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^{13}C NMR Spectroscopy of Substituted Cyclohexanes

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New possibilities are demonstrated in the study of the conformations and dynamics of ring inversion in substituted cyclohexanes by ^{13}C NMR spectroscopy compared with other methods of chemical and physical analysis.
The bibliography includes 106 references

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I. INTRODUCTION

^{13}C NMR spectroscopy employing the natural abundance of the ^{13}C isotope (~1.1%) has become extremely common in recent years. Progress in the technique of the recording of weak NMR signals, due to the introduction of pulsed Fourier transform NMR spectroscopy (FT),[1] permitted a wide-scale employment of this method in studies on complex objects, particularly natural products. The general principles of ^{13}C NMR and its applications are described in a number of reviews[2,3] and monographs[4-6]. Among the applications of the method, special mention should be made of stereochemical research associated with the determination of the steric structures of organic molecules. The term "stereochemical research" is used in its widest sense, including the study of the possible conformations (conformational analysis) and the kinetics of intramolecular rearrangements (dynamic stereochemistry).

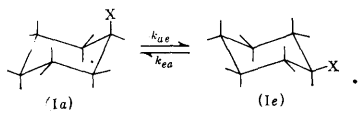
The aim of the present review is to analyse the results of the application of the ^{13}C NMR method to the study of substituted cyclohexanes. These compounds are of practical interest for organic chemistry and are traditional objects of classical conformational analysis[7].

II. CONFORMATIONAL ANALYSIS AND DYNAMIC STEREOCHEMISTRY OF SUBSTITUTED CYCLOHEXANES

Studies on the structures of cyclohexane derivatives have an extremely long history, the main landmarks of which are the classical studies by Sachse[8], Hassel[9], and Barton[10]. Starting from the 1950s, these compounds have been vigorously investigated with the aid of various chemical and physical methods; the numerous publications on this topic are analysed in a number of monographs[11,12] and reviews[13-15].

The present review deals only with the problems of experimental conformational analysis. Dashevskii's monograph[12] gives some idea about the tasks of theoretical conformational analysis, associated with calculations of the energies and geometrical structures of the conformers.

The aims of conformational analysis and the fundamental terminology employed in reports on the structures of substituted cyclohexanes can be illustrated in relation to monosubstituted derivatives $C_6H_{11}X$. One usually considers the equilibrium between only two forms (conformers), with the axial and equatorial orientations of the substituent X respectively:



(Ia) (Ie)

The conformational equilibrium is regarded as involving a rapid interconversion or inversion of the ring, (Ia) ⇌ (Ie), which can be described by two rate constants:

$$k_{ae} = \varkappa \frac{kT}{h} \exp(-\Delta G^{\neq}_{ae}/RT),$$
$$k_{ea} = \varkappa \frac{kT}{h} \exp(-\Delta G^{\neq}_{ea}/RT), \quad (1)$$

where κ is the transmission coefficient and $\Delta G^{\neq}$ the free energy of activation;

$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}, \quad (2)$$

where $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are the enthalpy and entropy of activation. In the general case $k_{ae} \neq k_{ea}$ (a non-degenerate process). The equilibrium in the reaction (Ia) ⇌ (Ie) may be characterised by the equilibrium constant K:

$$K = p_e/p_a = k_{ae}/k_{ea} = \exp(-\Delta G^0/RT), \quad (3)$$

where p_a and p_e are the equilibrium concentrations of the axial and equatorial conformers, it being assumed that

$$p_a + p_e = 1. \quad (4)$$

The quantity $-\Delta G^\circ$ is called the conformational energy; the term "A-value" is frequently used:

$$A = -\Delta G^0 = G_a - G_e, \quad (5)$$

where G_a and G_e are the free energies of the axial and equatorial conformers.

In the general case, when several substituents are present, the conformational equilibrium also involves only two conformers (A_1 and A_2); the equilibrium constant and the conformational energy for the process (A_1) ⇌ (A_2) are defined as follows: $K = p_2/p_1$ and $-\Delta G^\circ = G_1 - G_2$. In the specific instance of monosubstituted cyclohexanes it is assumed that A_1 = (Ia) and A_2 = (Ie).

Conformational Analysis

The main task in conformational analysis is the experimental determination of the equilibrium concentrations of the conformers. Evidently this task includes as a necessary stage the proof that only two forms are involved in the equilibrium at appreciable concentrations. Together with the *a*- and *e*-conformers examined above, which are derived from the chair conformation, other conformers derived from the boat (II) or twist-boat (III) conformations are also sometimes considered:



(II) (III)

Numerous theoretical estimates of the energies of a wide variety of non-chair forms of cyclohexane [16,17] have shown that the hypothesis that the chair form is most favourable is in fact justified, but the experimental proof of this was obtained only quite recently by Anet and coworkers [18]. These investigators detected the non-chair forms of cyclohexane by the method involving rapid freezing of the high-temperature equilibrium. For this purpose, gaseous cyclohexane, heated to approximately 800 K, was condensed, after vacuum evaporation, onto a CsI plate cooled to 20 K. It was thus possible to assume that the composition of the conformers in the condensate reflects the nature of the conformational equilibrium at high temperatures. It was shown by infrared spectroscopy that, together with the chair form, the condensate contains the twist-boat form. Estimates showed that the enthalpy of the twist-boat conformation exceeds by 5.5 kcal mole^{-1} that of the chair conformation. Assuming that the entropy contribution is close to zero, one may conclude that the content of the twist-form at room temperature does not exceed 0.01%. In the study of the conformational equilibria of substituted cyclohexanes, the negligible contribution of the non-chair forms is assumed without proof.

In order to determine the conformational equilibrium constant K, various methods have been used; Jensen and Bushweller [15] concluded on the basis of a comparison of numerous investigations that the method involving the measurement of the integrated intensities in high-temperature ^{1}H NMR spectra is the most accurate. On the basis of this method, the authors [15] proposed a system of "best" (i.e. most accurate) A-values for a number of substituents X. However, in view of the difficulty of the interpretation of the ^{1}H NMR spectra, the method cannot be regarded as a universal procedure for the measurement of the equilibrium constants K, which has been confirmed by the results of certain studies [13,15].

Investigators as a rule confine themselves to the determination of the conformational equilibrium constant at a single temperature, which permits the subsequent determination of the free energy ΔG_T at the same temperature. Naturally, on a wider scale conformational analysis involves the determination of the values of K over a fairly wide range of temperatures and the calculation from the $K(T)$ relation of the enthalpies and entropies of the reversible process (ΔH° and ΔS°).

An important feature of studies on conformational equilibria, consisting in the necessity to take into account the influence of intermolecular interactions (i.e. of the medium), should be noted. In many instances the influence of the medium is very significant [14,19]; this factor hinders the comparison of the results of different studies carried out in different media. As a rule equilibrium constants are measured by NMR in solutions where the test compound can be subjected to different chemical or physical influences. Thus there is a risk of the incorrect application of the parameters of the conformational equilibrium obtained in one solvent (for example in carbon disulphide, which is most suitable for NMR studies) to other conditions.

This factor, in particular, necessitates a certain amount of caution in comparing the results of studies on conformational equilibrium in almost neutral solutions and in solutions with added paramagnetic shift reagents [20], where additional complex-formation processes undoubtedly occur.

The Study of the Properties of Individual Conformers

This involves the investigation of the complete geometry of the conformers and also, in principle, the study of their other chemical and physical properties. This aspect is in fact of fundamental interest for theoretical organic chemistry in connection with the search for conformational features of molecules responsible for the selective courses of chemical reactions. Studies in this field constitute an important stage on the way to an effective employment of cyclohexane derivatives in fields such as pharmacology and the chemistry of insecticides and perfumes.

The Study of the Dynamics of the Conformational Transformation (Ring Inversion)

This involves the determination of the rate constants for ring inversion k_{ae} and k_{ea} and the calculation from these data of the free energies of activation $\Delta G^{\neq}_{ae}$ and $\Delta G^{\neq}_{ea}$. Within a wider framework, the study of the dynamics of ring inversion includes the determination of the rate constants over a wide temperature range and the calculation of the enthalpy ($\Delta H^{\neq}$) and entropy ($\Delta S^{\neq}$) of activation. The easiest method for the investigation of the dynamics of ring inversion in substituted cyclohexanes is NMR, which makes it possible to determine the rates of chemical processes from characteristic dynamic effects in the spectra [21-23].

The solution of the above problems requires the use of the entire set of the chemical and physical methods available at present. However, the specific limitations characteristic of particular methods sharply restrict the region of their applicability. Furthermore, there exist many limitations due to the specific features of the compound investigated, namely the chemical instability of the compound, its low solubility, and the narrow range of temperatures employed. Attention should also be drawn to certain limitations which are rarely mentioned in the literature but which are extremely fundamental. One of these is associated with the methodological difficulties in the isolation of the individual conformers, which requires the use of a special low-temperature technique. Only one report is at present available [24], concerning the isolation by low-temperature multistage recrystallisation of the equatorial conformer of chlorocylcohexane. Analysis of studies on polysubstituted cyclohexane has shown that even the much simpler problem of separating a mixture of isomers entails significant technical difficulties [45]. These difficulties apparently arise from the inadequate knowledge of the adsorption of substituted cyclohexanes. Another fundamental difficulty is caused by the lack of methods for

the investigation of strongly displaced equilibria (in other words of high-energy conformations). The relative error of the methods of measurements used in conformational analysis as a rule increases sharply with increase of the equilibrium constant. A conformational energy ≥ 2 kcal mole^{-1} corresponds to equilibrium constants of 200 and above and the study of the conformational equilibrium becomes virtually impossible.

New possibilities arising from ^{13}C NMR spectroscopy in the solution of the problems formulated above are discussed below. Before describing them, we shall deal with the general characteristics of the method.

III. ^{13}C NMR SPECTROSCOPY. GENERAL CHARACTERISTICS, SCOPE, AND LIMITATIONS

The vast majority of measurements of ^{13}C NMR spectra are nowadays performed by pulsed Fourier NMR. As a rule the ^{13}C NMR spectra are recorded under the conditions of the complete suppression of spin–spin interaction with protons. In commercial NMR spectrometers the suppression of the interaction with protons (or proton decoupling) is achieved with the aid of the noise modulation of the high-frequency field, the carrier frequency of which is the same as the resonance frequency of protons. Proton decoupling is accompanied not only by the merging of the multiplets but also by an increase of the integrated signal intensities as a result of specific cross-relaxation phenomena arising on proton pumping (the so called Nuclear Overhauser Effect (NOE). Thus proton uncoupling leads to an evident simplification of the spectra; one line in the $^{13}C-\{H\}$ NMR spectrum corresponds to each chemically non-equivalent carbon atom in the molecule. The position of this line in the spectrum relative to the line of the reference substance, which is tetramethylsilane $(CH_3)_4Si$, or the chemical shift of the ^{13}C nucleus is the most important spectroscopic parameter. Numerous data quoted in monographs[4,5] have shown that ^{13}C nuclei are more effective "indicators" of chemical non-equivalence than, for example, protons. Comparison of the range of variation of the chemical shifts of ^{13}C and ^{1}H nuclei, $\Delta\delta(^{13}C)$ and $\Delta\delta(^{1}H)$, carried out in a number of studies[4,5,25] for the corresponding series of model compounds showed that

$$\Delta\delta(^{13}C) = k\Delta\delta(^{1}H), \quad (6)$$

where the proportionality coefficient is 10–30 (depending on the series of compounds).

These two factors, namely the simple form of the $^{13}C-\{H\}$ NMR spectra and the high sensitivity of the chemical shift of ^{13}C nuclei to changes in the electronic environment were in fact responsible for the great interest by chemists in ^{13}C NMR.

In order to assess the nature and amount of information which can be obtained from ^{13}C NMR spectra, it is sufficient to examine the results of the study of the conformational state of chlorocyclohexane, a compound typical for the series under consideration[26]. The $^{13}C-\{H\}$ NMR spectra of chlorocylcohexane, measured in the temperature range from 193 to 273 K, are presented in Fig. 1. The changes observed in the spectra with increase of temperature indicate the occurrence of chemical exchange [in the present case of the conformational transformation $(Ia) \rightleftharpoons (Ie)$]. Two groups of signals (four signals in each group with the intensity ratios 1 : 2 : 2 : 1) can be distinguished in the spectrum measured at 193 K and referring to the conformers (Ie) and (Ia). The lower-intensity signals refer to the conformer (Ia), since it had been shown previously for chlorocyclohexane[9] that $K = p_e/p_a > 1$. Further assignment of the signals to $C_\alpha(C_1)$, $C_\beta(C_2, C_6)$, $C_\gamma(C_3, C_5)$, and $C_\delta(C_4)$ carbon atoms of each conformer is possible. This assignment is based on the integrated intensities, the analysis of the dynamic broadening of individual spectral lines, the employment of other recording techniques, as well as literature data for chloro-substituted hydrocarbons[27]. Only four signals are observed in the spectrum obtained at 273 K, which indicates the rapid inversion of the ring in chlorocyclohexane. The assignment of the spectra lines measured at 273 K follows from the assignment of the signals in the low-temperature spectrum but it can also be based on independent data[28].

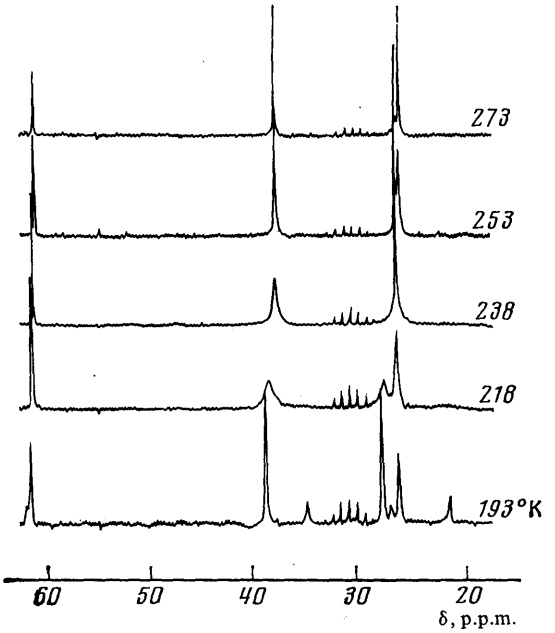


Figure 1. ^{13}C NMR spectra of chlorocyclohexane with complete proton coupling. The lower-intensity signals in the low-temperature spectrum refer to the axial conformer. The multiplet in the region of 30 p.p.m. is the signal of deuteroacetone used as the reference signal.

In conformity with the problems described above, it is possible to arrange systematically in the following manner the information which follows from the temperature-dependent ^{13}C NMR spectra.

1. Conformational Analysis

The number of conformers may be determined from spectra measured at 173–193 K. Using the integrated intensities I of the signals of the individual conformers A_1 and A_2, one can determine the equilibrium constant K:

$$\alpha_i = I_2/I_1 = K, \quad (7)$$

where subscript i corresponds to the ith pair of carbon atoms. The concentrations of individual conformers may be determined from the spectra measured at room

temperature using the following equation for the spectral parameter averaged with respect to the conformers:

$$\langle\theta\rangle = \sum_i p_i\theta_i = p_1\theta_1 + p_2\theta_2, \quad (8)$$

where the chemical shifts δ or the spin–spin coupling constants J may be used as θ.

2. Dynamics of Ring Inversion

Using the parameters of the line form in the NMR spectra in the regions corresponding to intermediate exchange and the well developed procedures for the treatment of such temperature-dependent spectra[21-23], it is possible to determine the rate constants k_{ae} and k_{ea}. If such measurements are carried out over a wide range of temperatures, the activation parameters for the process can be found: $\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$.

3. Chemical Shifts and the Spin–Spin Coupling Constants

The chemical shifts of the ^{13}C NMR signals of the individual conformers, δ_i^1 and δ_t^2, can be determined from spectra measured at 173–193 K. If the test compound contains other magnetic nuclei (^{19}F, ^{31}P, etc.) then information about the spin–spin ^{13}C–X coupling constant (where X is the ^{19}F, ^{31}P, etc. isotope) may be derived from ^{13}C NMR spectra under the conditions of complete decoupling from protons. Unfortunately it is so far impossible to obtain information about the $J(^{13}C-^{1}H)$ constants, which is due to the difficulties in the recording and analysis of monoresonance ^{13}C NMR spectra. Definite advances have been achieved in recent years in the analysis of monoresonance ^{13}C NMR spectra of certain types of organic compounds[29]. This suggests that eventually it will be possible to use information about the $J(^{13}C-^{1}H)$ constants also for substituted cyclohexanes, which is of significant stereochemical interest.

The ^{13}C NMR method suffers from certain limitations.

(a) Limitations due to the low value of the "signal/noise" ratio. Despite the advances towards an increase of sensitivity achieved in recent years as a result of the introduction of pulsed FT,[30] the problem of sensitivity in the measurement of ^{13}C NMR spectra remains extremely urgent. In particular, each spectrum illustrated in Fig. 1 required the accumulation of ~1000 pulses for a solution concentration of about 30 wt.%. With overall 10 s intervals between the pulses, the recording of each spectrum required ~3 h. Reduction of the solution concentration by a factor of 2 would entail an increase in the time required for the experiment by a factor of 4. This factor precludes studies on sparingly soluble substances.

(b) Limitations due to the distortions of signal form. When ^{13}C NMR spectra are recorded under the conditions of complete decoupling from protons using pulsed methods (FT), the NMR signal form (particularly the integrated intensity) may be distorted by a number of factors. The most important of these are (1) the non-identical increase of the intensities of the signals due to different ^{13}C nuclei owing to the different values of the NOE factors, (2) signal saturation arising as a consequence of unduly short periods of pulse repetition, (3) errors introduced by the limited power of the computer, and (4) other sources of apparatus error associated with the presence of lateral signals due to rotation, the contribution of dispersion to the recorded signal, the frequency dependence of the signal intensity, and the influence of the inhomogeneity of the exciting field $\dot{\gamma}H_1$ ($\dot{\gamma} = \gamma/2\pi$, γ being the gyromagnetic constant). A more detailed analysis of these factors may be found in the papers by Freeman and Hill[31] and by Jones and Sternlicht[32].

(c) Limitations associated with the necessity for the complete assignment of the spectrum. ^{13}C NMR spectra with complete decoupling from protons show only singlet lines due to non-equivalent carbon atoms. Although in many instances the assignment of the lines is fairly evident, in practice, for example in the analysis of complex mixtures, the problem of the assignment of the lines is not trivial. Various methods have been described for the assignment of spectral lines using modifications of ^{13}C–$\{^{1}H\}$ double resonance[34], additive schemes for the calculation of ^{13}C chemical shifts[25,27], spin–lattice relaxation times for ^{13}C nuclei (T_1),[35,69] and induced shifts resulting from the addition of paramagnetic shift reagents have been described[20]. Although the use of these methods does increase the total amount of work which must be performed in the investigation, it results, in principle, in the solution of the assignment problem in almost all cases.

Analysis of the scope and limitations of the ^{13}C NMR method have shown that in principle the method can be used to solve all the problems formulated above. An important limitation concerns the study of the influence of the medium, because the measurement of ^{13}C NMR spectra in dilute solutions is difficult (certain data of this kind are described by Schneider and Freitag[33] and Pehk et al.[36]). Studies on substituted cyclohexanes have so far been made only in concentrated solutions. The problem of the investigation of the properties of individual conformers within the framework of ^{13}C NMR spectroscopy naturally reduces merely to the interpretation of the information which follows from the NMR spectra, i.e. the chemical shift of the ^{13}C nuclei and the spin–spin coupling constants involving such nuclei. Furthermore, useful information about the correlation times for molecular motion can be obtained by measuring the spin–lattice relaxation times and NOE factors.

IV. CONFORMATIONAL ANALYSIS USING ^{13}C NMR

1. TEMPERATURE RANGE

The experimental data available at the present time have shown that the accuracy of the measurement of the conformational equilibrium constant K is to a large extent determined by the temperature range employed. The following characteristic temperature ranges can be distinguished for NMR spectroscopy.

Temperatures Below 173 K

In this temperature range ring inversion becomes very slow (here and henceforth we are considering the NMR time (scale), so that the signals of the individual conformers should be observed. However, owing to experimental difficulties (the choice of solvent, the establishment of a high concentration in the solution, and the design characteristics of the transducers), studies in this temperature range have not so far been made with the aid of ^{13}C NMR.

Temperatures in the Range 173–193 K

Here ring inversion is slow and the signals of individual conformers are observed. They are adequately resolved, which permits correct integration and determination of the equilibrium constant.

Temperatures in the Range 193–243 K

An intermediate rate of inversion obtains. This leads to a significant broadening of the spectral lines and their overlapping (Fig. 1), which prevents the separate integration of the signals due to the conformers. The study of conformational equilibrium in this temperature range requires prolonged experiments with calculation of the total spectral line form. It is perhaps possible to quote only one example of a fairly thorough analysis of spectra in this temperature range carried out by Bovey et al.[37] for the inversion of fluorocyclohexane (joint analysis of ^{19}F and ^{1}H NMR spectra).

Temperatures above 243 K

Ring inversion is rapid and the ^{13}C NMR spectra show averaged signals. This temperature range is of particular interest, since it includes room temperature—the most important for practical purposes. The ratio of the concentrations of the conformers p_1 and p_2 may be estimated by Eqn. (8). It must be emphasised that there are many specific problems which significantly hinder the use of equations for the average parameters (see the reviews of Jensen and Bushweller[15] and Garbish[38]). Such estimates frequently lead to a decrease of the accuracy of the calculated equilibrium constants or in general to doubtful and contradictory results.

2. ASSIGNMENT OF THE SPECTRAL LINES

In conformational analysis the correct assignment of the spectral lines is of greatest importance. The assignment procedure presents no difficulties, provided that the chemical shifts of non-equivalent carbon atoms differ by more than 2–3 p.p.m. For the correct assignment of the lines in the spectra of monosubstituted compounds, it is sufficient to use symmetry considerations, integrated signal intensities, and data concerning the influence of the substituent on the chemical shift of the ^{13}C nuclei in model saturated hydrocarbons[39–42]. An extremely effective procedure for the assignment of the lines of polysubstituted compounds, involves the comparison of the experimental shifts with calculated additive data[43–45]. Among the special assignment methods useful for the analysis of the spectra of substituted cyclohexane, mention should be made of the procedure based on the study of the dynamic broadening of the spectral lines, which permits the identification of the signals due to pairs of nuclei undergoing exchange. One should also note that the employment of integrated intensities should be approached with a certain amount of caution, because incorrectly selected conditions for the recording of the spectrum in pulsed FT may lead to considerable distortions of the signal intensities up to the disappearance of certain signals from the spectrum.

3. EQUILIBRIUM BETWEEN THE CONFORMERS AT TEMPERATURES IN THE RANGE 173–193 K

The constant K for the equilibrium between two conformers A_1 and A_2 of a substituted cyclohexane is determined from the integrated signal intensities in low-temperature spectra. Since several ^{13}C signals are observed for each conformer (six in the general case), there is a possibility of averaging with respect to the corresponding pairs of signals:

$$K = \frac{1}{N}\sum_{i=1}^{N} \alpha_i. \qquad (9)$$

The problem of the accuracy of the measurement of the conformational equilibrium constants is of significant interest for conformational analysis. Since the integrated intensities are influenced by many distortions, the problem of the errors of the measurements requires special examination. Subject to certain simplifying assumptions, the ratio of the integrated intensities of two signals in the spectrum (for pulsed FT) is related to the required quantity $K = p_2/p_1 = M^i_{Z,2}/M^i_{Z,1}$, where M_Z is the projection of the nuclear magnetisation vector onto the z axis) by the expression

$$\alpha_i = \frac{I_i^2}{I_i^1} = \frac{(\eta(C_i^2)+1)}{(\eta(C_i^1)+1)} \cdot \frac{[1-\exp(-t/T_1(C_i^2))]}{[1-\exp(-t/T_1(C_i^1))]} \cdot K, \qquad (10)$$

where the first term takes into account the difference between the Nuclear Overhauser effects for the ith pair of signals C_i^1 and C_i^2, while the second term defines the difference between the saturation factors for the same signals[31,32]; $\eta = \mathrm{NOE} - 1 = I_p/I_0 - 1$, where I_p and I_0 are the integrated signal intensities with and without proton decoupling respectively. The correct employment of Eqn. (10) for quantitative analysis thus requires data for NOE factors and the spin–lattice relaxation times $T_1(^{13}C)$. The time t in Eqn. (10) corresponds to the total interval between the pulses, equal to the sum of the sampling time of the free induction signal and the arrest time[4]. Technical difficulties in the measurement of NOE and of the relaxation time T_1 constitute serious obstacles to the use of ^{13}C NMR data in quantitative analysis. More detailed analysis shows[39,46,50,80] that the relaxation times of protonated carbon atoms (i.e. atoms forming part of methylidyne and methylene groups) are almost fully determined by the dipole–dipole mechanism and the NOE factors for such nuclei are therefore close to the theoretical value of 2.99.[3,4] There are also data showing that the relaxation times of the ^{13}C nuclei of substituted cyclohexanes do not exceed 3 s at 173–193 K.[69] Hence it follows, in particular, that the distortions due to the differences between the relaxation times may be significantly reduced by using intervals of 8–10 s between the pulses. The accuracy of the measurement of the equilibrium constant K also depends on the value of the latter, the errors being a minimum for almost degenerate equilibria and increasing almost linearly with increase of K. Despite the fact that in most cases the correct analysis of the errors has not been carried out, presumably in real systems it is very difficult to achieve an accuracy better than to within 10%.

The results of a study of the conformational equilibria for a series of monosubstituted cyclohexanes at 163 to 204 K are presented in Table 1. It follows from these results that the standard relative error $\Delta\Delta G^\circ/\Delta G^\circ$ of the conformational energies in the range -0.3–1.8 kcal mole^{-1} is about 10%. The ^{13}C NMR data can be compared with those of Jensen and Bushweller[15] ("best" A-values)

(Fig. 2). Evidently the results obtained by these two methods of measurement of conformational energies are correlated, but the conformational energies found from ^{13}C NMR spectra are systematically higher by 20% than the values derived from ^{1}H NMR spectra. These discrepancies may be caused, particularly, by the fact that ^{13}C NMR measurements are made as a rule in much more concentrated solutions than those used for the measurement of low-temperature ^{1}H NMR spectra. The discrepancies are largest for X = F (37%) and X = OCH_3 (36%). The problem of the true causes of these discrepancies is still obscure and requires a more detailed analysis of the errors of both methods.

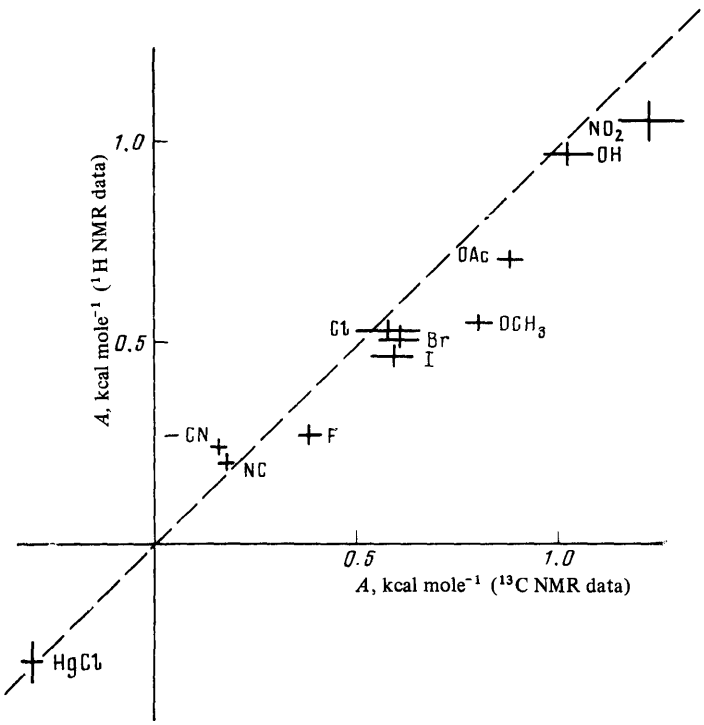


Figure 2. Comparison of the conformational energies obtained with the aid of ^{13}C and ^{1}H NMR for certain substituents in monosubstituted cyclohexanes.

Despite the fact that the problem of the relative accuracies of different methods of measurement of conformational energies has not been finally elucidated, ^{13}C NMR has already permitted progress in several important cases. In particular, it has been possible to obtain for the first time spectroscopic evidence for the existence of the axial conformer of methylcyclohexane—the classical object of conformational analysis—and to measure $-\Delta G_{173^\circ} = 1.8 \pm 0.1$ kcal mole^{-1}.[42] Previous attempts to solve this problem[51] were based on indirect reasoning and yielded significantly divergent values (ranging from 1.5 to 2.0 kcal mole^{-1}).[7,52] This and other examples (nitrocyclohexane, cyclohexanol[42]) have shown that ^{13}C NMR is the most suitable method for the investigation of high-energy conformations. Another example of the successful application of ^{13}C NMR is provided by the study of mercury-substituted cyclohexanes[49]. Earlier conformational analysis of these compounds was complicated by the difficulty of interpretating the ^{1}H NMR spectra[53]. When ^{13}C NMR was used, it was possible to assign the signals on the basis of the $J(^{13}C-^{199}Hg)$ constants[54] and to show that the axial conformer predominates ($-\Delta G_{183^\circ} = -0.30$ kcal mole^{-1}). The mercury-substituted compounds constitute the only example of systems with the preferential axial orientation of the substituent in a series of monosubstituted cyclohexane derivatives. This stabilisation is probably due to weak coordinate bonds formed between the hydrogen atoms in the γ-positions and the mercury atom, with participation of vacant 5*d* orbitals. Presumably such "anomeric" effects can be observed also for other organometallic derivatives of cyclohexane[84] (see also Table 1).

The still limited data available for polysubstituted cyclohexane derivatives do not allow a detailed elucidation of the characteristics of the conformational equilibrium over a fairly wide range of conditions (temperature, solvent) and types of substituents. The most interesting results were obtained with the aid of ^{1}H NMR[19,55-57] and ^{19}F NMR[58,59] but these methods cannot be regarded as universal either.

The attempts to employ ^{13}C NMR to investigate polysubstituted cyclohexanes using integrated spectral intensities are still not numerous[45,60-63], but they clearly show that the method makes it possible to overcome successfully the difficulties associated with the isomeric purities of the test systems.

In considering the conformational equilibria involving disubstituted cyclohexanes it is useful to divide the equilibria into two types: (1) the equilibrium between the *aa*- and *ee*-conformers, which obtains in 1,2-*trans*-, 1,3-*cis*, and 1,4-*trans*-isomers; (2) the equilibrium between the *ae*- and *ea*-conformers in 1,1-, 1,2-*cis*-, 1,3-*trans*-, and 1,4-*cis*-isomers. When the substituents are the same, the conformational transformation of type (2) is degenerate, so that $\Delta G = 0$. The experimental conformational energies $A_{exp}(X, Y)$ for compounds of types (1) and (2) are listed in Tables 2 and 3 respectively. In addition, the tables list the conformational energies obtained by the additive approach. The additive conformational energy A_{add} can be represented as the sum (or difference) of the conformational energies of both substituents, i.e.

$$A_{add}(X, Y) = A(X) + A(Y) \quad (\text{for } aa \rightleftharpoons ee), \qquad (11)$$
$$A_{add}(X, Y) = A(X) - A(Y) \quad (\text{for } ae \rightleftharpoons ea).$$

The data quoted in Table 1 may be used as the A-values for specific substituents. The factors R, which are a measure of conformational non-additivity, may be determined from the experimental values of $A_{exp}(X, Y) = -\Delta G^\circ(X, Y)$ and the calculated values of A_{add}:

$$R = A_{add}(X, Y) - A_{exp}(X, Y). \qquad (12)$$

The following features may be deduced from the results (see also other studies[15,59] where other methods were used).

1. The *ee*-form is destabilised in the presence of bulky substituents (Br, Cl, CH_3), in *trans*-1,2-isomers (or the *aa*-form undergoes additional stabilisation), the destabilisation factor varying from 0.1 kcal mole^{-1} (for fluoroiodocyclohexane[59]) to 2 kcal mole^{-1} (for di-iodocyclohexane[64]); it probably increases with increase of the bulk of the substituent.

Table 1. Comparison of the conformational energies ($-\Delta G^{\circ}$) for monosubstituted cyclohexanes obtained from ^{13}C and ^{1}H NMR data*.

Substituent	^{13}C NMR				^{1}H NMR			
	solvent	T, K	$-\Delta G^{\circ}$, kcal mole^{-1}	Refs.	solvent	T, K	$-\Delta G^{\circ}$, kcal mole^{-1}	References
$HgOCOCH_3$	$CDCl_3$	183	−0.30±0.03	49	$CDCl_3$	183	−0.30±0.05	49
$HgOCOCH_3$	—	—	—	—	CS_2	193	0.61	15
CN	CF_2Cl_2	190	0.152±0.005	40	CS_2	194	0.24±0.003	15,53
NC	CF_2Cl_2	180	0.182±0.015	40	CS_2	193	0.21±0.013	15,53
F	CS_2	183	0.380±0.03	39	CS_2	187	0.276±0 02	15,53,37
F	CF_2Cl_2	180	0.360±0.025	40	—	—	—	—
Cl	CS_2	193	0.53±0.05	39	CS_2	192	0.528±0.02	15,53
Cl	CF_2Cl_2	180	0.62±0.04	40	—	—	—	—
Br	CS_2	198	0.61±0.05	39	CS_2	192	0.476±0.02	15,53
Br	CF_2Cl_2	200	0.585±0.025	40	—	—	—	—
I	CS_2	195	0.59±0.05	39	CS_2	193	0.468±0.02	15,53
I	CF_2Cl_2	180	0.455±0.025	40	—	—	—	—
$Pb(CH_3)_3$	CD_2Cl_2	204	0.67±0.06	84	—	—	—	—
OCH_3	CF_2Cl_2	180	0.75±0.035	40	CS_2	191	0.547±0 019**	15,53
$OSi(CH_3)_3$	CF_2Cl_2	170	0.735±0.015	48	—	—	—	—
$OCOCH_3$	CF_2Cl_2	180	0.885±0.03	40	CS_2	185	0.71±0.05	15,53
OH	CS_2	183	1.02±0.1	42	CS_2	190	0.97	15,53
OH	CF_2Cl_2	180	>1.4	40	—	—	—	—
$Sn(CH_3)_3$	CD_2Cl_2	204	1.06±0.14	84	—	—	—	—
NO_2	CS_2	183	1.27±0.2	42	CS_2	183	1.05±0.14	15,53
CH_3	pure compound	183	1.6	41	—	—	—	—
CH_3	CS_2	173	1.80±0.1	42	—	—	—	—
CH_3	$CFCl_3$—$CDCl_3$	172	1.74±0.06	106	—	—	—	—

*The low-temperature NMR spectra; the method of integrated intensities was used [Eqns. (3) and (7)].
**Data for the OCD_3 substituent.

2. The diaxial form of *cis*-1,3-isomers is exceptionally unfavourable as a result of 1,3-*syn*-diaxial interactions of the bulky substituents. Theoretical estimates for such interactions have been carried out by Bailey et al.[57] in relation to the *syn*-diaxial interaction of the methyl group and fluorine, chlorine, bromine, or iodine atoms. The calculated energies of these interactions, amounting to 0.34, 7.34, 15.07, or 28.37 kcal mole^{-1} respectively (the calculations were performed with the aid of the Hill potential[65]), show that the repulsion energy for the substituent increases with increasing bulk of the latter, causing the destabilisation of the diaxial conformer.

Table 2. Equilibria of the type *aa* ⇌ *ee* for disubstituted cyclohexanes according to ^{13}C NMR data (173–193 K)*.

Compound	$A_{exp}(X, Y)$, kcal mole^{-1}	$A^{**}_{add}(X, Y)$, kcal mole^{-1}	R, kcal mole^{-1}	References
trans-1,2-Dichlorocyclohexane	0.34	1.06	0.72	61
trans-1,2-Dichlorocyclohexane	0.47***	1.06	0.69	45
cis-1,3-Dichlorocyclohexane	>1.5***	1.06	<−0.50	45
trans-1,4-Dichlorocyclohexane	0.03***	1.06	1.03	45
trans-1,2-Dibromocyclohexane	−0.76	1.22	1.98	61
trans-1-Chloro-2-methoxycyclohexane	0.29	1.28	0.99	61
trans-1-Bromo-2-methoxycyclohexane	0.48	1.36	0.88	61
trans-1-Hydroxy-2-methoxycyclohexane	1.05	1.77	0.72	61
trans-1-Hydroxy-2-methylcyclohexane	>1.4	2.8	<1.4	62
trans-1-Hydroxy-4-methylcyclohexane	>1.4	2.8	<1.4	62
cis-1-Hydroxy-3-methylcyclohexane	>1.4	2.8	<1.4	62

*For solutions in CS_2; method of integrated intensities.
**The conformational energies obtained from ^{13}C NMR spectra were used in the calculation of A_{add} (see Table 1).
***For a mixture of isomers of *trans*-1,2-, *cis*-1,3-, and *trans*-1,4-dichlorocyclohexanes.

3. The *aa*-form of *trans*-1,4-isomers undergoes additional stabilisation ($R_{14} > 0$). An attempt at a theoretical explanation of this effect, based on the consideration of the energy of the electrostatic interaction in 1,4-dihalogenocyclohexanes, has been made[19].

Table 3. Equilibrium of the type *ae* ⇌ *ea* for disubstituted cyclohexanes according to ^{13}C NMR data (173–193 K)*.

Compound	$A_{exp}(X, Y)$, kcal mole^{-1}	$A^{**}_{add}(X, Y)$, kcal mole^{-1}	R, kcal mole^{-1}
cis-1-Hydroxy-4-methylcyclohexane	0.74	0.76	0.02
trans-1-Hydroxy-3-methylcyclohexane	0.94	0.76	−0.18
cis-1-Hydroxy-2-methylcyclohexane	0.53	0.76	0.23

*Method of integrated intensities[62] (for solutions in CS_2).
**The conformational energies based on ^{13}C NMR data (for solutions in CS_2) were used in the calculation of $A_{add}(X, Y)$.

4. The deviations from additivity for 1,4-*cis*-, 1,3-*trans*-, and 1,2-*cis*-isomers involved in transformations of the *ea* ⇌ *ae* type are comparatively small (the values of R are ~±0.2 kcal mole^{-1}) and on the whole the additive scheme can be used to predict the conformational composition of such isomers.

The conformational equilibria of polysubstituted (three and more substituents) cyclohexanes have not been investigated so far by ^{13}C NMR in the range 173–193 K. It is to be expected that the method will find applications in the immediate future in the study of these and related systems (decalins, tetralins, steroids, etc.)

4. CONFORMATIONAL EQUILIBRIUM AT TEMPERATURES NEAR 300 K

In the high-temperature region the equilibrium parameters are determined using the equation for average parameters [Eqn. (8)]. If it is assumed that only two conformers are involved in the equilibrium (the equatorial and axial conformers in the case of monosubstituted cyclohexanes), then it follows from Eqn. (8) that

$$p_i = \frac{\langle\theta\rangle_i - \theta_i^a}{\theta_i^e - \theta_i^a} \qquad (13)$$

and

$$K = \frac{\langle\theta\rangle_i - \theta_i^a}{\theta_i^e - \langle\theta\rangle_i}. \qquad (14)$$

Thus, provided that the spectroscopic parameters θ_i^a and θ_i^e are known under stereochemically rigid conditions, it is possible to determine from the average value the fractions of the conformers and the equilibrium constants.

It is noteworthy that the problem of the interpretation of the averaged spectroscopic parameters measured at temperatures ensuring a rapid conformational transformation is of general interest for the conformational analysis of organic compounds. This is due to the fact that in many systems which are of interest as regards their conformations [12,13] (cyclopentanes, cycloheptanes, cyclohexanones, dioxans, piperidines, etc.) it is extremely difficult to create conditions sufficient to "freeze out" individual conformations. In systems of this kind this requires measurements at temperatures in the range 123–173 K, which is not always possible. This fact explains the great interest in the interpretation of averaged spectroscopic parameters in terms of conformational equilibria [66]. The available reviews on the application of the method of averaged parameters (substituted cyclohexanes [13,15], rotational isomers of ethane-like molecules [38,67]) show that this method of studying equilibria should be used with much caution. The fundamental difficulties make it necessary to take into account the temperature dependence of the spectroscopic parameters of rigid systems. This implies that in principle one cannot use in Eqns. (13) and (14) the parameters θ_i^a and θ_i^e obtained from low-temperature measurements.

In describing the results of the application of the method of averaged parameters to substituted cyclohexanes, it is useful to consider separately the chemical shift data and the spin–spin coupling constants. The former are of considerable practical interest, since they can be measured in all cases. On the other hand, the use of averaged spin–spin coupling constants (in those cases where the relevant data may be determined from the spectrum) apparently leads to more accurate results, because according to some data [66] the constants are less affected by temperature.

Eqns. (13) and (14) can be used in two ways [62]. One of them, which may be called experimental, involves the use as θ_i^e and θ_i^a of the experimental chemical shifts of the ^{13}C nuclei of individual conformers obtained from spectra measured at 173–193 K. In principle, the method can be modified by studying experimentally the temperature dependence of the chemical shifts in the accessible temperature range (123–200 K) and extrapolating the relation obtained to higher temperatures. However, ^{13}C NMR studies of this kind have not so far been made and the chemical shifts δ_i^e and δ_i^a were assumed to be independent of temperature, which probably introduced a systematic error. The second way of using Eqns. (13) and (14), which may be referred to as the computational procedure, consists in using the chemical shifts calculated in accordance with some scheme; different empirical and semiempirical methods may be used in the calculation. The evident requirement which must be met by the computational scheme is that the calculated chemical shifts should be sufficiently accurate. The required level of accuracy ($\Delta\delta$) follows directly from Eqns. (13) and (14): the error must be significantly less than the range of variation of the shift, i.e. $\Delta\delta < |\delta_i^e - \delta_i^a|$.

A satisfactory computational scheme for the calculation of chemical shifts has not so far been proposed for monosubstituted cyclohexanes and the experimental method was therefore used in the study of the conformational equilibria at 300 K. [39] The only attempt to employ the computational method, undertaken by Pehk and Lippmaa [28], involved the use of the chemical shifts for the corresponding t-butyl derivatives $(CH_3)_2XCH$. [4-6] When the chemical shifts of the conformers cannot be measured experimentally at low temperatures (for example, owing to the limited solubility of the corresponding monosubstituted compound), this procedure is the only one available for the estimation of the equilibrium constant. However, the analogy with the t-butyl derivatives is probably extremely approximate and the method can be recommended only for qualitative estimates.

Table 4. Parameters of the conformational equilibria for halogenocyclohexanes at 298 K according to ^{13}C NMR chemical shifts and their comparison with the results obtained by other methods.

Halogen	Parameter	Position of carbon atom				^{13}C NMR	Results obtained by other methods**	
		α	β	γ	δ	$\langle p_e \rangle$	p_e	method
F	δ*	63.29	4.82	−4.76	−2.25			
	p_e	0.67	0.73	0.64	0.30	0.65	0.57	^{19}F NMR
	f_t	0.22	0.19	0.23	0.01			
Cl	δ	32.24	9.68	−2.09	−1.60			
	p_e	3.00	0.75	0.70	0.75	0.79	0.73	^1H NMR
	f_t	0.09	0.25	0.40	0.05			
Br	δ	25.06	10.51	−1.02	−1.42			
	p_e	1.00	0.68	0.65	1.00	0.74	0.72	^1H NMR
	f_t	0.22	0.25	0.47	0.06			
I	δ	4.38	12.52	0.40	−1.40			
	p_e	0.91	0.80	0.71	0.65	0.80	—	—
	f_t	0.40	0.23	0.33	0.04			

*The chemical shifts are expressed in p.p.m. relative to C_6H_{12} (from the paper by Subbotin and Sergeyev [39]).
**Taken mainly from Squillacote et al. [18] (see also Refs. 53 and 37).

Both the averaged chemical shifts (see also Table 4) and the shifts of the individual conformers (see Table 11) of many monosubstituted cyclohexanes are known [39-42], which makes it possible to examine the problem of the applicability of the experimental method to the study of the conformational equilibrium at 298 K. The corresponding results are presented in Table 4 for halogenocyclohexanes.

In the calculation of the fraction of the equatorial conformer p_e by Eqn. (13) the experimental chemical shifts of the ith carbon atoms ($i = \alpha, \beta, \gamma$, or δ) taken from Subbotin and Sergeyev [39] were used for the a- and e-conformers. Table 4 presents for comparison the fractions of the equatorial conformer obtained from results found by other methods (^{1}H NMR and ^{19}F NMR) using an analogous procedure [15].

It follows from the data in Table 4 that the values of p_e corresponding to different atoms are significantly scattered. In certain cases absurd results ($p_e > 1$) are obtained. The above deficiencies are a consequence of the temperature dependence of the chemical shifts of the individual conformers. The available estimates of the influence of temperature on the chemical shifts of individual substances quoted in the literature have shown [68-70] that the "temperature coefficients" may reach 1 p.p.m. per 100°C. The experimental method for the investigation of high-temperature equilibria is therefore ineffective when the difference between the chemical shifts of the ith atoms of the conformers is small (1 p.p.m. and less). In particular, this is characteristic of the δ-carbon atoms in monosubstituted cyclohexanes.

The error in the calculation in accordance with this scheme may be reduced by several formal procedures. Firstly, it is possible to exclude from consideration the results to which correspond relatively small differences $|\delta_i^e - \delta_i^a|$. Secondly, in the calculation of the average value it is possible to introduce "statistical weights" for the results of individual measurements [62]:

$$\langle p_e \rangle = \sum_i f_i p_e^i \qquad (15)$$

where

$$f_i = \frac{|\delta_i^e - \delta_i^a|}{\sum_{i=1}^{N} |\delta_i^e - \delta_i^a|} \qquad (16)$$

is the "statistical weight" of p_e^i.

In this procedure more reliable estimates of p_e^i, obtained for larger differences $|\delta_i^e - \delta_i^a|$, have a larger statistical weight and formally one can permit the inclusion of results leading to $p > 1$ or $p < 0$. Data obtained by this method are in reasonable agreement with literature estimates (see Table 4). For polysubstituted compounds, the computational as well as the experimental method may be used to measure the constant K and the additive values of the chemical shifts of the conformers may be used as the calculated values.

Both methods for the investigation of the high-temperature equilibria based on calculations in accordance with an additive scheme have been used to investigate the conformations of isomeric methylcyclohexanols [62]. It follows from the data in Table 5 that the two methods give similar results. The conformer with the equatorial orientation of the methyl group (the *ea*-conformer in terms of the notation of Subbotin et al. [62]) predominates in all cases. The fraction of this conformer is a minimum for the 1,2-*cis*-isomer and a maximum for the 1,3-*trans*-isomer. The above tendency has been confirmed by low-temperature measurements (Table 5).

As regards the use of spin–spin coupling constants in the study of high-temperature equilibria, we may note that the experimental data available hitherto are extremely limited and refer mainly to fluorinated cyclohexanes [39,71], i.e. consist of $J(^{13}C-^{19}F)$ constants. By analogy with averaged chemical shifts, here too it is possible to distinguish two procedures for the interpretation of the results, but, since a satisfactory scheme for the calculation of spin–spin coupling constants does not yet exist, only the experimental procedure has so far been tested. Constants for the spin–spin coupling of the ^{19}F nuclei with all the non-equivalent ^{13}C nuclei of fluorocyclohexane have been found for both conformers at 183 K as well as the average spin–spin coupling constants at 300 K. These data can be used in Eqn. (14) to estimate the fraction of the equatorial conformer at 300 K, as was done in the analysis of the chemical shift (i.e. the "statistical weights" of the individual measurements are introduced) (Table 6).

Table 5. The fraction of the dominant conformer $\langle p_e \rangle$ in isomeric methylcyclohexanols (according to the conformationally averaged ^{13}C NMR chemical shifts at 300 K [62]).

Compound	$\langle p_e \rangle_{exp}$	$\langle p_e \rangle_{calc}$	$p_e^{l.t.}$*
cis-1-Hydroxy-2-methylcyclohexane	0.74	0.84	0.81
trans-1-Hydroxy-3-methylcyclohexane	0.83	0.96	0.93
cis-1-Hydroxy-4-methylcyclohexane	0.81	0.85	0.88

*Obtained from low-temperature ^{13}C NMR spectra by measuring the integrated signal intensities for the individual conformers.

Table 6. The spin–spin coupling constants $J(^{13}C-^{19}F)$ for fluorocyclohexane at 300 K and the fractions of the equatorial conformer.

Parameter	Position of carbon atom			
	α	β	γ	δ
J (^{13}C—^{19}F), HZ	170.6	19.0	7.6	1.5
p_e^*	0.69	0.66	0.64	0.50
f_i	0.26	0.20	0.51	0.05

*The value averaged with respect to the positions of the carbon atom is $\langle p \rangle = 0.66$.

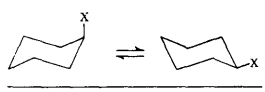
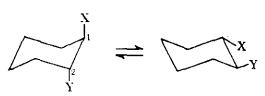
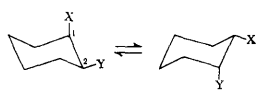
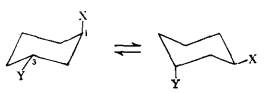
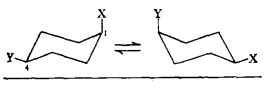
The average fraction of the equatorial conformer thus obtained (0.66) agrees with the value found from the chemical shifts (0.65; Table 4). Since the spin–spin coupling constants are less influenced by factors such as temperature and the solvent, one may expect their successful application in conformational analysis.

5. ENTHALPIES AND ENTROPIES OF THE REVERSIBLE CONFORMATIONAL TRANSFORMATION ACCORDING TO ^{13}C NMR DATA

From the theoretical standpoint, the enthalpy ΔH° and entropy ΔS° of the conformational transformation are of greatest interest rather than its free energy ΔG°_T because

these quantities are related to the structures of the conformers. However, their experimental determination is extremely difficult, because it requires the measurement of the equilibrium constants over a very wide temperature range. The experimental data on this problem are extremely fragmentary[15] and have not been subjected to a critical analysis. Since ^{13}C NMR permits measurements of the equilibrium constant K in two temperature ranges (173–193 K and in the vicinity of 300 K), attempts have been made to determine ΔH° and ΔS° from ΔG_{183° and ΔG_{300°.[61,62] The results of these estimations for a series of substituted cyclohexanes are compiled in Table 7; however, one should note that, despite the relatively greater accuracy of the determination of ΔG° (on average to within 10–20% for ΔG°—to within a quantity of the order of 0.5 kcal mole^{-1}), the enthalpies and entropies of the reversible conformational transformation determined from the difference of two ΔG°_T values at close temperatures are obtained with an accuracy to within ~0.3 kcal mole^{-1} and 1.5 e.u. respectively[72]. It follows from the analysis of the errors that the accuracy diminishes rapidly with increase of the equilibrium constant (for $K > 1$). It is therefore hardly useful to pose the question of the theoretical interpretation of the enthalpies and entropies of the reversible conformational transformation. At any rate, the available data (Table 7) show that the entropies of the transformation are as a rule in the range ±1 e.u. This implies that the qualitative interpretation of the temperature dependence of the conformational equilibrium may be based on the hypothesis that there is no entropy contribution.

Table 7. The conformational energies and the enthalpies and entropies of the reversible conformational transformations for a series of substituted cyclohexanes[61,62].

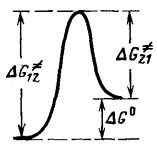
Inversion process	Substituent	$-\Delta G^\circ_{183^\circ}$, kcal mole^{-1}	$-\Delta G^\circ_{300^\circ}$, kcal mole^{-1}	$-\Delta H^\circ$, kcal mole^{-1}	$-\Delta S^\circ$, e.u.
	F	0.380	0.368	0.40	0.1
	Cl	0.530	0.790	0.02	—2.6
	Br	0.610	0.625	0.59	—0.1
	I	0.590	0.820	0.13	—2.3
	*trans*-1,2-(Cl, Cl)	0.34	0.19	0.61	1.4
	trans-1,2-(Br, Br)	—0.76	—0.51	—1.14	—2.0
	trans-1,2-(OCH_3, OH)	1.05	1.42	2.38	3.2
	trans-1,2-(OCH_3, Cl)	0.29	0.26	0.34	0.3
	trans-1,2-(OCH_3, Br)	0.48	0.37	0.67	1.0
	*cis*-1,2-(CH_3, OH)	0.53	0.62	0.40	0.75
	*trans*-1,3-(CH_3, OH)	0.94	0.94	0.94	0.0
	*cis*-1,4-(CH_3, OH)	0.74	0.86	0.56	—1.0

V. DYNAMICS OF RING INVERSION IN SUBSTITUTED CYCLOHEXANES

As already pointed out, the changes in the NMR spectrum occurring when the specimen temperature is altered (Fig. 1) may be used to analyse the dynamics of ring inversion (to solve this problem, it is necessary to find four activation parameters: the values of $\Delta H^\neq_{12}$ and $\Delta S^\neq_{12}$ characterising the transformation of the more stable conformer into a less stable one ($e \rightarrow a$ for monosubstituted cyclohexanes) and the values of $\Delta H^\neq_{21}$ and $\Delta S^\neq_{21}$ characterising the reverse process. Here we have

$$\Delta G^\neq_{12} = \Delta H^\neq_{12} - T\Delta S^\neq_{12}; \quad \Delta H^\neq_{12} = \Delta H^\neq_{21} - \Delta H^0; \qquad (17)$$
$$\Delta G^\neq_{21} = \Delta H^\neq_{21} - T\Delta S^\neq_{21}; \quad \Delta S^\neq_{12} = \Delta S^\neq_{21} - \Delta S^0.$$

If the equilibrium parameters ΔH° and ΔS° are known, the problem reduces to determining two parameters (for example, $\Delta H^\neq_{12}$ and $\Delta S^\neq_{12}$; see the scheme below).



Before proceeding to the analysis of the results of the study of ring dynamics obtained with the aid of ^{13}C NMR, it is necessary to consider certain characteristics of the NMR method. In the first place we may note that the method is perhaps the only available procedure for the investigation of the dynamics of ring inversion in substituted cyclohexane. Data found by other methods are extremely limited (see, for example, Refs. 73 and 74) and have not been analysed critically. Among the different versions of the NMR method, ^1H NMR [55] and ^{19}F NMR [37,59] have become common. Studies by ^{19}F NMR are naturally restricted to fluorinated cyclohexanes (the so called method of the fluorine label proposed by Roberts[75]). When ^1H NMR is used, a fundamental difficulty arises because of the complex multiplet nature of the spectra due to the strong coupling between the spins in the spectra of substituted cyclohexanes. A correct interpretation of the dynamic effects requires in this case the use of the formalism of the density matrix[21,22]. The degrees of the systems of equations and the dimensions of the corresponding matrices obtained in this type of description increase rapidly with increase of the number of interacting spins. As a rule powerful computers must be used even for three spins, and, when there are five non-equivalent groups of interesting spins, the problem is virtually insoluble even when the best of modern computers are used. For certain special systems (for example, deuterated compounds), the degree of the systems of equations may be significantly reduced[76] but hitherto the formalism of the density matrix has not been used in studies on the dynamics of the inversion of cyclohexane derivatives.

It is also necessary to consider the general limitations in the study of the form of the potential surface for the ring inversion reaction by NMR. In examining these limitations one may begin with the phenomenological Bloch–McConnell equations for two-position exchange[23,77]. All inversions in substituted cyclohexanes belong to this type of exchange with two stable A_1 and A_2 states. Fig. 3 shows the region where NMR may be used to investigate two-position exchange (the shaded region). The limitations arise from the following considerations. Firstly, the modulus $|\Delta G^\neq_{12} - \Delta G^\neq_{21}|$ must not exceed 2 kcal mole^{-1}, which implies that the study of strongly displaced equilibria (or high-energy conformations) is difficult. Secondly, the values of $\Delta G^\neq_{12}$ and $\Delta G^\neq_{21}$ are limited from below by the low temperatures actually attained (6 kcal mole^{-1} for

120 K and 8 kcal mole^{-1} for 170 K). Thirdly, the limitations at the upper end are caused by the maximum attainable temperature in NMR transducers (473 K, which corresponds to ΔG = 24 kcal mole^{-1}). The region actually investigated proves to be even narrower, bearing in mind that the accuracy of the measurement of the dynamic broadening decreases rapidly with increase of the "degree of non-degeneracy" of the process. This fact reflects the real situation, which arises, in particular, in the study of substituted cyclohexanes. In fact the majority of the investigations of the dynamics of ring inversion by ^{1}H NMR [55,76,78] were devoted to degenerate systems. The inversion of non-degenerate systems has been studied using three models (fluorocyclohexane[37], 1,2-*trans*-fluoroiodocyclohexane[59], and 3-chloro-1,1-difluorocyclohexane[58]) by ^{19}F NMR. Some of the results obtained by ^{1}H and ^{19}F NMR are compiled in Tables 8 and 9.

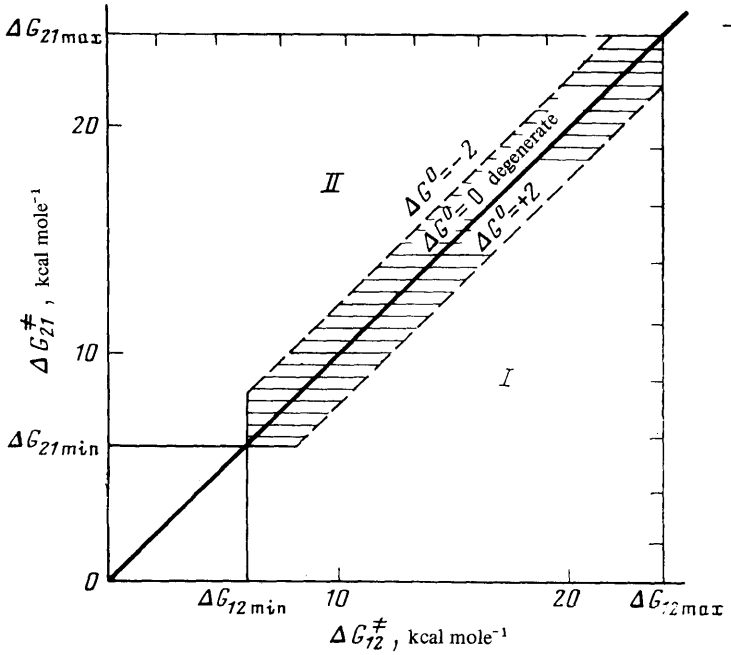
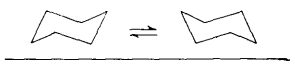
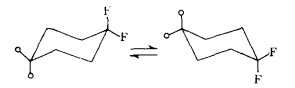
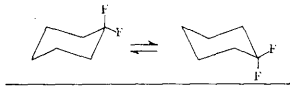
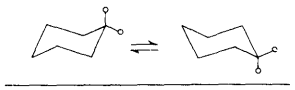
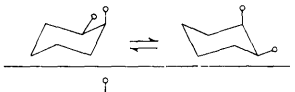
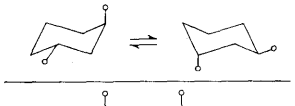
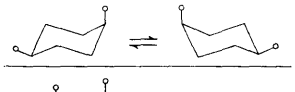
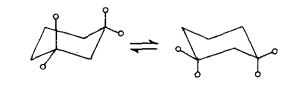
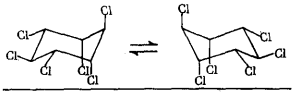


Figure 3. Energy diagram for the $(A_1) \rightleftharpoons (A_2)$ transformations. The values of ΔGmax and ΔGmin correspond to the maximum and minimum free energies of activation which can be measured by NMR; I—region where conformer A_1 predominates; II—region where conformer A_2 predominates.

^{13}C NMR also has many practical advantages over other versions of the NMR method in the study of intramolecular dynamic processes[27,81]. The most important advantage is that ^{13}C NMR spectra measured under the conditions of complete decoupling from protons do not contain spin multiplets and therefore permit the employment of a simpler formalism based on the Bloch–McConnell equation. The second advantage consists in a wider range of variation of the chemical shifts (exceeding by a factor of ~20 the range of the proton chemical shifts), which makes it possible, in principal, to carry out measurements on faster processes. However, one should note that studies on ring inversion processes in substituted cyclohexanes by ^{13}C NMR have so far been comparatively restricted and devoted mainly to degenerate processes (see Table 8). Non-degenerate inversion has been studied in only one instance, namely the inversion of chlorocyclohexane (see Table 9). In this last instance the prospects for the employment of ^{13}C NMR are so far extremely problematical. The data presented for degenerate processes undoubtedly show that the ^{13}C NMR method is more universal.

Table 8. The activation parameters for ring inversion in substituted cyclohexanes (the degenerate case).

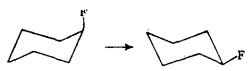
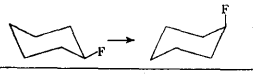
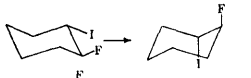
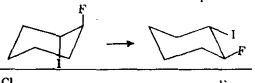
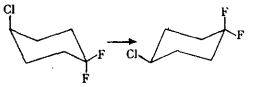
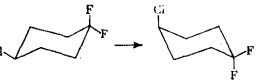
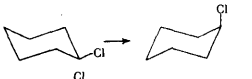
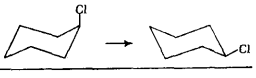
Inversion process*	$\Delta G^{\neq}_{300°}$, kcal mole^{-1}	$\Delta H^{\neq}$, kcal mole^{-1}	$\Delta S^{\neq}$, e.u.	T_r, K**	NMR method	Refs.
	10.0	10.8±0.1	2.8±0.5	178	^{1}H—{^{2}H}	76
	10.5	8.9±0.5	−5.4±2	169	^{19}F	58
	9.5	10.4±0.4	3.0±2	170	^{19}F	58
	10.2	11.3±0.7	3.7±3	182	^{13}C—{^{1}H}	79
	10.3	9.3±0.7	−3.5±3	168	^{13}C—{^{1}H}	79
	9.8	11.1±0.7	4.5±3	178	^{13}C—{^{1}H}	79
	9.8	11.0±0.7	4.1±3	177	^{13}C—{^{1}H}	79
	10.4	6.4±0.2	−13.2±1	142	^{13}C—{^{1}H}	96
	12.2	9.9±0.6	−7.7±2.5	196	^{13}C—{^{1}H}	68

*The methyl group is designated by a circle.
**T_r is the temperature of stereochemical rigidity at which the rate of exchange is 1 s^{-1}. The values of T_r were determined from the approximate formula $T_r \simeq \Delta H/(\Delta S + 58.2)$, which follows from Eqn. (1) for $k = 1$ s^{-1}.

Despite the achievements in the experimental studies on inversion processes, a consistent method for the interpretation of these data has not so far been put forward in

the literature. This is due to the general state of the theoretical description of the process under consideration[12,16,17]. The available estimates[17], carried out by Westheimer's method (a version of the method of atom–atom potentials) are in only qualitative agreement with experimental data and in all cases the accuracy of the latter is significantly higher than that of the calculation.

Table 9. The activation parameters for ring inversion in substituted cyclohexanes (the non-degenerate case).

Inversion process	$\Delta G^{\neq}_{300°}$, kcal mole^{-1}	$\Delta H^{\neq}$, kcal mole^{-1}	$\Delta S^{\neq}$, e.u.	Method	Refs.
	10.15	9.40	2.51	ЯМР	37
	10.32	9.87	−1.46	^{19}F	
	10.20	10.83	2.1	ЯМР	59
	9.54	10.17	2.1	^{19}F	
	9.8	10.2	1.4	ЯМР	58
	10.1	10.8	2.5	^{19}F	
	10.7	12.6±0.4	6.4±0.5	ЯМР	26
	11.4	13.0±0.4	5.3±0.5	^{13}C—{^{1}H}	

In view of the present lack of a quantitative theory of conformational transformations, many investigators are rightly interested in various approximate methods for the analysis of the inversion dynamics, which make it possible to establish the occurrence of ring inversion and to determine the approximate thermodynamic characteristics of this process. The free energies of activation, calculated directly from the rate constants defined by Eqn. (1) at a specified temperature, may be used as characteristics of this kind. Sometimes the specified temperature is the temperature of stereochemical rigidity T_r,[82] which is determined from the nature of the broadening of the lines in the slow exchange stage (T_r is the temperature at which the exchange rate constant is 1 s^{-1}). For degenerate inversions investigated by ^{13}C NMR, the values of T_r are listed in Table 8. One should note that T_r varies within wide limits (142–196 K). We may point out that quite recently it proved possible to establish with the aid of ^{13}C NMR that γ-hexamethyl-(*aeaeae*)-cyclohexane is rigid even at room temperature and undergoes inversion only on heating to 370 K; estimates of the free energy of activation gave 17.6 kcal mole^{-1}.[83] The ^{13}C NMR method is the most effective and universal procedure in the search for anomalous inversion barriers.

VI. CHEMICAL SHIFTS OF ^{13}C NMR NUCLEI IN INDIVIDUAL CONFORMERS OF SUBSTITUTED CYCLOHEXANES

In those cases where there are adequate grounds for the assumption that the conformational equilibrium is strongly displaced towards one conformer, it is possible to employ high-temperature spectroscopic data (for 300 K) as the individual spectroscopic characteristics of the dominant conformer. This approximation is valid for the majority of alkyl groups; the corresponding chemical shifts are listed in Table 10. However, in the general case where the nature of the conformational equilibrium is unknown, it is necessary to investigate low-temperature spectra. The relevant data for monosubstituted cyclohexanes are listed in Table 11. Data obtained by optimising the additive scheme for the determination of chemical shifts are quoted for the methyl group[44].

Table 10. ^{13}C NMR chemical shifts (δ, p.p.m.) in monosubstituted cyclohexanes $C_6H_{11}X$ (X is a substituent with a conformational energy ≥2 kcal mole^{-1}).

X	Position of carbon atom			
	α	β	γ	δ
C_2H_5	12.6	6.1	−0.5	−0.2
n-C_4H_9	10.8	6.5	−0.5	−0.3
t-C_4H_9	21.2	0.5	0.1	−0.5
C_5H_{11}	16.7	3.2	−0.2	−0.2
C_6H_5	17.5	7.3	−0.2	−0.9

*Relative to cyclohexane (according to Pehk and Lippmaa[28])

In general, additive schemes for the compilation of ^{13}C chemical shifts have been widely used (see, for example, the selection of data in the review of Martin et al.[25]), particularly as one of the most effective methods for the assignment of spectral lines. Additive schemes are devised with the aid of a system of increments $\Delta_i(X)$, each of which characterises the influence of the substituent X on the shifts of the *i*th atom of the unsubstituted molecule. The index *i* describes the possible positions of a cyclohexane carbon atom relative to the substituent. Thus the ^{13}C NMR chemical shifts adjusted to the chemical shift of cyclohexane (27.50 p.p.m. relative to tetramethylsilane in terms of the δ-scale) can be regarded as the increments $\Delta_i(X)$.

Additive schemes for the calculation of ^{13}C NMR chemical shifts have been used successfully in the analysis of the spectra of dichlorocyclohexanes[45], methylcyclohexanols[62], a series of 1,2-disubstituted compounds[61], polymethylcyclohexanes[43], methyl derivatives of methylcyclohexanol[85], chloromethyl derivatives[86], etc. In most cases the deviations did not exceed 2 p.p.m. Appreciable upfield deviations (>2 p.p.m.) have been observed systematically in only one case—in the analysis of the shifts of the $C_{(1)}$ and $C_{(2)}$ atoms in 1,2-disubstituted compounds. The non-additivity of the shifts observed for 1,2-disubstituted cyclohexanes is probably general, because analogous deviations (sometimes referred to as the "*ortho*-effect") have been found also for other 1,2-disubstituted compounds: benzene[4], cyclopropane[87], ethylene[88], and cyclo-octane[99] derivatives. We may note that, for the

diaxial orientation of the substituents, this effect is a maximum (Table 12). Thus the phenomenon is probably due to the overall influence of electronic and steric factors.

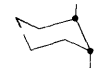
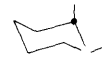
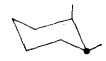
Table 11. The ^{13}C NMR chemical shifts (δ, p.p.m.) relative to C_6H_{12} for monosubstituted cyclohexanes.

X	δ, p.p.m.	Position of carbon atom				Solvent	Refs.
		α	β	γ	δ		
F	δ_i^e	64.38	5.53	−3.46	−2.57	CS_2	39
	δ_i^a	61.12	2.93	−7.11	−2.11		
	$\delta_i^a - \delta_i^e$	−3.26	−2.60	−3.65	0.46		
Cl	δ_i^e	32.80	10.62	−0.14	−1.81	CS_2	39
	δ_i^a	33.12	6.89	−6.61	−0.97		
	$\delta_i^a - \delta_i^e$	0.32	−3.73	−6.47	0.84		
Br	δ_i^e	25.13	11.75	1.35	−1.41	CS_2	39
	δ_i^a	28.35	7.90	−5.48	−0.55		
	$\delta_i^a - \delta_i^e$	3.22	−3.85	−6.83	0.86		
I	δ_i^e	3.64	13.40	2.28	−1.67	CS_2	39
	δ_i^a	11.30	9.04	−4.19	−0.89		
	$\delta_i^a - \delta_i^e$	7.66	−4.36	−6.47	0.88		
OH	δ_i^e	42.59	8.51	−1.65	−1.03	CS_2	42
	δ_i^a	37.92	5.28	−6.73	−0.61		
	$\delta_i^a - \delta_i^e$	−4.67	−3.23	−5.08	0.42		
OCH_3	δ_i^e	51.80	4.49	−2.80	−1.76	CF_2Cl_2	40
	δ_i^a	47.05	1.75	−7.23	−1.37		
	$\delta_i^a - \delta_i^e$	−4.75	−2.74	−4.43	0.39		
$OCOCH_3$	δ_i^e	45.79	5.03	−2.38	−1.73	CF_2Cl_2	40
	δ_i^a	42.08	2.76	−6.34	—		
	$\delta_i^a - \delta_i^e$	−3.71	−2.27	−6.72	—		
NO_2	δ_i^e	57.59	3.88	−2.78	−2.41	CS_2	42
	δ_i^a	54.02	1.10	−5.85	−1.26		
	$\delta_i^a - \delta_i^e$	−3.57	−2.78	−3.07	1.15		
NC	δ_i^e	24.86	6.67	−2.64	−1.82	CF_2Cl_2	40
	δ_i^a	23.29	3.52	−6.87	−1.82		
	$\delta_i^a - \delta_i^e$	−1.57	−3.15	−4.23	0.0		
CN	δ_i^e	1.38	2.81	−1.93	−1.93	CF_2Cl_2	40
	δ_i^a	0.09	−0.93	−4.53	−1.41		
	$\delta_i^a - \delta_i^e$	−1.29	−3.74	−2.60	0.52		
HgOAc	δ_i^e	20.30	—	—	—	$CDCl_3$	49
	δ_i^a	24.78	—	—	—		
	$\delta_i^a - \delta_i^e$	4.48	—	0.0	—		
CH_3	δ_i^e	5.96	9.03	0.05	−0.22	*	44
	δ_i^a	1.40	5.41	−6.37	−0.06	*	
	$\delta_i^a - \delta_i^e$	−4.56	−3.62	−6.42	0.16		
$Sn(CH_3)_3$	δ_i^e	−2.75	3.37	1.48	−0.57	CD_2Cl_2	84
	δ_i^a	—	—	−1.61	—		
	$\delta_i^a - \delta_i^e$	—	—	−3.09	—		
$Pb(CH_3)_3$	δ_i^e	8.54	6.16	2.56	−0.85	CD_2Cl_2	84
	δ_i^a	11.22	4.69	−1.62	−0.85		
	$\delta_i^a - \delta_i^e$	2.68	−1.47	−4.18	0.0		

*Data obtained by optimising the additive scheme for the calculation of the chemical shifts for polysubstituted compounds.

In principle the inclusion of non-additive corrections may lead to an improvement of the agreement between the experimental and calculated chemical shifts. An improved scheme of increments has been proposed so far only for polymethylcyclohexanes[44] and it was possible to achieve agreement with experiment within the limits of several tens of p.p.m. As regards the increments $\Delta_i(X)$ themselves, the upfield shift of the signal of the γ-carbon atom in the axial conformer (on average by 5–6 p.p.m. relative to the equatorial conformer) is the most interesting feature. This shift (the so called γ-effect), first observed by Grant and Cheney[89] for methylcyclohexanes, is interpreted in the general case as reflecting the interaction "through space" of the hydrogen atoms attached to the γ-carbon atoms in the ring with the substituent.

Table 12. The non-additive corrections for the calculation of ^{13}C NMR chemical shifts for substituted carbon atoms in 1,2-derivatives of cyclohexane (in p.p.m.).

Conformation*	Substituents		
	CH_3, CH_3	Cl, Cl	Br, Br
	2.45[44]	4.7[42]	6.5[61]
	—	6.7[42]	9.2[61]
	3.43[44]	6.9[42]	—
	2.91[44]	6.9[42]	—

*The atom considered is designated by a filled circle.

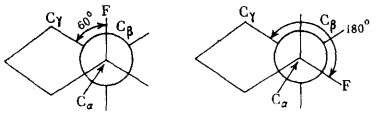
According to Grant and Cheney[90], the γ-effect depends on the distance r_{CH} and the angle θ which the C–H bond of the methyl group makes with the C...H line. The above dependence is described by the formula

$$\Delta\gamma = 1680 \cos\theta \cdot \exp(-2.67 r_{CH}). \quad (18)$$

The simplicity of this purely geometrical model explains why γ-effects have aroused interest in the literature on the conformational analysis of six-membered heterocycles[91,92]. It is noteworthy that in certain cases the γ-effect is weaker (for example, in the case of the F, OCH_3, and NO_2 substituents; see Table 11) and is altogether absent for mercury-substituted compounds[49]. The attempts at experimental determination of the dependence of Δγ on r_{CH} (or r_{CX}) were unsuccessful (see, for example, the analysis of the γ-effects in fluorine-substituted steroids[93]).

By considering now the narrower class of halogenocyclohexanes, it is possible to trace the dependence of the chemical shifts on the electronegativity of the substituent (Fig. 4). With increase of Pauling's electronegativity E, the chemical shifts of the α-carbon atom increase, those of the β- and γ-atoms decrease, and for β-atoms the dependence is close to linearity. The corresponding differences $\Delta\delta = \delta_i^e - \delta_i^a$ are $\Delta\delta_\alpha = -7$–5, $\Delta\delta_\beta = 2.5$–4.5, $\Delta\delta_\gamma = 4$–6, and $\Delta\delta_\delta = 0$–-1 (all the values are expressed in p.p.m.).

Comparatively little is known about the spin–spin coupling constants[44] involving ^{13}C nuclei (in substituted cyclohexanes); some results may be found in the papers of Subbotin and Sergeyev[39] and Weigert and Roberts[71]. A study of the low-temperature spectra of fluorocyclohexane showed all the $^{13}C-^{19}F$ spin–spin coupling constants for the interaction involving the carbon atoms in the individual conformers are different (these constants are listed in Tables 13). The $^3J(^{13}C-^{19}F)$ constant undergoes the most pronounced changes. The difference between the corresponding constants is probably due to the dependence of the constant $^3J(^{13}C-^{19}F)$ on the dihedral angle Φ between the $FC_\alpha C_\beta$ and $C_\alpha C_\beta C_\gamma$ planes. The dihedral angles are 60° and 180° for the axial and equatorial conformers respectively.



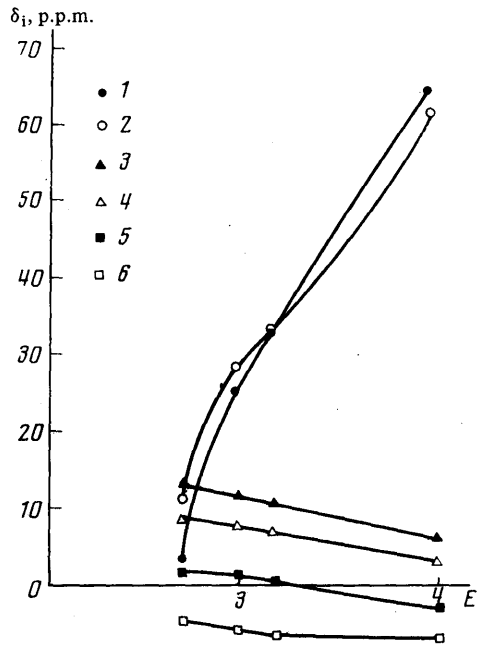


Figure 4. Dependence of the ^{13}C NMR chemical shift of the α-, β-, and γ-carbon atoms in the axial (a) and equatorial (e) conformers of halogenocyclohexanes on Pauling's electronegativity: 1) α_e; 2) α_a; 3) β_e; 4) β_a; 5) γ_e; 6) γ_a.

Assuming that the dependence of the constants $^3J(^{13}C-^{19}F)$ on the dihedral angle Φ is described by the "Karplus" curve corresponding to a function of the type $A + B\cos^2\Phi$, it is possible to estimate from the data in Table 13 the coefficients A and B, which yields $A = -2.5$ Hz and $B = 14$ Hz; thus the constant $^3J(^{13}C-^{19}F)$ probably changes sign in the vicinity of $\Phi = 0$. The absolute sign of the constant $^3J(^{13}C-^{19}F)$ is discussed by Hinton and Jaques[94].

There is at present no reliable information about the constants $J(^{13}C-H)$ for the compounds under consideration. The limited data obtained from ^{13}C NMR spectra of certain cyclic compounds[4,95] show that the constants $^1J(^{13}C-H)$ can be used in stereochemical studies, since a difference is observed between the constants for the axial and equatorial protons†.

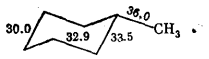
Table 13. The spin–spin coupling constants $J(^{13}C-^{19}F)$ (Hz) for fluorocyclohexane conformers at 183 K.[39]

SSC constant	Position of carbon atom			
	α	β	γ	δ
J_a,	167.0	21.5	1.0	<1
J_e,	172.2	17.7	11.5	2.0
$\lvert J_e - J_a \rvert$	5.2	3.8	10.5	~1

The constants $J(^{13}C-^{13}C)$ for coupling between carbon atoms linked by a σ bond may become yet another useful source of information. In recent years there has been a significant growth of interest in studies on these spin–spin coupling constants[97,98] in connection with advances in the technique of the recording of ^{13}C NMR spectra and in the calculation of spin–spin coupling constants. In particular, Gunther and Herrig[98] proposed on the basis of a compilation of experimental data an equation describing the dependence of $^1J(^{13}C-^{13}C)$ on the C–C bond length. If both carbon atoms are sp^3-hybridised, the equation becomes

$$J(^{13}C-^{13}C) = (-167.2 \pm 9.4)\,r_{CC} + (294.4 \pm 13.5). \qquad (19)$$

The constants $J(^{13}C-^{13}C)$ for the class of compounds under consideration have been reported so far only in the case of methylcyclohexane[42] (equatorial conformer). The $^{13}C-^{13}C$ constants for the corresponding C–C bonds are indicated below:



The similarity of the constants for the given compound shows that the C–C bond lengths differ very insignificantly (not more than by 0.02 Å).

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Thus ^{13}C NMR spectroscopy has permitted definite progress in the solution of the classical problem of conformational analysis involving the study of equilibria between the conformers of substituted cyclohexanes. This progress consists in a significant expansion of the range of objects investigated, the discovery of universal methods for the measurement of equilibrium constants, and experimental study of ring inversion dynamics. In certain cases

†The $^{13}C-H$ constants for cyclohexane itself have been obtained in a recent study[105] of the low-temperature ^{13}C NMR spectra of $[D_{11}]$cyclohexane: $^1J(^{13}C-H_a) = 122.44$; $^1J(^{13}C-H_e) = 126.44$; $^2J(^{13}C-H_a) = -3.94$; $^2J(^{13}C-H_e) = -3.69$; $^3J(^{13}C-H_a) = 2.12$; $^3J(^{13}C-H_e) = 8.12$; $^4J(^{13}C-H_a) = -0.31$; $^4J(^{13}C-H_e) = -0.50$ (all the values are expressed in Hz).

the accuracy of these methods, based on ^{13}C NMR spectra, is not inferior to that of other physical and chemical methods.

We may recall that ^{13}C NMR spectroscopy has been used recently to solve also other more complex problems of dynamic stereochemistry. In particular it has been possible to achieve with the aid of ^{13}C NMR a definite understanding of the conformational transformations in cyclo-octane [99], some of its derivatives [100,101], certain moderately large and large saturated rings [102], and cyclic ketones [103,104].

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