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Directly Bonded $^{13}C-^{13}C$ Spin-Spin Coupling Constants in Structural Studies

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The review presents the present state of research into the directly bonded $^{13}C-^{13}C$ spin-spin coupling constants (SSCC)—the parameters of NMR spectra which are most difficult to measure and which contain unique structural information. The principal factors determining the magnitude of the direct $^{13}C-^{13}C$ SSCC, namely the hybridisation of the interacting atoms, the electronic influence of substituents, steric and solvation effects, and the influence of the unshared electron pairs of the heteroatoms, are analysed. The possibilities of using the directly bonded $^{13}C-^{13}C$ SSCC for the solution of a wide variety of structural problems in chemistry are examined; special attention is devoted to the prospects for the employment of these parameters in stereochemistry and conformational analysis.
The bibliography includes 232 references.

CONTENTS

I. Introduction	1
II. The nature of the spin-spin coupling between directly bonded carbon nuclei	3
III. The principal factors determining the variation of the directly bonded $^{13}C-^{13}C$ SSCC	4
IV. Structural applications	9

I. INTRODUCTION

The measurements of the constants for the spin–spin coupling between ^{13}C nuclei ($^{13}C-^{13}C$ SSCC or $^{n}J_{SS}$) under the conditions of the natural abundance of this isotope (~1.1%) involves the recording of the ^{13}C NMR spectra of molecules containing simultaneously two ^{13}C nuclei. The fraction of such molecules in the natural mixture of isotopomers is only ~0.01%, i.e. one molecule out of 10 000. This fact and also the low relative sensitivity of the ^{13}C NMR method make the $^{13}C-^{13}C$ SSCC the parameters of the high-resolution NMR spectra of organic compounds which are most difficult to obtain.

The first studies involving the experimental measurement of $^{13}C-^{13}C$ SSCC date back to the beginning of the 1960s [1–3] and were carried out for model compounds enriched in ^{13}C. The complexity of the synthesis of a wide range of such compounds was one of the reasons why such studies have been non-systematic during the last 10–15 years. The situation changed significantly at the end of the 1970s with the appearance of commercial Fourier Transform NMR spectrometers improved by the incorporation of pulse type programmers and highly sensitive devices for the recording of the signal ensuring a real increase of the sensitivity of the method, amounting on average to two orders of magnitude. Together with successes in the synthesis of ^{13}C-labelled compounds, this led to a vigorous growth of studies on the $^{13}C-^{13}C$ SSCC.[4–10] Thus, whereas in 1979 about 700 experimental values of the direct $^{13}C-^{13}C$ SSCC ($^{1}J_{CC}$) were known, in 1981 as many as approximately 1800 were measured.[10]

The method for the observation of ^{13}C satellites in the ^{13}C NMR spectra under the conditions of the "suppression" of the signals of the principal isotopomers, developed by Bax,

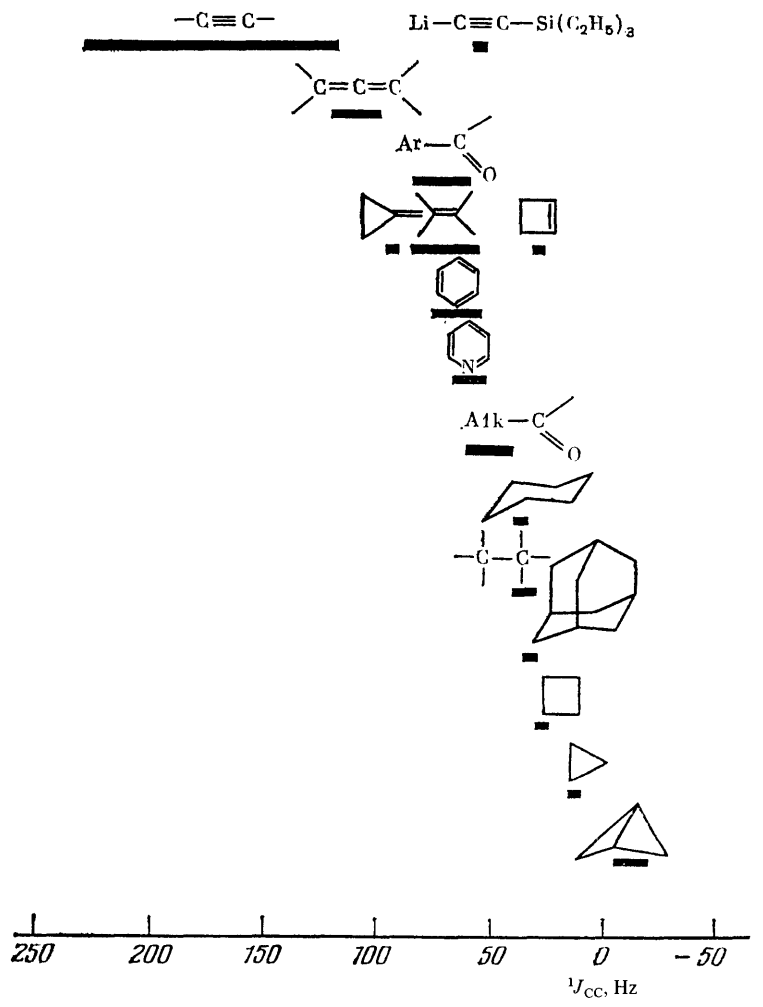


Figure 1. The ranges of variation of the directly bonded $^{13}C-^{13}C$ SSCC for different classes of organic compounds.[8,9]

Freeman, and Kempsell,[11,12] occupies a special place in the development of the research into the $^{13}C-^{13}C$ SSCC. The essential feature of the method, which the authors called INADEQUATE (Incredible Natural Abundance Double Quantum Transfer Experiment), consists in the conversion of the magnetisation of the satellites into the "two-quantum coherence" state $\mathcal{F}_2$ with subsequent separation of the components of $\mathcal{F}_2$ and the component of magnetisation $\mathcal{F}_0$ corresponding to ^{13}C nuclei without $^{13}C-^{13}C$ SSCC. Without increasing the sensitivity compared with the usual procedure for the recording of ^{13}C signals, the method facilitates significantly the measurement of weak signals due to $^{13}C-^{13}C$ SSCC in specimens with a natural isotopic content, because it eliminates the problem of their overlap with the strong signals of the main isotopomers, the signals of impurities, and also the signals modulated by the rotation of the tube. A two-dimensional version of the basic inadequate INADEQUATE method [13–15] and also a version which has been modified and combined with certain other pulse sequences[16–24] were realised subsequently. As a result, the measurement of $^{13}C-^{13}C$ SSCC on modern spectrometers has now become just as easy as the recording of the ^{13}C NMR spectra themselves 15 years ago.

This review surveys the available data solely on the directly bonded $^{13}C-^{13}C$ SSCC, because the geminal, vicinal, and long-range $^{13}C-^{13}C$ constants have already been the subject of a recent careful examination.[8,9] As can be seen from the correlation diagram presented (Fig.1), the range of variation of the directly bonded $^{13}C-^{13}C$ SSCC is exceptionally large: from −20 Hz in bicyclobutanes to +230 Hz in acetylenes.† Their information content is also high, because the accuracy of the measurement of these SSCC is to within 0.1 Hz and less. Attention is concentrated on the principal applications of $^1J_{CC}$ which have arisen in the solution of a wide variety of structural problems of organic chemistry such as the use of $^1J_{CC}$ in stereochemistry and conformational analysis, the study of the effects of substitution and the

† The few experimental measurements of the signs of $^nJ_{CC}$ suggest that all the direct and vicinal $^{13}C-^{13}C$ SSCC are positive (with the exception of sterically strained systems of the bicyclobutane series), while the geminal constants are of variable sign.[5,6]

properties of substituents, the establishment of methods for the biosynthesis and the determination of the structures of complex synthetic and natural products, and the structural studies of the nature of the carbon–carbon bond (estimation of the amounts of *s* character, i.e. of the contributions of the 2*s* orbitals of the carbon atoms to the corresponding hybrid atomic orbitals, of the degree of hybridisation of the interacting atoms, of the bond lengths and bond force constants, and certain other important characteristics). The experimental results of individual studies are resorted to to a minimal extent and are used as specific examples. The consideration of the structural applications of the directly bonded $^{13}C-^{13}C$ SSCC is preceded by sections dealing with the state of the theoretical calculations of these constants and the analysis of the structural factors determining their values.

II. THE NATURE OF THE SPIN–SPIN COUPLING BETWEEN DIRECTLY BONDED CARBON NUCLEI

Calculation of the directly bonded $^{13}C-^{13}C$ SSCC on the basis of the modern theory of spin–spin coupling do not as a rule lead to quantitative agreement with experiment, but make it possible in a number of instances to understand the principal trend in the variation of the experimental values of $^1J_{CC}$. This Section deals briefly with the main results of the theoretical study of $^1J_{CC}$; a more detailed discussion of the theoretical problems and of the problem concerning the calculation of $^1J_{CC}$ may be found elsewhere.[25,26]

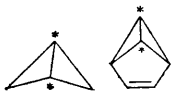
1. The Coupling Mechanisms

The magnetic moments of two directly bonded ^{13}C nuclei interact via the spin polarisation mechanism. The directly bonded $^{13}C-^{13}C$ SSCC corresponding to this interaction are determined by three contributions arising via three independent mechanisms of the spin–spin coupling: the Fermi-contact mechanism (contact electron–nucleus interaction), the spin–orbital mechanism (the interaction of the orbital electron currents with the nuclear moments), and the dipole–dipole mechanism (the interaction of electronic and nuclear dipoles).[27]

The Fermi-contact contribution is proportional to the product of the *s* orbital densities at the corresponding nuclei, while the two non-contact contributions are proportional to the products of the one-centre integrals of the valence *p* electrons of the interacting carbon nuclei. The first acceptable algorithm for the calculation of the above contributions was proposed by Blizzard and Santry,[28,29] who established that in many instances the Fermi-contact contribution only is sufficient for the calculation of $^1J_{CC}$; the inclusion in the calculation of the non-contact contributions leads in the general case to an improvement of the agreement between the theoretical and experimental values of $^1J_{CC}$, which is shown particularly for the $^{13}C-^{13}C$ SSCC for the triple bond.

The problem of the ratio of the contributions to the directly bonded $^{13}C-^{13}C$ SSCC has been studied thoroughly using a wide variety of non-empirical and semiempirical methods.[28–43]

In the general case the Fermi-contact contribution ($^1J^{Fc}$) is positive and as a rule predominates, the spin–orbital contribution ($^1J^{SO}$) is negative, and the dipole–dipole contribution ($^1J^{dd}$) has a variable sign and is insignificant. The non-contact interactions become significant for unsaturated and especially sterically strained systems with "unusual" hybridisation. In the latter, the role of the non-contact interactions increases mainly as a result of the decrease of the Fermi-contact contribution, which may be negative in the given instance.[44–48] For example, in the molecules of bicyclobutane (I) and benzvalene (II), a structural isomer of benzene, all three contributions to $^1J_{CC}$ by the bridging carbon atoms# are comparable in magnitude and negative,[44] i.e. the theory predicts in this case the negative sign of the resulting constant, which was subsequently confirmed experimentally.[49,50]



(I) (II)

Another extreme example is provided by acetylene derivatives in which all three contributions are positive.[26,39–41]

Table 1. The relative contributions of $^1J^{Fc}$, $^1J^{SO}$, and ^1Jdd (Hz) to the directly bonded $^{13}C-^{13}C$ SSCC for ethane, ethylene, and acetylene calculated using various methods.[26]

Method of calculation	H_3C-CH_3		$H_2C=CH_2$		$HC\equiv CH$	
	^1JFC	^1JSO + ^1Jdd	^1JFC	^1JSO + ^1Jdd	^1JFC	^1JSO + ^1Jdd
Non-empirical method with scanning of molecular orbitals	19.7	—	53.9	—	14.9	—
Non-empirical method involving direct summation with respect to states	17.4	0.6	69.2	—1.2	190.7	2.2
Non-empirical generalised Hartree–Fock method	—	1.2	—	—7.4	—	19.7
Method of finite perturbations in terms of the INDO approximation	41.5	—	82.1	—	163.8	—
Self-consistent theory of finite perturbations in terms of the INDO approximation	35.6	—2.2	70.6	—14.7	140.8	31.9
Method of finite perturbations in terms of the MINDO/3 approximation	29.9	0.2	72.3	2.5	84.0	87.5
Method involving direct summation with respect to states in terms of the INDO approximation with localised molecular orbitals	27.2	—1.1	71.6	—2.7	141.6	3.6
Experiment (Ref.2)	34.6		67.6		171.5	

It is noteworthy that the results of the study of the ratio of the contributions to $^1J_{CC}$ depend greatly on the computational methods employed, and they should therefore be interpreted with a certain amount of caution. Table 1 presents the values of the Fermi-contact contributions and the sums of the non-contact contributions ($^1J^{dd}$ + $^1J^{SO}$), calculated by several methods for ethane, ethylene, and acetylene molecules. Different methods yield a very significant scatter both in the estimates of the relative significance of the individual contributions and in the calculated $^1J_{CC}$, which is manifested particularly strikingly for the acetylene molecule. The method of finite perturbations in terms of the MINDO/3 approximation is apparently least applicable to the calculation of $^1J_{CC}$ for acetylenic compounds in view of the fact that the relative role of non-contact interactions is then found to be clearly too high.

Here and henceforth the asterisk denotes the interacting carbon nuclei.

2. The Types of Coupling

The three mechanisms of the coupling of the ^{13}C nuclear spins enumerated above can involve the participation of orbitals of the σ or π type. In order to separate these two types of coupling, the method of partly restricted and molecular orbitals was used in terms of the INDO approximation and it was shown that the Fermi-contact coupling takes place mainly via the σ system, while both types of non-contact coupling involve almost completely the π-electron system.[51] Using the method of direct summation with respect to states, it was established, in terms of the INDO approximation, that the spin–spin coupling between the ^{13}C nuclei linked directly in the acetylene, ethylene, and benzene molecules takes place via the σ mechanism.[52] A similar conclusion was reached as a result of the calculation of $^1J_{CC}$ for the same molecules by the method of the self-consistent theory of finite perturbations in terms of the INDO approximation with subsequent exclusion of the one-centre exchange integrals between the 2*s* orbital and one or more of selected 2*p* orbitals of one of the interacting carbon atoms.[53]

Thus, in the case where the Fermi-contact contribution predominates (which is the case in almost all compounds), the spin–spin coupling between carbon nuclei linked directly takes place via the σ-electron system.

III. THE PRINCIPAL FACTORS DETERMINING THE VARIATION OF THE DIRECTLY BONDED $^{13}C-^{13}C$ SSCC

1. Hybridisation of the Interacting Atoms

The main factor determining the variation of the directly bonded $^{13}C-^{13}C$ SSCC is the hybridisation of the interacting carbon atoms. In the very first experiment, it was already observed that the $^1J_{CC}$ increase sharply with increase of the amount of *s* character, i.e. the contribution by the 2*s* orbitals of the carbon atoms involved in the formation of the corresponding carbon–carbon bond.[1–3]

The observed variation becomes understandable if account is taken of the fact that the Fermi-contact contribution $^1J^{Fc}$ (which, as mentioned above, predominates in the vast majority of cases) is proportional to the *s* character of the bond in terms of the "average excitation energy" approximation:[27]

$$^1J^{Fc} = \frac{64\pi^2\beta^2}{9(\Delta E)}\langle s_A|\delta(r_A)|s_A\rangle\langle s_B|\delta(r_B)|s_B\rangle P^2_{s_As_B}. \quad (1)$$

where β is the Bohr magneton, ΔE the average excitation energy, $\langle s_A|\delta(r_A)|s_A\rangle$ and $\langle s_B|\delta(r_B)|s_B\rangle$ are the one-centre integrals for the 2*s* orbitals of the carbon atoms A and B, and $P_{s_As_B}$ is the corresponding first order density matrix of the valence *s* electrons.

(a) The Formal Relation with Hybridisation

The first quantitative description of the directly bonded $^{13}C-^{13}C$ SSCC in the context of the hybridisation of the interacting atoms was proposed by Frei and Bernstein, who measured $^1J_{CC}$ for thirteen ^{13}C-labelled compounds corresponding to six formal types of hybridisation of the interacting atom and established that the SSCC $^1J_{CC}$ (Hz) is proportional to the product of the *s* characters of the hybrid orbitals forming the corresponding carbon–carbon bond:[3]

$$^1J_{AB} = 576 s_As_B - 3.4 \quad (2)$$

Later, an analogous relation was obtained by Günther and Herrig.[54]

A more accurate description of this relation was proposed by Newton et al.,[44] who observed a correlation between the experimental $^1J_{CC}$ (Hz) and the products of the *s* characters of the hybrid orbitals calculated by the method of finite perturbations in terms of the INDO approximation for sixteen hydrocarbons of different structure:

$$^1J_{AB} = 621 s_As_B - 10.2 \quad (3)$$

The last relation differs from Eqn.(2) by a significant negative constant term, which is important, as will be shown below, for the description of the variation of $^1J_{CC}$ for sterically strained systems.

An attempt has been made[55] to include in the correlation equations of types (2) and (3) the overlap integral of the hybrid orbitals of the interacting atoms, but the relation obtained has not been widely used.

If it is assumed that the one-centre overlap integrals of the 2*s* orbitals of the carbon atoms in Eqn.(1) are constant, then, under conditions where the Fermi-contact interaction predominates, the SSCC $^1J_{CC}$ should be proportional to the square of the corresponding element of the density matrix $P^2_{s_As_B}$. Similar relations have been noted in other studies.[53,56,57] Recalculation of the data of Maciel et al.[53] by the method of least squares using the experimental values of $^1J_{CC}$ known at the present time led us§ to Eqn.(4) describing the variation of 60 values of $^1J_{CC}$ for 47 compounds with different hybridisation of the interacting atoms ($r = 0.956$, $s = 3.5$ Hz):

$$^1J_{AB} = 475.7\,(\pm 19.0)P^2_{s_As_B} + 6.6\,(\pm 1.8) \quad (4)$$

The description of the variation of $^1J_{CC}$ in the context of the hybridisation has been satisfactorily confirmed experimentally for various compounds,[54–56] including charged systems.[61]

(b) The Inadequacy of the Hybridisation Model

The successful description of the variation of $^1J_{CC}$ within the framework of the concept of hybridisation has become possible only for a set of systems with a wide variation of the *s* character of the bonds being compared and without substituents having markedly different electron-donating (electron-accepting) and steric properties. A number of examples are known where the hybridisation model does not reflect even the principal trend in the variation of $^1J_{CC}$.[62–66] There may be several reasons for the inadequate description in this instance.

The constant term in the correlation equations (2)–(4) corresponds to a constant overall contribution of the non-contact interactions independent of the *s* character of the bond.[30] Therefore the inconstancy of the non-contact interactions may introduce a significant error in the calculation of $^1J_{CC}$ by means of these equations, which applies in the first place to the spin–orbital contribution.

On the other hand, the effect of substituents, which is underestimated or, conversely, overestimated in the formal calculations of the amount of *s* character of the hybrid orbitals or the elements of the density matrix of the valence *s* electrons (different electronic and steric effects, the effect

§ L.B.Krividin, S.V.Zinchenko, V.V.Shcherbakov et al., Zhur.Org.Khim., 1987 (in the Press).

of unshared electron pairs of heteroatoms, etc.) can induce a significant variation of $^1J_{CC}$. For example, the range of variation of $^1J_{CC}$ for a triple bond, caused by the influence of substituents, is ~170 Hz (Fig.1).

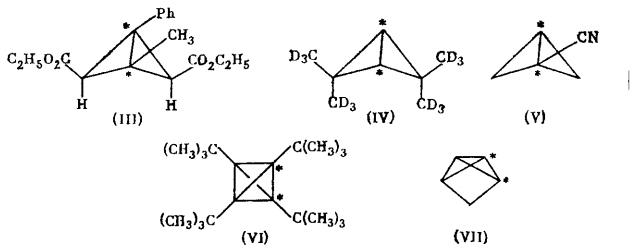
The correlation of $^1J_{CC}$ with various characteristics of the *s* character of the bond are based on the fairly rough (average excitation energy) approximation, which has been used to eliminate summation with respect to triplet states in the second-order perturbation theory.[33] The use of various quantum-chemical methods leads to an appreciable scatter of the *s* character of the bond, which also affects the overall quality of correlations of types (2)–(4). For example, the sum of the amounts of *s* character of the four equivalent hybrid orbitals of the central carbon atom of neopentane, calculated using the most accurate Eqn.(2), is 136%, i.e. it exceeds by 36% the maximum permissible value.[67]

The sterically strained mono-, di-, and poly-cycloalkanes—compounds with "unusual" hybridisation—constitute a special case. For example, the bond between the bridging carbon atoms in bicyclobutane is believed to be of the sp^{24}–sp^{24} type (which corresponds to 4% of the *s* character of the hybrid orbitals forming the bridge bond).[68] The interest in the ^{13}C–^{13}C SSCC for these compounds is therefore understandable.[44–50,68–79]

On the basis of the simplest model of the structure of the cyclopropane ring, each carbon atom forms two exocyclic hybrid orbitals with 33% of *s* character of the sp^2 type and two endocyclic orbitals with 17% of *s* character, which corresponds approximation to sp^5 hybridisation. The use of the classical Frei–Bernstein equation [Eqn.(2)] leads to $^1J_{SS} \cong$ 16 Hz as the directly bonded ^{13}C–^{13}C SSCC between two ring carbon atoms of the cyclopropane ring,[70] which is close to the experimental value of 12.4 Hz.[47]

In the case of bicyclobutane, even the Frei–Bernstein equation predicts a negative value of the constant ($^1J_{CC} \cong$ −3 Hz) for the coupling between the bridging carbon atoms, while according to the more accurate Eqn.(5), the value in this case should be above −10 Hz.[44] As mentioned above, the same result follows also from the calculation of the three theoretical contributions to the given constant.[44,75]

The theoretical prediction of the negative sign of the directly bonded ^{13}C–^{13}C SSCC between the bridging carbon atoms in systems of the bicyclobutane type has been confirmed experimentally by Pomerantz and Finkelmeier, who carried out unique experiments involving the measurement of the signs of the ^{13}C–^{13}C SSCC for 1-methyl-[3-^{13}C]phenylbicyclo[1.1.0]butane-1,3-*exo*,*endo*-2,4-dicarboxylate (III) ($^1J_{CC}$ = −5.4 ± 0.5 Hz [49]) and 2,2,4,4-tetra(trideuteriomethyl)bicyclo[1.1.0][1,3-$^{13}C_2$]butane (IV) ($^1J_{CC}$ = −17.49 ± 0.2 Hz [50]). In the light of these data, the corresponding SSCC $^1J_{CC}$ for 1-cyanobicyclobutane (V) ($^1J_{CC}$ = 16.0 Hz [71,72]), tetra-t-butyltetrahedrane (VI) ($^1J_{CC}$ = 9.2 Hz [48]), and tricyclo[2.1.0.$0^{2,5}$]pentane (VII) ($^1J_{CC}$ = 19.0 Hz [76]) should also be regarded as negative.



As already mentioned, the hybridisation $^1J_{CC}$ model suffers from a number of limitations. In sterically strained systems, the limitation associated with failure to take into account the geminal (for three-membered rings) and vicinal (for four-membered rings) ^{13}C–^{13}C interactions, which involves independent pathways and lead to an additive contribution to the direct constant, assumes special importance.[30,47,48] For example, according to Stöcker's data,[47] the geminal interaction in cyclopropane leads to the contribution $^2J'_{CC}$ = −20.08 Hz, while the direct interaction leads to the contribution $^1J'_{CC}$ = 33.45 Hz, which results in the constant $^1J_{CC}$ = $^1J'_{CC}$ + $^2J'_{CC}$ = 12.47 Hz, agreeing exactly with the experimental value $^1J_{CC}$ = 12.4 Hz.[47] In the given interpretation, cyclopropane is a molecule with the "usual" sp^3 hybridisation.

Thus, in describing the variation of $^1J_{CC}$ within the framework of a simple hybridisation model, much care must be exercised in taking into account more secondary factors such as the electronic and steric effects of the substituents, the ratio of the contributions of the non-contact interactions in the series of compounds compared, and certain others.

2. Effects of Substitution

A factor of secondary importance, determining the variation of $^1J_{CC}$, is the electronic influence of substituents via the system of bond electrons (the steric effects of substituents will be considered separately). Derivatives of acetylene,[39,80–82] ethylene,[57,83–90] ethane,[56,91,92] benzene,[31,37,93–103] pyridine,[104] adamantane and diamantane,[106–108] and also, to a lesser extent, those of other compounds,[34,47,62,63,70,77,109–122] have been most thoroughly investigated in this sense. This Section deals with the general consideration of the effects of substitution without presenting extensive factual data; these data have been partly included in two compilations.[5,6]

(a) General Characteristics

The linear increase of $^1J_{CC}$ with increasing electronegativity of the first atom of the substituent (E_X)[37,39,88] or other characteristics reflecting its induction properties and acting via the system of σ-bonds of the molecule[81,94,95,123] has been noted in a series of studies of the influence of substituents on directly bonded ^{13}C–^{13}C SSCC. For example, for monosubstituted ethylene and acetylenes, these relations have the following form respectively:[39,88]

$$^1J_{CC} = 14.4E_X + 33.1 \quad (5)$$

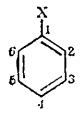
$$^1J_{CC} = 43.4E_X + 17.3 \quad (6)$$

According to the results obtained by the method of finite perturbations in terms of the INDO approximation, electronegative substituents X in the C–C–X fragment diminish the *s* character of the hybrid carbon orbital involved in the formation of the C–X σ-bond, which leads in its turn to an increase of the *s* character of the second hybrid orbital of the same carbon atom forming the C–C bond.[92] This increases the contribution of the Fermi contact interaction of the two carbon atoms considered and hence increases the constant $^1J_{CC}$, which is apparently a general principle for any system. These ideas have been confirmed by the results of calculations of ~70 values of $^1J_{CC}$ for more than 40 derivatives of ethane, ethylene, acetylene, and benzene by the self-consistent finite perturbation theory in terms of the INDO approximation.[32] According to the results of the last study quoted, the influence of substituents on $^1J_{CC}$ for a neighbouring carbon–carbon bond is exerted mainly as a result of the alteration of the Fermi-contact contribution to the ^{13}C–^{13}C SSCC.

The only known exceptions are cyclopropane derivatives in which the electronegative substituents CO_2H, CN, and COR (R = H or alkyl) decrease $^1J_{CC}$ compared with the unsubstituted cyclopropane; this may be explained by the interaction of the *p* orbitals of the α-carbon atom of the substituent with the "Walsh orbitals" of the cyclopropane ring, which decreases the *s* character of the endocyclic hybrid carbon orbital forming a carbon–carbon ring bond.[47] Account must also be taken of the fact that the spin–orbital interaction, sensitive to the redistribution of π-electron density,[51] makes a major contribution in the given instance to the ^{13}C–^{13}C constant.[44–48]

The influence of substituents on $^1J_{CC}$ decreases rapidly with increase in the number of intervening bonds separating the interacting atoms from the site of substitution.

For example, the ranges of the variation of $^1J_{CC}$ in the series of monosubstituted benzenes (VIII) are respectively Δ^1J_{CC} = 21.3 Hz, $\Delta^1J_{2,3}$ = 4.7 Hz, and $\Delta^1J_{3,4}$ = 1.9 Hz.[37]



(VIII)

An analogous relation is characteristic also of adamantane,[107] diamantane,[108] and pyridine[104] derivatives. The character of the dependence of $^1J_{CC}$ for the ^{13}C nuclei in the β- and γ-positions relative to the site of substitution on the electronegativity of the substituent may be directly opposite for different compounds.[37,104,107,108] It can be assumed that $^1J_{CC}$ for the even more remote bonds is almost insensitive to the influence of substituents transmitted via the system of σ-bond electrons.

A dependence of $^1J_{CC}$ on the π-electronic properties of substituents has been noted in some cases[31,38,47,93,96,99,100,101] but in most cases these effects are apparently associated with the π-induced redistributions of *s*-electron density, i.e. ultimately with the change in the *s* character of the bond.

The question of the additivity of the effects of substitution, which has so far been scarcely investigated, is extremely interesting for the practical application of $^1J_{CC}$ in structural studies. The additivity of the effects of substitution in the benzene rings of aromatic ethers and sulphides on $^1J_{CC}$, with the exception of instances of specific interaction of substituents in close proximity, has been noted.[124] The additivity of the influence of the phenyl group on $^1J_{CC}$ for the double bond has also been established.[38] A distinct non-additivity has been observed for the ^{13}C–^{13}C SSCC for the cyclopropane ring[47] and the triple bond.[80,125] For example, the experimental values of $^1J_{CC}$ for compounds (IX), (X) and (XI) exceed the values of this constant calculated using an additive scheme respectively by 10.2, 12.0 and 32.0 Hz:[125]

$(C_2H_5)_3Si{-}C{\equiv}C{-}Si(C_2H_5)_3$ (IX)

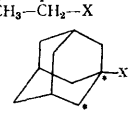
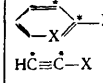
$(C_4H_9)_3Sn{-}C{\equiv}C{-}Sn(C_4H_9)_3$ (X)

$(CH_3)_3Sn{-}C{\equiv}C{-}Si(CH_3)_3$ (XI)

(b) Comparative Analysis of the Effects of Substitution

Table 2 gives a compilation of the increments Δ^1J_{CC} for the commonest substituents in certain model systems corresponding to different types of hybridisation of the interacting atoms. The Δ^1J_{CC} increase sharply with the increasing *s* character of the corresponding carbon–carbon bonds, which

Table 2. The substitutional increments in $^1J_{CC}$ (Hz) for the commonest substitutents[a].

Formal type of hybridisation	System	Substituents X										Refs.
		$Si(CH_3)_3$	CH_3	$COCH_3$	CO_2CH_3	CN	NH_2	Cl	Br	I	OCH_3	
sp^2–sp^2		—	+0.9	-2.2[b]	-2.6[c]	−1.5	—	+1.5	+0.9	+0.5	—	[47]
sp^3–sp^3	$\dot{C}H_3{-}\dot{C}H_2{-}X$	-2.8[d]	−1.6	+0.9	+0.2[c]	−1.6	+1.2	+1.5	+1.4	+1.2	+4.2	[56,92]
sp^3–sp^3		—	+0.3	−0.1	-0.3[c]	−0.1	+2.2	+1.7	+1.1	+0.7	+3.3[e]	[107]
sp^3–sp^2	$\dot{C}H_3{-}\dot{C}(=CH_2)X$	—	−0.1	—	+2.7	+3.0	—	+6.6	—	—	+9.9[f]	[57]
sp^3–sp^2	$\dot{C}H_3{-}\dot{C}(=O)X$	—	+0.7	—	—	—	+12.8[g]	+16.7	+14.7	+7.1	+19.4[f]	[62]
sp^2–sp^2	$H_2\dot{C}{=}\dot{C}H{-}X$	-8.2[h]	+2.4	—	+0.7	+3.0	+8.4[i]	+9.9	+8.7	—	+11.0	[5,88]
sp^2–sp^2		-6.5[k]	+1.1	+1.8	+2.3	+4.1	+5.1	+9.2	+7.7	+5.0	+11.1	[37,96]
sp^2–sp^2		—	+1.9	—	+5.3	+7.3	—	+13.1	+10.6	—	+16.4	[104]
sp–sp	$H\dot{C}{\equiv}\dot{C}{-}X$	−39.0	+0.4[l]	+8.4[m]	+7.3[c]	+24.1[m]	+7.5[o]	+23.7[m]	+21.3[m]	—	+58.4[p]	[39,81]

[a] $\Delta^1J_{CC} = {}^1J_{CC}(X) - {}^1J_{CC}(H)$. [b] For the substituent CO–; [c] For the substituent CO_2H. [d] For the substituent $SiH(C_2H_5)_2$. [e] For the substituent OH. [f] For the substituent OC_2H_5. [g] For the substituent $N(C_2H_5)_2$. [h] For the substituent $Si(CH_3)_2Cl$. [i] Estimated on the basis of an additive scheme for the substituent $N(C_2H_5)_2$. [k] For the substituent SiH_3. [l] For the substituent C_4H_9. [m] For the substituent $COCH(CH_3)_2$. [n] Estimated on the basis of an additive scheme. [o] Estimated on the basis of an additive scheme for the substitutent $N(CH_3)_2$. [p] Estimated on the basis of an additive scheme for the substituent $4\text{-}CH_3C_6H_4O$.

also demonstrates the dependence, presented in Fig. 2 of the Δ^1J_{CC} for the substituents $Si(CH_3)_3$, $COCH_3$, CN, and OCH_3 on the product of the *s* characters of the interacting atoms. This is most notable when the values of $^1J_{CC}$ for the "strongest acting" substituents $Si(CH_3)_3$ and OCH_3, amounting to −40 and +60 Hz respectively for acetylene derivatives corresponding to the *sp*–*sp* hybridisation, are compared.

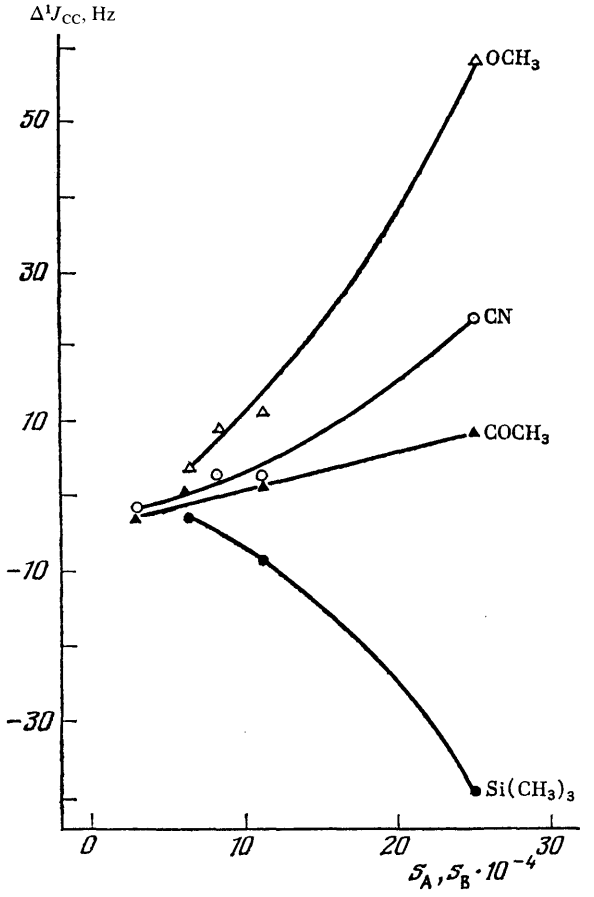


Figure 2. Variation of the increments Δ^1J_{CC} for certain substituents with the product of the amounts of *s* character of the interacting atoms.

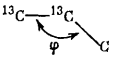
3. Steric Effects

The directly bonded $^{13}C-^{13}C$ SSCC are stereospecific with respect to the spatial distribution of individual structural fragments of the molecule, which makes it possible to use these parameters for the solution of a wide variety of stereochemical problems. The principal types of steric effects of substituents reflected in the values of $^1J_{CC}$ are briefly considered below.

(a) Effects Association with Changes in Valence Angles

The steric interactions of substituents are capable of inducing changes in molecular geometry leading to changes in the hybridisation of individual orbitals (which is determined in the first place by the bond angles) and hence to changes in the *s* characters of the bond and the corresponding $^{13}C-^{13}C$ SSCC. The first experimental manifestation of such effects has been observed in a study of $^1J_{CC}$ for ethane derivatives.[92] At first sight the unexpected increase in $^1J_{CC}$ on successive increase in the number of methyl groups at one of the interacting carbon atoms becomes understandable if account is taken of the fact that this leads to a gradual increase in the bond angle in the $^{13}C-^{13}C-CH_3$ fragment compared with the tetrahedral bond angle (by 5° [92]) and hence to an increase in the *s* character of its hybrid orbitals and correspondingly in the Fermi-contact contribution to the constant $^1J_{CC}$.

A quantitative description of this relation has been proposed by Pomerantz and Bittner,[126] who established that $^1J_{CC}$ for the fragment (XII) in a series of monohydrocarbons with a known geometry exhibits a quadratic dependence on the bond angle:



(XII)

$$^1J_{CC} = -0.00566\,\varphi^2 + 1.377\,\varphi - 49.04. \quad (7)$$

When ϕ is increased from 60° to 126.5°, $^1J_{CC}$ increases from 13.3 to 35.14 Hz.[126]

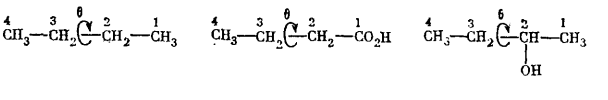
In a later study,[78] it was shown that, when cyclopropane, for which the observed $^1J_{CC}$ is the sum of the SSCC for two independent types of spin–spin coupling, is excluded from consideration, the observed dependence is linear:

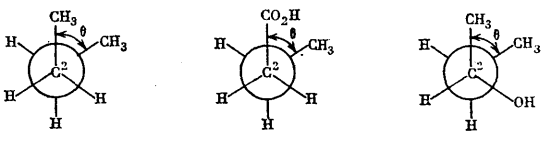
$$^1J_{CC} = 0.166\,\varphi + 14.91 \quad (8)$$

Extrapolation of Eqn. (8) to ϕ = 60° leads to the "true" value of the directly bonded carbon–carbon constant for cyclopropane: $^1J_{CC} \cong 25$ Hz.[78]

(b) Effects Associated with Changes in the Mutual Orientation of the Bonds

Calculation of $^1J_{CC}$ by the method finite peturbations in terms of the INDO approximation for butane (XIII), butyric acid (XIV), and 2-butanol (XV) revealed a distinct stereospecificity of $^1J_{1,2}$ with respect to the mutual orientation of the C(1)–C(2) and C(3)–C(4) bonds, i.e. the dependence of $^1J_{CC}$ on the dihedral angle θ:[33]



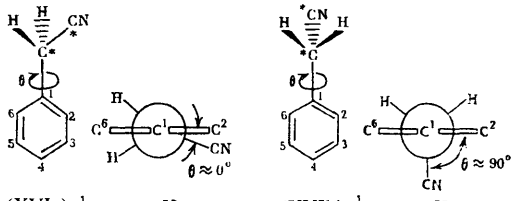


(XIII) (XIV) (XV)

The increase in θ from 0° to 180° reduces $^1J_{CC}$ by 4.5–6 Hz.

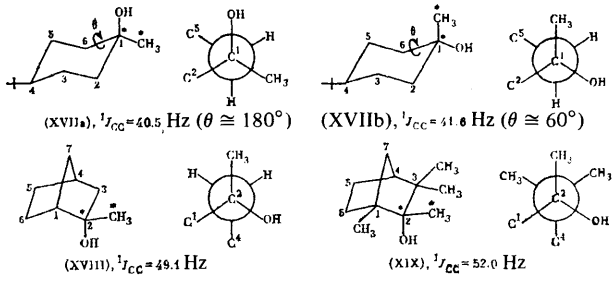
A difference between the theoretical values of $^1J_{CC}$ calculation was performed taking into account only the Fermi-contact contribution) for the planar and orthogonal conformers of benzyl cyanide (XVIa, b) has been noted.[127] This too can be explained by the change in the C(2)–C(1)–CH_2–CN

dihedral angle θ.



(XVIa), $^1J_{CC}$ = 76.3 Hz (XVIb), $^1J_{CC}$ = 75.0 Hz

The experimental values of $^1J_{CC}$ for *cis*- and *trans*-4-t-butyl-2-methylcyclohexanols (XVIIa, b), *exo*-2-methyl-2-norborneol (XVIII), and *exo*-2-methyl-2-fenchone (XIX) [33] reflect the same relation.

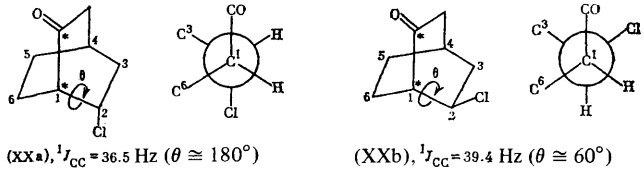


(XVIIa), $^1J_{CC}$ = 40.5 Hz ($\theta \cong 180°$) (XVIIb), $^1J_{CC}$ = 41.6 Hz ($\theta \cong 60°$)

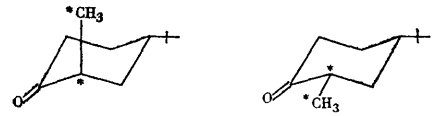
(XVIII), $^1J_{CC}$ = 49.1 Hz (XIX), $^1J_{CC}$ = 52.0 Hz

Analogous effects have also been noted in certain diamantane derivatives. [108]

The relation discussed above has also been observed in the $^{13}C-^{13}C-C-X$ fragment, where X is a heteroatom, as happens in the *exo*- and *endo*-derivatives of bicyclo[2.2.2]octanone (XXa, b) [128] and the pairs of 4-t-butyl-2-methyl-cyclohexanone diastereoisomers (XXIa, b). [129]



(XXa), $^1J_{CC}$ = 36.5 Hz ($\theta \cong 180°$) (XXb), $^1J_{CC}$ = 39.4 Hz ($\theta \cong 60°$)

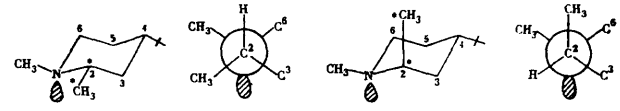


(XXIa), $^1J_{CC}$ = 33.8 Hz (XXIb), $^1J_{CC}$ = 37.6 Hz

The striking stereospecificity of $^1J_{CC}$ with respect to the orientation of neighbouring bonds makes it possible to employ these constants also for the solution of various problems in conformational analysis.

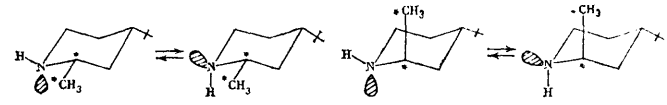
4. Effects of Unshared Electron Pairs of Heteroatoms

The stereospecificity of the directly bonded $^{13}C-^{13}C$ SSCC with respect to the orientation of the unshared electron pair of the nitrogen atom was first noted by Barna and Robinson for pairs of diastereoisomers of piperidine derivatives. [129] $^1J_{CC}$ for the *cis*-isomer of 4-t-butyl-2-*N*-dimethylpiperidine (XIIa) with the *gauche*-disposition of the C(2)–CH_3 bond and the unshared electron pair of the nitrogen atom is greater by 4 Hz than the corresponding constant for the *trans*-isomer (XXIIb):



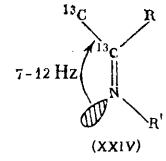
(XXIIa), $^1J_{CC}$ = 39.3 Hz (XXIIIb), $^1J_{CC}$ = 35.3 Hz

The difference between the constants for the corresponding NH derivatives is reduced to ~2 Hz as a consequence of the shift of the conformational equilibrium of the *trans*-isomer (XXIIIb) towards the form with the *gauche*-orientation of the unshared electron pair and of the carbon–carbon bond considered:



(XXIIIa), $^1J_{CC}$ = 38.4 Hz (XXIIIb), $^1J_{CC}$ = 36.5 Hz

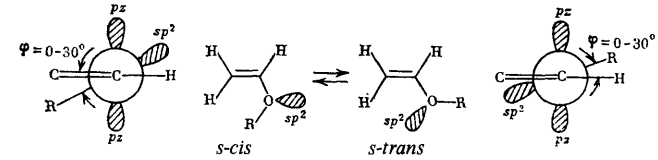
The effect of the unshared pair of the imino-nitrogen, leading to an additional contribution to $^1J_{CC}$ for the neighbouring carbon–carbon bond of the fragment (XXIV), amounting to up to 12 Hz, which permits an unambiguous identification of the configurations of a wide variety of imines, has been noted in a series of studies. [123,130–135]



(XXIV)

An analogous influence of unshared electron pairs has also been established for a series of oxygen-containing compounds. [90,124,136,137]

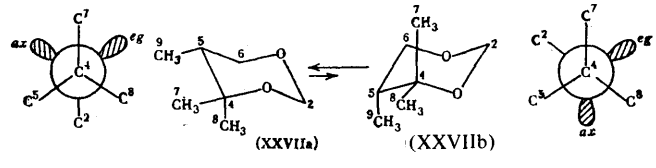
The shift of the conformational equilibrium in a series of alkyl vinyl ethers towards the *s-trans*-conformer with the *cis*-orientation of the sp^2-hybridised unshared electron pair of oxygen with respect to the double bond leads to an additional contribution to the corresponding $^{13}C-^{13}C$ constant up to ~4 Hz: [136]



s-cis *s-trans*

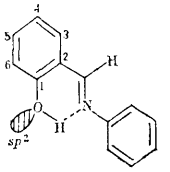
R = CH_3 (XXV), $^1J_{CC}$ = 78.6 Hz; R = $C(CH_3)_3$ (XXVI), $^1J_{CC}$ = 82.2 Hz

The same effect has been observed also for the sp^3-hybridised unshared electron pairs of the oxygen atom of 4,4,5-trimethyl-1,3-dioxan (XXVII). [137] The equilibrium in this compound is displaced towards the conformer (XXVIIa). The constant $^1J_{4,7}$ exceeds $^1J_{4,8}$ by ~3.5 Hz owing to the additional contribution to the former by the axial sp^3-hybridised unshared pair of the neighbouring oxygen atom in the preferred conformer (XXVIIa), while the contributions of the equatorial unshared electron pair to the two constants are the same.



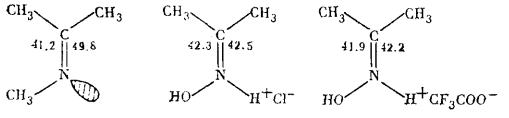
(XXVIIa) (XXVIIb)

According to Krivdin et al.,[124] the contribution of the hybridised unshared pair of the oxygen of the hydroxy-group in compound (XXVIII), rigidly fixed in the *cis*-position with respect to the C(1)–C(6) bond as a consequence of the formation of a strong intramolecular hydrogen bond, is ~7 Hz, which is comparable to the contribution by the unshared electron pair of the imino-nitrogen.



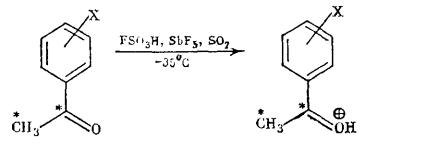
(XXVIII)

In view of the practical importance of the effects considered in stereochemical studies on heteroatomic compounds, the elucidation of the nature of the influence of the unshared electron pairs of the heteroatoms on the $^{13}C-^{13}C$ SSCC is of great interest. In their first study,[129] Barna and Robinson suggested that the observed effect is caused by the steric overlapping of the unshared electron pair of the heteroatom with the antibonding orbitals of the neighbouring C–C bonds, which increases $^1J_{CC}$ for the *cis*- and *gauche*-orientations and decreases this constant for the *trans*-orientation of the unshared pair and of the corresponding bonds.[129] However, the results for the protonation of the acetoxime (XXIX) support the view that the unshared electron pairs of the heteroatoms give rise to an additional contribution to the $^1J_{CC}$ for the neighbouring bond in the *cis*-position and hardly influences the $^1J_{CC}$ for the bond having the *trans*-orientation.[138] The constants $^1J_{CC}$ (Hz) for acetoxime (XXIX) and its protonated forms (XXIXa, b) are presented below.[138] They demonstrate unambiguously that the positive contribution to $^1J_{CC}$ for the neighbouring bond having the *cis*-orientation is in fact "removed" on protonation of the unshared electron pair.



(XXIX) (XXIXa) (XXIXb)

The "unexpected" decrease in $^1J_{CC}$ by ~5 Hz on protonation of the carbonyl oxygen in substituted acetophenones (XXX) with formation of the stable oxonium ions (XXXI)¶ [100] should also be apparently explained by the removal of the additional positive contribution of the unshared electron pair of the carbonyl oxygen to the corresponding constant.



(XXX), $^1J_{CC}$ = 43–44 Hz (XXXI), $^1J_{CC}$ = 38–40 Hz

So far nothing is known about the influence of the unshared electron pairs of other heteroatoms on the directly bonded $^{13}C-^{13}C$ SSCC. According to our own preliminary data,† one can assume that the effect under discussion is insignificant for the halogens, sulphur, and phosphorus.

5. Effects of the Medium

The effects of the medium are manifested in the variation of three main contributions to the direct SSCC caused by the influence of the solvent: the magnetic shielding induced by the magnetic moments of neighbouring molecules, dispersion effects of the exchange type, and intermolecular electrostatic interactions.[139] In the absence of specific solvation effects, the theory predicts the variation of the directly bonded SSCC for the two interacting A and B nuclei as a function of the dielectric constant of the solvent ε in accordance with Eqn.(9), which reflects mainly the variation of the contribution by the intermolecular electrostatic interactions:[140]

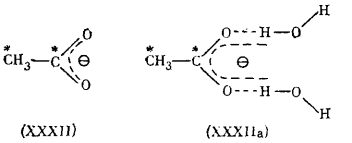
$$^1J_{AB} = a\left(\frac{\varepsilon-1}{\varepsilon}\right)^2 + b\left(\frac{\varepsilon-1}{\varepsilon}\right) + c \qquad (9)$$

However, the changes in the experimental values of $^1J_{CC}$ are comparable to the accuracy of the measurement of the constants even for a wide range of variation of the polarity of the medium.[34,80,123,141,142]

The few measurements of the temperature dependence of $^1J_{CC}$ indicate a low sensitivity of the $^{13}C-^{13}C$ SSCC to temperature.[39,123,142] For example, the constants $^1J_{CC}$ for a series of halogeno-derivatives of ethane, acetonitrile, and acetic acid increase by only 0.1–0.3 Hz when the temperature is raised by 100 °C.[142] The constants $^1J_{CC}$ are almost independence of the concentrations of the test compounds.[123]

The weak sensitivity of the $^1J_{CC}$ to solvation effects permits a correction comparison of the constants measured under different experimental conditions and, what is particularly important, in different solvents.

Like the conformational changes in the molecules induced by the solvent, in individual instances the specific associative processes may induce very large changes in the $^{13}C-^{13}C$ SSCC. For example, the calculated constants $^1J_{CC}$ for the acetate anion (XXXII) and its solvated form (XXXIIa) differ by ~35 Hz:[53]



(XXXII) (XXXIIa)

IV. STRUCTURAL APPLICATIONS

1. The Nature of the Carbon–Carbon Bonds and the Properties of Substituents

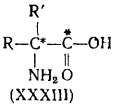
The direct $^{13}C-^{13}C$ SSCC can be used to estimate the hybridisation of individual atoms, and *s* characters of the bonds, and the *s* characters of individual orbitals and also

¶ In superacid media at −35 °C.

† L.B.Krivdin, V.V.Shcerbakov, and G.A.Kalabin, "Konstanty Spin–Spin Vzaimodeistviya $^{13}C-^{13}C$ Geteroatomnykh Soedinenii" (The $^{13}C-^{13}C$ Spin–Spin Coupling Constants for Heteroatomic Compounds) (Edited by V.A.Koptyug et al.), NIOKh Sibir.Otd.Akad.Nauk SSSR, Novosibirsk, 1988 (in the Press).

to refine the distribution of *s* electron density on carbon nuclei. The values of $^1J_{CC}$ are also reflected by the product of "empirical factors",[143] including the elements of the relative *s*-electron density, the C–C bond order, and the singlet–triplet excitation energy. A dependence of $^1J_{CC}$ on the π-bond order calculated by the Hückel method has been noted for a series of condensed aromatic hydrocarbons.[38,105,116,120]

On the other hand, the dependence of $^1J_{CC}$ on the *s* electron density and the weak sensitivity to π-electronic effects permit a wide-scale use of these parameters in the study of the induction properties of substituents in various systems.[37,39,81,88,94,95,123] One of the practical applications of such relations is in the method for the determination of the pK_a for carboxy-groups based on the dependence of $^1J_{CC}$ for the interaction of the carboxy-carbon atom with the neighbouring α-carbon atom in aminoacids (XXIII) on the degree of ionisation of the carboxy-group:[144–148]



(XXXIII)

On passing from an acid to a neutral medium, $^1J_{CC}$ for aminoacids diminishes by ~6 Hz; a further increase in pH, accompanied by a transition of the carboxy-group from the zwitterionic state to the anionic state, leads to a successive decrease in $^1J_{CC}$ by ~1 Hz.[145] The relation under discussion provides a unique possibility for the selective titration of individual amide groups in natural and synthetic peptides labelled with the ^{13}C isotope and for the determination of the degree of their ionisation in the active centres of enzymes.

The relation between $^1J_{CC}$ and the internuclear distances r_{CC} (Å) is of great interest. Eqn.(10) for the hybridisation of the interacting sp^3–sp^3, sp^3–sp^2, and sp^2–sp^2 atoms and Eqn.(11) for sp^3–sp, sp^2–sp, and sp–sp can be fitted to the available data:[54]

$$^1J_{CC} = -167r_{CC} + 294 \quad (10)$$

$$^1J_{CC} = -571r_{CC} + 855 \quad (11)$$

Eqns.(10) and (11) reflect the general trend involving a decrease of $^1J_{CC}$ with increase of the distance between the interacting atoms and can be used solely for rough estimates of r_{CC}.

More accurate equations have been obtained for a narrow range of condensed aromatic hydrocarbons, naphthalene, anthracene, phenanthrene, pyrene, and benzo[a]pyrene:[149]

$$^1J_{CC} = -143r_{CC} + 257 \quad (12)$$

$$^1J_{CC} = -119r_{CC} + 227 \quad (13)$$

Eqn.(12) corresponds to the case of the interaction of the methylidyne and quaternary ^{13}C nuclei, whilst Eqn.(13) corresponds to two methylidyne carbon nuclei.

The directly bonded dipole–dipole ^{13}C–^{13}C SSCC for partly oriented molecules in the nematic phase contain a large contribution due to the anisotropy of indirectly bonded carbon–carbon constants and their use for the determination of the internuclear distances r_{CC} is therefore limited.[150]

A study of the relaxation of the ^{13}C satellites in the carbon spectrum of phenylacetylene established that the ratio of the relaxation times for the pairs of satellites being compared corresponds exactly to the theoretical ratio of the dipole–dipole contributions to relaxation, which are proportional to r_{CC}^{-6}.[151] Thus the relaxation times of the ^{13}C satellites can also be used to estimate bond lengths.

A correlation between $^1J_{CC}$ and the bond force constants K_{CC}, whose experimental measurement is frequently difficult, has been observed.[152,153] The form of the equations depends on the hybridisation of the interacting atoms:

$$sp^3 - sp^3: K_{CC} = 0.0344\,^1J_{CC} + 3.25 \quad (14)$$

$$sp^2 - sp^2: K_{CC} = 0.1800\,^1J_{CC} - 3.25 \quad (15)$$

$$sp - sp: K_{CC} = 0.0295\,^1J_{CC} + 11.04 \quad (16)$$

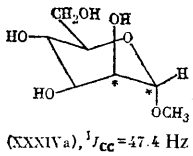
The use of these equations made it possible to define the bond force constants for a series of compounds, including epoxyethane, propene, butadiene, and diacetylene.[152]

The directly bonded ^{13}C–^{13}C SSCC made it possible to expand significantly the ideas about the nature of the carbon–carbon coordinate bonds in transition and non-transition metal complexes.[154–157] In particular, it has been established that, in a series of allyl complexes, there is a strong "reverse donation" from the highest occupied molecular orbits of the ligand to the unoccupied orbitals of the metal, which is manifested by a sharp decrease of the constant $^1J_{CC}$ for the bonds in the ligand.[156]

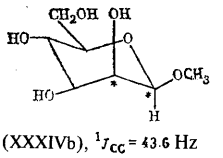
2. Stereochemical Studies

The marked stereospecificity of the directly bonded ^{13}C–^{13}C SSCC gives rise to major prospects for the use of these parameters in stereochemistry and conformational analysis. A series of problems associated with the steric orientation of the unshared electron pairs of heteroatoms have been solved with the aid of the ^{13}C–^{13}C SSCC: a new universal method has been developed for the determination of the configurations of compounds with imino-nitrogen;[123] the conformational analysis of a wide range of unsaturated and aromatic ethers and sulphides has been carried out;[90] a new method has been proposed for the identification of azole isomers;[158] the steric structure of pyrazolines—the products of the incomplete reduction of pyrazoles—has been studied.[159]

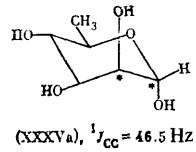
The directly bonded ^{13}C–^{13}C SSCC have found extensive applications in the stereochemistry of biologically important carbohydrates.[160,161] The constants $^1J_{CC}$ are presented as an example for methyl α- and methyl β-D-mannopyranosides (XXXIVa, b) and α-L- and β-L-rhamnoses (XXXVa, b). Here the constants are stereospecific with respect to the orientation of the substituent (OH, OCH_3) at C(1) and can thus be used to determine the steric structure of related glycosides and free sugars:[161]



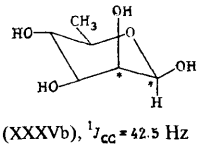
(XXXIVa), $^1J_{CC}$ = 47.4 Hz



(XXXIVb), $^1J_{CC}$ = 43.6 Hz



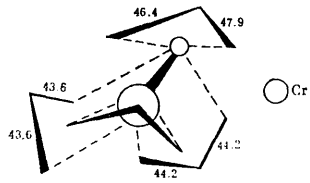
(XXXVa), $^1J_{CC}$ = 46.5 Hz



(XXXVb), $^1J_{CC}$ = 42.5 Hz

In the studies of Benn and Rufinska,[155,156] the constants $^1J_{CC}$ were used to investigate the stereochemistry of allyl complexes of metals. For example, the measurement of $^1J_{CC}$ (Hz) for the dinuclear chromium complex (XXXVI) makes it possible to determine unambiguously the bridging η^3-allyl

groups, for which the values of $^1J_{CC}$ are significantly smaller:

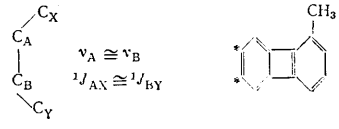


(XXXVI)

Thus the application of the directly bonded $^{13}C-^{13}C$ SSCC to the solution of a wide variety of stereochemical problems has led to the creation of a new promising method for the determination of the conformation and configurational structures of molecules.

3. Tracing Out the Carbon Skeleton of Complex Molecules

A universal method for the assignment of the ^{13}C NMR signals, which has come to be called "tracing out the carbon skeleton" has been developed using the directly bonded $^{13}C-^{13}C$ SSCC.[162] In the two-dimensional version of INADEQUATE, the carbon skeleton of the molecules is traced out by observing the two-quantum frequencies in the dimension $\mathcal{F}_1$ to which the usual carbon spectrum with ^{13}C satellites corresponds in the dimension $\mathcal{F}_2$; the ^{13}C nuclei linked directly are then readily identified from the identical two-quantum frequencies.[162] The use of this method is especially effective when the chemical shifts of the interacting nuclei are almost identical and the constants for their interaction with the neighbouring carbon nuclei are so close that they cannot be distinguished to within the accuracy of the experimental measurement, as happens, for example, in 1-methylbiphenylene (XXXVII):[163]



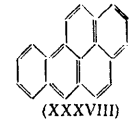
(XXXVII)

Despite the advantages noted above, when the two-dimensional version of INADEQUATE is used, two difficulties are encountered: the extremely acute problem of sensitivity, which frequently cannot be overcome even in the most sophisticated NMR spectrometers (in order to record a single two-dimensional INADEQUATE spectrum, it is necessary to obtain at least ~1000 ^{13}C satellite carbon spectra) and, on the other hand, the low numerical resolution in the transformed spectra which precludes the measurement of $^1J_{CC}$ with the necessary accuracy.

The alternative one-dimensional version of the INADEQUATE method is free from the above disadvantages. In this method, the carbon skeleton is traced out by identifying the carbon–carbon bonds as a result of the successive comparison of the values of $^1J_{CC}$ measured for each signal in the ^{13}C NMR spectrum. The COSMIC [164] and CABSA [165] programs ensure the complete automation of such an experiment.

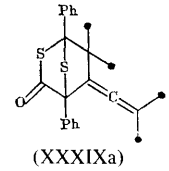
In the case of a high spectral signal density, the use of the DOUBTFUL pulse sequence[166] makes it possible to achieve an unambiguous assignment of the quaternary signals under INADEQUATE conditions with their preliminary filtration.

The method discussed is used widely for the assignment of the ^{13}C signals for complex organic compounds containing up to 40 carbon atoms. In a number of instances, the signals have been reassigned.[149,167–177] For example, the application of this method resulted in the reassignment of 11 out of the 20 ^{13}C NMR signals of the benzo[*a*]pyrene (XXXVIII) molecule.[149]

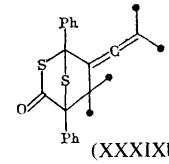


(XXXVIII)

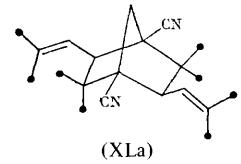
The isomers (XXXIXa, b),[178] (XLa, b),[179] and (XLIa, b),[180] which have very similar structures and cannot be distinguished on the basis of the ^{13}C NMR spectra, have been identified with the aid of this method.



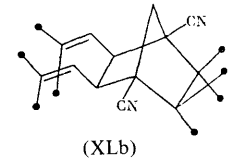
(XXXIXa)



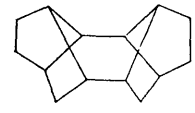
(XXXIXb)



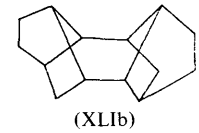
(XLa)



(XLb)

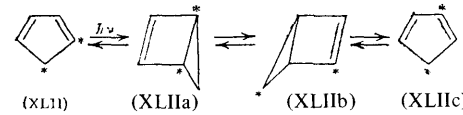


(XLIa)



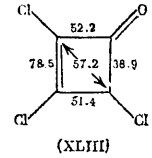
(XLIb)

The method for tracing out the carbon skeleton has already found application in the determination of the reaction mechanisms and for the identification of the intermediates.[76,181,182] An elegant example of studies of this kind is the determination of the pathway followed in the photoisomerisation of [1,2-$^{13}C_2$]cyclopentadiene (XLII):[76]

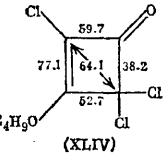


(XLII) (XLIIa) (XLIIb) (XLIIc)

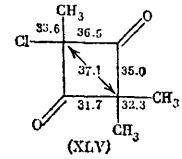
The unusually high values (tentatively positive) of the geminal constants $^2J_{CC}$ for the polychloro-derivatives of cyclobutenone and cyclobutanedione (XLIII)–(XLV), which can reach and actually exceed the values of $^1J_{CC}$, constitute a serious obstacle to the use of the method:[183]



(XLIII)



(XLIV)



(XLV)

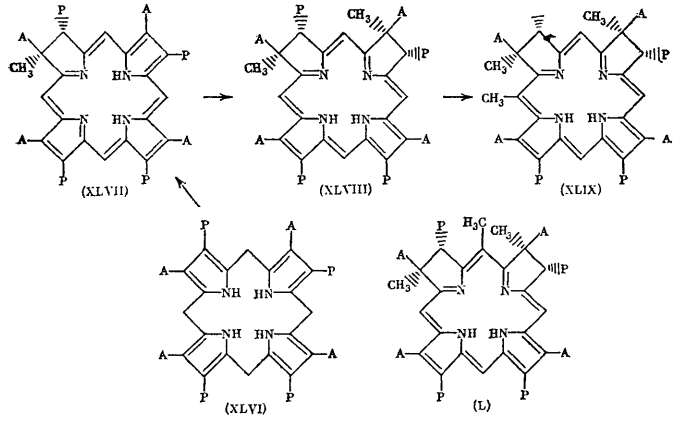
The two-dimensional version of the method discussed can be used to assign the repeating structural fragments in polymers without measuring the constants $^1J_{CC}$. The principal structural units (guaiacyl, syringyl, and pinoresinol) of the natural polymer lignin have been unambiguously assigned in this way.[184]

Thus, the method for tracing out the carbon skeleton is one of the most promising and rapidly developing applications of the direct $^{13}C-^{13}C$ SSCC in structural studies.

4. Determination of Biosynthetic Pathways

Directly bonded $^{13}C-^{13}C$ SSCC are widely used to determine the biosynthetic pathways for complex natural products.[9,185,186] The selective introduction of the ^{13}C isotope into the precursor molecule not only makes it possible to trace by the NMR method the fate of an individual atom as it passes through a sequence of biochemical reactions *in vivo* but also to determine unambiguously the site where ^{13}C is incorporated and to establish the structure of the compounds formed by the method for tracing out the carbon skeleton.

For example, the use of directly bonded $^{13}C-^{13}C$ SSCC makes it possible to establish, in the biosynthesis of vitamin B_{12}, the chain of successive transformations of intermediate precursors—sirohydrochlorin (XLVIII)—urogen-III (XLVI) derivatives.[187,188] The structure (L) had been attributed earlier erroneously to compound (XLIX).



The majority of studies concerning the use of $^1J_{CC}$ for the determination of biosynthetic pathways were based on the investigation of microbial metabolites enriched in [1,2-$^{13}C_2$]-acetate in the biosynthetic process. The earliest example of such investigations dates back to 1973: the incorporation of [1,2-$^{13}C_2$]acetate in dihydrolatumcidin.[189] The principles underlying the above study are widely used nowadays. In connection with the devlopment of the methods of synthesis of compounds enriched in the ^{13}C isotope, the most varied ^{13}C-labelled precursors, such as, for example, [U-$^{13}C_6$]-D-glucose,[190] [3,5-$^{13}C_2$]-L-tyrosine and [1,2-$^{13}C_2$]glycine,[191] [4,5-$^{13}C_2$]lysine,[192] [3,4-$^{13}C_2$]glutamate,[193] [1,2-$^{13}C_2$]propionate,[194] [2,3-$^{13}C_2$]succinate,[195,196] [5,6-$^{13}C_2$]nicotinic acid,[197,198] and certain others[199,200] have been used with increasing frequency in recent years.

The structures of about 300 most important products of the metabolism of animals and plants—polyketides, mixed metabolites, terpenes and steroids, aminoacids, and amino-acid metabolites—have now been determined with the aid of the $^1J_{CC}$ constants.

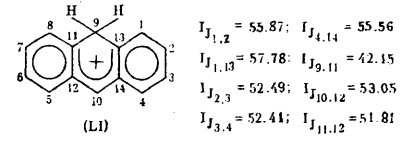
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During the preparation of the manuscript for printing, a number of studies dealing with the improvement of methodological procedures for the experimental measurement of $^{13}C-^{13}C$ SSCC, relating to problems of increasing the sensitivity of the basic INADEQUATE method in its one-dimensional and two-dimensional versions, the compensation for non-resonance effects, the development of new pulse sequences, and also for the elucidation of the possibility of measuring directly bonded $^{13}C-^{13}C$ dipole–dipole SSCC in the ^{13}C NMR spectra of solids have been published.[201–208]

The studies of the stereospecificity of the $^{13}C-^{13}C$ SSCC with respect to the orientation of the unshared electron pairs of heteroatoms (nitrogen[209,210] and oxygen[211–213]) have continued. The new experimental data confirm the conclusion that the additional contributions of the unshared pairs of these heteroatoms to the $^{13}C-^{13}C$ SSCC for neighbouring bonds are positive.

The structures of α-longipinene (a sesquiterpene),[214] the product of the cyclisation of the sesquiterpene hydrocarbon caryophyllene,[215] 1-methoxy-*endo*-tetracyclo[6.3.0.$0^{2,11}$.$0^{3,7}$]-undec-9-ene—the product of the photochemical cycloaddition of anisole to cyclopentene,[216] and the complex condensed heterocycle benzo[*b*]phenanthro[4,3-*d*]thiophen have been determined using the methods for tracing out the carbon skeleton, and their signals in the ^{13}C NMR spectra have been fully assigned.

There has been significant progress in studies on the $^{13}C-^{13}C$ SSCC for charged systems—carbonium ions of the bis-homotropylium type,[218] α-cyanodiaryl- and 1,1-diaryl-2-butynyl cations,[219] and also six-membered heteroatomic cations—the pyrylium, thiapyrylium, and seleninium ions.[220] In the last study,[220] the fundamental conclusion was reached that the lower values of $^1J_{CC}$ for positively charged systems compared with their neutral analogues can be accounted for by charge polarisation. This conclusion has been confirmed by the results of a unique experiment involving the measurement of $^1J_{CC}$ (Hz) for the anthracenium cation (LI) with the natural isotopic abundance.[221]



Progess has been noted in the theoretical study of $^{13}C-^{13}C$ SSCC. In this connection, special mention should be made of the study of Fronzoni and Galasso concerning the use of the non-empirical *ab initio* method to calculate $^1J_{CC}$ for monoheterocyclopropanes and cyclopropenes.[222] The work on the creation of a set of quantum-chemical programs IPPP RPA INDO (Inner Projections of the Polarisation Propagator at the Random Phase Approximation level using the INDO method), which makes it possible to investigate the mechanisms of the transfer of individual contributions to $^{13}C-^{13}C$ SSCC (fermi-contact, spin–orbital, and dipole–dipole) via bonds, individual molecular orbitals (including antibonding orbitals), and unshared electron pairs of heteroatoms is being completed.[223]

The work on the compilation of extensive experimental data has been completed and a survey of $^{13}C-^{13}C$ SSCC for the triple bond in a series of organoelemental and heteroatomic derivatives of acetylene is being prepared for printing.[224] Directly bonded $^{13}C-^{13}C$ SSCC have been used[225–232] for the solution of specific structural problems in the chemistry of saturated and carbocyclic, unsaturated, and aromatic, as well as heterocyclic compounds having different structures.

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