounds in liquids and solutions. The application of the NMR method to the study of the structures of heterocyclic compounds is particularly effective. The presence of an endocyclic heteroatom leads to an increase in the internal chemical shift between the methylene and methylidyne protons and also between the nuclei of carbon-13, and this facilitates the qualitative interpretation and quantitative analysis of the NMR spectra.

This review is devoted to general problems in the application of NMR spectroscopy to the study of conformations, primarily those of saturated heterocycles. In this paper we will not set out to give a review of all of the extensive information devoted to the determination of the three-dimensional structures of heterocycles by the NMR method; only those publications that most clearly illustrate the general approach in a methodical respect will be discussed, although the scientific and practical value of other studies not mentioned here may undoubtedly be very great.

The currently accepted classification of nuclear spin systems and the methods for extraction of the principal spectral parameters — the chemical shifts (δ_i) and spin–spin coupling constants (SSCC) — from the NMR spectra have been described in monographs [1-6], reviews [7, 8], and special manuals [9]; catalogs and atlases of NMR spectra [10] are of great assistance in studies of this kind. After determination of the δ_i shifts and SSCC, one faces the problem of their use for the establishment of the three-dimensional structure of the molecules of the investigated compound.

A fragmentary summary of the most important stereochemical NMR dependences of the $^nJ_{NN'}$ and δ_i parameters in a form suitable for practical use is presented below. The problem of the proton–proton geminal and vicinal SSCC is described within a more general framework in a review by V. F. Bystrov [11].

PART I. SPIN – SPIN COUPLING CONSTANTS
AND CONFORMATIONS OF HETEROCYCLES

1. Dependence of the Vicinal $^3J_{HH'}$ Constant on the Dihedral
Angle. Effect of the Electronegativities of the Heteroatoms

The vicinal $^3J_{HH'}$ proton–proton SSCC has the most extensive application in the conformational analysis of hydrogenated heterocycles by the ^1H NMR method. The dependence of this constant on the dihedral angle (θ) in ethane has been examined repeatedly theoretically by the valence bond (VB) [12] and MO [13, 14] methods and is satisfactorily described by the Karplus equation [12]

$$^3J^{\circ}_{HH'} = A + B \cdot \cos\theta + C \cdot \cos 2\theta, \tag{1}$$

where the values A = 7 Hz, B = −1 Hz, and C = 5 Hz are assumed on the basis of experimental data [15]. It was later [16] proposed that the angular dependence be represented in the form

$$^3J_{HH'} = \begin{cases} 8.5\cos^2\theta - 0.28, & 0° \leqslant \theta \leqslant 90°; \\ 9.5\cos^2\theta - 0.28, & 90° \leqslant \theta \leqslant 180°. \end{cases} \qquad (2)$$

Dependences (1) and (2) and dependences similar to them [17, 18] fit into the sufficiently broad cross-hatched region of $^3J_{HH'}$ values shown in Fig. 1. It is apparent from Fig. 1 that the $^3J_{HH'}$ constant reaches its maximum value of 9.5-16 Hz when $\theta = 180°$, is 6.0-10 Hz when $\theta = 0°$, and becomes small or equal to zero in the vicinity of a right angle. The scatter in the $^3J_{HH'}$ values for a given θ is due to the effect on the coupling nuclei of a number of electronic and geometrical factors. The most important factors are listed below.

1) A change in the electronegativities (EN) of substituents X attached to the fragment under consideration; the average vicinal constant decreases linearly as the sum of the EN of the substituents increases in accordance with the additive equation [15, 19-22]

$$^3J^{\,exp}_{HH'} = {}^3J^{\circ}_{HH'} \left(1 - \lambda \sum_i \Delta E_i\right), \qquad (3)$$

where $^3J^{\circ}_{HH'}$ is the coupling constant for the unsubstituted ethane fragment, ΔE is the difference in the EN of the substituent and the hydrogen atom,* and constant $\lambda = 0.07$ satisfactorily describes the phenomenon in compounds with free rotation or pseudorotation (in the rings) about the $C-C$ bond in the ethanelike fragment. Here the changes in $^3J_{HH'}$ correspond physically to electron transfer from the $C-H$ bonding to the $C-X$-antibonding MO.

2) A change in the $H-C-C$ valence angles; an increase in these angles usually leads to a decrease in the coupling constant.

3) A change in the $C-C$ bond length; an increase in R_{C-C} leads to a decrease in the coupling constant.

4) A change in the hybridization of one of the carbon atoms; the $^3J_{HH'}$ constant is usually smaller for $H-C_{sp^3}-C_{sp^2}-H$ than for $H-C_{sp^3}-C_{sp^3}-H$; this decrease is manifested more markedly in the interval $0° \leq \theta \leq 50°$ than in the interval $50° \leq \theta \leq 130°$, whereas, on the other hand, the constants increase and are not equal to zero when $\theta \sim 90°$ [11].

If one of the carbon atoms is included in the composition of three-membered heterocycles containing O and S atoms, the vicinal constant is described by the equation [23]

$$^3J_{HH'} = 5.1\cos^2\theta, \; 0° \leqslant \theta \leqslant 90°. \qquad (4)$$

It would seem that the relatively broad range of $^3J_{HH'}$ values presented in Fig. 1 lowers the potential value of the dependence of $^3J_{HH'}$ for purposes of conformational analysis. However, experience has shown that this is not so. This can be illustrated in the case of the analysis of the PMR spectrum of 3,4-dimethyl-6-phenyltetrahydro-1,3-oxazine (I) (Fig. 2). In this case one can, in principle, assume chair and twist conformations and several boat forms for the heteroring or the existence of ring interconversion. From the assignment of the lines and the scheme of the spin-spin splittings presented in Fig. 2 it may be seen that the spectrum corresponds primarily to a chair conformation for the ring and cis-4-methyl-6-phenyl configuration for I. The chair conformation can be judged from the fact of reversal of the chemical shifts of the methylene protons attached to the $C_{(5)}$ atom (the equatorial proton resonates at higher field than the axial proton). This phenomenon is typical for 1,3-heterocycles (O and N) in the chair conformation [24, 25]; the $^3J_{4a5a} = 11.0$ and $^3J_{6a5a} = 10.7$ Hz values for the vicinal constants, in conformity with the graphs in Fig. 1, indicate an axial-axial ($\theta = 180°$) orientation of the $C-H$ bonds at the $C_{(4)}$ and $C_{(6)}$ atoms and the $C-H_a$ bond at $C_{(5)}$, whereas the $^3J_{6a5e} = 3.3$ and $^3J_{4a5e} = 3.5$ Hz values, which correspond to a dihedral angle θ of $\sim 60°$, confirm the correctness of the selected orientation of the substituents and the form of the carbon portion of the heteroring. The absence of reversal of the chemical shifts of the 2-H_e and 2-H_a protons repudiates any unsymmetrical boat conformation [25], and the geminal $^2J_{2a2e}$ value of -10.7 Hz constitutes evidence for an axial orientation of the $N-CH_3$ bond (see point 5c below) and corresponds to the chair form. If the primary conformation were the 2,5- or 1,4-twist form, the form of the spectrum and the $^3J_{HH'}$ values would have been completely different,† just as in the case of fast (on the NMR time scale) conformational transitions.

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*The introduction into our examination of differences ΔE_i in place of the E_i values themselves is convenient in that the $^3J^{\circ}_{HH'}$ coefficient in front of the parenthesis in Eq. (3) is a constant for ethane for the θ value under consideration.

†Cases of this type will be discussed in the second part of the review, which is devoted to the stereochemical factors that affect the chemical shifts and to the application of the SSCC and δ_i values to the study of the three-dimensional structures of the molecules of specific heterocyclic compounds.
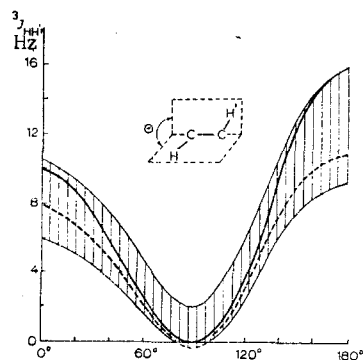
Fig. 1. Dependence of the vicinal proton–proton
constant on dihedral angle θ. The continuous
heavy line corresponds to the data in [17], while
the broken line corresponds to the data in [14].
The upper and lower boundaries of the cross-
hatched region include cases in which one of the
intermediate carbon atoms is in the sp^2-hybrid-
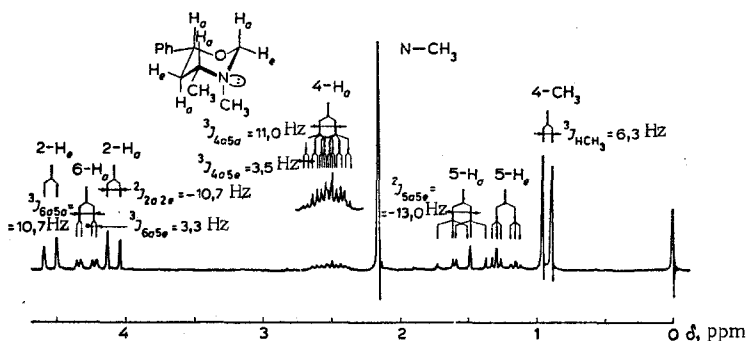ized state.

Fig. 2. PMR spectrum of 3,4-dimethyl-6-phenyltetrahydro-1,3-oxazine (I)
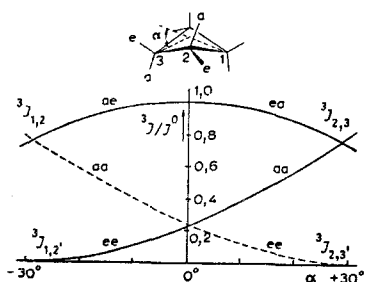(10% by volume solution in CCl at 28°C and 100 MHz).

Fig. 3. Character of the change in the vicinal
$^3J_{HH'}^{cis} = {}^3J_{ae}$ and $^3J_{HH'}^{trans} = {}^3J_{aa}$ constants in four-
membered rings as a function of α.

The example examined above shows the fruitfulness of the use of the Karplus dependence $^3J_{HH'} = f(\theta)$ in
the analysis of six-membered heterocycles. The application of this dependence to stereochemical problems of
five-membered heterocycles leads to extremely approximate data on the geometry of the molecule. A more
accurate approach requires allowance for the effect of the electronegativity and the orientation of the hetero-
atoms on $^3J_{HH'}$; this will be examined in detail below, while the conformational analysis of five-membered
heterocycles on the basis of PMR data will be discussed in part II of this review.

TABLE 1. Comparison of Torsion Angles ψ and θ_{ae} Found by the R-Factor Method and Calculated with Allowance for the Electronegativites and Orientations of the Substituents in Conformationally Labile Six-Membered Heterocycles

Compound	$^3J_{ae}$, Hz		Torsion angles, deg.	
	calc.	exptl.	ψ	θ_{ae}
Piperazine [33]	3,14	3,04	58	60
1,3-Dioxane [36]	2,29	2,78	58	57
1,4-Dioxane [33]	2,29	2,78	58	57
Morpholine [37]	2,75	3,04*	58	58
1,3-Dithiane [38]	2,75	3,5	59	61
1,4-Dithiane [33]	3,75	2,40	65	66
1,4-Oxathiane [37]	3,14*	2,65*	62	62
1,4-Diselenane [33]	3,81	2,43	64	66
d_2-4,4-Tetrahydropyran [39]	3,14*	3,87*	56	57
d_2-4,4-Piperidine [39]	3,48*	3,77*	57	59
d_2-4,4-Thiane [39]	3,75*	3,26*	61	62
d_2-4,4-Selenane [39]	3,78*	3,09*	61	63
d_2-4,4-Tellurane [39]	3,91*	3,12*	61	63
d_8-3,3,4,4,5,5,6,6-Cyclohexane [40]	3,75	3,73	58	60

*The $^3J_{HH'}^{cis}$ value presented is the average of two different $^3J_{a'e}$ and $^3J_{ae'}$ constants.

TABLE 2. Calculated Torsion Angles ψ and θ in Conformationally "Rigid" (primary chair conformations) Six-Membered Heterocycles

Compound	Coupling protons	$^3J_{HH'}^{calc*}$, Hz	$^3J_{HH'}^{obs}$, Hz	Torsion angles, deg	
				ψ	θ
cis-2-(5-Bromo-2-furyl)-4-methyl-1,3-dioxane (VII)†	6e5e	1,69	2,0	54	58
	6e5a	4,18	5,0		58
	6a5e	2,0	2,9		56
	6a5a		11,3		
2-tert-Butyl-1,3-dioxane (XII) [41]	4e5e	1,69	1,3	53	63
	4e5a	4,18	5,0		57
	4a5e	2,0	2,6		56
	4a5a		10,8		
cis-2-Phenyl-3,4-dimethylmorpholine (XIII) [42]	2a3e	1,94	2,7	—	55
1,3-Propanediol sulfite (XIV) [24]	4e5e	1,69	3,0	57	50
	4e5a	4,18	4,56		59
	4a5e	2,0	3,0		53
	4a5a		12,0		
1,3-Propanediol selenite (XV) [24]	4e5e	1,69	3,0	57	50
	4e5a	4,18	4,6		59
	4a5e	2,0	3,0		53
	4a5a		12,0		
trans-2-Methoxy-4-methyl-1,3,2-dioxaphosphorinane (XVI)†	6e5e	1,69	2,0	57	58
	6e5a	4,18	4,5		59
	6a5e	2,0	2,5		56
	6a5a		12,5		

*Calculated under the assumption that ψ =60°.

†According to the data of the present research.

The justification for the direct application of dependences (1)-(3) to four- and three-membered heterocycles is not obvious. Experience shows that in four-membered rings the vicinal constants between the cis protons usually have higher values than those between the trans protons [26]. This observation does not contradict the Karplus dependence of the form $^3J = J° \cdot \cos^2\theta$. It may be understood that saddle angle $\beta = 180° - \alpha$ determined dihedral angle θ between the C−H bonds. This dependence for valence angle $\gamma = 109°28'$ is depicted in Fig. 3 in terms of the ratio $^3J/J° = \cos^2\theta$ for the constants $^3J_{HH'}^{cis} = J_{ea}$ and $^3J_{HH'}^{trans} = J_{aa}$ (or J_{ee}). The realiza-
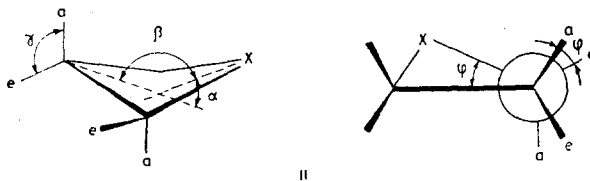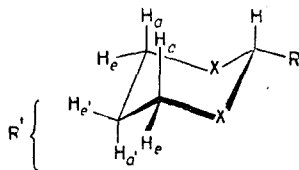
TABLE 3. Vicinal $^3J_{HH'}$, SSCC, R Factors Calculated from Them, and Torsion Angles ψ and θ_{ae} in 2,5-Disubstituted 1,3-Dioxanes and 1,3-Dithianes

X	R	R'	Isomer	bp, °C (mm)	SSCC, Hz				R factor	Torsion angle, deg	
					$^3J_{aa'}$	$^3J_{ee'}$	$^3J_{ae'}$	$^3J_{ea'}$		ψ	θ_{ae}
O	CH$_3$	i-C$_3$H$_7$	trans	58,6 (12)	10,5	3,0*	—	4,5	1,78	55	56
			cis	50 (12)	12*	2,5	3,1	—	1,91	56	52
O	i-C$_3$H$_7$	i-C$_3$H$_7$	trans	80,5 (11)	10,3	3,0*	—	4,7	1,72	54	55
			cis	74,5 (11)	12*	1,9	3,0	—	1,81	55	53
S	CH$_3$	CH$_3$	trans	mp 54,5°	9,0	4,4†	—	4,5	1,49	52	56
			cis	58 (2)	12,4†	3,1	4,5	—	1,72	54	56
S	CH$_3$	i-C$_3$H$_7$	trans	72 (1)	9,0	4,4†	—	5,0	1,34	50	54
			cis	69 (1)	12,4†	4,0	4,0	—	2,05	57	58
S	i-C$_3$H$_7$	CH$_3$	trans	73 (1)	9,0	4,4†	—	4,0	1,67	54	58
			cis	71 (2)	12,4†	3,0	4,5	—	1,71	54	56
S	i-C$_3$H$_7$	i-C$_3$H$_7$	trans	mp 41°	9,0	4,4†	—	4,5	1,49	52	56
			cis	98 (2)	12,4†	4,2	4,2	—	1,97	57	57

*Taken from [24].

†Taken from [46]

tion of the relationship $J^{cis} > {}^3J^{trans}$ or $^3J^{trans} > {}^3J^{cis}$ depends not only on deformation angle α but also on the form of heteroatom X in the ring. If one disregards the electronegativity and the orientation of X, for the trans constants one can write the expressions

$$J_{aa} = J°(180°) \cdot \cos^2(\gamma' + \varphi);$$
$$J_{ee} = J°(180°) \cdot \cos^2(\gamma' - \varphi), \tag{5}$$

where φ is the angle of rotation about the C–C bond (see formula II), and γ' is the projection of valence angle γ on the plane of the Newman projection. One can then determine φ from the J_{aa}/J_{ee} ratio [27]:

$$\tan \varphi = \frac{b-1}{b+1} \tan(\gamma' - 90°), \tag{6}$$

where $b = \sqrt{J_{aa}/J_{ee}}$. Angles φ and α are related by the expression $\sqrt{2} \tan \frac{\alpha}{2} = \tan \varphi$; consequently, taking expression (6) into account, we have

$$\tan \frac{\alpha}{2} = \frac{1}{\sqrt{2}} \frac{b-1}{b+1} \tan(\gamma' - 90°). \tag{7}$$

An analysis of the PMR spectra of 2-substituted oxetanes (X=O) shows that $J^{cis} > J^{trans}$ and that, according to expression (7), deformation angle $\alpha \sim 5°$, whereas in 2,3-disubstituted oxetanes [28], $J^{trans} > J^{cis}$, and the deformation angle should then increase. In 2-substituted (CH$_3$ and Ph) azetidines (X=NR) $J^{trans} > J^{cis}$, and the deformation angle lies in the 15-20° range [27].

Conformational problems are absent in three-membered heterocycles. Here, according to Eq. (4), the vicinal $^3J_{HH'}$ constants should be smaller than those expected from expressions (2). In fact, in monosubstituted oxiranes $^3J_{HH'}^{cis} \sim 3.6$-5.5 and $^3J_{HH'}^{trans} \sim 1.5$-2.8 Hz [29, 30], as in the case of ethylene sulfide ($^3J_{HH'}^{cis} = 7.1$ and $^3J_{HH'}^{trans} = 5.6$ Hz [31]).

2. Vicinal $^3J_{HH'}$ Constants, "R Factors," and Ring

Torsion Angles ψ in Six-Membered Heterocycles

Above in the case of the 1,3-oxazine ring we demonstrated that in the case of six-membered heterocycles one can select from the vicinal $^3J_{HH'}$ constants one of the possible canonical forms (chair, half-chair, twist, boat, and others) as the primary form or establish within which set of conformations the conformational transitions occur. One can further set up for oneself the following problem with respect to the estimation of the
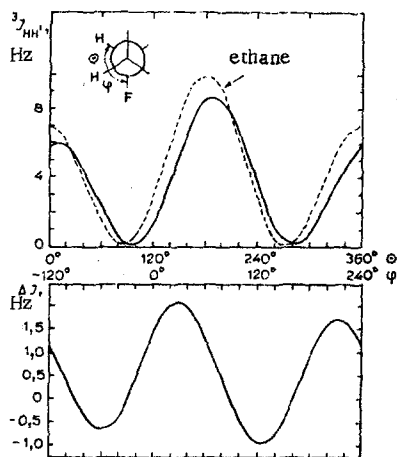
Fig. 4

Fig. 5

Fig. 4. Dependence of the calculated vicinal constants for ethane and fluoroethane on dihedral angle θ (upper graphs) and the difference $\Delta J = J_{HH'}^{ethane} - J_{HH'}^{fluoroethane}$ as a function of phase angle $\varphi = \theta - 120°$ (lower graph).
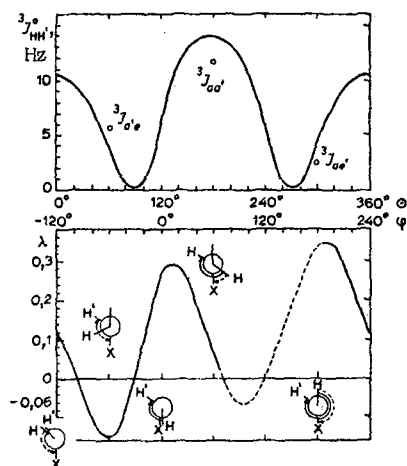
Fig. 5. Dependence of the "ethanelike" experimental vicinal $^3J_{HH'}$ constant on dihedral angle θ (shown by the continuous arc on the Newman projections and of coefficient λ on phase angle $\varphi = \theta - 120°$ (shown by the broken arc). The points correspond to the experimental $^3J_{HH'}$ constants in the "rigid" 1,3-dioxane ring.

degree of distortion of the "ideal" (canonical) conformation as a function of the configuration of the stereoisomers and the character and position of the substituents. One of the methods for the estimation of the distortion of a conformation is the R-factor method. This method was proposed by Buys [32] and does not require one to take into account the various effects that influence the $^3J_{HH'}$ constant. The R factor [33] is equal to the
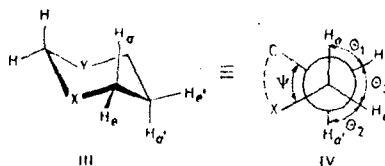
ratio of the average values $\langle ^3J_{HH'}^{trans} \rangle$ and $\langle ^3J_{HH'}^{cis} \rangle$ (the angular brackets designate averaging):

$$R = \frac{<^3J_{HH'}^{trans}>}{<^3J_{HH'}^{cis}>} = \frac{\frac{1}{2}\,(^3J_{aa'} + {}^3J_{ee'})}{\frac{1}{2}\,(^3J_{ae'} + {}^3J_{a'e})}. \tag{8}$$

Proceeding from expressions of the Karplus form, one can link the R factor with ring torsion angle ψ (see structural formulas III and IV) by means of the dependence

$$\cos \psi = \left[\frac{3}{4R+2}\right]^{1/2}. \tag{9}$$

The R value can be determined only for compounds that have one of the structural fragments listed below [34]:

a) an $X-CH_2CH_2-Y$ or $X-CH_2CHR-Y$ group in molecules with two rapidly inverting equivalent conformers;

b) an $X-CH_2CH_2-Y$ group in an absolutely rigid molecule (a canonical or primary conformation);

c) a $CHRCH_2CHR'$ group in a rigid molecule with R and R' trans-oriented with respect to one another.

Thus it is apparent from formula (8) that the R-factor method requires a knowledge of either four $^3J_{HH'}$ SSCC between coupling protons or two averaged constants between two exchanging pairs of protons. It was found that the R ratio does not depend on the electronegativity of the X and Y atoms [32, 34]. The measured R

values range from 1.1 to 3.9. In six-membered rings without distortions the torsion angle lies in the 55-58° range, whereas in the case of compression of the carbon portion of the ring ψ is lower than these values, and the ψ angles increase in the case of great flexibility. In 1,3-dioxane torsion angle ψ is 54°, which is in excellent agreement with the results of x-ray diffraction analysis [32, 35]. The ψ values for some other six-membered heterocycles are presented in Tables 1 and 2. The R-factor method can be regarded as a method for the approximate quantitative characterization of the conformations for five-membered heterocycles (see Part II) and as a better approximation for six-, seven-, and eight-membered heterocycles. For example, in the stereo-isomeric 2,5-dialkyl-1,3-dioxanes and 1,3-dithianes [38, 43-45], in which primarily chair conformations are realized, the torsion angles vary from 52-57° (Table 3). It is apparent from Table 3 that $\psi = 52 \pm 2°$ for the trans isomer (V) and $56 \pm 2°$ for the cis isomer (VI) of 1,3-dithiane. The cis isomers consequently experience somewhat less distortion of the "ideal" chair conformation than the trans isomer. This should be understood to be the result of the more favorable orientation of substituent R in the $C_{(5)}$ axial position as compared with the usual cyclohexane equatorial position because of weakening of the 1,3-interactions and the existence of "spatial freedom" in the region of the position of the ring sulfur atoms. This phenomenon is in opposition to the tendencies of the changes in ψ in cyclohexane and 1,3-dioxane derivatives.
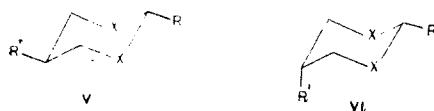

A method for estimation of dihedral angles θ with respect to the vicinal $^3J_{HH'}$ constants [dihedral angle estimation by the ratio method (DAERM) [46]] has been proposed; this method, like the R-factor method, makes it possible to establish the conformations without prior determination of the $J°$ constants in the Karplus Eq. (2), but the applicability of the method is limited to the electronegativity of substituent R in the $-CHRCH_2-$ fragment. The error introduced is a maximum when substituent R is anti-periplanar with respect to one of the protons under consideration. The method examined below does not have this disadvantage.

3. Allowance for the Effect of the Orientation of the Heteroatom on the Vicinal $^3J_{HH'}$ Constant

The effect of the electronegativity of the substituent depends on the relative spatial orientation of the substituent relative to the coupling protons and has its maximum value when their orientation is trans coplanar [47]. This was initially observed for the staggered conformers in such "rigid" structures as steroids [48], cyclohexane derivatives, and six-membered heterocyclic compounds [49] and was later observed in noncyclic compounds during a study of 1,2-disubstituted ethanes [50]. A study of bicyclic systems with eclipsed CH_2CHX groups [51, 52] led to different linear relationships between the $^3J_{HH'}$ (0°) and $^3J_{HH'}$ (120°) constants and the electronegativities of the substituents.

The effect of the orientation of the $C-H$ bonds under consideration relative to the heteroatom can be graphically seen in the case of 2-(5-bromo-2-furyl)-4-methyl-1,3-dioxane (VII)* and two isomers of alkoxy-cyclohexane (IX and X).
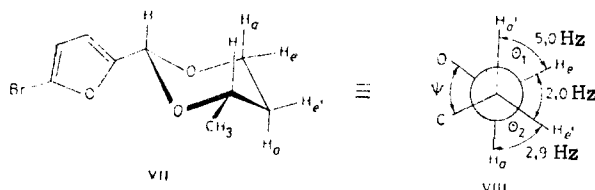
In 1,3-dioxane VII, regardless of the distortions of the ring conformation (angle ψ), dihedral angles θ_1 and θ_2 of the $C_{(5)} - C_{(6)}$ fragment (VIII) should be identical and equal to angle ψ. In fact, $^3J_{6a\,5e}$ $(\theta_2) = 2.9$ Hz and $^3J_{5a6e}(\theta_1) = 5.0$ Hz differ markedly. Since the sum of the electronegativities ($\sum_i \Delta E_i$) with respect to the $^3J_{6a5e}$ constants is identical, it would seem that when $\theta_1 = \theta_2$ these constants should be identical, but this is not actually observed. This is evidently due to the fact that the oxygen atom has a trans orientation (5-H$_e$) with respect to one of the coupling vicinal partners, whereas it has a gauche orientation (5-H$_a$) with respect to the other. The $C_{(4)}$ atom has a similar orientation with respect to the other partners (6-H$_a$ and 6-H$_e$). The ΔE_i

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*In this compound both substituents act as conformation-fixing groups.

differences are substantially different for the O and C atoms (on the Huggins scale [53] $\Delta E_O = 1.3$ and $\Delta E_C = 0.4$). Both the O and C atoms have trans orientations with respect to the 5-H_e and 6-H_e protons, and the $^3J_{5e6e}^{gauche}$ constant (2.0 Hz) is therefore smaller than the previous values.

IX   2–3 Hz   X   ~5 Hz   XI
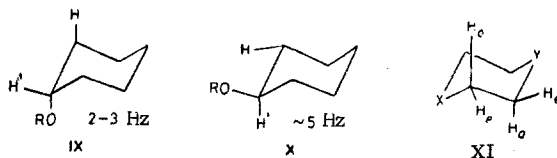
Forrest [54] has made a detailed analysis of the $^3J_{HH'}^{gauche}$ constants in the ethane fragment of diverse compounds in order to ascertain the relationship between the $^3J_{HH'}^{gauche}$ constants, the electronegativities of the substituents, and their orientation with respect to the coupling protons. He found that the expected $^3J_{HH'}^{calc}$ (60°) value for dihedral angle $\theta = 60°$ can be estimated [47] from expression (10):

$$^3J_{HH'}^{calc} (60°) = (4.1 + 0{,}63 \sum_i \Delta E_i)(1 - 0.462\Delta E_1)(1 - 0.462\Delta E_2), \tag{10}$$

where ΔE_1 and ΔE_2 are the differences in the electronegativities of the two substituents in an anti-periplanar orientation (trans orientation) relative to the coupling protons, and the electronegativities of both substituents, irrespective of their orientation, are included in $\sum \Delta E_i$.

It has been proposed that this approach be used for the quantitative description of the deviations of the dihedral angles from the "normal" values. The J° constant in expressions of the form $^3J = J° \cdot \cos^2 \theta - C$ [see Eq. (2)] varies from compound to compound in an indefinite manner, but it can be found for a given compound from Eq. (11):

$$^3J_{HH'}^{calc} = J° \cdot \cos^2 60° - 0.3, \tag{11}$$

where the $^3J_{HH'}^{calc}$ value is calculated from formula (10). By substitution of the J° value found into explicit expression (12) one can estimate angle θ_{ae}:

$$\cos \theta_{ae} = [(^3J_{HH'}^{exp} + 0.3)/J°]^{1/2}. \tag{12}$$

For example, in 1,4-dioxane the expected $^3J_{HH'}^{calc}$ value from Eq. (10) is 2.06 Hz, whereas the experimental $^3J_{HH'}^{exp}$ value is 2.78 Hz [33]. Estimation from formulas (11) and (12) leads to dihedral angle $\theta_{ae} = 57°$. The R-factor method gives $\psi = 58°$ for the same compound. Since angles ψ and θ_{ae} should virtually coincide in six-membered rings, the observed agreement constitutes evidence that the Forrest method, which can be regarded as a first approximation, and the R-factor method lead to similar results in conformational analysis.

A list of the θ_{ae} and ψ values in a number of conformationally labile heterocycles is presented in Table 1; for comparison, cyclohexane, which will be subsequently used for a more detailed discussion of orientation effects, is included in Table 1. In those compounds in Table 1 in which X and Y differ (XCH_2CH_2Y), the observed $^3J_{HH'}^{exp} = J^{cis}$ constant is the average of two completely different gauche constants $^3J_{2a3e}$ and $^3J_{3a2e}$ (XI), and the average constant from the two calculated $^3J_{2a3e}^{calc}$ and $^3J_{3a2e}^{calc}$ values is therefore used to find the J° value. Dihedral angles θ_{ae} and ψ in a number of six-membered heterocycles, the molecules of which under normal conditions exist primarily in the chair conformation, are presented in Table 2. In the case of 1,3-heterocycles VII, XII, and XIII alkyl or aryl substituents act as "conformation-fixing" groups, whereas in the case of sulfite XIV, selenite XV, and phosphorinane XVI the conformational "rigidity" of the ring is due to the high stability of the pyramid of bonds of sulfur, selenium, and phosphorus (for example, in the case of XVI inversion of the pyramid of bonds of phosphorus is characterized by a potential barrier of ~30 kcal/mole [55]).

XIV   XV   XVI
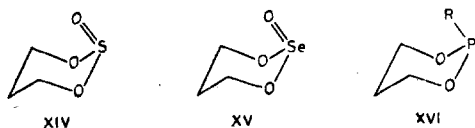
4. Theoretical and Empirical Dependence $^3J_{HH'} = f(\theta)$ with Allowance for the Orientation of the Endo- and Exocyclic Heteroatoms

The problem of the effect of the orientation of the heteroatoms on the vicinal $^3J_{HH'}$ constant has been examined theoretically [MO LCAO Extended Hückel Method (EHM)] [56-59] within a more general framework than the Forrest approach. The vicinal constants in mono- and disubstituted ethanes XCH_2-CH_2Y, where X and $Y=H$, CH_3, NH_2, OH, and F, were calculated in [59] on the basis of the Pople-Santry approximation [61]. The $^3J_{HH'} = f(\theta)$ dependences for $X=Y=H$ and $X=H$, $Y=F$ are presented in Fig. 4, in which the lower graph illustrates the contribution of the orientation of X by the difference in the SSCC for ethane and fluoroethane $\Delta J = J_{ethane} - J_{fluoroethane}$.

The $^3J_{HH'} = f(\theta)$ curve for ethyl derivatives is shifted with respect to phase relative to ethane (Fig. 4). The asymmetry of the curves for the monosubstituted ethanes is the result of the contribution of two different constants (for identical dihedral angles θ), which depend on the corresponding angle φ between the β proton under consideration and substituent X:

$$\varphi_{XH} = \theta - 120°. \tag{13}$$

The results show that although the electronegativity of the substituent decreases the average vicinal constant, for certain θ values (30-90° and 210-280°) substituent X leads to an increase in $^3J_{HH'}$ as the electronegativity of the substituent increases; this has been experimentally confirmed [62, 63].

The continuous curve $^3J_{HH'} = f(\theta)$ (Fig. 4) can with high accuracy be approximated by the equation [57]

$$^3J_{HH'}(\theta, E_X) = (A_0 - \lambda_A \cdot E_X) + (B_0 - \lambda_B E_X)\cos\theta + (C_0 - \lambda_C E_X)\cos 2\theta +$$
$$+ (D_0 - \lambda_D E_X)\sin\theta + (E_0 - \lambda_E E_X)\sin 2\theta, \tag{14}$$

in which sinusoidal terms are added to the original equation (1) in order to take into account the asymmetry of the curves relative to $\theta = 0°$.

In [64], Eq. (14) was used with A, B, C $(D=E=0)$, and λ_i constants found on an empirical basis relying on $^3J_{aa} = 13.12$, $^3J_{ae} = 3.73$, and $^3J_{ee} = 2.96$ Hz for cyclohexane [40]; this equation was used in the conformational analysis of 2-alkoxy derivatives of 1,4-benzodioxane and 1,4-benzoxathiane [64].

Several empirical approaches [11, 66] with specific $\lambda_i = F(\varphi)$ graphs* have been proposed to take into account the orientation effect of substituents on $^3J_{HH'}$ in terms of the λ_i parameter in Eq. (3). In [67] this approach was examined in greater detail, and modified expressions for the vicinal constants were obtained in the form

$$^3J_{HH'} = (10.6\cos^2\theta + 1.5\sin^2 2\theta)(1 - \sum_i \lambda_i^\varphi \Delta E_i); \tag{15}$$

$$0° \leqslant \theta \leqslant 90°, \quad 270° \leqslant \theta \leqslant 360°;$$

$$^3J_{HH'} = (14\cos^2\theta + 2.66\sin^2 2\theta)(1 - \sum_i \lambda_i^\varphi \Delta E_i); \tag{16}$$

$$90° \leqslant \theta \leqslant 270°.$$

Here the λ_i^φ parameters are determined by the lower $\lambda_i^\varphi = F(\varphi)$ graph presented in Fig. 5, in which phase angle φ is found from expression (13). The dependence $^3J_{HH'}^0 = f(\theta)$ for ethane $(\Delta E_i = 0)$ can be constructed from Eqs. (15) and (16). This dependence is presented in Fig. 5, in which three values of vicinal constants $^3J_{a'e}$, $^3J_{aa'}$, and $^3J_{ae'}$ found from the experimental spectrum of 2-tert-butyl-1,3-dioxane, which exists primarily in the chair conformation, are shown. With allowance for the lower curve in Fig. 5, these values are very satisfactorily described by Eqs. (15) and (16).

During the derivation of expressions (15) and (16) in implicit form it was assumed that the heteroatoms in the α position have cylindrical symmetry, i.e., it was assumed that the orientation of the orbitals of the unshared electron pairs (UEP) of the substituents has no effect, whereas it is known that the orientation of the

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*A $\lambda_i = F(\varphi)$ graph in which dihedral angle φ lies in the range $0° \leq \varphi \leq 180°$ is presented in a dissertation [66] with a reference to the unpublished research of S. Vottero. It follows from this review that such limits for the change in angle φ are inadequate for the complete description of the orientation effect of a substituent on $^3J_{HH'}$.

TABLE 4. Estimated Values of the $^3J_{HH'}$ Constants (Hz) in Six-Membered Heterocycles for the Canonical Chair Conformation (ψ = 60°) and Experimental $^3J^{exp}_{HH'}$ Values
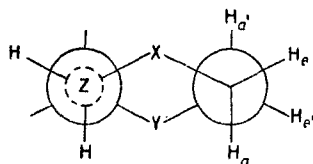
X	Y	Z	Constant	According to Forrest[47]	According to Viktorova[64]	Modified method[67]	$_3J^{exp}_{HH'}$
O C O 1,3-Dioxane			$^3J_{a'e}$	4,18	4,06	4,05 (5,1)*	5,0†; 5,0[41]
			$^3J_{ae'}$	2,00	3,06	2,35 (2,9)*	2,9†; 2,7[41]
			$^3J_{ee'}$	1,69	2,88	1,6 (1,34)*	2,0†; 1,3[41]
			$^3J_{aa'}$		12,4	12,3 (12,8)*	11,3†
S C S 1,3-Dithiane			$^3J_{a'e}$	3,76		3,5	3,9†
			$^3J_{ae'}$	3,76		3,5	2,7†
			$^3J_{ee'}$	3,06		2,75	3,9†
			$^3J_{aa'}$	—		13,2	11,8†
O O C 1,4-Dioxane			$^3J_{a'e}$	2,3	3,48	2,9	2,66 [69]; 4,0 [70]
			$^3J_{ae'}$	2,3	3,48	2,9	
			$^3J_{ee'}$	0,92	2,3	0,44	~ [71]; 0,62 [69]
			$^3J_{aa'}$	—	11,65	11,4	10,2 [37]; 11.7 [71]
O S C 1,4-Oxathi-ane			$^3J_{a'e}$	4,2	3,95	3,5	$<J$cis$>$=2,65 [35]
			$^3J_{ae'}$	2,0	3,15	3,5	
			$^3J_{ee'}$	1,7	2,77	2,75	
			$^3J_{aa'}$	—	12,27	13,2	12,5[37];
O N C Morpholine			$^3J_{a'e}$	3,3		3,5	$<J$cis$>$=3,04 [37]
			$^3J_{ae'}$	2,2		2,6	
			$^3J_{ee'}$	1,33		1,0	
			$^3J_{aa'}$	—		11,9	

*The estimated values for torsion angle ψ =55° are indicated in parentheses.

†The experimental values for 2-(5-bromo-2-furyl)-4-methyl-1,3-dioxane at +26°C are presented.

‡The values correspond to the spectrum of cis-2a,4e-dimethyl-2e-tert-butyl-1,3-dithiane at −50°C.
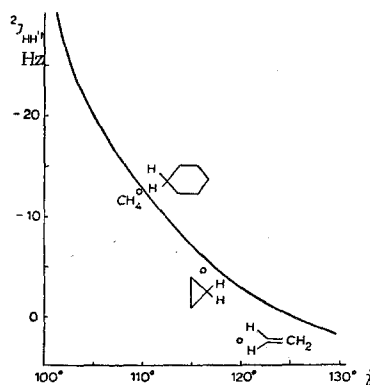

Fig. 6. Dependence of the geminal $^2J_{HH'}$ constant on the valence angle in accordance with the calculated values [84] and the experimental data (negative sign).
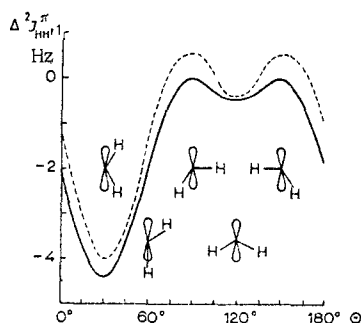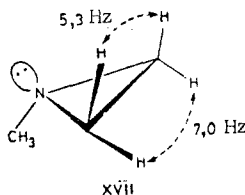
Fig. 7. Orientation dependence of the π contribution to the $^2J_{HH'}$ constant.

UEP makes a certain and sometimes substantial contribution to the geminal ($^2J_{HCH'}$, $^2J_{PCH}$) and vicinal ($^3J_{HH'}$) constants. This contribution in N-methylethyleneimine (XVII) reaches +1.7 Hz in the case of a transoid orientation of the C−H bond closest to the substituent and the axis of the UEP [11, 68].

XVII

Let us examine the data in Table 4 for a comparative evaluation of the degree of agreement between the calculated $^3J_{HH'}$ constants and the calculated values in some six-membered heterocycles. It can be seen that estimation by the modified method [67] gives numerical values of the $^3J_{HH'}$ constants that are in closer agreement with the experimental values. However, in the case of 1,3-dioxanes estimation of the $^3J_{aa'}$ constant by all methods gives a value of $\sim$ 12.5 Hz instead of the experimental $^3J_{aa'}^{exp}$ value of 10.8 Hz. However, this constant is closer to the estimated values in other heterocycles. For example, in 1,3-propanediol sulfite (XIV), which, like 1,3-dioxane, contains an − OCH_2CH_2O − fragment and is distinguished by high rigidity of its chair conformation, the $^3J_{aa'}$ constant is 12.8 Hz, i.e., it is close to the calculated value. Thus a contribution by the alternative conformation evidently exists in those heterocycles in which the experimental $^3J_{aa'}$ constant is lower than the expected value. In the case of bilateral exchange this contribution can be estimated from the explicit expression

$$3J_{aa'}^{exp} = {}^3J_{aa'}^{canon}(1-\chi) + {}^3J_{ee'}^{canon}\chi, \tag{17}$$

where χ is the fraction of the alternative conformation. In the case of VII and assuming $^3J_{aa'}^{canon} = 12.5$ Hz and $^3J_{ee'}^{canon} = 1.3$ Hz we obtain $\chi = 0.16$,* i.e., the contribution by the alternative chair conformation is significant (16%).

5. Stereospecificity of the Geminal $^2J_{HH'}$ Constant

The geminal $^2J_{HCH'}$, $^2J_{PCH'}$, and other constants have exceptionally high stereospecificity. However, until recently they were rarely used in conformational analysis because of the lack of sufficiently complete experimental confirmations of the theoretical predictions. The $^2J_{HH'}$ values usually range from +42.4 to −21 Hz [72]. A qualitative examination of the $^2J_{HH'}$ constant in the X−CH_2−Y fragment shows that its magnitude depends on the following factors [73, 74]: on the hybridization of the carbon atom and, consequently, on the valence angle between the C−H and C−H' bonds, on the electronegativities of substituents X and Y; on the lengths of the C−H, C−X, and C−Y bonds; on the orientation of the valence orbitals or the orbitals of the unshared electron pairs (UEP) of the X and Y atoms relative to the σ (C−H) bonds; on the nature of the β substituent and the solvent. According to theory [75-78] and the experimental data [79-82], the effect of temperature

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*Estimates of this sort should not be considered to be quantitative. In fact, the possible change in the ψ angle, which also leads to a decrease in the $^3J_{a'a}$ constant and an increase in the $^3J_{a'e}$ constant, is not taken into account in such calculations. Strict separation of the contribution of the alternative conformation and the change in angle ψ can be achieved after thorough low-temperature studies of the NMR spectrum.
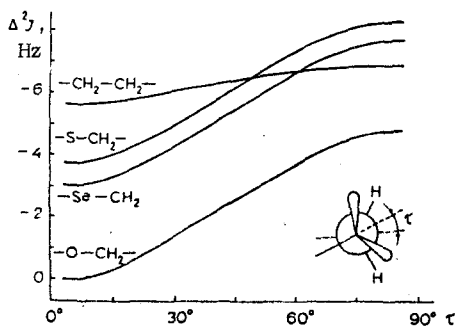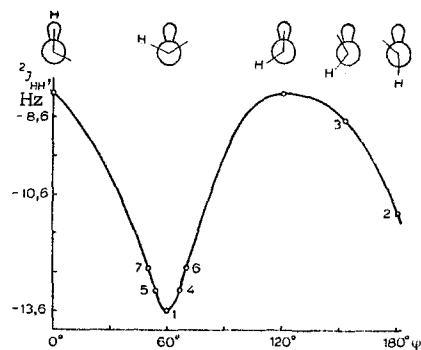
Fig. 8

Fig. 9

Fig. 8. Contributions of $\Delta^2 J$ to the geminal $^2J_{HH'}$ constant as a function of the orientation of the adjacent heteroatom and the CH_2 group as a function of torsion angle τ. The graphs are applicable to any heterocycles except those with small rings.

Fig. 9. Dependence of the geminal $^2J_{HH'}$ constant in the CH_2-N fragment on the orientation of the orbital of the unshared electron pair (UEP) of the nitrogen atom: 1) piperidine with an equatorial orientation of the UEP (see Scheme 2); 2) for an anti-coplanar orientation with adoption of an average contribution of +2.4 Hz; 3) from a comparison of syn-perhydropyrido-[1,2-c;2',1'-f]pyrimidine (XXVI) and syn-perhydropyrido[1,2-c;2',1'-e]imidazole (XXVII) in which angle φ changes from 180° to 150°, which makes the contribution for one fragment +2.5 Hz; 4) and 5) spectrum of XXVIII; 6) and 7) XXIX.
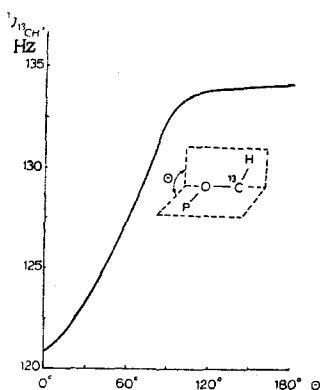

Fig. 10. Angular dependence of the direct $^1J_{13CH}$ constant in the CH_3OPCl_2 molecule.

can be disregarded. Let us examine in greater detail those factors that are of greatest interest in a stereochemical respect.

a) Dependence of $^2J_{HH'}$ on Valence Angle γ. The dependence of $^2J_{HH'}$ on valence angle γ between the C – H bonds is presented in Fig. 6. It is apparent that this constant increases (becomes more positive) as the s character of the carbon orbitals increases [83]. The first calculation by the valence bond (VB) method [84-86] showed approximately the same dependence, but the result had the opposite sign. The sign and general character of the dependence of $^2J_{HH'}$ on γ were correctly predicted by the MO method with allowance for overlap [partial neglect of differential overlap (PNDO) and complete neglect of differential overlap (CNDO)]; however, their numerical values differ somewhat from the experimental values [60, 87-89].

b) Effect of a π System Adjacent to the CH_2 Fragment. If the methylene group forms a part of the cyclic system, by examining the $^2J_{HH'}$ constants in various molecules that exist in the primary conformations one can perceive the dependence of $^2J_{HH'}$ on the orientation of the adjacent π orbital [83]. The theoretical dependences [73] of the π contribution to $^2J_{HH'}$ on the dihedral angle between the methylene group and the adjacent π bond are presented in Fig. 7.
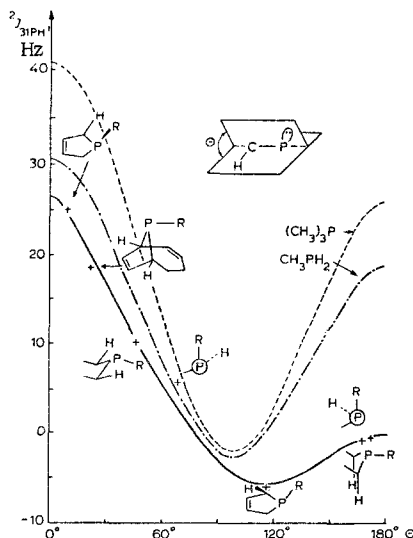
Fig. 11. Angular correlation for the $^2J_{PCH}$ constant. The continuous line corresponds to the experimental data [107, 108], and the upper curves were obtained by the CNDO/SP method [106].

c) Effect of the Electronegativities, Bond Lengths, and Orientation of the Orbitals of Heteroatoms X and Y. According to theory, the $^2J_{HH'}$ constant in the $-CH_2-X-$ fragment should become more positive both as a result of inductive σ-electron withdrawal from the symmetrical bonding orbital and as a consequence of transfer of a pseudo-π electron of the unshared electron pair (UEP) of heteroatom X to the methylene group. The inductive effect does not depend on the angle of rotation about the $C-X$ bond, but the contribution of hyperconjugation should depend markedly on the dihedral angle between the orbitals of the UEP and the CH_2 group. The contribution of the second effect should be maximal when the intranuclear $H-H$ axis is perpendicular to the $C(H_2)-X-R$ plane and should be zero when one of the H atoms lies in this plane.

It is also known that the direct $^1J_{^{13}CH}$ constant may serve as a measure of the s character of the $C-H$ bond. On the other hand, a satisfactory linear dependence between $^2J_{HH'}$ and $^1J_{^{13}CH}$ is sometimes experimentally observed. The $^2J_{HH'}$ constant consequently should also depend on the length of the $C-H$, $C-X$, and $C-Y$ bonds.

Anteunis and coworkers [74] used an iteration procedure to thoroughly analyze the experimental data on the $^2J_{HH'}$ constants in the case of six- and five-membered 1,3-diheterocycles, alicycles, and noncyclic compounds containing O, S, and Se atoms and found the expression

$$^2J_{HH'} = 2.19 \sum_i^4 d_i + 2.52 \sum_i^n E_i + 4.85 \sum_i^4 [\chi \cdot \sin^2 \tau_i + (1-\chi) \sin^2 \tau_i]$$

$$+ 1.31 \sum_i^{4-n} [\chi \cdot \sin^2 \Phi_i + (1-\chi) \sin^2 \Phi_i] - 2.1n - 53.95, \tag{18}$$

where d_i are the lengths of the bonds of the $X-CH_2-Y$ fragment; E_i are the Pauling electronegativities of substituents X and Y; τ_i and Φ_i are the torsion angles between the bisectrices that divide valence angle $H-C-H$ and the angle between the p or σ orbitals of the adjacent heteroatoms (see Fig. 8); n is the number of orbitals of the unshared electron pairs (UEP); (4 - n) is the number of adjacent σ bonds; and χ is the mole fraction of one conformation in a system with two possible conformations.

Graphs of the Δ^2J increments (Fig. 8) convenient for practical application in conformational analysis can be constructed for heterocycles with X=O, S, Se, and C on the basis of Eq. (18). For example, in the case of 1,3-dioxanes the portion of the ring with $O_{(1)}-CH_2-O_{(3)}$ atoms in the canonical chair conformation is characterized by angle $\tau \sim 60°$. We find the increment $\Delta^2J = -3.65$ Hz from the lower curve in Fig. 8. The expected value of the geminal constant at the $C_{(2)}$ atom for the chair conformation should consequently be equal to twice the increment, i.e., $^2J_{HH'} = 2(-3.65) = -7.3$ Hz, whereas $^2J_{HH'} = -3.65 + (-1.2) = -4.85$ Hz for the unsymmetrical boat conformation $(\tau_1 = 60°, \tau_2 = 30°)$. In fact, the experimentally observed $^2J_{HH'}$ constants are close to the values calculated from Eq. (18), as can be seen from Scheme 1. The fact that experiments show a somewhat smaller constant $(^2J_{HH'} = -6.2$ Hz) than the expected value in the case of the chair form of XVIII is evidently due

either to the contribution of the alternative conformation, for example, half-chair XXI, in which torsion angle τ_i are 0 and 15° and the expected $^2J_{HH'}$ constant is consequently -0.4 Hz, or to a somewhat different torsion angle. The orientation of the unshared electron pair of the nitrogen atom also has a pronounced effect on the magnitude of the $^2J_{HH'}$ constant. This effect has been examined by Chivers and coworkers [91, 92] in the case of methyl-substituted perhydropyrido[1,2-c]pyrrolo[2,1-c]imidazoles (XXIII), syn- and anti-perhydro-7,11-methanopyrido[1,2-c][1,3]diazocines (XXIV, XXV), in which the geometry of the $N-CH_2$ fragment is fully determined, and other nitrogen-containing five- and six-membered mono-, bi-, and tricyclic compounds.
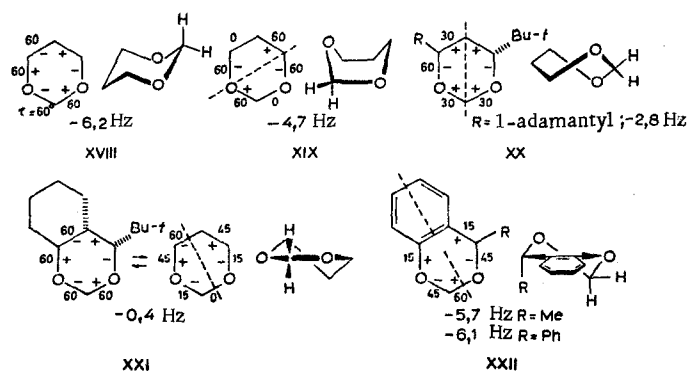
Scheme 1. Some canonical conformations of 1,3-dioxane systems and their corresponding experimental $^2J_{HH'}$ constants in the $-O-CH_2-O-$ fragment [74].
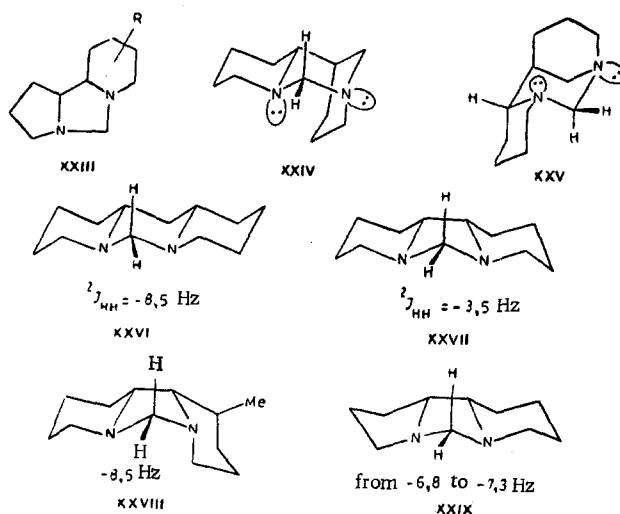
The $^2J_{HH'}$ constants for the chair form of six-membered heterocycles with a definite spatial orientation of the orbital of the unshared electron pair of the nitrogen atom are presented in Scheme 2, and an empirical graph that illustrates this angular dependence is presented in Fig. 9. This (see Scheme 2, next page) graph is applicable only to the endocyclic nitrogen atom. In addition, one must bear in mind that correlations similar to that presented in Fig. 9 can serve as a conformational criterion only in series of related compounds [93, 94].

It is interesting to note that the orientation of the orbitals of the sulfoxide group in derivatives of 1,4-oxathiane S-oxide fit into the same scheme [95]. Molecules of compounds of this type exist in equatorial (XXX) and axial (XXXI) conformations with respect to the $S \rightarrow O$ bond. Formally speaking, the valence electrons of the excited sulfur atom with sp^3d^2 hybridization can be allocated over the tetrahedrally oriented orbitals, in which case one of the unshared electron pairs (UEP) of tetravalent sulfur can be placed in the hybridized orbital, which in the case of form XXX is anti-coplanar relative to the $C-H_a$ bond ($\varphi = 180°$), and a higher value can be expected for the $^2J_{HH'}$ constant than in the case of the axial conformation of $S \rightarrow O$, in which the orbital of the
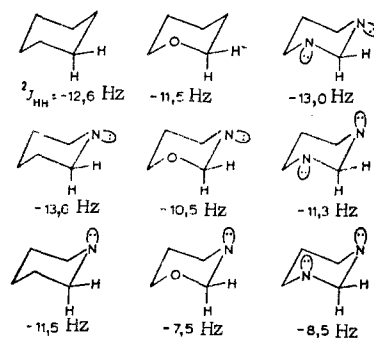
Scheme 2. Examples illustrating the contribution of the orientation of the orbital of the unshared pair of electrons of the nitrogen atom to the geminal $^2J_{HH'}$ constant in six-membered hererocycles.

UEP forms dihedral angle $\varphi = 60°$. In fact, experiments show that in the case of form XXX one observes $^2J_{3a3e} = -11.3$ and $^2J_{5a5e} = -12.0$ Hz, whereas for XXXI one observes $^2J_{3a3e} = -13.8$ Hz and $^2J_{5a5e} = -14.2$ Hz.
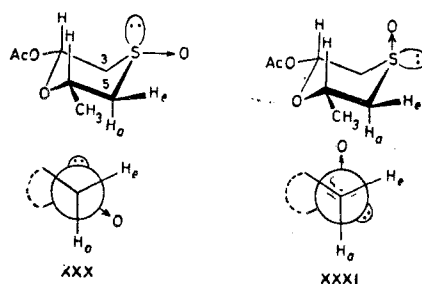
6. Stereospecificity of the Constants of Spin – Spin Coupling between the Protons and the ^{13}C, ^{14}N, ^{15}N, ^{19}F, ^{31}P, ^{119}Sn, and ^{199}Hg Nuclei

a) Direct $^1J_{13CH}$ and $^1J_{31PH}$ Constants. The $^1J_{13H}$ constant is proportional to the order of the bond between the coupling nuclei and is a measure of the s character of the bonding orbitals of carbon [96-98]; in the $H-C-X$ fragment it increases as the electronegativity of substituent X increases [97, 99].

Little study has been devoted to the stereospecificity of the direct constants. The effect of the orientation of the unshared electron pair (UEP) of the nitrogen atom [100] on $^1J_{13CH}$ is due to partial delocalization of the UEP over the $C-H$ bond [101, 102]. The same problem has been examined by the Hückel method [103] in $CH_2-\ddot{N}$ and $CH_2-\ddot{O}$ fragments [103]. The angular dependence of the $^1J_{13CH}$ constant in groups with a cationic carbon atom was discussed in [104, 105]. Calculation of the $^1J_{13CH}$ constant within the CNDO/SP (complete neglect of differential overlap according to Santry – Pople) approximation in methyl dichlorophosphite indicates its clear dependence on the orientation of the $O-P$ bond [106] (Fig. 10). This dependence can apparently be used for the assignment of the spatial orientation of the $C-H$ bonds in phosphorus- and oxygen-containing rings.

In a stereochemical respect little study has been devoted to the $^1J_{31PH}$, $^1J_{31P15N}$, $^1J_{31P13C}$, and $^1J_{13C13C}$ constants.

b) Geminal $^2J_{31PCH}$, $^2J_{13CCH}$, and $^2J_{19FCH}$ Constants. The first of these constants is of great value in the conformational analysis of cyclic phosphorus-containing compounds. The dependence of $^2J_{31PCH}$ on the orientation of the unshared electron pair (UEP) of trivalent phosphorus relative to the $P-C-H$ plane (Fig. 11) was constructed on the basis of experimental data for cyclic phosphines [107, 108]. Calculation by the CNDO/SP method [106] basically confirms the experimentally observed tendency, with the exception of angles θ, which correspond approximately to an anti-coplanar orientation of the orbital of the UEP of phosphorus and the $C-H$ bond.

The problem of the stereospecificity of the $^2J_{31PCH}$ constant for pentavalent phosphorus has been touched upon only in part [109], and it has been shown that in 2-methyl-2-oxo-3-phenyl-4-methyl-1,4,2-oxazophosphorinane with a gauche orientation of the $P-O$ bond (XXXII) this constant is -2.3 Hz, whereas it is -19.3 Hz in the
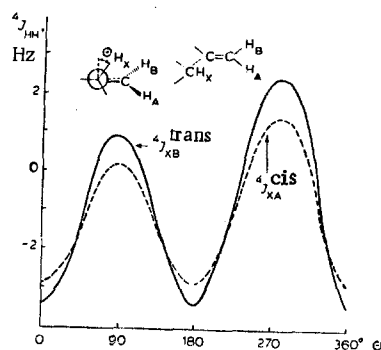
Fig. 12. Dependence of the cisoid and transoid allyl
$^4J_{HH'}$ constant on the orientation of the C—H$_X$ bond
relative to the nodal plane of the C=C bond.

case of an anti-coplanar orientation relative to C—H (XXXIII). Calculation within the Pople—Santry approximation for methyldichlorophosphine oxide [CH$_3$P(O)Cl$_2$] shows a similar tendency [106].

The geminal $^2J_{13CCH}$ constant in the case of five-membered unsaturated rings with two sulfur atoms in the 1 and 3 positions has been experimentally determined [110]. In this study the $^2J_{13CCH}$ constants were discussed from the point of view of the effects of hyperconjugation, and it was concluded that participation of the d orbitals in the bonds of the unsaturated carbon atom with the sulfur atom does not play any role whatsoever. However, this does not mean that the $^2J_{13CCH}$ constant is not stereospecific. This problem requires further detailed experimental and theoretical study.
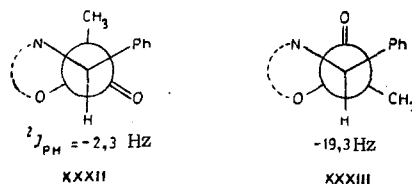
The spin—spin coupling constants with participation of ^{19}F nuclei in fluorine-containing heterocycles are stereospecific [1, 111, 112], but this problem has not been investigated in detail for the $^2J_{19FCH}$ and $^2J_{19FC19F}$ constants.

c) Vicinal Constants with the Participation of Protons and the Nuclei of ^{13}C, ^{14}N, ^{15}N, ^{19}F, ^{29}Si, ^{31}P, ^{119}Sn, and ^{199}Hg Isotopes. The experimental and theoretical data show that the $^3J_{13CCCH}$ constant follows dependences of the Karplus form [113-115]. Angular correlations of the $^3J_{15NCCH}$ constants have been examined by the PNDO (partial neglect of differential overlap) method by Solkan and Bystrov [116] for a peptide fragment. The applications of a similar constant in biologically important systems have been fully described in a review [117]. A dependence of the Karplus form is characteristic for the vicinal $^3J_{14,15NCCH}$ constants [118-122].

Theoretical and experimental studies [123-128] have been devoted to the establishment of the dependence of the vicinal $^3J_{19FCCH}$ constant on the dihedral angle.

A paper [129] in which it was demonstrated that the reduced constant $^3K_{29SiCCH} = \dfrac{2\pi}{\hbar\gamma_{Si}\gamma_H}\,^3J_{29SiCCH}$ lies on the Karplus curve was devoted to the study of the stereospecificity of the $^3J_{29SiCCH}$ constant.

The angular dependence for the vicinal $^3J_{31PH}$ constant is of great significance in the study of the three-dimensional structures of heterocyclic organophosphorus compounds. In the P—X—C—H fragment this constant depends on many parameters [108, 130-141]; among these, the most important are dihedral angle θ between the P—X—C and X—C—H planes, the valence state of phosphorus (P^{III} and P^V), the character of heteroatom X (S, O, N, Se, etc.), the hybridization state of carbon (if X=C) [138], the orientation of the orbital of the unshared electron pair of the P^{III} atom or the P=O bond of tetracoordinated phosphorus relative to the X—C—H plane, and the electronegativities and orientations of the substituents attached to the fragment.

The following expressions were found empirically [139] in the case of a pentavalent tetracoordinated phosphorus atom in the P—C$_{(sp^3)}$—C$_{(sp^3)}$—H fragment by analysis of the PMR spectra of a number of phosphonates with rigid geometries and an exocyclic P(O)(OCH$_3$)$_2$ group:

$$^3J_{^{31}P^VCCH} = 18\cos^2\theta; \quad 0° \leqslant \theta \leqslant 90°;$$
$$^3J_{^{31}P^VCCH} = 41\cos^2\theta; \quad 90° \leqslant \theta \leqslant 180°. \tag{19}$$

In this case the contribution of the orientation of the P=O bond is averaged due to the relatively free rotation of the $P(O)(OCH_3)_2$ fragment. If one of the carbon atoms has sp^2 hybridization or the hybridization of the cyclopropane ring, the observed constants deviate from dependence (19) [138]. A change in the H–C–C and P–C–C valence angles has a small effect on the constant [139]. A change in the electronegativity of the substituent attached to one of the carbon atoms gives rise to variation in the $^3J_{^{31}PCCH}$ constant over a range of 0-2 Hz.

The complete dependence $^3J_{^{31}PCCH} = f(\theta)$ for trivalent phosphorus has not been studied.

A correlation similar to the Karplus curve [141-146] was proposed for the dependence of the $^3J_{^{31}POCH}$ constant on dihedral angle θ from the very beginning. As a rule, the values of the $^3J_{POCH}$ (60°) and $^3J_{POCH}$ (180°) constants for 1,3,2-dioxaphosphorinanes with participation of P^{III} are approximately half the values observed in the case of pentavalent phosphorus with a P=O(S) bond. It is therefore meaningless to speak of a $^3J_{POCH} = f(\theta)$ dependence in general form, as one can see from the experimental $^3J_{POCH}$ values for phosphites and thiophosphates [147]. If the carbon atom in the P^VOCH fragment has sp^2 hybridization, the gauche constant is $^3J_{POCH}$ (60°) ~1.5 Hz, i.e., its value is considerably lower than in the case of sp^3 hybridization (4-12 Hz), whereas trans constant $^3J_{POCH}$ (180°) retains a higher value (20-28 Hz [148]).

The following dependence was used during a study of the conformations of 3',5'-cyclic nucleotides [149]:

$$^3J_{^{31}P^VOCH} = 16.3\cos^2\theta - 4.6\cos\theta. \tag{20}$$

This expression must be used with caution and only for semiquantitative estimates, since it includes many assumptions.

Despite the complexity of the problem of the specific form of the $^3J_{POCH} = f(\theta)$ dependence, the use of the expression $J° \cdot \cos^2\theta$ without a knowledge of the magnitude of the $J°$ coefficient makes it possible to perform conformational analysis even in the case of noncyclic organophosphorus esters [150]. In the case of phosphorus-containing heterocycles the solution of conformational problems is simplified, since it is necessary to operate with $^3J_{POCH}$ values in the vicinity of dihedral angles $\theta = 60$ and 180°, at which the former differ substantially.

The dependence of the averaged $^3J_{PNCH}$ constant on the orientation of the unshared electron pair of trivalent phosphorus was touched upon in [151-153].

The problem of the stereospecificity of the $^3J_{PH}$ constants in structures with trigonally bipyramidal or square-pyramidal structures of the bonds at the phosphorus atom remains virtually unsolved.

Vicinal constants with the participation of the nuclei of ^{119}Sn and ^{199}Hg isotopes have been discussed as a function of angle θ in experimental and theoretical studies [154-157].

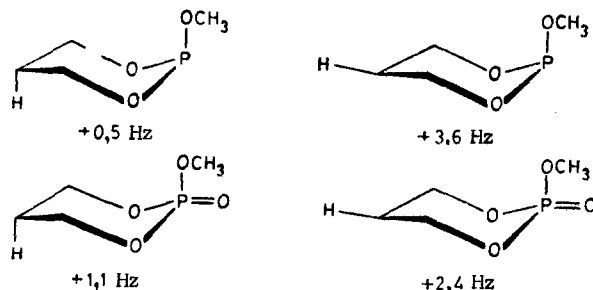## 7. Stereospecificity of the Long-Range Spin – Spin Coupling Constants

Spin–spin couplings through more than three chemical bonds are united under the general title of long-range spin–spin coupling. The long-range $^4J_{HH'}$, $^4J_{PH}$, $^5J_{HH'}$, and other constants are strictly stereospecific; however, many factors affect them, and little study of the details of the stereospecificity of such constants has been accomplished. It has been shown for some specific systems that an interaction due to direct overlapping of the orbitals of the atoms is also superimposed on the angular dependence of the long-range constants; this introduces an additional complication in the pattern of the stereospecificity. It is precisely the long-range constants that contain sometimes deficient or supplementary information during the study of the three-dimensional structures of heterocycles.

It has been experimentally established that if the carbon skeleton of the fragment under consideration and the C–H bond form a zigzag plane of the "M" (or "W") form, the $^4J_{HH'}$ constant is positive [158, 159] and larger than in the case of other forms, for which the $^4J_{HH'}$ values are usually negative. This means that if the six-membered heterocycle exists in the chair conformation, the long-range spin–spin coupling between the two equatorial protons of the 1,3-carbon atoms is characterized by a larger constant (0.8-1.2 Hz) than, for example, in the case of axial–axial coupling. However, these qualitative generalizations must be used with caution, since exceptions are also known. Many of the experimental facts were confirmed in a theoretical study [163] in which the relative roles of "indirect" and "direct" mechanisms in $^4J_{HH'}$ spin–spin coupling were uncovered in a number of specific cases.

Axial—axial coupling of a proton and a vicinal methyl group is usually realized with a larger $^4J_{HCCCH_3}$ constant (~ 0.8 Hz; the line of the methyl protons is broader [164]) in six-membered heterocycles than in the case of axial—equatorial coupling of the proton and the methyl group (the line is narrower). This feature can be successfully used for the determination of the axial or equatorial orientation of a methyl substituent.

In the study of the stereochemistry of heterocycles containing unsaturated C=C bonds the allyl cisoid and transoid long-range $^4J_{HH'}$ constants sometimes contain additional stereochemical information (Fig. 12) [83]. It can be seen from the graphs that the $^4J_{HH'}$ constants may be negative or positive, depending on dihedral angle θ.

The long-range constants with the participation of the nuclei of "other" isotopes are also stereospecific. For example, in the case of 1,3,2-dioxaphosphorinane systems this can be seen from Scheme 3. Other examples of long-range couplings through four bonds have been presented in a previous review [83].

+0,5 Hz   +3,6 Hz

+1,1 Hz   +2,4 Hz

Scheme 3. Stereospecificity of the long-range $^4J_{POCCH}$ constant in 1,3,2-dioxaphosphorinanes.

The long-range $^5J_{HH'}$ constants, including the so-called homoallyl constants (in H−C−C=C−C−H and H−C=C−C−C−H fragments), also have

XXXIV   XXXV
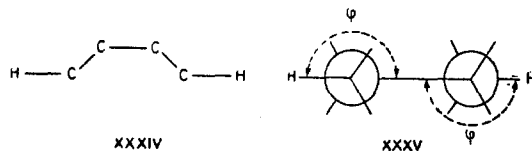
stereochemical applications [165]. According to [166], an indirect mechanism for coupling through five bonds leads to dependences of the form

$$^5J_{HH'} = (A \cdot \cos^2 \varphi + B \cdot \cos \varphi + C)(A \cdot \cos^2 \varphi' + B \cdot \cos \varphi' + C), \qquad (21)$$

where φ and φ' are dihedral angles that include the terminal C−H bonds (see formula XXXV). The maximum $^5J_{HH'}$ constant is observed when $\varphi = \varphi' = 180°$ and is independent of the dihedral angle in the vicinity of the central C−C bond (XXXIV). The stereochemical applications of homoallyl constants in cyclohexene structures are discussed in [167, 168].

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