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The Application of Nuclear Magnetic Resonance in the Study of the Conformational Equilibria of Cyclic Compounds

T.M.Ivanova and G.P.Kugatova-Shemyakina

The NMR spectroscopic methods used to investigate mobile conformational equilibria and to determine the rate constants are discussed. A critical comparison has been made of the accuracy of the results obtained by high-resolution and spin-echo NMR methods. A systematic account of the thermodynamic parameters of the ring inversion of cyclic compounds obtained by NMR methods has been given. The possibility of employing NMR spectra for the determination of conformational equilibrium constants is discussed.
The bibliography includes 224 references.

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I. INTRODUCTION

In recent years there has been an intense development of the field of structural chemical studies which has come to be called conformational analysis. The development of Barton's ideas[1] concerning the relation between the physical and chemical properties of molecules, in particular between reactivity and the steric position of atoms and groups of atoms, proved to be extremely fruitful in a wide variety of chemical fields. Particularly important advances have been made in the conformational analysis of cyclic compounds for which a comparatively small number of conformations (in many cases not more than two) is possible owing to the limitations imposed on structural isomers. The interest in conformational studies has been largely reflected by the simultaneous publication of two extensive monographs[2,3].

Both chemical methods, based on definite reactions of model compounds, and many physical methods, with the aid of which it is possible to establish either the complete structure of the molecule (X-ray analysis, electron diffraction, microwave spectra) or certain details of this structure (dipole moments, vibrational spectra, NMR spectra, optical rotatory dispersion) are used at present to investigate conformations. Among the latter group of methods, NMR spectra occupy a special place. By virtue of their specificity, NMR spectra permit in many cases a rapid and reliable determination of the steric orientation of groups containing magnetically active nuclei and the relative amount of such groups in the molecule. They are more selective, than, for example, dipole moments and vibrational spectra; in the latter the vibrations of individual bonds and groups are frequently not entirely characteristic, which may lead to conclusions with little justification. Moreover, NMR spectra permit the investigation of processes involving the attainment of conformational equilibrium and the determination of the lifetime of the molecule in each form, while with the aid of other methods only indirect conclusions concerning such problems may be made. Although the method began to be developed comparatively recently, extensive data have now accumulated on fixed conformations and also on the inversion of cyclic systems. Without exaggeration, one may say that conformational analysis has to a large extent stimulated the development of the NMR method for the study of mobile equilibria. A number of techniques have been developed permitting the determination of the thermodynamic parameters of the ring inversion of cyclic systems. The most extensive studies of this kind have been made for cyclohexane derivatives, but there are also data on the inversion of other cyclic compounds, in particular medium-ring and heterocyclic compounds. Extensive data on the NMR spectra of rigid polycyclic systems, mainly steroids, are given in the book of Bhacca and Williams[4].

This review deals with the application of NMR spectra in the study of mobile conformational equilibria, mainly of monocyclic systems. Initially, methods which have now been developed for the investigation of ring inversion will be considered and their comparative accuracy will be estimated. The second part of the review gives a systematic account of the data on the thermodynamic parameters of the inversion of cyclic compounds obtained with the aid of NMR methods. The scope of the use of NMR spectra for the determination of conformational energies in six-membered rings is also briefly discussed. The majority of published results concern proton magnetic resonance spectra, but in recent years interesting data have been obtained with the aid of the fluorine resonance, also discussed in the review.

II. METHODS FOR THE INVESTIGATION OF RING INVERSION

The conformational hypotheses concerning the structure of cyclohexane and many other derivatives are based on the concept of the rapid conversion of one chair form of the molecule into another with the boat forms as intermediates. In this process the axial bonds of one chair conformation become the equatorial bonds in the other and conversely. Since it was shown in early studies that the axial and equatorial protons of six-membered rings are magnetically non-equivalent, the study of the inversion of cyclic systems is a special case of the study of the exchange of protons (or

other magnetically active nuclei) between non-equivalent positions; hindered rotation and intermolecular exchange in chemical reactions belongs to the same class of problems.

In recent years the "kinetic" field of NMR spectroscopy has been developing very vigorously. A number of methods and theoretical procedures have been developed, whereby one can use all the parameters of NMR spectra which vary with the rate of exchange of the nuclei: the multiplicity of the spectrum, intensity ratios, chemical shifts, and component widths.

The existing methods belong mainly to two categories: high-resolution and spin-echo spectroscopy. Their fundamental principles and practical applications in the study of ring inversion will be discussed below. The applicability of the method is undoubtedly not limited to the inversion of cyclic compounds; all the relations between the parameters of the spectrum and the rates of exchange may be applied to hindered rotation and, after appropriate modification, to the study of chemical reaction kinetics. In the investigation of mobile conformational equilibria, one usually employs the methods of high-resolution spectroscopy, which have been developed in detail. Detailed descriptions of these procedures are given in a number of monographs [5,6] and in this review only their principal postulates will be briefly described. The double-resonance and spin-echo methods, recently proposed for the investigation of ring inversion, will be considered in greater detail.

1. High-resolution NMR Spectroscopic Methods

The theoretical basis of these methods is the semi-classical treatment of Gutowsky et al. [7], who examined the Bloch equations for two protons with resonance frequencies ω_A and ω_B undergoing exchange between equilibrium positions A and B (it is assumed that the lifetime $\tau_A = \tau_B = \tau$). The expression for the total magnetisation averaged with respect to proton exchange is [7]:

$$G = \overline{G}_A + \overline{G}_B = \frac{-2\omega M_0 \tau\,[2+(1/T_2 - i\Delta\omega)\,2\tau]}{(1+2\alpha_A\tau)\,(1+2\alpha_B\tau)-1}, \qquad (1)$$

where, as usual, $\alpha_A = 1/T_2 - i(\Delta\omega + \delta\omega/2)$, $\alpha_B = 1/T_2 - i(\Delta\omega - \delta\omega_2)$, M_0 is the equilibrium value of nuclear magnetisation, $\Delta\omega$ the difference between the applied radio-frequency ω and the frequency of the midpoint between two resonance components, and T_2 is the transverse relaxation time. Eqn. (1) was obtained on the basis of simple considerations by McConnell [8], who included directly in the Bloch equations terms taking into account the exchange: G_A/τ and G_B/τ. For non-identical probabilities $p_A \neq p_B$ of the presence of the proton in A and B (p_A and p_B may be regarded as the "molar concentrations" of A and B),

$$p_A + p_B = 1 \quad \tau_A/p_A = \tau_B/p_B, \qquad (2)$$

analytical expressions defining the total magnetisation were obtained by Gutowsky and Saika [9] and subsequently by other investigators [10,11].

It follows from Eqn. (1) that the form of the NMR spectrum is determined by $\delta\omega$, T_2, and the rate of proton exchange $1/\tau$. At high rates of exchange ($\tau\delta \ll 1$) one signal with a frequency ω_0 is observed; with increase of τ, the signal gradually widens, and for $\tau > \sqrt{2}/2\pi\delta\omega$ two broad signals are observed. The value of τ corresponding to the merging of the signals may be called the coalescence point. On further growth of τ, the width of the signals diminishes and the distance between them increases to $\delta\omega$ (Fig. 1).

Eqn. (1) contains an implicit relation between all the parameters of the NMR spectrum and the rate of exchange, but for the solution of practical problems it is convenient to obtain analytical relations between $1/\tau$ and quantities measured directly from the spectrum. Such relations have been obtained for three readily measurable parameters: (a) the distance between the lines (for $\tau\delta \ll 1$); [13] (b) the intensity ratios I_{max}/I_{min} for incomplete resolution of the doublet [14-16]; (c) the line widths in the limiting cases of rapid and slow exchange [17,18].

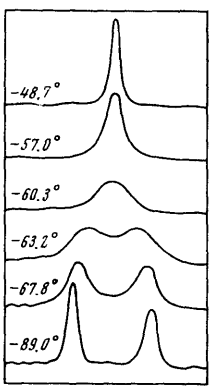


Figure 1. Spectra of $C_6D_{11}H$ at different temperatures [12].

a. Change in the distance between the components of the spectrum. An explicit expression relating the distance between the signals to the rate of exchange was obtained by Gutowsky and Holm [13]. Starting with Eqn. (1), they obtained an equation of the fifth degree in $\Delta\omega$, which becomes very simple when the width of the lines $1/T_2$ is small compared with the distance $\delta\omega$ between them:

$$\delta\omega_e = (1-2/\tau^2\delta\omega^2)^{1/2}\,\delta\omega; \quad \tau\delta\omega > \sqrt{2}. \qquad (3)$$

Thus, when measuring the distance $\delta\omega_e$ between the components under various conditions (usually the lifetime is varied by altering the temperature), it is possible to determine τ by Eqn. (3) provided that the distance $\delta\omega_\infty$ is known for $\tau \to \infty$. In practice, however, failure to take into account the widths of the components may introduce a significant distortion into the results already when $1/T_2\delta\omega > 1/3$. [13] Gutowsky and Holm showed that this is equivalent to applying a correction to $\delta\omega_\infty$. The true distance $\delta\omega$ may be obtained from a plot of $\delta\omega/\delta\omega_\infty$ against $2/T_2\delta\omega_\infty$. [13] In practice T_2 may be determined from the line width when $\tau \to 0$; $\delta\omega_\infty$ is measured at $\tau \to \infty$.

b. Intensity ratio in the spectrum. Starting with postulates analogous to those discussed above, it is possible to express the average lifetime τ of the protons undergoing exchange in terms of the ratio r of the intensity at the maximum of the signal to the intensity in the centre of the spectrum, between the signals, when the symmetrical doublet (or other symmetrical multiplet signal) is completely resolved [14-16]. The expression is of the form

$$\tau\delta\omega = \sqrt{2}\,[r + (r^2 - r)^{1/2}]^{1/2}; \quad \tau\delta\omega > \sqrt{2}. \qquad (4)$$

The determination of the rate of exchange reduces in this case to the measurement of the intensity at the maximum and the minimum intensity in the "hollow" between the signals for different degrees of incomplete resolution. It is also necessary to know the distance $\delta\omega$ between the components at $\tau \to \infty$. Expressions of this kind, relating τ to the peak intensity of the signal for rapid[10] and slow[11] exchange, have been obtained in a number of studies.

c. Change in signal width. The applicability of the methods described above is restricted to the range of comparatively low rates of exchange. In order to obtain the necessary parameters, all the measurements must be made over a narrow temperature range below the point of coalescence. Moreover, it is also necessary to know the chemical shift $\delta\omega$ at $\tau \to \infty$, which sometimes gives rise to additional difficulties. Meiboom and coworkers[15,17] and Piett and Anderson[18] suggested that the variation of the transverse relaxation time with τ be used for the estimation of the rates in the extreme cases of rapid and slow exchange. Employing the approach of Gutowsky and Saika[9], Piett and Anderson[18] showed that, for low rates of exchange, the observed line width is

$$1/T_2' = 1/T_2 + 1/\tau, \qquad (5)$$

where T_2 is the transverse relaxation time in the absence of exchange and T_2' is the "new" transverse relaxation time. When the rate of exchange diminishes, the width of each component will tend to an effective natural value. For rapid exchange, the following expression was obtained:

$$1/T_2' = 1/T_2 + p_A p_B (\delta\omega)^2 \tau. \qquad (6)$$

The line width can be determined either directly from the high-resolution spectrum or by the usual methods based on measurements of signal decay. It is significant that the temperature variation of line widths may be slower and may be observed over a wider range than, for example, the temperature variation of the distance between the components described by Eqn. (3). Therefore the above methods greatly extend the range of measurable rates of exchange.

2. Methods Based on Complete Calculation of the Spectrum

In recent years a new approach to the determination of the rates of exchange from NMR spectra became possible as a result of the availability of high-speed computers. It reduces to the complete analysis of the outline of an AB or more complex systems as a function of the lifetime τ. A general quantum-mechanical theory of the effect of exchange on the parameters of the NMR spectrum, based on the time variation of the components of the density matrices, was developed by Kaplan[19] and Alexander[20]. The corresponding expressions for the system AB were obtained by Heidberg et al.[21]. The method involving the complete calculation of the spectrum requires the derivation of the equations and their numerical solution for each specific problem. The value of τ, which gives the best description of the spectrum when the other parameters are specified is determined by an iterative procedure. As a rule, the calculated and observed spectra are compared visually. However, recently Jonáš et al.[22] developed a convenient program for the comparison of the observed and calculated outlines by means of a computer.

3. Double Resonance

Recently a double-resonance technique was proposed for the investigation of the rates of exchange. The method was developed by Forsen and Hoffman[23,24] and applied in the study of the rate of inversion of cyclohexane by Anet and Burn[25]. The idea of the method is as follows. Suppose that there is exchange between two non-equivalent positions A and B, and the following two obligatory conditions are fulfilled: (1) the lifetimes τ_A and τ_B must be sufficiently long for a satisfactory resolution of the signals A and B; (2) the lifetime τ_A must be comparable to the spin-lattice relaxation time T_{1A}. If the signal B is saturated instantaneously, the signal A will decay exponentially with the time constant τ_{1A}:

$$M_z^A = M_0^A [\tau_{1A}/\tau_A \exp(-t/\tau_{1A}) + (\tau_{1A}/T_{1A})], \qquad (7)$$

where M_0^A is the initial magnetisation of A. The new "generalised" relaxation time τ_{1A} is defined thus:

$$1/\tau_{1A} = 1/\tau_A + 1/T_{1A} \qquad (8)$$

and the new equilibrium magnetisation is given by

$$M_z^A(t \to \infty) = M_0^A(\tau_{1A}/T_{1A}). \qquad (9)$$

Thus the ratio of the initial and final magnetisations M_0^A/M_Z^A, which can be readily obtained experimentally, yields τ_{1A}/T_{1A}; by plotting $\lg[M_Z^A(t) - M_Z^A(t \to \infty)]$ against t, we obtain a straight line with slope τ_{1A}. It is then easy to determine τ_A and T_{1A} from Eqn. (9).

When the saturating field at B is removed, the A signal returns to its initial value M_Z^A, but the corresponding relation is not exponential; in the general case it cannot be described with the aid of a single time constant[23,24]. Forsen and Hoffman examined also two other possibilities: the return of the magnetisation of the signal to the initial value after saturation of the same signal and after the simultaneous saturation of the A and B signals[23]. Subsequently the same workers[24] applied the method to the study of exchange between several non-equivalent positions. As already stated, the double-resonance method can be applied only over a very restricted range of rates of exchange, since the lifetime must be comparable to the spin–lattice relaxation time. The latter may be varied somewhat by the addition of paramagnetic substances. The lower limit to the measured rates is imposed by the requirement that the signals do not overlap, i.e. the lifetime must be greater than the reciprocal of the distance between the corresponding lines.

The advantages of the method are due primarily to the fact that the lifetimes measured with its aid cannot be determined by other high-resolution procedures. Moreover, it is noteworthy that the experiment in which two parameters (rate of exchange and spin–lattice relaxation times) are measured simultaneously is relatively simple and the amount of calculation in the interpretation of the data is also small. The method does not require a very high resolution and an accurate determination of the chemical shifts. However, a high sensitivity of the detecting system is essential.

4. The Spin-echo Method

Recently Gutowsky, Allerhand and coworkers[26-31] developed a fundamentally new approach to the determination of the rate of proton exchange from NMR spectra. It

is based on the observation of spin-echo signals† when a chain of high-frequency pulses in the Carr–Purcell sequence [32] is applied to the spin system investigated: at time $t = 0$ a 90° pulse is applied and then at times $(2n - 1)t_{av}$ a sequence of 180° pulses is observed. These pulses generate a spin echo at times $2nt_p$ (here t_p is the period between the 90° pulse and the first 180° pulse). In the general case the amplitudes of the observed echo signals are functions of the shift $\delta\omega$, the spin–spin coupling constant J, the transverse relaxation time T_2^0 in the absence of exchange‡, the distance between the 180° pulses, t_{av}, the population of the p_A and p_B levels, and the rate of exchange $1/2\tau$. It is important that the duration of the pulses is short compared to T_2 (and to the spin–lattice relaxation time T_1) and also to the intervals between the pulses, so that the relaxation and exchange effects during the application of the pulse may be neglected.

The simplest relations between these quantities are obtained for the AB system when $J = 0$. For this case, Allerhand and Gutowsky [26,27] employed a semiclassical approximation taking into account the exchange terms [7,8,13]. Earlier Luz and Meiboom [33] obtained an approximate analytical expression for the decay of the spin-echo signals under conditions where (1) the distance between the 180° pulses is small ($t_{av} \ll T_2$) and (2) the exchange is fairly rapid ($1/2\tau \gg \delta\omega$):

$$1/T_2 = 1/T_2^0 + p_A p_B (\delta\omega)^2 \tau [(1 - 2\tau/t_{av}) \tanh t_{av}/(2\tau)]. \quad (10)$$

Gutowsky and Allerhand showed [26,27] that, although Eqn. (10) may be applied over a fairly wide range of values of the independent variables, for high values of t_{av} and for slow exchange its application leads to significant errors. Their general examination of the problem led to the conclusion that the expression for the variation of the magnetisation component may be represented by two terms, one of which varies exponentially with time and the other is pseudoexponential. However, the latter is small in most practical cases, so that only the contribution of the exponential term need be considered.

The following expression was obtained for identical populations $p_A = p_B = 0.5$: [27]

$$1/T_2 = 1/T_2^0 + 1/2\tau + 1/t_{av} \sinh^{-1} F,$$

where

$$F = (1/\tau\sigma) \sinh (t_{av}\sigma/2); \quad \sigma = [(1/\tau)^2 - (\delta\omega)^2]^{1/2}. \quad (11)$$

In the limiting cases Eqn. (11) leads to the following relations. (1) Slow exchange ($1/\tau < \delta\omega$):

$$1/T_2 = 1/T_2^0 + 1/2\tau. \quad (12)$$

(2) Rapid exchange ($1/\tau \geq \delta\omega$):

$$1/T_2 = 1/T_2^0 + 1/2\tau - 1/2[(1/\tau)^2 - (\delta\omega)^2]^{1/2}. \quad (13)$$

For very rapid exchange ($1/\tau \gg \delta\omega$), Eqn. (13) yields the result obtained on the basis of another approximation by Piett and Anderson [18]:

$$1/T_2 = 1/T_2^0 + 1/4(\delta\omega)^2\tau. \quad (14)$$

Eqn. (13) can also be used to determine the rates of exchange from the line widths in high-resolution NMR spectra; it can be applied in the case of much lower rates of exchange than Eqn. (14).

When the distance between the pulses diminishes ($t_{av} \to 0$), $1/T_2$ approaches asymptotically the effective natural line width (independent of the rate of exchange).

† For transient processes, see Ref. 6, p. 61.

‡ It is assumed that the transverse relaxation times for positions A and B are equal.

This gives rise to the possibility of determining T_2^0 from spin-echo experiments with very rapid repetition of pulses.

Thus the rate of exchange $1/\tau$ may be determined by measuring the spin-echo signal decay as a function of the distance between the 180° pulses. Since Eqn. (11) includes, apart from τ and t_{av}, also the two independent variables T_2^0 and $\delta\omega$, it is usually solved by iterative methods [26,27]. Allerhand and Gutowsky developed programs whereby it is possible to obtain "true" values of the parameters after, as a rule, not more than ten iterations. The initial values of $1/\tau$ and $\delta\omega$ may be chosen with the aid of the Luz–Meiboom equation [Eqn. (10)].

The spin-echo method has the advantage that in this case there is no need for a direct determination of the parameters $\delta\omega$ and T_2^0; they are obtained additionally in the iterative process from the functional relation between $1/T_2$ and $1/t_{av}$. We may note that, in order to calculate the amplitude of the echo signals, it is by no means obligatory to express the variation of T_2 in an analytical form: it is possible to solve directly modified Bloch equations in a numerical form by means of appropriate programs. Although such calculations do require a considerable machine time, accurate values are then obtained over the entire range of variation of the parameters. However, for the majority of practical problems, the relation between T_2 and $1/t_{av}$ is satisfactorily described by Eqn. (11).

The semiclassical approach described above can be applied only to a system AB. If the coupling constant J_{AB} is comparable to the chemical shift, $\delta\omega$, significant changes may be introduced into the results of the spin-echo experiments. Allerhand and Gutowsky [31] examined, using a quantum-mechanical approach, the time variation of the components of the density matrix [20,21] for the system AB under conditions corresponding to the application of a Carr–Purcell sequence of pulses. In the general case eight recurrent equations were obtained, the coefficients of which are complex functions of the experimental quantities. However, as in the case examined above, a significant success may be achieved here by the numerical solution of the equations. By varying the independent variables τ, $\delta\omega$, J, and t_{av} over a wide range, Allerhand and Gutowsky showed that the results obtained [26,27,30] for an AB system with $J = 0$ are not applicable to interacting nuclei for low rates of exchange. When $1/2\tau$ (s^{-1}) is small compared with the geminal coupling constant J, modulation of the echo signal amplitudes should be observed. The modulation frequency depends on the distance between the pulses t_{av}, the constant J, and also $\delta\omega$, particularly if $J/\delta\omega \simeq 1$. In the limiting case where $J = 0$, the same results are obtained as in the semiclassical theory. The modulation greatly depends also on the rate of exchange. When $1/2\tau$ increases, the modulation frequency falls and the time variation of the echo signal amplitude approaches the exponential form. When $1/2\tau \geq 20J$, the relation is rigorously exponential and can be described by a single decay constant. Thus in spin-echo experiments geminal coupling may be neglected only at high rates of exchange. In particular, for cyclohexane, which is an A_6B_6 system, $J_{HH} = 12.6$ Hz, [34] and therefore the semiclassical approach may be employed here at rates of inversion $k > 1/200$ s^{-1}. All these results have been qualitatively confirmed in spin-echo experiments with 1,1-difluorocyclohexane [31].

Gutowsky et al. [29] also developed a general theory of the effect of rates of exchange on the spin-echo signal amplitudes based on the formal matrix approach of Anderson and Weiss [35–37]. Among the series of interesting consequences

of this treatment, the authors demonstrated an analogy between the exchange effects and the quadrupole spin–lattice relaxation effects and showed that in principle quadrupole relaxation times may be measured by spin-echo methods§.

5. Accuracy of the Determination of the Rate Constant by Different NMR Methods

When a particular method is employed, it is necessary to bear in mind the resulting accuracy in the determination of the rate constant and then in the thermodynamic parameters of the system. Frequently, as experimental data accumulated, it became clear that many NMR methods probably involve serious systematic errors. The determination of the barrier to the hindered rotation of *NN*-dimethylformamide constitutes a striking example; its estimates vary from 7 to 24 kcal mole^{-1}, [23] while the experimental error quoted in each case does not exceed 1 kcal mole^{-1}.

Apart from the purely experimental errors (instability of the field, incorrect calibration, inaccuracies in temperature measurement), systematic errors can arise as a result of an incorrect choice of the model for the description of the real system. The simple semiclassical model for an AB system with $J = 0$ [7,9,13] becomes inapplicable in more complex cases where it is necessary to estimate the rate from equations for a system with $J \neq 0$. [19,20,39] However, even if the application of the semiclassical model is justified, usually further simplifications are made in order to obtain analytical relations and to employ readily available parameters: differences between the chemical shifts, intensity ratios, and line widths.

High-resolution NMR methods permit the measurement of the rate constant within very narrow ranges. The least accurate is the widely used method for the determination of the rate constants based on the merging of the signals at the coalescence temperature. In the first place the coalescence temperature cannot be determined with sufficient accuracy. This method yields no information about the process kinetics unless one assumes that Eyring's pre-exponential factor may be used and a transmission coefficient of unity is adopted.

The methods for the determination of τ from the change in the chemical shift and the intensity ratio are suitable only for low rates of exchange at temperatures below the coalescence point. Usually $\delta\omega_e$ is small and varies within a narrow temperature range; for example, for cyclohexane appreciable changes in $\delta\omega_e$ are observed between 64° and 72 °C, i.e. over a range of only 6 deg. In order to increase $\delta\omega$, it is necessary to employ spectrometers with a higher field strength. $\delta\omega_\infty$ must be measured fairly accurately; a 10% error in the measurement of $\delta\omega_\infty$ leads to a much greater error in the thermodynamic parameters. A high accuracy in the measurements of $\delta\omega_e$ is also necessary, particularly when $\delta\omega_e$ approaches $\delta\omega_\infty$, i.e. in the region where $\delta\omega$ is already relatively insensitive to changes in temperature. Moreover, there is a possibility of a temperature variation of $\delta\omega_\infty$, [26,40] and failure to take this into account must lead to an additional systematic error in the determination of the rate of inversion. For very low rates of exchange, Eqn. (3) leads to large errors in the determination of τ and may not be used [16].

§ Powles and Strange [38] examined approximately the determination of the rate of intermolecular exchange for an AB system from spin-echo experiments.

Allerhand, Gutowsky, and coworkers [41] analysed Eqns. (3) and (5) and showed that they yield high values of the rates, the error depending on the ratios of three parameters: $\delta\omega$, $1/\tau$, and the transverse relaxation time T_2^0. In particular, when Eqn. (3) is used, the error for a chosen pair of values of $\delta\omega$ and $1/\tau$ increases as T_2^0 falls.

Since both methods yield rate constants over a limited range of temperatures, small systematic errors in the measurement of τ may lead to considerably greater errors in the activation parameters. To extend the range of measured rates, the relation between line width and τ is employed in high-resolution methods at temperatures above the coalescence point. Here the inaccuracies may be attributed to the employment of temperatures close to the coalescence point of approximation (6), which is suitable only for very high rates of exchange [41]. However, it is precisely in the range of temperatures close to T_c that the contribution of the "exchange term" is most significant. In this case one may employ a more general expression for line width [10,40]. With increase in the rate, the contribution of the exchange term becomes extremely small and approaches the experimental error in the determination of line widths. In practice such a limiting value of the broadening due to exchange amounts to 0.05 Hz. Evidently, for systems which are not very complex, the most reliable values of τ may be obtained by complete calculation of the outline of the spectrum for various values of τ and subsequent comparison with the experimental spectra [21,22].

The spin-echo method developed by Gutowsky, Allerhand, and coworkers has a fundamental advantage: it permits the determination of the rates of exchange over a much wider range than high-resolution NMR methods. In particular, this applies to the region of high rates, where (for specified values of $\delta\omega$ and T_2^0) the maximum measurable rate depends on the accuracy with which it is possible to determine T_2^0/T_2 when this quantity tends to unity. In this case the limit of the possible errors in τ measured by the spin-echo method is

$$^1/_2\tau \leqslant p_A p_B T_2^0 (\delta\omega)^2 . \qquad (15)$$

Such rates of exchange are not measurable by high-resolution NMR methods. The most favourable situation for measurement by the spin-echo method obtains in the case where the transverse relaxation time of the test substance is high, as, for example, in $C_6D_{11}H$ ($T_2^0 = 10$ s at −100° and 85 s at 25 °C). The spin-echo method permits the investigation of the ring inversion of deuterocyclohexane in the range where the rate varies by five powers of ten [30]: from 0.5 s^{-1} to 4×10^4 s^{-1}, extending thereby the range of attainable τ by a factor of more than 50. These data were obtained by Allerhand, Chen, and Gutowsky on a 24 MHz spectrometer. Evidently, by employing spectrometers with a higher field strength, the range of rate constants may be extended further by a factor of several units. The accuracy of the determination of τ by spin-echo methods does not exceed the accuracy of the high-resolution NMR method (10–20%), but, since τ is measured over a much wider range, the thermodynamic parameters obtained should be more reliable.

Spin-echo measurements have yet another advantage: they permit the determination at the same time of $\delta\omega$ and T_2^0, and $\delta\omega$ may be obtained at high rates of exchange for which high-resolution NMR spectroscopy is inapplicable.

Despite its undoubted advantages, the spin-echo method is comparatively rarely used to determine the rates of exchange. To a large extent, this is because the method has been developed quite recently. It requires additional

apparatus, which has only now begun to be produced commercially outside the USSR and is more time-consuming than high-resolution NMR methods. The interpretation of the results is laborious and requires special programs and considerable machine time. Probably spin-echo measurements also include some phenomenological errors the source of which is as yet obscure. The point is that these measurements tend to yield high values for $\delta\omega$. Thus low-temperature NMR spectra yield $\delta\omega = 0.48$ p.p.m. for $C_6D_{11}H$ [12,42,43] and $C_6D_8H_3$, [44] while the value obtained from spin-echo results for the same temperatures is higher by approximately 30%. In the study of 1,1-difluorocyclohexane [31] by the spin-echo method it was necessary to adopt $\delta\omega = 18.5$ p.p.m.; the value $\delta\omega = 15.6$ p.p.m., determined from low-temperature NMR spectra [22], gave a poor agreement between the results. The possible reasons for these discrepancies have been discussed [29]. The inconsistency is probably associated with the fact that the approximation in which the decay of the echo signal amplitudes is described by a single constant T_2 becomes inapplicable and it is necessary to take into account the pseudoexponential terms.

III. ENERGY PARAMETERS OF THE INVERSION OF CYCLIC COMPOUNDS

1. Cyclohexane

The classical model for the investigation of ring inversion by NMR spectroscopy is cyclohexane. The interest in this molecule is due, on the one hand, to the fact that it occupies a central place in the theory of conformational analysis. On the other hand, the rates of inversion of cyclohexane are in a favourable range and therefore it is frequently used to test a particular method.

Cyclohexane and its derivatives have been investigated by all the NMR spectroscopic methods developed hitherto (Table 1). At the coalescence temperature and below the

Table 1. Thermodynamic parameters of ring inversion in cyclic compounds.

No.	Compound	$\Delta H^{\neq}$ (E_a), kcal mole^{-1}	$\Delta F^{\neq}$ (°C), kcal mole^{-1}	ΔS e.u.	Solvent	Method	Refs.
1	Cyclohexane	11.5±0.2[1]	10.1±0.1 (−67)	—	CS_2	*b*	45
2	Cyclohexane	9.0±0.2	10.6 (−67)	−7.9[2]	CS_2	*d*, *e*[3]	46
3	Cyclohexane	11.5	10.7 (−67)	+4.0[4]	CS_2		47
4	Cyclohexane (C_6HD_{11})	10.9±0.6 (11.3)	10.3 (−67)	+2.9±2.3	CS_2	*b*, *e*	42
5	Cyclohexane (C_6HD_{11})	10.5±0.5	10.2 (−67)	+1.4±1.0	CS_2	*c*, *e*	12,43
6	Cyclohexane	9.1±0.5 (9.5)	10.3 (−68)	−5.8±2.4	CS_2	*f*	30
7	Cyclohexane (C_6HD_{11})	9.1±0.1 (9.5)	10.3 (−68)	−5.8±0.4	CS_2	*f*	30
8	Cyclohexane	10.8	10.2	+2.8[4]	CS_2	*d*, *g*, *i*	25
9	Fluorocyclohexane	9.6±0.4	9.7 (−57)	−0.8±0.5	$CFCl_3$	*d*, *e*	48
10	Chlorocyclohexane	—	10.5	—	CS_2	*a*	49
11	Chlorocyclohexane	—	11.7 (−65)	—	CS_2	*a*	50
12	Bromocyclohexane	—	10.8	—	CS_2	*a*	49
13	Bromocyclohexane	—	11.7 (−65)	—	CS_2	*a*	50
14	Iodocyclonexane	—	11.7 (−65)	—	CS_2	*a*	50
15	Cyclohexanol	—	11.7	—	CS_2	*a*	50
16	3,3,5,5-Tetradeutero-1,1-dimethylcyclohexane	—	10.4 (−60)	—	CS_2	*a*	51
17	*trans*-1,2-Dichlorocyclohexane	—	11.9 (−45)	—	CS_2	*a*	52
18	*trans*-1,2-Dibromocyclohexane	—	11.8 (−45)	—	CS_2	*a*	52
19	*trans*-1,3-dichlorocyclohexane	—	9.8 (−79)	—	CS_2	*a*	53
20	*trans*-1,3-Dibromocyclohexane	—	9.9 (−79)	—	CS_2	*a*	52
21	1,1-Difluorocyclohexane	10.4 (10.9)	9.7[5]	+3.0±2	propene	*g*[6]	54
22	1,1-Difluorocyclohexane	9.04 (9.5)	9.8 (−46)	−3.3	CS_2	*g*[7]	22
23	Ditto	8.6 (9.1)	9.8 (−46)	−5.0	$CFCl_3$	*g*[7]	22
24	"	9.4 (9.8)	9.5	−0.6	CS_2	*f*	31
25	1,1,4,4-Tetramethylcyclohexane	—	11.6 (−53)	—	CS_2	*a*	51
26	Ditto	13.3 (13.7)	11.4	+9.1	CS_2	*c*, *d*	55
27	6,6-Dimethoxy-1,1-dimethylcyclohexane	—	11.0 (−70)	—	CS_2	*a*	51
28	1,1,4,4-Tetramethylcyclohexane	8.6±1.2	10.5±0.4[4]	−9.5±6[4]	toluene	*g*	56
29	1,1-Difluoro-4,4-dimethylcyclohexane	8.9[5] (9.4)	10.2[5]	−5.4±2	propene	*g*[6]	54
30	1,1-Difluoro-4-ethyl-4-methylcyclohexane	7.92[5] 8.4	9.84[5]	−8.3±2	propene	*g*[6]	54
31	1,1,2,2-Tetrafluorocyclohexane	7.51[5] (8.0)	10.87[5]	−13.6±2	propene	*g*[6]	54
32	4-chloro-1,1-difluorocyclohexane	10.79[5]	10.21[5]	+2.5±1	propene	*g*[6]	54
33	Perfluorocyclohexane	7.5±0.3	9.9 (−66.5) 10.9 (+25)	— −10.7	CCl_3F $C_6H_5CF_3$	*d*, *e* *d*, *e*	57 57
34	Ditto	9.9±0.2 (10.5)	11.2	−4.4	liquid, isopentane	*f*	58
35	Isomers of fully acetylated inositol						
	cis-	6.6	15.4 (+18)	−30.1	$CHCl_3$	*b*	59
36	*allo*-	5.5	12.6 (−34)	−29.6	$CHCl_3$	*b*	
37	*muco*-	4.7	10.5 (−77)	−29.2	$CHCl_3$	*b*	59
38	Cyclohexene	5.3	5.3 (−164)	0[8] 1.3[9]	CF_3Br	*a*	60
39	4-Bromocyclohexene	6.1	5.9±0.1 (−148)	+1.4	$CD_2=CDCl$	*b*	61
40	1,1-Difluoro-4,4-dimethylcycloheptane	(6)	—	—		*f*	62
41	Cyclo-octatetraene	—	7.8 (−64) 7.8 (−110)	+0.3 −5.7	CS_2 CF_2Cl_2	*f* *f*	47 47
42	Cyclo-octane	7.7±0.3	8.1 (−115)	−4.4	$CCl_2=CHCl$	*b*, *e*	63
43	Cyclo-octatetraene	13.7	13.7 (−10)	0	CS_2	*a*	64
44	Fluoro-cyclo-octatetraene	—	12.0 (−33)	—	CS_2	*a*	65
45	2,3,4,5,6,7-Hexadeutero-cyclo-octatetraenyldimethylmethanol	15.4	17.4 (+41)	−6.3	CCl_4	*b*	66
46	2,3,4,5,6,7-Hexadeuteroethylcyclo-octatetraene carboxylate	12.8	15.3 (+40)	−8.0	CCl_4	*b*	66
47	*cis*-1,2-Dibromocyclo-octatriene	—	13.0 (−16)	—	$CDCl_3$	*a*	67
48	3,5,7-cyclo-octatrienone	11.9	—	—	CS_2	*g*	68
49	*cis*-Hydrindane	—	6.4 (−133)	—	CS_2	*a*	69
50	2,2-Difluoro-*cis*-decalin	15.0±0.9	12.3	8±5	acetone	*g*	70
51	1,1,3,3-Tetradeutero-2,2-difluoro-*cis*-decalin	13.4±0.8	12.4	2±3	propene	*g*	70
52	2,2-Difluoro-9-methyl-*cis*-decalin	9.1±0.6	12.1	−13±3	propene	*g*	70
53	2,2-Difluoro-10-methyl-*cis*-decalin	10.6±0.6	12.8	−10±3	acetone	*g*	70

Table 1 (contd.).

No.	Compound	$\Delta H^{\neq}$ (E_a), kcal mole^{-1}	$\Delta F^{\neq}$ (°C), kcal mole^{-1}	ΔS e.u.	Solvent	Method	Refs.
54	9-Ethyl-2,2-difluoro-*cis*-decalin	9.5±0.5	11.8	−11±4	acetone	*g*	70
55	Pentamethylene sulphoxide	—	14.2 (−70)	—	CH_2Cl_2	*a*	71
56	Pentamethylene sulphone	—	14.9 (−63)	—	CH_2Cl_2	*a*	71
57	Tetrahydro-thiopyran	—	11.6 (−93)	—	CH_2Cl_2	*a*	71
58	Tetrahydro-pyran	—	10.7 (−80)	—	CD_3OD	*a*	71
59	Piperidine	—	14.5 (−63)	—	CD_3OD	*a*	71
60	3,3,5,5-Tetra-deuteropiperidine	(14.5)	—	—	CH_3OH	*g*	72
61	Tetradeutero-*N*-methylpiperidine	(14.4)	—	—	CH_3OH	*g*	72
62	Tetradeutero-*N*-t-butylpiperidine	(14.0)	—	—	CH_3OH	*g*	72
63	Perfluoro-piperidine	5.7±1.5	8.9 (−67)	−15.5	$CFCl_3$		73
64	4,4,5,5-Tetradeutero-1,2-dithiane	11.5	11.7	0	CS_2		71
65	Ditto	—	11.6 (−43)	—	CS_2	*a*	74 75
66	3,3,6,6-Tetramethyl-1,2-dithiane	15.6 (16.1)	13.8 (−2)	+6.7	CS_2	*b*	75
67	4,5-*cis*-Di-acetoxy-1,2-dithiane	12.0	13.9 (−8)	−7.2	CS_2		71
68	1,3-Dithiane	—	9.4 (−80)	—	CS_2	*a*	76
69	5,5-Dimethyl-1,3-dithiane	—	10.3 (−70)	—	CS_2	*a*	76
70	2,2-Dimethyl-1,3-dithiane	11.2	9.8 (−80)	—	CS_2	*a*	76
71	1,3-Dioxane	—	9.7 (−82)	—	acetone	*a*	76
72	1,3-Dioxane	10.2±1.0	9.0 (−73)	+6±5	acetone	*d*	77
73	2,2-Dimethyl-1,3-dioxane	6.3	7.8 (−73)	−7	CCl_2F_2	*d*	77
74	5,5-Dimethyl-1,3-dioxane	12.4±0.8	10.5 (−73)	+9±4	acetone	*d*	77
75	2,2,5,5-Tetramethyl-1,3-dioxane	9.1±0.9	8.2 (−73)	+4±5	acetone	*d*	77
76	5,6-Dimethyl-1,3-dioxane	12.8±2	11.2 (−50)	+7.3	acetone	*a*	76
77	2,2-Dimethyl-1,3-dioxane	—	<8.0	—	acetone	*a*	76
78	3,3,6,6-Tetra-methyl-1,2-di-oxane	17.9 (18.5)	14.6 (+12)	+14.4	CS_2	*a*, *b*	75
79	3,3,6,6-Tetra-methyl-1,2-dioxane	(11.7)	—	—	CH_2Cl_2		78
80	*N*-Methyl-morpholine	—	11.5 (−31)	—	CH_2Cl_2	*a*	79
81	*NN*-Dimethyl-piperazine	—	12.6 (−8.5)	—	CH_2Cl_2	*a*	79
82	*NN*-Dimethyl-piperazine	—	13.0	—	CH_2Cl_2	*d*, *e*	80
83	*NNN'N'*-Tetra-methylpiperazine dichloride	9.3±1.2	12.9[4] (0)	−13.5±5.6	CS_2	*g*	56
84	Tetramethyl-*s*-tetrathiane	—	16.1±1 (+50)	—		*a*	81
85	Acetone diperoxide	11.7	15.4 (+29)	−12.1	CS_2	*c*, *d*	55
86	Acetone diperoxide	12.3	15.4 (+29)	−12.1	$CDCl_3$	*b*	82
87	2,3-Diazabicyclo-[2,2,1]hept-5-ene	16.9±0.6 16.2±0.8	14.5±0.2 (−9) 13.9±0.2 (−5)	+8.3±2.1 +7.6±2.6	$CDCl_3$ pentane	*b*, *d* *b*, *d*	83 83
88	2,3-Diazabicyclo-[2,2,1]-heptane	14.8±0.5 15.7±1.0	13.0±0.2 (−9) 12.6±0.4 (−5)	+6.0±2.0 +11.5±4	$CDCl_3$ pentane	*b*, *d* *b*, *d*	83
89	2,3-Diazabicyclo-[2,2,2]-octane	14.9±0.8 12.4±0.6	12.2±0.2 (−9) 11.8±0.3 (−5)	+10.0±3 +2.8±2.5	$CDCl_3$ pentane	*b*, *d* *b*, *d*	83 83
90	Dimethyl 3,6-diphenyltetra-hydropyridazine-1,2-dicarboxylate	16.4±1	18.5 (97)	−7±3		*d*	84
91	Diethyl ester of above acid	—	18.5 (95)	—	pentane	*a*	84
92	Dimethyl 4,5-dimethyltetra-hydropyridazine-1,2-dicarboxylate	—	19.7 (123)	—	pentane	*a*	84
93	Diethyl ester of above acid	—	20.3 (133,5)	—		*a*	84
94	Dimethyl 3,6-diphenylpiperida-zinedicarboxylate	15.6±1	16.7±0.3 (55)	±3		*d*	84

Table 1 (contd.).

No.	Compound	$\Delta H^{\neq}$ (E_a), kcal mole^{-1}	$\Delta F^{\neq}$ (°C) kcal mole^{-1}	ΔS e.u.	Solvent	Method	Refs.
95	Dimethyl 4,5-dimethylpiperida-zinedicarboxylate	—	19.4±0.4 (74)	—		*a*	84
96	*N*-Methyl-hexahydro-1,3,5-tri-azine	14.2±1.5	12.6±0.1 (0)	2.2±5.5	pentane	*g*	85
97	*N*-Ethylhexa-hydro-1,3,5-tri-azine	12.1±0.8	11.9±0.1 (0)	−3.4±2.9	pentane	*g*	85
98	*N*-Isopropyl-hexahydro-1,3,5-triazine	11.3±1.1	10.8±0.1 (0)	−2.6±4.0	pentane	*g*	85
99	*N*-t-Butylhexa-hydro-1,3,5-triazine	10.8±0.7	10.2±0.1 (0)	−1.8±2.6	pentane	*g*	85
100	1,3,5-Trimethyl-hexahydro-1,3,5-triazine	15.2±0.2 (15.7)	13.2±0.2 (−6)	7.5	$CHFCl_2$ $CDCl_3$	*g* *g*	86
101	1-Methyl-aziridine	(19)	—	—	liquid	*b*	87
102	1-Methyl-2,2-dimethyaziri-dine	(6.8±0.7) (7.8±0.8) (10.0±1.0)	— — —	— — —	CH_3OH CCl_4 liquid	*e* *e* *e*	88 88 88
103	1-Methyl-2-methylene-aziridine	(6.4±0.6)	—	—	liquid	*e*	88
104	1-Phenyl-aziridine	—	12.8 (−40)	—	CS_2	*a*	89
105	1-Methane-sulphonylaziridine	—	14.0 (−25)	—	$CDCl_3$	*a*	89
106	*NN*-Dimethyl-carbamoyl-aziridine	—	10.8 (−86)		$CH_2=CHCl$	*a*	89
107	1-Methoxycarbonyl-aziridine	—	7.6 (−138)	—	$CH_2=CHCl$	*a*	89
108	1-Phenylsulphonyl-aziridine	10.9±2	10.0±0.1	3.6±6	$CDCl_3$	*d*	90

Remarks. Designation of methods: (*a*) from coalescence temperature; (*b*) from temperature variation; (*c*) from intensity ratio *r*; (*d*) from signal width in high-resolution spectra; (*e*) from signal width in rapid sweep method; (*f*) spin-echo method; (*g*) total calculation of spectrum; (*i*) double-resonance method; +—approximate estimate.

[1]Erroneous value; according to Jensen et al.[45], the value should be $\Delta H = 5.9$ kcal mole^{-1}.

[2]For chair–chair ring inversion. [3] At 40 MHz.

[4]Chair–boat. [5]Value averaged with respect to the temperature range investigated. [6]Calculation by Alexander's method[20]. [7]Calculation for case AB.[20]

[8]For half-chair–half-chair inversion.

[9]For half-chair–boat inversion.

cyclohexane (C_6H_{12}) spectrum consists of a twelve-spin system, is extremely complex, and cannot be approximated by a simple doublet[45] or quartet[46]. However, these difficulties are eliminated when deuterated derivatives are employed[12,25,30,42]. At low temperatures the $C_6D_{11}H$ spectrum consists of two broad lines of equal intensity; the signal width may be greatly reduced with the aid of H–D double resonance[25,42,43]. With increase of temperature, the signals become broader and merge at the coalescence temperature (−61.4 °C), above which a single narrow line is observed (Fig. 1).

If the rate constant is determined for a number of temperatures, the thermodynamic parameters of the inversion process may be obtained from the usual relations:

$$k = \frac{kT}{h} \exp(\Delta S^{\neq}/R) \exp(-\Delta H^{\neq}/RT), \quad (16)$$

$$\Delta H^{\neq} = -R(\partial \ln k/\partial T^{-1})_p - RT, \quad (17)$$

$$\Delta S'^{\neq} = (\Delta H^{\neq} - \Delta F^{\neq})/T, \quad (18)$$

$$k = {}^1/_{2\tau} = A \exp(-E_a/RT). \quad (19)$$

The data in Table 1 show that the Gibbs free energies of activation for the inversion of cyclohexane agree to within 0.2 kcal mole^{-1} in six cases out of seven¶, while the values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ differ significantly. Only the parameters obtained by high-resolution methods agree satisfactorily[25,42,43]. The ring inversion of cyclohexane has been investigated over the widest temperature range by the spin-echo method[30], which should apparently have yielded the most accurate values of the energy parameters. However, the results of Allerhand, Chen, and Gutowsky do not agree with the results from high-resolution spectra†, the differences being illustrated in Fig. 2.

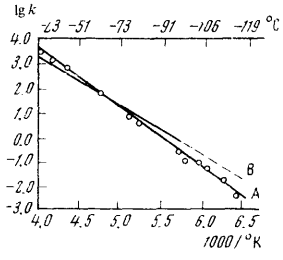


Figure 2. Temperature variation of the rate constant for ring inversion in cyclohexane determined by high-resolution (B) and spin-echo (A) methods[46].

The discrepancies are evidently associated with large systematic errors in the determination of the temperature variation of the rate constant. There are particularly large differences in the entropies found by different workers: they vary from +4.9 to −6.5 e.u. These results show that the experimental values of $\Delta S^{\neq}$ must be treated with caution in a discussion of the mechanism of ring inversion and the structure of the molecule in the transition state. In a number of studies attempts were made to estimate the entropy on the basis of the possible symmetry of the intermediate form[12,46,98]. If the rotational and vibrational contributions are neglected, such estimates may be made either by taking into account the symmetry numbers σ and the statistical weight w,[12,46] or by calculating directly the number of possible ways in which one form can be converted into another[25,98]. If the half-chair form is adopted for the intermediate state, the number of such ways is six and $S = R \ln n = 3.6$ e.u. Calculation from the expression $\Delta S = R \ln(w^{\neq}/w)(\sigma/\sigma^{\neq})$ also yields a positive entropy[98]. Harris‡ pointed out that the entropies can be negative only when the intermediate state has a planar shape in the ring inversion process. However, according to calculations[99], the energy of this state should be of the order of 30 kcal mole^{-1}. The agreement between the ΔS values predicted on the basis of symmetry and the experimental data from high-resolution spectra[25,42,43] may be evidence of a high reliability of the latter.

Recently computational methods have been widely used for the investigation of the conformations of cyclic compounds[99-104]. They are based on the calculation of the energy of the molecule by classical methods for specified potential functions, taking into account mainly the extension of the bonds, the deformation of valence angles, the torsional strain, and the interaction of atoms not linked by valence bonds. Cyclohexane was investigated in greatest detail by Hendrickson[99,104]. Fig. 3, taken from Hendrickson's paper[104], shows the geometry of the intermediate states in the chair–boat inversion of the symmetrical forms. The boat–skew boat conversion is achieved by a pseudorotation the potential barriers for which are low, in contrast to the barriers in symmetrical transitions. Hendrickson obtained the following values for the barriers in the transitions: chair–chair 11.0 kcal mole^{-1}, chair–boat 6.4 kcal mole^{-1}, and chair–twist-boat 5.6 kcal mole^{-1}. Evidently all the calculated values agree very well with experiment.

It is noteworthy that in all the conformational calculations for cycloalkanes a considerable improvement is achieved when the valence angles corresponding to minimum strain are assumed to be not tetrahedral but 112°,[102-104] which agrees with the latest electron diffraction data for cyclohexane[105] and certain cycloalkanes[106].

2. Cyclohexene

Compared with cyclohexane, the ring inversion of cyclohexene and its conformations have been investigated in much less detail. Nevertheless the conformational studies on these molecules are just as important, since the cyclohexene ring is included in a large number of natural compounds and determines their structure to a great extent.

The geometry of the cyclohexene ring is determined to a considerable degree by the presence of a double bond: four carbon atoms must be located in one plane. As a result, cyclohexene can adopt the form either of a half-chair or a boat (Fig. 4). Thermodynamic calculations showed that[107] the boat form is less stable to the extent of 2.7 kcal mole^{-1} than the half-chair. However, the valence angles of the trigonal and tetrahedral carbon atoms in both conformations must be distorted. Corey and Sneen[108] determined by vector analysis the cyclohexane (half-chair) model for which the simultaneous distortion of all the valence angles is a minimum. A similar determination was made by Boucourt and Hainaut[109], who suggested that 112° be adopted for all the tetrahedral angles in cyclohexene.

Many experimental data now show that cyclohexene and some of its derivatives exist in the half-chair conformation[110-114]. The frequencies of the skeletal vibrations and the CH vibrations in the infrared and Raman spectra of gaseous, liquid and solid cyclohexene also agree better with the half-chair form[115].

¶ It is interesting to compare the parameters of the ring inversion of cyclohexane obtained from NMR spectra with data derived by other methods. The first estimates of the height of the barrier in cyclohexane varied from 10 to 14 kcal mole^{-1}.[91,92] Later direct measurements of the decay of ultrasound yielded 8.3 kcal mole^{-1} [93] and 10.8 kcal mole^{-1}.[94] The following values have been obtained for the energy of the labile intermediate form, which cannot be estimated directly from NMR spectra: 5.9 kcal mole^{-1},[95] 5.5 kcal mole^{-1},[96] and 4.8 kcal mole^{-1}.[97]

† The spin-echo results agree with those of Harris and Sheppard[46], who also determined the rate constants over a fairly wide temperature range. However, subsequently Harris and Sheppard[98] reinterpreted their measurements in a different way and obtained $H = 10.3$ kcal mole^{-1}, in agreement with the enthalpies found by Anet and coworkers[25,42].

‡ Ref. 40 in the paper of Bovey et al.[48]

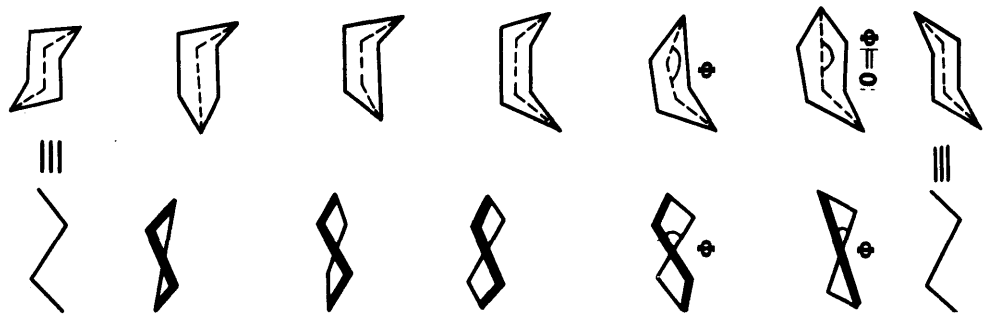


Figure 3. Intermediate states in the symmetrical ring inversion of cyclohexane[104].

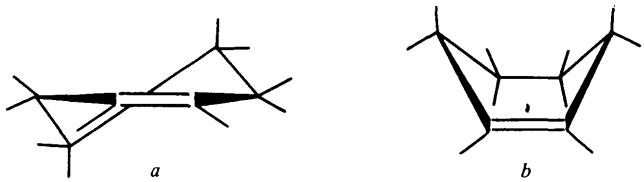


Figure 4. Cyclohexene conformations: *a*) half-chair; *b*) boat.

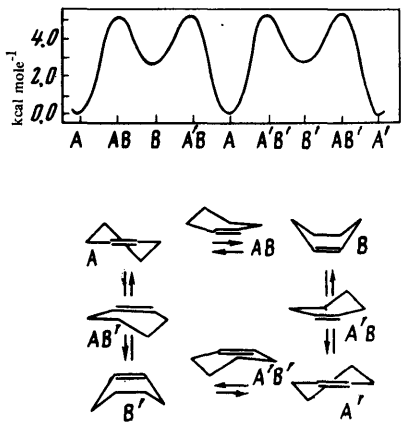


Figure 5. Intermediate forms and the energy barrier in the ring inversion of cyclohexene[60].

As for cyclohexane, one conformer of cyclohexene may be converted into another. Until recently, the rate of conversion and the potential barrier separating the conformers were unknown. It might have been supposed that, in view of the characteristics of the structure of cyclohexene, the half-chair–half-chair conversion would be much faster than the chair–chair conversion. Recently Anet and Hag[60] showed that the rate of inversion of cyclohexene approaches the upper limit accessible to NMR methods. At room temperature the NMR spectrum of cyclohexene shows the signal due to the olefin protons (5.59δ) and the complex multiplets of the allylic (1.96δ) and homoallylic (1.65δ) protons[116]. Anet and Hag[60] investigated *cis*-3,3,4,5,6,6-hexadeuterocyclohexene. At −150°C the band due to the homoallylic protons is significantly split and becomes a doublet at −164°C. Since at −170°C δ_{a-e} does not yet reach a constant value, it may be supposed that δ_{a-e} for cyclohexene is actually 24 Hz§.[60] The rate constant determined from the coalescence temperature of the signals is $k = 53\ s^{-1}$, whence the free energy of activation $\Delta F^{\neq} = 5.3$ kcal mole^{-1}. Thus in cyclohexene the height of the barrier in the ring inversion process is smaller by a factor of approximately two than in cyclohexane. Since the energy of the boat form is higher than that of the half-chair form[107], it may be supposed that the boat form is intermediate in the inversion process. The possible pathways in the inversion process and the corresponding forms of the barrier proposed by Anet and Hag[60] are presented in Fig. 5. The authors adopted a structure with five carbon atoms in one plane (AB, AB′, A′B′) as the transition state, since the distortion of the valence angles and the interaction between methylene groups would be too high for the completely planar form. The enthalpy and entropy of activation for the inversion process cannot be determined directly from the NMR spectroscopic data[60]. The values quoted in Table 1 were obtained by taking into account the symmetry of the possible transition states and the statistical factors. The average lifetime of the cyclohexene molecule before inversion at 25°C may be calculated from $\Delta H^{\neq}$ and $\Delta S^{\neq}$. It proved to be about 10^{-9} s, i.e. smaller by five powers of ten than the lifetime of the cyclohexane molecule (4×10^{-4}).

Apart from unsubstituted cyclohexene, the inversion of 4-bromocyclohexene was also investigated[61]. At −159°C Jensen and Buchweller[61] observed a complete separation of the signals due to the tertiary proton corresponding to the axial and equatorial orientations with $\delta_{a-e} = 27.3$ Hz. The rate constant ($k = 47.7$ s at −124°C) and the height of the barrier ($\Delta F^{\neq} = 5.93 \pm 0.1$ kcal mole^{-1}) obtained by these investigators are very close to the corresponding values for unsubstituted cyclohexene. Jensen and Buchweller also determined the conformational energy of bromine in the cyclohexene ring (about 0.1 kcal mole^{-1}), which proved to be smaller almost by a factor of four than the energy of the substituent in cyclohexane. This result is in qualitative agreement with Sakashita's data obtained

§ The assignment of the signal in the weak field to an equatorial proton and that in the strong field to an axial proton was made by analogy with cyclohexane. It has been confirmed by the study of the ring inversion of 4-bromocyclohexene[61].

from vibrational spectra[117]. In practice, however, the values determined both from the vibrational spectra and NMR spectra are smaller than the experimental errors and therefore one may suppose that in 4-bromocyclohexene the axial form has no advantage over the equatorial form on energy grounds. However, the axial form of 3-halogenocyclohexenes is probably more favourable[118].

In a number of studies attempts were made to determine the preferred conformations of cyclohexene derivatives from the widths of the NMR signals[119-121]. Some information about the geometrical structure of the cyclohexene ring can be derived also from the vicinal coupling constants. The values of J_{HH} were determined for three cyclohexene derivatives[122-124]. The dihedral angles for the half-chair forms of conduritols[124] were calculated from the Karplus equation and compared with the values determined from Barton's models[123,125] and calculated by Corey and Sneen[108]. All three methods give similar valence angles, but these are only approximate.

The long-range coupling constants for allylic ($J_{He'}$ = −0.5 Hz, $J_{Ha'}$ = −2.1 Hz) and homoallylic (J = 1−3 Hz) protons have been determined[122-124] and interaction via four saturated bonds (about 0.5−2 Hz) has been observed.

3. Cyclobutane

In the crystalline phase certain cyclobutane derivatives (tetraphenylcyclobutane[126] and *trans*-1,3-cyclobutanedicarboxylic acid[127]) have a planar ring structure but, according to electron diffraction, cyclobutane itself is non-planar[128]. NMR spectroscopic studies have shown[129] that the cyclobutane molecule undergoes interconversion between two equivalent forms (Fig. 6), in which the orientation of the substituent may be referred to as axial or equatorial by analogy with the nomenclature for six-membered rings; the structure with a pseudoaxial substituent is more planar. According to the estimates of Meiboom and Snyder[129], the dihedral angle θ is 18°.

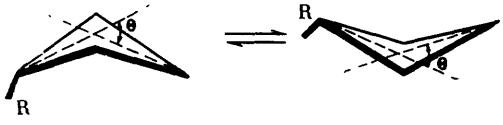


Figure 6. Ring inversion in cyclobutane.

The barrier in the ring inversion of cyclobutane is probably low, but has not been estimated experimentally at present¶. However, the chemical shift and the coupling constants of the signals due to geminal fluorine-19 nuclei[130] in the NMR spectra of certain fluorinated cyclobutane derivatives, used to calculate the free energy differences between the two conformers, were found to vary with temperature. For R = C_6H_5, this difference is about 1 kcal mole^{-1}, which is consistent, as regards order of magnitude, with the value calculated by Allinger et al.[102] Allinger's calculations also showed that the buckled form is more favourable than the planar form to the extent of about 1 kcal mole^{-1} and yields the angle θ = 20°.

The NMR spectra of 3-isopropylcyclobutanols and 3-isopropylcyclobutylamines[131] are also consistent with the non-planar structure of the cyclobutane ring.

4. Cycloheptane

The cycloheptane molecule does not have a highly symmetrical form analogous to the chair form of cyclohexane. The four conformations of cycloheptane with the minimum energy, the geometry of which was calculated by Hendrickson[104], are shown in Fig. 7. The most stable is the twist-chair form. As in the boat form of cyclohexane, which can be converted into a series of twist-boat forms by pseudorotation, in cycloheptanes pseudorotation can take place for the chair−twist-chair and boat−twist-boat conformations. The boat and chair conformations can be interconverted by symmetrical inversion. The barrier to pseudorotation is represented by a simple sinusoidal curve, the symmetrical forms corresponding to its maxima and minima. The energy differences in pseudorotation are small and cannot be estimated from the NMR spectra.

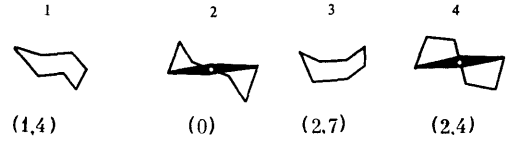


Figure 7. Stable conformations of cycloheptane: 1) chair; 2) twist-chair; 3) boat; 4) twist-boat; the relative energies are indicated in brackets[104].

The ring inversions in a number of substituted cycloheptanes were investigated by Roberts using the resonance of the fluorine-19 nuclei[62]. The fact that the spectra of 1,1-difluorocycloheptane and 1,1,3,3-tetrafluorocycloheptane do not show a temperature variation up to −180°C agrees best with the existence of cycloheptane in the twist-chair form, which undergoes rapid pseudorotation. At the same time the spectrum of 1,1-difluoro-4,4-dimethylcycloheptane does alter significantly as the temperature is reduced. On the basis of these changes, one may conclude that fluorine atoms are present in positions resembling equatorial and axial positions. The barrier to the interconversion of the two forms (or two sets of equivalent forms) is low and amounts to 6 kcal mole^{-1} according to preliminary estimates[62].

5. Cyclo-octane

The ring inversion of cyclo-octane was investigated by Meiboom[47], Harris and Sheppard[46], and Anet and coworkers[68,133]. On lowering the temperature, the proton signal in the $C_8D_{15}H$ spectrum broadens and at −111°C two

¶ In oxetan, where as a result of the replacement of a methylene group by a heteroatom in the four-membered ring several 1,2- and 1,3-interactions are eliminated, the barrier in the ring inversion process is only 35 cm^{-1} according to the estimate of Chan et al.[132]

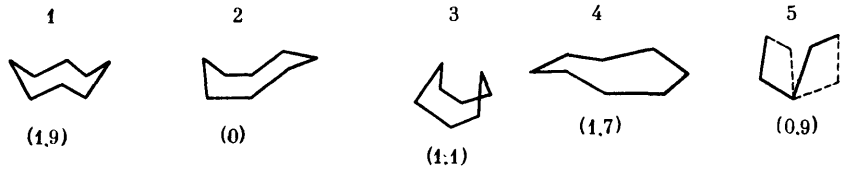


Figure 8. Cyclo-octane conformations with minimum energies: 1) chair–chair; 2) boat–chair; 3) boat–boat; 4) twist-chair–chair; 5) S_4; the relative energies are indicated in brackets[104].

sharp lines separated by about 19 Hz are observed[133]. The activation parameters for the inversion process were calculated from the temperature variation of the band outline (Table 1, Nos. 41 and 42). However, it is impossible to arrive at unambiguous conclusions concerning the nature of the conformations undergoing interconversion. From the conformational standpoint, cyclo-octane is probably the most complex cyclic molecule. Theoretical analysis shows[100,104] that there exist a large number of conformations of cyclo-octane with approximately the same energy. The boat-chair form (C_S symmetry) is probably the most favourable on energy grounds[100,104]. However, the energies of five other symmetrical forms are in the range of 2 kcal mole^{-1}: chair–chair (extended crown), boat–boat (saddle, symmetry D_{2d}), twist-chair–chair (D_2), twist-chair–boat, and the form with symmetry S_4 (Fig. 8). The regular crown form of cyclo-octane, in contrast to the "crown" of cyclohexane (chair), does not correspond to an energy minimum; according to Hendrickson's calculations[104], its energy is higher by 2.8 kcal mole^{-1} than the energy of the boat–chair form. The transitions between the cyclo-octane conformations can take place, apart from the interconversion of symmetrical forms, via a pseudorotation, the barriers to which are not high. Thus the signals in the NMR spectrum at a low temperature may correspond to a whole set of conformations, provided that pseudorotation is sufficiently rapid. By studying the temperature variation of the NMR spectra of three deutero-derivatives of cyclo-octane ($C_8D_{14}H_2$) and alkyl-substituted cyclo-octanes, Anet and St. Jacques[133] concluded that they agree best with the boat–chair form. X-Ray diffraction studies showed that many cyclo-octane derivatives have the same conformation[134]. However, in order to interpret the NMR spectra of fluorinated cyclo-octanes, Roberts[62] chose the S_4 form (twist-boat). Since the energy of the S_4 form differs only by 1 kcal mole^{-1} from that of the boat–chair form[104], the replacement of a hydrogen atom by a fluorine atom can shift the conformational equilibrium towards the S_4 form.

The cyclo-octane conformations were examined theoretically also by Bixon and Lifson[103] and Allinger et al.[102] In all these studies the energy minimum was obtained for the boat–chair form.

Recently ring inversion in eight-membered unsaturated systems was investigated by NMR spectroscopy: cyclo-octatetraene[64,66], fluorocyclo-octatetraene[65], cyclo-octatrienone[68], and substituted cyclo-octatriene[67].

In cyclo-octatetraene derivatives[64-66] bond displacement may occur as well as the interconversion of two boat forms (*t* and *b*, symmetry D_{2d}) (Fig. 9). The transition state for both processes is probably a planar form. Calculation of the barrier to the inversion of cyclo-octraene, taking into account the σ-strain of the system[69], yielded results in good agreement with experiment.

6. Decalin

An interesting example of complex systems undergoing ring inversion is provided by *cis*-decalin derivatives. While the NMR spectrum of *trans*-decalin, which has a fixed conformation, consists of a complex multiplet, in the *cis*-decalin spectrum there is a comparatively narrow singlet even at −120°C.[135,136] On this basis, it was initially suggested that the barrier to the ring inversion of *cis*-decalin is low, not exceeding 6 kcal mole^{-1}; however, recently it was suggested[137] that the low width of the signal may be due not to rapid ring inversion but to the similarity of the chemical shifts of the axial and equatorial protons.

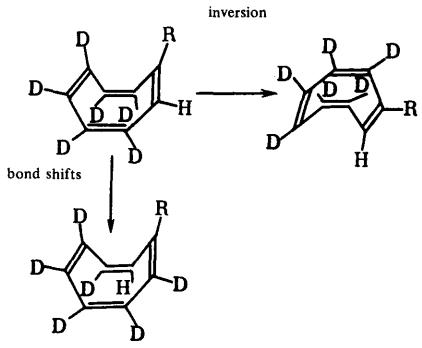


Figure 9. Ring inversion and bond shifts in cyclo-octatetraene[66].

The ring inversion of *cis*-decalin derivatives was investigated by Roberts[62,70] using fluorine-19 resonance. In the spectrum of 2,2-difluoro-*cis*-decalin two AB quartets, corresponding to the axial and equatorial positions of fluorine atoms, appear in place of the average signal when the temperature is reduced. The activation energy for the ring inversion proved to be somewhat higher than for cyclohexane (Table 1, No. 50). Since the bulk of the fluorine atoms is small, it may be supposed that in unsubstituted *cis*-decalin the inversion barrier is approximately the same. The introduction of a methyl group in the 9- or 10-position of 2,2-difluoro-*cis*-decalin results in a lowering of the barrier. This is apparently due to the fact that for both forms undergoing interconversion there is a *syn*-axial interaction of the methyl group with the fluorine atom.

The NMR spectra of 1-methyl-, 3-methyl-, 6-methyl-, and 6,9-dimethyl-*cis*-decalin do not show a temperature

variation, in agreement with the existence of a single energetically favourable conformation.

Theoretical calculations have been made for the conformations of decalin [101,102] and show that, in contrast to the earlier hypothesis [138], the double chair conformation is the most favourable for both *cis*-decalin and *trans*-decalin.

7. Heterocycles

Compared with hydrocarbons, in heterocyclic systems there are a number of additional factors which may influence the ring-inversion parameters. Apart from different bond lengths and valence angles, as a result of which the ring geometry and the intensities of interactions between atoms not linked by valence bonds are different from those in the hydrocarbon analogues, electronic effects due to the presence of unshared electron pairs, vacant *d* orbitals, and conjugation may play a major role in heterocycles.

Although the amount of data obtained up to the present time on the ring inversion of heterocyclic compounds is small, it is evident that they cannot be interpreted by simple analogy with the hydrocarbons. In some cases the corresponding parameters are in fact similar but the agreement may be the result of the opposed effects of several factors.

The barriers for pyran (10.7 kcal mole^{-1}) and thiopyran (11.6 kcal mole^{-1}) [71] are close to the corresponding value for cyclohexane, but in piperidine the barrier is probably higher [71,72]. On the other hand, about 6 kcal mole^{-1} was obtained for perfluoropiperidine [73]. The barrier in *NN*-dimethylpiperazine, the geometry of which is close to that of the cyclohexane ring [79] according to electron diffraction data [105], is almost the same as in cyclohexane. The barriers in hexahydro-1,3,5-triazines [85], the skeleton of which consists exclusively of C–N bonds, are also close to this value. However, the data obtained for triazines and the mechanisms proposed for ring inversion differ somewhat [85,86]. A decrease of the barrier with increasing dimensions of the substituent of the nitrogen was also noted for 1,3,5-triazines [85]; this can probably be accounted for by a tendency of the pyramidal nitrogen atom to assume a more planar structure with increase of the size of the substituent.

The orientation of unshared electron pairs plays a major role in ring inversion processes in heterocyclic systems incorporating nitrogen, oxygen, and sulphur. For alkyl-substituted piperidines, it has been established with the aid of NMR spectra [72,139] and dipole moment studies [140] that the alkyl group is equatorial. However, there exist at present two opposed views concerning the orientation of the unshared pair in piperidine itself. According to the first view, the dimensions of the unshared pair exceed those of the hydrogen atom [72,139] and accordingly piperidine must be predominantly in the conformation with an axial hydrogen atom; according to the second view, the unshared pair is smaller [141,142]. The recent calculation by Allinger and coworkers [143] for piperidine conformations showed that hydrogen in the axial orientation has a small advantage on energy grounds (0.6 kcal mole^{-1}). Since the difference between the energies is small, evidently in real systems the presence of substituents or small deformations of the ring can displace the equilibrium in the opposite direction.

The available data on the ring inversion of substituted 1,3-dioxanes [77], containing two heteroatoms, show that the decisive factor in these compounds is probably the interaction of atoms not linked by valence bonds. The barrier in unsubstituted 1,3-dioxane is almost identical with that in cyclohexane [77]. As a result of intensive 1,3-*syn*-axial interactions, the energy of the ground state of 2,2-dimethyl-1,3-dioxane is increased, which leads to a decrease of the barrier†. At the same time in 5,5-dimethyl-1,3-dioxane, where such interactions do not occur, the barrier is 10.5 kcal mole^{-1} (Table 1, No. 74). It should also be noted that the conformational energies of the 5-alkyl substituents in 1,3-dioxanes are very much lower than the corresponding values for cyclohexane [145].

Among six-membered rings containing a large number of heteroatoms, acetone diperoxide [55,82], and tetramethyl-*s*-tetrathiane [81] were investigated. The barriers in these compounds are significantly higher than in tetramethylcyclohexane. Here non-valence interactions probably do not play a dominant role and other factors are more important; in particular, ring inversion can involve other intermediate forms than in cyclohexane. It has been suggested that the twist-boat form and not the chair form is the most stable for tetramethyl-*s*-tetrathiane [81,146]. The high barrier in this compound made it possible to isolate a stable conformer at −80°C, [146] as had been done for chlorocyclohexane [147].

The ring inversion of tetramethyl derivatives of 1,2-dithiane and 1,2-dioxane [75] has also been investigated. The difference between the barriers in these compounds has been explained by the absence of intermediate forms in ring inversion; the existence of a symmetrical boat form of tetramethyldioxane is impossible because of the interaction between the methyl groups; at the same time in tetramethyldithiane this form can be realised owing to the greater length of the C–S bonds.

The barriers to the inversion of tetra- and hexa-hydropyridazines are much higher [83] than in the corresponding hydrocarbons. While the barriers in cyclohexane and cyclohexane differ sharply, those in the above compounds are similar (Table 1, Nos. 90–95).

In heterocyclic systems containing nitrogen there is a possibility of yet another conformational transition–inversion at the nitrogen atom. In six-membered rings (piperazines [79] and triazines [85,86]) the rate of this process is still too high to investigate by NMR methods; however, in aziridine (ethyleneimine) derivatives, where the nitrogen atom is incorporated in a strained three-membered ring, the inversion is slower. A number of substituted aziridines have now been investigated [87-90,148-151] and attempts have been made to estimate the role of the various factors influencing the heights of the barriers in these compounds. Thus bulky substituents at the nitrogen atom apparently increase the rate of inversion [148], since they increase the steric strains in the ground state; these strains are removed in the transition state, which has a planar structure. The conjugation effect, which leads to a "flattening" of the pyramidal structure of the nitrogen atom, acts in the same direction: the rates of ring inversion in acetylaziridines [89] are much higher than in alkylaziridines. An "extreme" example in this case is formamide, which has

† Since the C–O bond is much shorter (1.43 Å) than the C–C bond (1.53 Å), the conformational energy of 2-alkyl substituents in 1,3-dioxane reaches 3 kcal mole^{-1} [99] (compared with 1.6 kcal mole^{-1} in cyclohexane). Eliel and Knoeler [144] showed that in the *trans*–*cis* isomerisation of 2-alkyl-5-t-butyl-1,3-dioxane the t-butyl group passes to the axial position. This is apparently the first example of the axial orientation of the t-butyl group in a six-membered ring. In the analogous situation cyclohexane goes over to the boat form [95].

an almost planar structure: here the barrier to the nitrogen inversion is only 1 kcal mole^{-1}.[152] Solvents have a considerable influence on the barriers to ring inversion in aziridines: in hydroxylated solvents the rate of inversion is significantly lower[87,148]. Probably in this case the solvent forms a weak bond of the hydrogen type with the unshared electron pair of the nitrogen atom.

Simultaneous inversion at the nitrogen atoms has also been observed in a series of diazabicycloheptanes and diazabicyclo-octanes[94].

IV. CONFORMATIONAL ENERGIES OF SUBSTITUENTS

It is by no means possible to obtain the absolute values of the thermodynamic parameters of ring inversion in all cyclic systems. However, it is possible to determine by a relatively simple procedure quantities which are sometimes of no less interest. These are the so called conformational energies of substituents, i.e. the differences between the free energies of the conformers with R in the axial and equatorial positions. The equilibrium constant K for this process is defined by the expression:

$$K = N_a/N_e\,, \qquad (20)$$

where N_a and N_e are the mole fractions of the axial and equatorial forms in the equilibrium mixture. The values of K may be determined with the aid of kinetic methods, for example, from the different reactivities of substituted cyclohexanes as a function of the orientation of the substituent. This approach has been developed independently and successfully employed for the determination of conformational energies by Eliel and coworkers[153] and Winstein[154]. Subsequently a number of physical methods were developed for the determination of the content of the conformers in the mixture, among which those based on vibrational and NMR spectra became most widely used. At present the conformational energies of a large number of substituted cyclohexanes have been determined. In this section the scope of the determination of conformational energies of substituents by NMR methods will be briefly discussed. Attention will be concentrated on a comparative estimate of the accuracy of the methods. The effects of various factors on the conformational energies have been discussed in reviews[155,156].

N_a and N_e may be determined most directly by measuring the areas of the signals corresponding to the two conformers in the low-temperature NMR spectra where these signals are completely or partly separated. The conformational energies of chloro- and bromocyclohexane[49,157], iodocyclohexane[157], and fluorocyclohexane[48,157] were determined in this way. In all these studies measurements were made of the intensities of signals due to the tertiary proton, which can be identified without error. However, in principle, one can employ for this purpose other signals, for example those of the hydroxyl and methyl protons[76,158,159].

However, this method for the measurement of conformational energies is not always feasible owing to experimental difficulties. Moreover, in this case one obtains the free energies for temperatures between −60° and −100°C. The use of these values at other temperatures is not always justified, since ΔG may vary with temperature.

In order to determine K from NMR spectra, it is possible to use parameters which differ for conformers with axial and equatorial orientations of the substituents and which become averaged out in the inversion process: chemical shifts, coupling constants, and signal widths. If the corresponding parameters are known for fixed conformations, it is possible to determine the relative concentrations of both forms in the equilibrium mixture and hence the equilibrium constant by Eqn. (20).

1. Determination of Conformational Energy from the Chemical Shift

If ring inversion takes place in a substituted cyclohexane, a chemical shift of the signal (usually of the tertiary proton) is observed in the NMR spectrum:

$$\delta = N_e\delta_e + N_a\delta_a\,, \qquad (21)$$

where δ_a and δ_e are the chemical shifts of the axial and equatorial forms, and N_a and N_e are their mole fractions. The method was proposed by Elial who used it to investigate the equilibrium in bromocyclohexane[160]. The shifts δ_a and δ_e may be determined from the low-temperature NMR spectra with "frozen" inversion. The compositions of the equilibrium mixtures of a number of halogeno-substituted cyclohexanes[49,50,52] and cyclohexyl ethers[161] were determined by this procedure. For substituents with high electronegativities, the difference δ_{a-e} between the chemical shifts of the signals due to the tertiary proton may become considerable (0.7−0.8 p.p.m.).[50]

However, methods in which model compounds with known conformations are used have become most widespread. Usually *cis*- and *trans*-4-t-butyl derivatives of cyclohexane are used as the "fixed" forms. Since the t-butyl group in the cyclohexane rings always occupies an equatorial position[154,162], the *cis*-isomer yields in this case δ_a and the *trans*-isomer δ_e‡. In some studies other 4-alkyl derivatives of cyclohexane[163] or 3-alkyl derivatives[164] were employed as model compounds. The method has been used to determine the conformational energy of the amino-group[163,164] and the nitro-group[165] and also in the investigation of the conformational equilibria in a number of other cyclohexane[166], cyclohexanol[167], and cyclohexanone[168] derivatives. The dependence of the conformational energy on the presence of hydrogen bonds has been established by this method for the amino-group: the relative constants of the conformers differ significantly in neutral, protonated, and proton-donating solvents (Table 2). In most studies the chemical shift of the tertiary proton was determined; however, the chemical shifts of the hydroxyl proton, for which the difference between the axial and equatorial positions amounts to about 30 Hz, were also employed for this purpose.

Evidently fixed models may be used only when the alkyl groups do not have a significant influence on the chemical shifts of the tertiary proton, do not distort the cyclohexane ring, and merely stabilise the conformation. The effect of the diamagnetic anisotropy of alkyl substituents in cyclohexane was studied in a number of investigations[175,180-184]. It has been shown experimentally that the effect of a 4-alkyl substituent is small[175]. However, an axial alkyl group in the 3-position displaces significantly the signal of an axial H_1 proton[175,183,184] and therefore the conformational energies obtained with 3-alkyl substituted model compounds are

‡ δ_a refers to the conformer in which the substituent occupies an axial position. This applies also to the coupling constant and signal widths discussed below. Since the chemical shifts of tertiary protons are usually investigated, this nomenclature is not altogether convenient.

probably unreliable. This has been demonstrated experimentally by Eliel and Martin[169] for halogeno-substituted cyclohexanes. Recently Jensen and Beck[171] compared the low-temperature NMR spectra of a number of cyclohexane derivatives with those of model compounds having a 4-t-butyl group. In all the compounds, the chemical shifts of the axial and equatorial α-protons differed at low temperatures from the chemical shifts of the corresponding 4-t-butyl derivatives. In all cases the conformational energies determined by Eliel's method proved to be lower than the result obtained by measuring the areas and by "freezing" the ring inversion with subsequent determination of δ_a and δ_e. Thus the fixed model method probably yields only semiquantitative results.

In addition the chemical shift method involves also a number of factors which may lead to significant errors in the determination of the conformational equilibrium position. Since the tertiary proton signal constitutes the X part of the ABX or A_2B_2X system and is greatly complicated as a result of spin–spin coupling, the chemical shifts cannot be determined with adequate precision. To eliminate this difficulty, the protons in the relevant positions are usually replaced by deuterium[154,173,185]. The accuracy of the determination of the equilibrium constant diminishes if the difference δ_{a-e} between the chemical shifts due to the fixed conformers is small (as in nitrocyclohexane[177,186]) or if the conformational equilibrium is strongly displaced towards one of the forms, in particular when $\delta - \delta_e$ is small[163,166]. The chemical shifts δ_a and δ_e have an "intrinsic" temperature variation and therefore in the extrapolation of the results obtained at low temperatures to other conditions it is necessary to apply corrections[171].

Table 2. Conformational energies of monosubstituted cyclohexanes obtained by NMR methods.

Substituent	−ΔG	t, °C	Solvent	Method	Refs.
1	2	3	4	5	6
F	0.24	−56	$CFCl_3$	*a*	48
	0.15	25	$CFCl_3$	*b*	48
	0.25	−93	CS_2	*a*	157
	0.24	room	CS_2	*b*	157
	0.15	25	+	*c*	169
Cl	0.44	25	+	*c*	169
	0.51	−81	CS_2	*a*	157
	0.49	25	CS_2	*b*	157
	0.41	−93	CS_2	*a*	49
	0.38	36	CCl_4	*c*	170
	0.43	36	*o*-dichlorobenzene	*c*	170
	0.49	−83	CS_2	*a*	171
	0.55		CS_2	*b*	171
Br	0.37	25	+	*c*	169
	0.53	−83	CS_2	*a*	171
	0.57		CS_2	*b*	171
	0.51	−81	CS_2	*a*	49
	0.48	−81	CS_2	*a*	157
	0.44	room	CS_2	*b*	157
	0.2	25	CCl_4	*c*	166
	0.24	25	liquid	*c*	162
	0.7	20	CCl_4	*d*	172
	0.37	35	CCl_4	*c*	170
	0.42	36	*o*-dichlorobenzene	*c*	170
I	0.43	−81	CS_2	*a*	157
	0.41	20	CS_2	*b*	157

Table 2 (contd.).

Substituent	−ΔG	t, °C	Solvent	Method	Refs.
1	2	3	4	5	6
OH	0.6	20	CCl_4	*c*	166
	0.73	30	CCl_4	*c*	167
	0.75	40		*c*	159
	0.43	20	CCl_4	*d*	172
	1.0	28	CCl_4	*d*	173
	0.82	36	CCl_4	*c*	174
	1.05	36	t-BuOH	*c*	174
	0.88	30	2D2PrOH	*c*	161
	1.07	20	CCl_4	*c*	175
OCH_3	0.6	20	CCl_4	*c*	166
OCD_3	0.56	−96	CD_2CDCl	*a*	147
OCHO	0.27	25	CS_2	*b*	161
$OCOCF_3$	0.68	25	CS_2	*b*	161
	0.54	−84	CS_2	*a*	171
	0.55		CS_2	*b*	171
$OCOCH_3$	0.68	25	CS_2	*b*	161
	0.66	28	CS_2	*e*	173
	0.7	25	CCl_4	*c*	166
	0.72	−83	CS_2	*a*	171
	0.64		CS_2	*b*	171
OT_s	0.6	25	CCl_4	*c*	166
ONO_2	0.59	25	CS_2	*b*	161
SH	0.9	25	CCl_4	*c*	174
SCH_3	0.7	25	CCl_4	*c*	174
SC_6H_5	0.8	25	CCl_4	*c*	166
NH_2	1.26	20	C_6H_6	*d*	172
	110	20	C_6H_6	*d*	172
	1.30	20	$CHCl_3$	*f*, *c*	164
	1.15	20	CCl_4, C_6H_{12}, CH_3CN	*c*	163
	1.45	20	$CDCl_3$, EtOH, t-BuOH	*c*	163
NH^+_3	1.7	20	CF_3COOH, HOAc	*c*	163
$NHCH_3$	1.1–0.9	25	$CHCl_3$	*c*	164
NO_2	0.78	37	liquid, $CDCl_3$	*d*	188
	1.02	25	$CDCl_3$	*f*	165
	1.3	25	$CDCl_3$	*f*	177
	1.1	25	$CDCl_3$	*d*	177
CH_3	1.78**	30	$CDCl_3$	*b*	178
	1.68	30	CCl_4	*c*	167
	1.70	32	CCl_4	*c*	170
C_2H_5	1.68	30	CCl_4	*c*	167
$CH(CH_3)_2$	2.22	30	CCl_4	*c*	167
	2.20	25	$CHCl_3$	*c*, *f*	164
C_6H_{11}	2.15	32	CCl_4	*c*	170
C_6H_5	3.0	25	$CDCl_3$	*f*	179
$CO_2C_2H_5$	1.1	25	CCl_4	*c*	166
C≡CH	0.18	41	CCl_4	*c*	158

Remarks: *a*) from measurements of signal areas at a low temperature; *b*) from chemical shifts (δ_a and δ_e obtained at a low temperature); *c*) from chemical shifts (δ_a and δ_e obtained from the spectra of *t*-butyl derivatives); *d*) from coupling constants (J_{HH} obtained from spectra of model compounds); *e*) from coupling constants (J_{HH} determined at a low temperature; *f*) from band width; +—value averaged for a number of solvents; **determined from the spectra of diazirines.

2. Determination of Conformational Energies from Spin–Spin Coupling Constants

The method is based on the difference between the vicinal coupling constant J_{HH} as a function of the axial or equatorial positions of the protons relative to the cyclohexane ring. Numerous experimental data show that J_{aa} varies in the range from 9 to 12.5 Hz and J_{ae} from 3.5 to 6 Hz.[187] The number of available measurements of J_{ee} is smaller; it probably does not exceed 2–3 Hz. The

approach to the determination of equilibrium constants based on J_{HH} values was developed for ethane derivatives[6] and was then employed in studies on ring inversion in substituted cyclohexanes[172,173]. If the equilibrium mixture contains x moles of one conformer and $1 - x$ of another, then, as a result of inversion, averaged constants will be obtained:

$$J_{12}^{av} = J_{14}^{av} = xJ_{ae} + (1-x)J_{ea} \simeq J_{ae}\,, \qquad J_{13}^{av} = J_{15}^{av} = xJ_{aa} + (1-x)J_{ee} \simeq J^*\,. \tag{22}$$

Thus, when the first-order condition $\delta_{12} \gg J_{12}$ holds, (which is usually the case for electronegative substituents), the α-proton signal will be a 1 : 2 : 1 triplet with spacings J^*; each component of the triplet will in turn be another triplet with spacings J_{ae}. In practice, however, the signal is rarely fully resolved. In some cases, as a result of the superposition of individual components, a symmetrical quintet[177] or septet is observed, as happens for nitrocyclohexane[176,188]. Usually the signal has an unresolved contour. Nevertheless in many cases it is possible to determine averaged constants either directly or from measurements of signal widths at a specified height[172]. J_{aa}, J_{ae}, and J_{ee} are frequently obtained from the spectra of *cis*- and *trans*-4-t-butylcyclohexyl-R.[173,188]

The method for the determination of the equilibrium positions from the averaged coupling constants becomes extremely approximate for small values of x ($x < 1/5$). Moreover it has a number of additional limitations. In particular, it has been shown that in cyclic systems $J_{ae} \neq J_{ea}$.[189-191] In the analysis of the spectra of the compounds investigated no account was taken also of long-range interaction constants which may reach 2 Hz for equatorial H_1 and H_3 protons[192].

3. Determination of Equilibrium Constants from Signal Widths

When the tertiary proton multiplet is unresolved, the conformational energies may be determined from the signal width. This parameter has been used in the very early studies to determine the configurations and fixed conformations of cyclohexane derivatives[193].

The equilibrium constant for a mixture of conformers is

$$K = \frac{w_a - w}{w_e - w}\,, \tag{23}$$

where w is the observed signal width, w_e the signal width for the conformer with a fixed equatorial position of the substituent, and w_a the signal width for a fixed axial position of the substituent. As in methods (a) and (b), the signal widths for *trans*- and *cis*-4-t-butylcyclohexyl-R are frequently adopted as w_a and w_e. This method is the most approximate, but in a number of cases it yields conformational energies in satisfactory agreement with the values obtained by other methods[165,177,194-197].

Table 2 lists the conformational energies of substituents in the cyclohexane ring and it is indicated which of the methods discussed above was used to obtain the value. The methods discussed can be arranged in the following sequence in terms of decreasing accuracy: chemical shifts > coupling constants > widths. However, frequently even approximate measurements of band widths yield satisfactory conformational energies and under favourable conditions the determination of K from NMR spectra is not inferior in accuracy to the most precise kinetic and thermodynamic methods.

V. APPLICATION OF FLUORINE-19 RESONANCE

In recent years ^{19}F NMR spectra have been used to investigate the mobile and fixed conformations of cyclic systems[62,198]. Perfluorocyclohexane[57], fluorocyclohexane[48], *gem*-difluorocyclohexane[22,62], substituted *gem*-difluorodecalins[70], cyclobutane derivatives[130], and large-ring systems have been investigated by this method[62,65].

The use of the chemical shifts of fluorine has a number of advantages, since they are more sensitive to the molecular environment and exceed by a factor of several tens the proton chemical shifts. In fluorine-substituted cyclohexanes the difference δ_{a-e} between the signals of the axial and equatorial fluorine atoms is 20 p.p.m., i.e. it exceeds by a factor of almost 50 the corresponding value for protons. The spin–spin coupling constants J_{FF} are of the order of 250–280 Hz and the constants J_{FaHa}§ also exceed the J_{aa} values for protons. The high values of δ_{a-c} permit the investigation of ring inversion in fluoro-substituted cyclic compounds over a wide range of temperatures by high-resolution NMR methods. Moreover, fluoro-substituted cyclohexanes are very convenient for the investigation of ring inversion by spin-echo methods for two reasons: (1) at the resonance frequencies employed in the spin-echo experiments $2\pi J_{FF} \lesssim \delta\omega$ and therefore it is possible to make measurements over a wide range of exchange rates; (2) the vicinal coupling constant J_{HF} is almost independent of the rate of exchange at very high and very low rates and does not affect the echo-signal amplitude, so that it can be disregarded in the determination of the rate[31].

The rates of inversion of fluorinated cyclohexane derivatives were determined by both high-resolution NMR methods[22,48,54] and by the spin-echo method[31,58]. The temperature variation of the chemical shift of fluorine was used to estimate the percentage contents of the conformers of 2,2-difluoro-*cis*-decalin[70] and alkyl derivatives of 1,1-difluorocyclohexane[54,62]. It has been shown[48] that the equatorial position is preferred for the fluorine atom to a much lesser extent than for chlorine and bromine atoms. The conformational energy of fluorine determined from the signal areas and from chemical shifts was found to be 0.153 and 0.242 kcal mole^{-1} respectively, in good agreement with the data derived by other methods[202,203].

For a correlation between the parameters of the fluorine-19 spectra and the structure of substituted cycloalkanes, further accumulation of experimental data is necessary. However, it is already evident that this method may be effective in studies on the conformations of cyclic compounds.

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After the manuscript had been sent to the editorial board, a large number of new data on the ring inversion of cyclic compounds were published. Those which are of greatest interest may now be indicated briefly.

With reference to p. 517: Allinger and coworkers calculated theoretically the conformations and energies of a large number of cycloalkanes and cyclic ketones[204]. The predicted barrier to ring inversion in cyclohexanone is 4.8 kcal mole^{-1}, which agrees well with recent experimental data by Gerig[205] and Jensen and Beck[206], who showed that

§ The vicinal coupling constants J_{FH} obtained in a number of investigations[130,199-201] show that the same relation applies to them as in the case of J_{HH}: J_{aa} is the maximum, J_{ee} is a minimum, and J_{ae} is intermediate.

the replacement in the cyclohexanone ring of one sp^3-hybridised atom by an sp^2-hybridised atom leads to an appreciable decrease of the barrier. A similar result was obtained for *cis*-decalones[207].

With reference to p. 519: Roberts and coworkers[208] investigated by the resonance of fluorine-19 nuclei the ring inversion in a number of cyclo-octane derivatives. They succeeded in detecting both types of conformational transitions: ring inversion and pseudorotation. For the majority of the compounds investigated, the boat-chair form is the most stable at low temperatures. Its stability has been confirmed recently by X-ray diffraction studies on *trans*-1,2-dichlorocyclo-octane[209]. It is interesting to note that the dihedral angles obtained in this investigation are in excellent agreement with the values predicted by Hendrickson[104].

The bond shift in cyclo-octatetraene was investigated by Anet and Bock[210]; Lack and Roberts[211] determined the barriers for *cis*-hydrindane derivatives.

With reference to p. 521: The conformational transitions in heterocyclic compounds were investigated: in difluoropiperidine[212], 1,3-dithiane derivatives[213], six-membered rings with silicon atoms[214,215], bicyclic diazo-compounds[216,217], and aziridines[218] and at tervalent oxygen[219] and arsenic[220] atoms. Jensen and Bushweller[221] continued their studies on the isolation of "pure" conformers of cyclohexane derivatives.

With reference to p. 524: Recently Jensen, Bushweller, and Beck determined the conformational energies of 22 functional groups in the cyclohexane ring; probably these are the most reliable data obtained hitherto. The conformational energies of ester groups[223] and amino-groups[224] have also been investigated.

REFERENCES

1. D. H. R. Barton, Experientia, 6, 316 (1950).
2. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis" (Translated into Russian), Izd. Mir., Moscow, 1969.
3. M. Hanack, "Conformational Theory", Academic Press, New York, 1965.
4. N. S. Bhacca and D. H. Williams, "Applications of Nuclear Magnetic Resonance in Organic Chemistry" (Translated into Russian), Inostr. Lit., Moscow, 1966.
5. J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy" (Translated into Russian), Izd. Mir, Moscow, 1968.
6. J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance" (Translated into Russian), Inostr. Lit., Moscow, 1962 [McGraw–Hill, New York, 1959].
7. H. S. Gutowsky, D. W. McCall, and C. P. Slichter, J. Chem. Phys., 21, 279 (1953).
8. H. M. McConnell, J. Chem. Phys., 28, 430 (1958).
9. H. S. Gutowsky and A. Saika, J. Chem. Phys., 21, 1688 (1953).
10. M. Takeda and E. O. Stejkal, J. Amer. Chem. Soc., 82, 25 (1960).
11. H. B. Charman, D. R. Vinard, and M. M. Kreevoy, J. Amer. Chem. Soc., 84, 347 (1962).
12. F. A. Bovey, F. P. Hood, E. W. Anderson, and R. L. Kornegay, J. Chem. Phys., 41, 2041 (1964).
13. H. S. Gutowsky and C. H. Holm, J. Chem. Phys., 25, 1228 (1956).
14. E. Grunwald, A. Loewenstein, and S. Meiboom, J. Chem. Phys., 27, 630 (1957).
15. A. Loewenstein and S. Meiboom, J. Chem. Phys., 27, 1067 (1957).
16. M. T. Rogers and J. C. Woodbrey, J. Phys. Chem., 66, 540 (1962).
17. M. Anbar, A. Loewenstein, and S. Meiboom, J. Amer. Chem. Soc., 80, 2630 (1958).
18. L. H. Piett and W. A. Anderson, J. Chem. Phys., 30, 899 (1959).
19. J. Kaplan, J. Chem. Phys., 28, 278 (1958); 29, 492 (1958).
20. S. Alexander, J. Chem. Phys., 37, 967, 974 (1962); 38, 1787 (1963).
21. J. Heidberg, A. Weil, G. A. Jannisonis, and J. K. Anderson, J. Chem. Phys., 41, 1033 (1963).
22. J. Jonáš, A. Allerhand, and H. S. Gutowsky, J. Chem. Phys., 42, 3396 (1965).
23. S. Forsen and R. A. Hoffman, J. Chem. Phys., 39, 2892 (1963).
24. S. Forsen and R. A. Hoffman, J. Chem. Phys., 40, 1189 (1964).
25. F. A. L. Anet and A. J. R. Burn, J. Amer. Chem. Soc., 89, 760 (1967).
26. A. Allerhand and H. S. Gutowsky, J. Chem. Phys., 41, 2115 (1964).
27. A. Allerhand and H. S. Gutowsky, J. Chem. Phys., 42, 1587 (1965).
28. H. S. Gutowsky and E. J. Wells, J. Chem. Phys., 43, 3414 (1965).
29. H. S. Gutowsky, R. L. Vold, and E. J. Wells, J. Chem. Phys., 43, 4107 (1965).
30. A. Allerhand, F. Chen, and H. S. Gutowsky, J. Chem. Phys., 42, 3040 (1965).
31. A. Allerhand and H. S. Gutowsky, J. Chem. Phys., 42, 4203 (1965).
32. H. Y. Carr and E. M. Purcell, Phys. Rev., 94, 630 (1954).
33. Z. Luz and S. Meiboom, J. Chem. Phys., 39, 366 (1963).
34. N. Muller and P. J. Schulz, J. Chem. Phys., 68, 2026 (1964).
35. P. W. Anderson and P. K. Weiss, Rev. Mod. Phys., 25, 269 (1953).
36. P. W. Anderson, J. Phys. Soc. Japan, 9, 316 (1954).
37. R. Kubo, J. Phys. Soc. Japan, 9, 935 (1954).
38. J. G. Powles and J. H. Strange, Mol. Phys., 8, 169 (1964).
39. C. S. Johnson, J. Chem. Phys., 41, 3277 (1964).
40. K. J. Dahlqvist and S. Forsen, J. Phys. Chem., 69, 4062 (1965).
41. A. Allerhand, H. S. Gutowsky, J. Jonáš, and R. A. Meinzer, J. Amer. Chem. Soc., 88, 3185 (1966).
42. F. A. L. Anet, M. Ahmad, and L. D. Hall, Proc. Chem. Soc., 145 (1964).
43. F. A. Bovey, F. P. Hood, E. W. Anderson, and R. L. Kornegay, Proc. Chem. Soc., 146 (1964).
44. N. Muller and P. J. Schulz, J. Phys. Chem., 68, 2026 (1964).
45. F. R. Jensen, D. S. Noyce, C. H. Sederholm, and A. J. Berlin, J. Amer. Chem. Soc., 84, 386 (1962).
46. R. K. Harris and N. Sheppard, Proc. Chem. Soc., 418 (1961).
47. S. Meiboom, "Symposium on High Resolution Nuclear Magnetic Resonance, Boulder, Colorado, 1962".
48. F. A. Bovey, E. V. Anderson, F. P. Hood, and R. L. Kornegay, J. Chem. Phys., 10, 3099 (1964).
49. L. W. Reeves and K. O. Stromme, Canad. J. Chem., 38, 1241 (1960).
50. W. C. Neikam and B. P. Daily, J. Chem. Phys., 38, 445 (1963).

51. H. Friebolin, W. Faisst, H. W. Schmidt, and S. Kabuss, Tetrahedron Letters, 1317 (1966).
52. L. W. Reeves and K. O. Stromme, Trans. Faraday Soc., 57, 390 (1961).
53. H. M. Van Dort and Th. J. Sekuur, Tetrahedron Letters, 1301 (1963).
54. S. L. Spassov, D. F. Griffith, E. S. Glazer, K. Nagarajan, and J. D. Roberts, J. Amer. Chem. Soc., 89, 88 (1967).
55. R. W. Murray and M. L. Kaplan, Tetrahedron, 23, 1575 (1967).
56. R. J. Abraham and D. B. Macdonald, Chem. Comm., 188 (1966).
57. G. van Dyke Tiers, Proc. Chem. Soc., 389 (1960).
58. H. S. Gutowsky and F. M. Chen, J. Phys. Chem., 69, 3216 (1965).
59. S. Brownstein, Canad. J. Chem., 40, 870 (1962).
60. A. F. L. Anet and M. Z. Hag, J. Amer. Chem. Soc., 87, 3147 (1965).
61. F. R. Jensen and C. H. Bushweller, J. Amer. Chem. Soc., 87, 3285 (1965).
62. J. D. Roberts, Chemistry in Britain, 2, 529 (1966).
63. F. A. L. Anet and J. S. Hartmann, J. Amer. Chem. Soc., 85, 1204 (1963).
64. F. A. L. Anet, J. Amer. Chem. Soc., 84, 671 (1962).
65. D. E. Gwynn, G. M. Whitesides, and J. D. Roberts, J. Amer. Chem. Soc., 87, 2862 (1965).
66. F. A. L. Anet, A. J. R. Bourn, and Y. S. Lin, J. Amer. Chem. Soc., 86, 3576 (1964).
67. R. Huisgen and G. Boche, Tetrahedron Letters, 1769 (1965).
68. C. Gunter, S. M. Pokras, and J. D. Roberts, J. Amer. Chem. Soc., 88, 4235 (1966).
69. N. L. Allinger, H. A. Miller, L. W. Chow, R. A. Ford, and J. C. Graham, J. Amer. Chem. Soc., 87, 3430 (1965).
70. J. T. Greig and J. D. Roberts, J. Amer. Chem. Soc., 88, 2791 (1966).
71. A. Luttringhaus, S. Kabuss, W. Maier, and H. Friebolin, Z. Naturforsch., 16b, 761 (1962).
72. J. B. Lambert, R. G. Keske, E. R. Carhart, and A. P. Jovanovich, J. Amer. Chem. Soc., 89, 3761 (1967).
73. L. W. Reeves and E. J. Welles, Discuss. Faraday Soc., 34, 177 (1962).
74. G. Claeson, J. M. Androes, and M. Calvin, J. Amer. Chem. Soc., 82, 4428 (1960).
75. G. Claeson, J. M. Androes, and M. Calvin, J. Amer. Chem. Soc., 83, 4357 (1961).
76. H. Friebolin, S. Kabuss, W. Maier, and A. Luttringhaus, Tetrahedron Letters, 683 (1962).
77. J. E. Anderson and J. C. D. Brand, Trans. Faraday Soc., 62, 39 (1966).
78. H. Freibolin and W. Maier, Z. Naturforsch., 16a, 640 (1961).
79. R. K. Harris and R. A. Spragg, Chem. Comm., 314 (1966).
80. L. W. Reeves and K. O. Stromme, J. Chem. Phys., 34, 1711 (1961).
81. C. H. Bushweller, J. Amer. Chem. Soc., 89, 5978 (1967).
82. R. W. Murray, P. R. Story, and M. L. Kaplan, J. Amer. Chem. Soc., 88, 526 (1966).
83. J. E. Anderson and J. M. Lehn, J. Amer. Chem. Soc., 89, 81 (1967).
84. J. E. Anderson and J. M. Lehn, Tetrahedron, 24, 137 (1968).
85. J. M. Lehn, F. G. Riddell, B. J. Price, and J. O. Sutherland, J. Chem. Soc., (B), 387 (1967).
86. H. S. Gutowsky and P. A. Temussi, J. Amer. Chem. Soc., 89, 4358 (1967).
87. H. S. Gutowsky, Ann. New York Acad. Sci., 70, 786 (1958).
88. A. Loewenstein, J. F. Neumer, and J. D. Roberts, J. Amer. Chem. Soc., 82, 3599 (1960).
89. F. A. L. Anet and J. M. Osyany, J. Amer. Chem. Soc., 89, 352 (1967).
90. F. A. L. Anet, R. D. Trepka, and D. J. Cram, J. Amer. Chem. Soc., 89, 357 (1967).
91. C. W. Shoppe, J. Chem. Soc., 1138 (1946).
92. C. S. Beckett, K. S. Pitzer, and R. Spitzer, J. Amer. Chem. Soc., 69, 2488 (1947).
93. M. E. Pedinoff, J. Chem. Phys., 36, 777 (1962).
94. J. E. Piersy, J. Acoust. Soc. Amer., 33, 198 (1961).
95. N. L. Allinger and L. A. Freiberg, J. Amer. Chem. Soc., 82, 2392 (1960).
96. W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, J. Amer. Chem. Soc., 83, 606 (1961).
97. J. L. Margrave, M. A. Frisch, R. G. Bautista, R. L. Clarke, and W. S. Johnson, J. Amer. Chem. Soc., 85, 546 (1963).
98. R. K. Harris and N. Sheppard, J. Mol. Spectroscopy, 23, 231 (1967).
99. J. B. Hendrickson, J. Amer. Chem. Soc., 83, 4537 (1961); 84, 3355 (1962).
100. K. B. Weiberg, J. Amer. Chem. Soc., 87, 1070 (1965).
101. N. L. Allinger, M. A. Miller, F. A. Van Catledge, and J. A. Hirsch, J. Amer. Chem. Soc., 89, 4345 (1967).
102. N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminsky, and F. A. Van Catledge, J. Amer. Chem. Soc., 90, 1199 (1968).
103. M. Bixon and S. Lifson, Tetrahedron, 23, 769 (1967).
104. J. B. Hendrickson, J. Amer. Chem. Soc., 89, 7036, 7043, 7047 (1967).
105. M. Davies and O. Hassel, Acta Chem. Scand., 17, 1181 (1963).
106. L. S. Bartell and D. A. Kohl, J. Chem. Phys., 39, 3097 (1963).
107. C. W. Beckett, N. K. Freeman, and K. S. Pitzer, J. Amer. Chem. Soc., 70, 4227 (1948).
108. E. J. Corey and R. A. Sneen, J. Amer. Chem. Soc., 77, 2505 (1955).
109. R. Boucourt and D. Hainaut, Compt. rend., 258, 3305 (1964).
110. O. Bastiansen and J. Markali, Acta Chem. Scand., 6, 442 (1952); 6, 875 (1952).
111. H. D. Orloff, A. J. Kolka, G. Galangaert, M. E. Griffing, and E. R. Kerr, J. Amer. Chem. Soc., 75, 4243 (1953).
112. A. E. Kolka, H. D. Orloff, and M. E. Griffing, J. Amer. Chem. Soc., 76, 1244 (1954).
113. R. S. Pasternak, Acta cryst., 4, 316 (1951).
114. J. M. Linsey and W. H. Barnes, Acta cryst., 8, 227 (1955).
115. K. Sakashita, J. Chem. Soc. Japan, 77, 1094 (1956); 79, 329 (1958).
116. K. B. Wiberg and B. J. Nist, J. Amer. Chem. Soc., 83, 1226 (1961).
117. K. Sakashita, Nippon Kagaku Zasshi, 80, 972 (1959).
118. K. Sakashita, Nippon Kagaku Zasshi, 81, 49 (1960).
119. A. Griswold and P. S. Starcher, J. Org. Chem., 31, 357 (1966).
120. W. Garbish, J. Org. Chem., 27, 4249 (1962).
121. E. W. Garbish, J. Amer. Chem. Soc., 85, 927 (1963).
122. L. D. Hall, J. Org. Chem., 29, 297 (1964).

123. L. D. Hall and L. F. Johnson, Tetrahedron, 20, 883 (1964).
124. R. J. Abraham, H. Gottschalk, H. Paulsen, and W. A. Thomas, J. Chem. Soc., 6268 (1965).
125. H. R. Barton, Chem. Ind., 1136 (1956).
126. T. N. Margulis, Acta Cryst., 19, 857 (1965).
127. T. N. Margulis and M. S. Fisher, J. Amer. Chem. Soc., 89, 223 (1967).
128. A. Allmeiningen and O. Bastiansen, Acta Chem. Scand., 15, 711 (1961).
129. S. Meiboom and L. S. Snyder, Chem. Eng. News, 44, 17, 51 (1966).
130. J. B. Lambert and J. D. Roberts, J. Amer. Chem. Soc., 87, 3884, 3891 (1965).
131. J. Lillien and R. A. Doughty, J. Amer. Chem. Soc., 89, 155 (1967).
132. S. I. Chan, J. Zinn, and W. D. Gwinn, J. Chem. Phys., 34, 1319 (1961).
133. F. A. L. Anet and M. St. Jacques, J. Amer. Chem. Soc., 88, 2585, 2586 (1966).
134. P. Groth, Acta Chem. Scand., 19, 1497 (1965).
135. W. Monitz and J. A. Dixon, J. Amer. Chem. Soc., 83, 1671 (1961).
136. N. Muller and W. C. Tosch, J. Chem. Phys., 37, 1170 (1962).
137. F. G. Riddell and M. J. T. Robinson, Chem. Comm., 227 (1965).
138. P. Geneste and G. Lamaty, Bull. Soc. chim. France, 2439 (1964).
139. J. B. Lambert and R. G. Keske, J. Amer. Chem. Soc., 88, 620 (1966).
140. R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katrizky, and R. J. Wyatt, J. Chem. Soc., (B), 493 (1967).
141. H. Booth and A. H. Bostock, Chem. Comm., 177 (1967).
142. H. Booth and J. H. Little, Tetrahedron, 23, 291 (1967).
143. N. L. Allinger, J. A. Hirsch, and M. A. Miller, Tetrahedron Letters, 3729 (1967).
144. E. L. Eliel and S. M. C. Knoeler, J. Amer. Chem. Soc., 88, 5347 (1966).
145. F. G. Riddell and M. J. T. Robinson, Tetrahedron, 23, 3417 (1967).
146. C. H. Bushweller, J. Amer. Chem. Soc., 90, 2450 (1968).
147. F. R. Jensen and C. H. Bushweller, J. Amer. Chem. Soc., 87, 4279 (1966).
148. A. T. Bottini and J. D. Roberts, J. Amer. Chem. Soc., 78, 5126 (1956).
149. V. F. Bystrov, R. G. Kostyanovskii, O. A. Pan'shin, A. U. Stepanyants, and O. A. Yuzhakova, Optika i Spektrosk., 19, 217 (1965).
150. A. B. Turner, H. H. Heine, J. Irving, and J. B. Bush, J. Amer. Chem. Soc., 87, 1050 (1965).
151. A. L. Logothetis, J. Org. Chem., 29, 3049 (1964).
152. C. C. Costain and J. M. Dowling, J. Chem. Phys., 32, 158 (1960).
153. E. L. Eliel and C. A. Luckach, J. Amer. Chem. Soc., 79, 5986 (1957).
154. S. Winstein and N. J. Hollness, J. Amer. Chem. Soc., 77, 5562 (1955).
155. E. L. Eliel, Angew. Chem., 77, 784 (1965).
156. H. Feltkamp and N. C. Franklin, Angew. Chem., 77, 798 (1965).
157. A. J. Berlin and F. R. Jensen, Chem. Ind., 998 (1960).
158. R. J. Quelett, J. Amer. Chem. Soc., 86, 3089 (1964).
159. R. J. Quelett, J. Amer. Chem. Soc., 86, 4378 (1964).
160. E. L. Eliel, Chem. Ind., 568 (1959).
161. E. A. Allan, E. Premuzic, and L. W. Reeves, Canad. J. Chem., 41, 204 (1963).
162. A. D. Stolow and M. M. Bonoventura, J. Amer. Chem. Soc., 85, 3636 (1963).
163. E. L. Eliel, E. W. Della, and T. H. Williams, Tetrahedron Letters, 831 (1963).
164. H. Feltkamp, N. S. Franklin, K. D. Thomas, and W. Brugel, Annalen, 683, 64 (1965).
165. H. Feltkamp and N. S. Franklin, J. Amer. Chem. Soc., 87, 1616 (1965).
166. E. L. Eliel and M. H. Gianni, Tetrahedron Letters, 97 (1962).
167. A. H. Levin and S. Winstein, J. Amer. Chem. Soc., 84, 2464 (1962).
168. E. W. Garbish, J. Amer. Chem. Soc., 86, 1780 (1964).
169. E. L. Eliel and R. J. L. Martin, J. Amer. Chem. Soc., 90, 682, 689 (1968).
170. J. Reisse, J. C. Celotti, D. Zimmerman, and G. Chiurdoglu, Tetrahedron Letters, 2145 (1964).
171. F. R. Jensen and B. H. Beck, J. Amer. Chem. Soc., 90, 3251 (1968).
172. H. Booth, Tetrahedron, 20, 2211 (1964).
173. F. A. L. Anet, J. Amer. Chem. Soc., 84, 1053 (1962).
174. E. L. Eliel and B. P. Till, Chem. Ind., 88 (1963).
175. E. L. Eliel, M. T. Gianni, T. H. Williams, and J. B. Stothers, Tetrahedron Letters, 741 (1962).
176. W. Hoffman, L. Stefaniak, T. Urbanski, and M. Witanowski, J. Amer. Chem. Soc., 86, 554 (1964).
177. N. C. Franklin and H. Feltkamp, Tetrahedron, 22, 2801 (1966).
178. J. J. Uebel and J. C. Martin, J. Amer. Chem. Soc., 86, 4618 (1964).
179. E. W. Garbish and D. B. Patterson, J. Amer. Chem. Soc., 85, 3228 (1963).
180. J. I. Musher, J. Chem. Phys., 35, 1159 (1961).
181. H. Booth, N. S. Franklin, and G. C. Gidley, Tetrahedron, 21, 1077 (1965).
182. H. Booth, Tetrahedron, 22, 615 (1966).
183. R. Bohlman, D. Schumann, and H. Schulz, Tetrahedron Letters, 173 (1965).
184. H. P. Hamlow, S. Okuda, and N. Nakagawa, Tetrahedron Letters, 2553 (1964).
185. R. U. Lemieux and J. W. Lown, Canad. J. Chem., 42, 893 (1964).
186. A. C. Huitric and W. F. Trager, J. Org. Chem., 27, 1926 (1962).
187. A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, Tetrahedron, 19, 2145 (1963).
188. W. F. Trager and A. C. Huitric, J. Org. Chem., 30, 3257 (1965).
189. N. S. Bhacca and D. H. Williams, J. Amer. Chem. Soc., 88, 2742 (1964).
190. H. Feltkamp and N. S. Franklin, Tetrahedron, 21, 1541 (1965).
191. J. T. Musher, Mol. Phys., 6, 93 (1963).
192. A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegel, Tetrahedron Letters, 233 (1964).
193. R. U. Lemieux, R. K. Kullning, and R. Y. Moir, J. Amer. Chem. Soc., 80, 2237 (1958).
194. H. Feltkamp and N. S. Franklin, Annalen, 683, 55 (1965).
195. H. Feltkamp, N. S. Franklin, W. Kraus, and W. Brugel, Annalen, 683, 75 (1965).
196. H. Feltkamp, N. S. Franklin, M. Hanak, and K. W. Heinz, Tetrahedron Letters, 3335 (1964).
197. J. Reisse, J. C. Celotti, and G. Chiurdoglu, Tetrahedron Letters, 397 (1965).

198. J. D. Roberts, Angew. Chem., 75, 20 (1963); Int. Ed., 2, 53 (1963).
199. H. S. Gutowsky, G. G. Belford, and P. E. McMahon, J. Chem. Phys., 36, 3353 (1952).
200. S. L. Stafford and J. D. Baldeschwieler, J. Amer. Chem. Soc., 83, 4473 (1961).
201. K. L. Williamson, Y. F. Li, F. U. Hall, and S. Swager, J. Amer. Chem. Soc., 88, 5678 (1966).
202. L. Pierce and J. F. Beecher, J. Amer. Chem. Soc., 88, 5406 (1966).
203. P. Anderson, Acta Chem. Scand., 16, 2337 (1962).
204. N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminsky, J. Amer. Chem. Soc., 90, 5773 (1968); 91, 337 (1969).
205. J. T. Gerig, J. Amer. Chem. Soc., 90, 1065 (1968).
206. F. R. Jensen and B. H. Beck, J. Amer. Chem. Soc., 90, 1066 (1968).
207. R. E. Lack, C. Ganter, and J. D. Roberts, J. Amer. Chem. Soc., 90, 7001 (1968).
208. J. E. Anderson, E. S. Galzer, D. L. Griffith, R. Knorr, and J. D. Roberts, J. Amer. Chem. Soc., 91, 1386 (1969).
209. I. V. Egmond and C. Romers, Tetrahedron, 25, 2693 (1969).
210. F. A. L. Anet and L. A. Bock, J. Amer. Chem. Soc., 90, 7130 (1968).
211. R. E. Lack and J. D. Roberts, J. Amer. Chem. Soc., 90, 6997 (1968).
212. G. A. Yousif and J. D. Roberts, J. Amer. Chem. Soc., 90, 6428 (1968).
213. E. L. Eliel and R. O. Hutchins, J. Amer. Chem. Soc., 91, 2703 (1969).
214. F. R. Jensen and C. H. Bushweller, Tetrahedron Letters, 2825 (1968).
215. R. W. Murrey and M. L. Kaplan, Tetrahedron, 25, 1651 (1969).
216. J. Wagner, W. Wojnarowski, J. E. Anderson, and J. M. Lehn, Tetrahedron, 25, 657 (1969).
217. J. M. Lehn and J. Wagner, Tetrahedron, 25, 677 (1969).
218. M. Jautelat and J. D. Roberts, J. Amer. Chem. Soc., 91, 642 (1969).
219. J. B. Lambert and D. H. Johnson, J. Amer. Chem. Soc., 90, 1349 (1968).
220. J. B. Lambert and G. F. Jackson, J. Amer. Chem. Soc., 90, 1350 (1968).
221. F. R. Jensen and C. H. Bushweller, J. Amer. Chem. Soc., 91, 3223 (1969).
222. F. R. Jensen, C. H. Bushweller, and B. H. Beck, J. Amer. Chem. Soc., 91, 344 (1969).
223. F. A. L. Anet and R. M. Henrichs, Tetrahedron Letters, 741 (1969).
224. G. Ransbotyn, J. C. Celotti, R. Ottinger, J. Reisse, and G. Chiordoglu, Tetrahedron, 24, 3647 (1968).

Institute of the Chemistry of
Natural Compounds,
USSR Academy of Sciences,
Moscow