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New Aspects of the Application of Nuclear Magnetic Resonance to the Study of Chemical Exchange Processes

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The application of the analysis of the total line shape (ATLS) in dynamic NMR to the investigation of complex chemical exchange is examined. Theoretical aspects of this problem, illustrated in relation to the available experimental data, are described. The methodological problems of dynamic NMR are discussed: the sources of error and the role of the medium, the interpretation of the activation parameters $\Delta H^{\neq}$, $\Delta G^{\neq}$, and $\Delta S^{\neq}$, and also the new varieties of the method and their applications.
The bibliography includes 171 references.

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I. INTRODUCTION

Since the publication of the first fundamental studies,[1-6] numerous reviews and monographs surveying the results of kinetic studies by the NMR method have appeared. General information can be found in a series of publications.[7-17] A more detailed description of the principles of the theory, method, and applications can be found in reviews.[18-24] The bibliography of the publications in 1970–1974 can be found in a periodical publication.[25] The appearance in 1975 of a fundamental collected volume[26] of review articles on all the most important problems of dynamic NMR (DNMR) heralded the completion of the first stage of its development and establishment. The review articles in the following period were devoted to special problems: dynamic ^{13}C NMR spectroscopy[27] and its application to the study of the dynamics of metal carbonyl[28] and cyclic organic[29] compounds, the application of the methods for the analysis of the total line shape to the examination of the chemical exchange mechanism,[30] and the physical aspects of the theory based on the influence of chemical exchange on relaxation processes[31] and the study of "rapid kinetics".[32] Special mention should be made of the publication of the first book on the general theory of the NMR of chemically exchanging systems[33] and the first monograph devoted to the methodological aspects of DNMR.[34]

Several varieties of the DNMR method are known. The non-selective pulse NMR is an independent method both as regards theory and the procedure used to obtain spectroscopic and kinetic data and as regards experimental technique. The principles of its application to kinetic studies have been described.[35]

Modern NMR Fourier spectrometers make possible experiments under both stationary and selective pulsed conditions. The use of the relaxation times T_1 and T_2, corresponding to the nuclear transitions between individual energy sublevels,

together with the chemical shift δ and the spin–spin coupling constant J, has therefore become a common feature of combined studies of chemical systems. The same universality is to be expected in kinetic investigations in the immediate future.

The DNMR method in the stationary regime is used in the range of reaction rate constants 10^{-1}–10^5 s^{-1} (^1H NMR). Selective pulse methods not only significantly expand the above range (in certain cases from 10^{-3} to 10^6 s^{-1}) but sometimes can yield unique information about the mechanisms of complex chemical exchange processes. It has now become possible to carry out kinetic studies at an extremely low concentration of magnetic nuclei (in gases, in solutions at infinite dilution but with a high natural abundance of magnetic nuclei in the specimen, by ^{13}C and ^{15}N NMR without enrichment in the usual solutions, etc.).

The applications of NMR to kinetic studies are extremely varied and numerous. A fairly completely survey of the research carried out in recent years can be given only within the framework of a collected volume analogous to that of Jackman.[26]

In the present review we shall consider new aspects of the application of NMR to the study of systems with a complex chemical exchange as well as the scope and applications of the new special methods. The most important publications of recent years will be mostly quoted. Brief information about the studies published in 1979–1983 can be found in the periodical reference publication.[36]

II. NMR IN SYSTEMS WITH CHEMICAL EXCHANGE. PROBLEMS OF THE ANALYSIS OF THE TOTAL LINE SHAPE

1. Principal Postulates of the Theory. Multiparameter Exchange. Difficulties and Limits of Applicability

The most interest and most important field in which analysis of the total NMR line shape is used in systems with chemical exchange (ATLS DNMR)† involves the study of the mechanisms of intramolecular and intermolecular exchange in chemical systems where the number of exchanging sites is greater than two and the transitions between them are characterised by different rate constants. Although the theory describing the effect of chemical exchange on NMR spectra has been established in a general form, in the interpretation of the temperature variation of the spectra and in the analysis of kinetic and activation parameters for the chemical exchange serious difficulties are encountered, which are probably not always surmountable. The study of such problems has not been reflected in the review articles quoted above.

The general postulates of the theory for many-sided exchange in systems where there is no direct spin–spin coupling of the nuclear spins have been formulated within the framework of a stochastic theory.[3,4] In another approach[5] modified Bloch equations are used. In a general form the theory has been described by Reeves and Shaw.[37] A detailed discussion of this question can be found in Johnson's[18] and Swift's[31] books and we shall confine ourselves only to brief remarks.

We shall consider a set of magnetic nuclei which can execute random jumps between n different magnetic environments (equilibrium positions). We shall characterise these magnetic environments by a set of Larmor precession frequencies ω_r and spin–spin relaxation times $^*T_{2r}$ (which do not take into account the effects of chemical exchange). The subscript r denotes the equilibrium position ($r = 1, \ldots, n$). In terms of a rotating coordinate system, the equation describing the movement of the xy component of the macroscopic magnetisation $M_{xy} = M_x + iM_y$ in these equilibrium positions under slow pass conditions can be represented in the following general form:[34]

$$\{-{}^*T_{2r}^{-1} + i(\omega_r - \omega)\} M_{xy}^r + \sum_s K_{sr} M_{xy}^r + i\omega_1 M_0 P_r = 0 , \qquad (1)$$

where ω_1 is the angular frequency of the microwave frequency field, M_0 the equilibrium magnetisation, P_r the probability of finding the nuclei in the position r with $\sum_{r=1}^{n} P_r = 1$, $K_{rr} = -\tau_r^{-1}$, and $K_{rs} = k_{rs}$, τ_r being the resonance time of the nucleus in the position r and k_{rs} the rate constant for the transition of the nuclei from the position r to the position s; $-\sum_s k_{rs} = \tau_r^{-1}$.

On solving a system of n linear equations (1) for M_{xy} and bearing in mind that $M_{xy} = \sum_{r=1}^{n} M_{xy}^r$, it is possible to find the required function of the line form. The results of the solution of this system of equations be be conveniently represented in a matrix form. The line form function Y (for the absorption component) can then be formulated thus

$$Y \simeq \mathrm{Re}\{P \cdot [-T_2^{-1} + i(\Omega - \omega) + K^{-1} \cdot 1\} , \qquad (2)$$

where Re is the real component, K the nth order exchange matrix whose elements are the same as in Eqn.(1), T_2^{-1} and Ω are diagonal matrices with the elements $^*T_{*r}$ and ω_r, 1 is a unit column matrix, and P a row matrix with the elements P_r. This equation can be easily solved on a computer provided with a translator enabling it to operate with complex numbers.

The quantum-mechanical theory describing the influence of chemical exchange on NMR spectra was first proposed by Kaplan[6] and is based on the examination of the evolution of the density matrix for the spin systems in the Gilbertian representation (a detailed description of NMR spectra with the aid of the density matrix can be found in Lynden-Bell[20] and Slichter[38]). We shall consider briefly the main postulates of this theory.

Suppose that ψ is the wave function of a "pure" state which can be expanded in a series in terms of the basis functions Φ_n: $\psi = \sum_n C_n \Phi_n$, $p_{ij} = C_i C_j^*$. The coefficients C_i and their complex conjugates C_j^* incorporates the entire time variation of the state of the system. The average value of the physical quantity Q, to which corresponds the quantum-mechanical operator $\hat{Q}$, is defined in the form

$$\langle Q \rangle = \langle \psi | \hat{Q} | \psi \rangle = \sum_{m,k} C_m^* C_k \langle \Phi_m | \hat{Q} | \Phi_k \rangle = \sum_{m,k} p_{mk} \langle \Phi_m | \hat{Q} | \Phi_k \rangle ,$$

where the elements of the density matrix p_{mk} can be represented as a result of the action of the density matrix operator $\hat{P}$:

$$p_{km} = C_k C_m^* = \langle \Phi_k | \hat{P} | \Phi_m \rangle .$$

Then

$$\langle Q \rangle = \sum_{m,k} \langle \Phi_k | \hat{P} | \Phi_m \rangle \langle \Phi_m | \hat{Q} | \Phi_k \rangle = \sum_k \langle \Phi_k | \hat{P}\hat{Q} | \Phi_k \rangle = \mathrm{Tr}\, \hat{P}\hat{Q} = \mathrm{Tr}\, \hat{Q}\hat{P} .$$

Thus $\langle Q \rangle$ is independent of the choice of the basis functions Φ_n. The spin state of a macroscopic system such as the substance in the cavity of the NMR spectrometer consists

† The terminology is discussed in Ref.25 (1973, p.218), in Jackman's book,[26] and by Sandstrom.[34]

of a mixture of states with the corresponding wave functions and cannot be described by a single wave function. However, such a system can be described with the aid of the general system of basis functions Φ_n and the density matrix ρ with the coefficient ρ_{km} averaged with respect to the total assembly:[34]

$$\rho_{km} = \overline{C_k C_m^*} = \langle \overline{\Phi_k | \hat{P} | \Phi_m} \rangle = \langle \Phi_k | \hat{\rho} | \Phi_m \rangle .$$

Then the expected physical quantity Q averaged with respect to the assembly of systems is defined by the relation

$$\langle \bar{Q} \rangle = \mathrm{Tr}\, \hat{Q}\hat{\rho} .$$

Assuming that the Hamiltonian is the same for all the members of the assembly, the Schrödinger time equation can be written in the form

$$d\hat{\rho}/dt = \frac{i}{\hbar} [\hat{\rho}, \hat{\mathcal{H}}] . \qquad (3)$$

The wave function ψ can be represented by the product of the spatial and spin wave functions. In describing NMR, only the spin functions are considered. The basis functions for nuclei with a spin of 1/2 are the eigenfunctions α and β of the operator $\hat{I}_z$ (the z components of the spin momentum operator $\hat{I}$).

The spin-Hamiltonian for a group of identical nuclear spins can be represented in the following form in terms of a rotating coordinate system:

$$\hat{\mathcal{H}} = \hat{\mathcal{H}}_0 + \hat{\mathcal{H}}_1 = \sum_i (\nu_i - \nu) \hat{I}_{zi} + \sum_{j<k} J_{jk} \hat{I}_j \hat{I}_i + \sum_i \nu_1 \hat{I}_{xi} , \qquad (4)$$

where the subscripts i and j refer to individual spins, J_{ij} is the spin–spin coupling constant, $\nu_i = \omega_i/2\pi$, $\nu_1 \hat{I}_{xi}$ describes the interaction with the microwave frequency field H_1 having a frequency ν_1, and $\hat{I}_x$ is the x component of the spin operator $\hat{I}$.

For a description of the resonance absorption under slow pass conditions ($d\rho/dt = 0$) and in the absence of saturation and chemical exchange, it is sufficient to introduce the relaxation term $\hat{\rho}^* T_2^{-1}$ in the right-hand side of Eqn.(3):

$$i [\hat{\rho}, \hat{\mathcal{H}}] - \hat{\rho}^* T_2^{-1} = 0 . \qquad (5)$$

The resonance absorption line form is described by the function

$$Y(\nu) = \mathrm{Im} \left(\mathrm{Tr}\, \hat{\rho} \sum_i \hat{I}_i^+ \right) ,$$

where Im denotes the imaginary component of the expression in brackets, $\hat{I}^+ = \hat{I}_x + i\hat{I}_y$, and the components of the operator $\hat{\rho}$ are found from the solution of Eqn.(5).

The effects of chemical exchange are taken into account by including in Eqn.(5) the term $(\hat{\rho}^{a.e.} - \hat{\rho})\tau^{-1}$, where $\tau(k^{-1})$ is the average residence time in the equilibrium states and $\hat{\rho}^{a.e.} = \chi\hat{\rho}\chi^{-1}$. The elements of the exchange operator χ are defined in the following manner in the simplest case of mutual exchange in a system of spins of one kind:

$$\chi_{kl} = \langle \Phi_l | \hat{\chi} | \Phi_k \rangle . \qquad (6)$$

Consequently the elements of the density matrix after exchange $\rho^{a.e.}$ are given by

$$\rho_{kl}^{a.e.} = \sum_{nm} \chi_{kn} \rho_{nm} \chi_{ml} .$$

In the presence of exchange, Eqn.(5) can then be rewritten as follows:[39,40]

$$k \left(\sum_{nm} \chi_{kn} \rho_{nm} \chi_{ml} - \rho_{kl} \right) - \frac{\rho_{kl}}{{}^*T_2} + i [\hat{\rho}, \hat{\mathcal{H}}]_{kl} = 0 , \qquad (7)$$

where

$$i [\hat{\rho}, \hat{\mathcal{H}}]_{kl} = i\rho_{kl} \left\{ \sum_i (\nu_i - \nu) [(\hat{I}_z^i)_{kk} - (\hat{I}_z^i)_{ll}] + \sum_{i<j} [(\hat{I}_z^i \hat{I}_z^j)_{kk} - (\hat{I}_z^i \hat{I}_z^j)_{ll}] \right\} +$$
$$+ \frac{i}{2} \sum_{i<j} J_{ij} [\rho, \hat{I}_+^i \hat{I}_-^j + \hat{I}_-^i \hat{I}_+^j]_{kl} + i\nu_1 (\rho_{kk} - \rho_{ll}) \sum_i (\hat{I}_x^i)_{kl} .$$

Bearing in mind that $H_1 \ll H_0$, the last term in Eqn.(7) can be replaced by the constant iC.

For a description of more complex cases of chemical exchange, such as non-mutual exchange, intermolecular exchange, exchange in a system of nuclear spins of different kinds or systems with multiparameter exchange, etc., the theory based on the use of exchange operators of the type found by Eqn.(6) is inapplicable; a different definition of the elements of the density and exchange matrices is necessary. Subsequently the approach based on the use of Eqn. (3) in the Gilbertian representation was developed and applied to the analysis of the exchange effects in a wide variety of spin systems.[33,41,42]

Calculations of the line form based on Binsch's unified density matrix method,[21,43–46] in which the formulation of Eqn.(3) in terms of the Liouville representation

$$d\vec{\rho}/dt = -i\hat{\mathcal{L}}\vec{\rho}$$

proposed by Johnson[18] is used, are much more common and probably more convenient in the study of multiparameter exchange, the elements of the Liouville operator matrix are made up of the matrix elements of the spin-Hamiltonian operator for the system (in s^{-1}) in the following manner

$$L_{\mu\nu,k\lambda} = 2\pi [\mathcal{H}_{\mu k}\delta_{\nu\lambda} - \mathcal{H}_{\lambda\nu}\delta_{k\mu}] ,$$

where δ is the Kronecker delta.

Using this representation of the density matrix ρ, Binsch[43] successfully combined the possible versions of the exchange process, including intermolecular exchange.

If the system is subdivided into r non-interacting and independent subsystems, it is possible to formulate the general vector for the system $\vec{\rho}_l$ in a space l, which is the sum of the subspaces $\vec{\rho}_r$. The elements of this vector are ρ_r with the multiplier $f_r = n m_r P_r \left(\sum_r^n m_r \right)^{-1}$, where m_r is the number of nuclei (with a spin of 1/2), P_r the relative population of the subsystem r, and n the number of types of the subsystem. It is postulated that the relaxation processes and the effects of the chemical exchange can be taken into account in describing the time variation of $\vec{\rho}_l$ by including the corresponding operators $\hat{R}_l$ and $\hat{\chi}_l$ defined in the $\vec{\rho}_l$ space:

$$d\vec{\rho}_l/dt = (-i\mathcal{L}_l + R_l + \chi_l)\vec{\rho}_l \equiv M\vec{\rho}_l . \qquad (8)$$

The relaxation operator matrix R_l contains only the diagonal element ${}^*T_2$. In describing the intramolecular exchange, the exchange operator matrix χ_l can be made up of the following elements according to Alexander:[40]

$$\chi_{\mu_r \nu_r k_s \lambda_s} = \delta_{\mu k}\delta_{\nu\lambda} \left[-\delta_{\mu s} \sum_{t(\neq r)} k_{rt} + (1 - \delta_{rs}) k_{sr} \right] ,$$

where k_{sr} is the rate constant for the transition of the spin from the state s to the state r, which has the same significance as in Eqn.(1).

Under the conditions of stationary NMR, Eqn.(8) assumes the form

$$(-i\mathcal{L}_l + R_l + \chi_l)\vec{\rho}_l = 0 . \qquad (9)$$

It is more convenient to represent the operator $\hat{\mathcal{L}}$ as the sum of the operators $\hat{\mathcal{L}}_0 + \hat{\mathcal{L}}_1$; the elements of the operator $\hat{\mathcal{L}}_0$ are

made up of the elements of the Hamiltonian $\hat{\mathscr{H}}_0$ (4), describing the interaction of the spin system with the field H_0, while $\hat{\mathscr{P}}_1$ is made up of the elements of the Hamiltonian $\hat{\mathscr{H}}_1$. Eqn.(9) then becomes

$$(-i\mathscr{P}_{0l} + R_l + \chi_l)\vec{\rho}_l = i\mathscr{P}_1\vec{\rho}_l = i\vec{\sigma} \quad \text{or} \quad M_0\vec{\rho} = i\vec{\sigma} .$$

The complex magnetisation is described by the expression

$$G = (\vec{I} + \vec{\rho}_l) = i(\vec{I}^+ M_0^{-1}\vec{\sigma}) ,$$

where $\vec{I} = \sum_i I_i^+$, and $\vec{\sigma}$ for the intramolecular exchange is determined by the elements $\sigma_{\mu\nu} = CP_r\beta_{\mu\nu}$, where $\beta_{\mu\nu} = 1$ when μ and ν refer to the eigenvalues I_z differing by unity, and $\beta_{\mu\nu} = 0$ in the remaining cases. The NMR absorption function is defined as follows:

$$Y = \mathrm{Im}(G) = \mathrm{Re}(-C(\vec{I}^+[-i\mathscr{P}_{0l} + R_l + \chi_l]^{-1}\vec{\sigma})) . \qquad (10)$$

The dimension of the matrix M_0 is defined in the general case by the relation $\sum_{r=1}^{n}(2^{2m_r})$ (n is the number of equilibrium positions). However, since many elements of the vectors $\vec{I}$ and $\vec{\sigma}$ are 0, the dimension of the matrices employed diminishes to $\sum_r W_r$, where W_r is the maximum number of the possible transitions for individual systems in the position r.

In those cases where the computer is not provided with a translator for operation with complex numbers, Eqn.(10) can be solved by the method proposed by Szymanski and Gyff-Keller.[45]

Thus the solution of Eqn.(2) or (10) can yield a function describing the NMR absorption line form, which in the general case depends on several variables:

$$Y = Y(C_0, \nu_{ri}, T_{2ri}, J_{ij}^{(r)}, P_r, k_{rs}) . \qquad (11)$$

It has been suggested that the constants k_{rs} in Eqns.(2) and (11) are interdependent, which means that under this condition, with the values of k_{rs} obtained from the analysis of the line form described by Eqn.(11), is it possible to compare the true values of the corresponding activation parameters $\Delta H_{rs}^{\neq}$, $\Delta S_{rs}^{\neq}$, and $\Delta G_{rs}^{\neq}$. It is evident, as will be illustrated below, that this condition by no means always holds. The interpretation of the temperature variation of the NMR spectra of such molecules is an extremely difficult problem whose solution has not been found in a general form.

There is no doubt that a more or less successful solution of the problem is possible provided that the parameters of the NMR spectra of the partners of the exchange, which enter into the function Y, are known, i.e. when the slow exchange limit had been attained, the complete line assignment was carried out and account was taken (where possible) of the different effects influencing these parameters. The next stage involves the setting up of exchange matrices corresponding to different versions of the exchange (among the number of the possible versions, naturally excluding those which are indistinguishable spectroscopically[47]). At first sight, this problem has been exhausted and we are dealing only with computational procedures whose success is wholly determined by the complexity of the exchanging spin system and the capacity of the computer (including the adequacy of the programmes). In fact the problem is much more complicated. Eqns.(2) and (10) do not yield an unambiguous solution—even if only one version of the exchange is possible, identical line form functions can correspond to different sets of variables k_{rs}. For example, this type of ambiguity can be observed in the simplest case of the two-sided non-mutual exchange with an appreciable temperature dependence of the relative populations P_r.[48]

A rigorous solution of Eqns.(2) and (10) for many-sided exchange can be obtained when the exchange is described by a single rate constant $k_{rs} = k$ (many-sided one-parameter exchange). For such systems, the selection of a unique exchange scheme, corresponding to a real process, can be achieved by comparing the calculated and observed line forms over the entire experimental temperature range.[30] Here success depends on the extent to which the spectrum is characteristic. In the general case of multiparameter exchange the ambiguity may be either not self-evident (and in this case can probably lead to considerable errors in the determination of the activation parameters) or can be explicit and gives rise as a consequence to the problem of the interpretation of the kinetic and activation parameters.

There is no doubt that the latter problem arises only when the NMR line form is determined by several constants k_{rs}. If the spectrum can be subdivided into subspectra in which the temperature measurements correspond to any one of the processes occurring in the system, the problem reduces to the analysis of two-sided exchange, because the kinetic matrices specified by Eqns.(2) and (10) are subdivided into a series of matrices, each of which includes only one constant k. This approach has been used, for example, in the study of the simultaneous hindered rotation about four bonds in polarised ethylenes.[49] In this review we shall not discuss studies of this kind.

2. Sources of Errors. The Medium Factor. Problems of the Interpretation of the Activation Parameters $\Delta H^{\neq}$, $\Delta G^{\neq}$, and $\Delta S^{\neq}$

The problems concerning the accuracy of kinetic measurements by the NMR method have always been the subject of special attention but their importance was only fully recognised after the activation data for the main types of chemical exchange had been arranged systematically. The essential feature of this situation is strikingly illustrated by the analysis of data for the inversion of six-membered rings (cyclohexane, its *gem*-substituted derivatives, 1,3-dioxans, etc.)—one of the intermolecular exchange processes which have been investigated in greatest detail and in which "anomalies" due to the effects of the medium are least to be expected. The first most striking fact is that the error in the determination of the enthalpy of activation $\Delta H^{\neq}$ quoted in different communications varies within wide limits (from 2–3% to 20–25%). Furthermore, even for the classical cyclohexane molecule, the differences between the $\Delta H^{\neq}$ reported by different workers but obtained under similar experimental conditions (from 38.0 to 48.1 kJ mol^{-1}) greatly exceed the experimental errors quoted in the relevant communications (±0.4–1.0 kJ mol^{-1}). A selection of data can be found in a number of communications.[14,15,50,51] These factors in essence ruled out a comparative analysis, because the real effects were in most cases concealed in the actual errors of the method. There existed also the no less important problem of explaining the anomalously large negative and positive activation entropies $\Delta S^{\neq}$ (~25 e.u. for a reported accuracy to within 3–4 e.u.)[34] for a wide variety of compounds. The anomalies enumerated above are observed more strikingly in the analysis of data characterising the rotation about the partially double C–N bond in amides and related systems.[10,34,52] These anomalies, which were not explained at the time, to some extent discredited the DNMR method.

We shall briefly consider the problems relating to the mutual exchange processes for which a general analysis of the sources of experimental and computational errors has

been carried out.[34] With small stipulations, the conclusions reached can be wholly applied also to the case of non-mutual two-sided exchange.

Intramolecular exchange processes are known to be described by the Eyring and Wynn-Jones equations:[53,54]

$$\ln(k/T) = -\Delta H^{\neq}/RT + \Delta S^{\neq}/R \qquad (12)$$

$$-\Delta G^{\neq} = RT \ln \frac{kh\varkappa}{k_b T} \qquad (13)$$

Since the free energy of activation $\Delta G^{\neq}$ is determined "at a point", its values depend only slightly on the systematic errors and can be determined with a high degree of accuracy.[34,46,55,56] In precision experiments, where the temperature is determined to within not more than 0.5 K and the rate constant k is found by the ATLS method, the error of the estimate of $\Delta G^{\neq}$ may not exceed ±0.15 kJ mol^{-1}. In the standard kinetic studies, an accuracy to within a quantity of the order of 0.8 kJ mol^{-1} can be readily attained. It is of interest to note that a relative 100% error in the determination of k for a hypothetical exchange model ($T = 300$ K, $k = 100$ s^{-1}), with an error of ±6 K in the determination of temperature, leads to a relative error in the estimate of $\Delta G^{\neq}$ at the level of only 4.5%.

The enthaly $\Delta H^{\neq}$ and entropy $\Delta S^{\neq}$ of activation are found as the coefficients of the linear relation between $\ln(k/T)$ and T^{-1} based on Eqn.(12). The use of the Arrhenius equation $k = A_0 \exp(-E_a/RT)$ is less preferable because the condition that the frequency factor A_0 and the activation energy E_a are independent of temperature holds less vigorously. Calculation of $\Delta G^{\neq}$ by the equation

$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq} \qquad (14)$$

is unjustified, because the advantage of accuracy, which is guaranteed by the direct calculation using Eqn.(13), is thereby lost.

The accuracy of the estimation of the constant k depends mainly on the extent to which the optimum experimental conditions can be fulfilled, because there are no fundamental difficulties in the mathematical treatment of the spectra. The constant k can be estimated in two ways: by the one-parameter procedure or by the ATLS method. In the one-parameter method simple analytical relations between the constant k and some spectroscopic parameter, which can be obtained in the simplest cases, are used. The methods involving these relations have been discussed in detail.[18,19,31,34,50] An exhaustive analysis of the limits of applicability of the approximate formulae and the errors in the determination of k has been carried out.[34,57] The principal difficulty consists in the fact that the use of approximate relations yields a number of experimental points which is inadequate for a statistical treatment and as a result gives rise to a large random error. The size of the deviations depends on how rigorously the conditions of the approximation hold and in certain cases can exceed the random errors to such an extent that the value of the activation data obtained becomes doubtful. These systematic errors, which are difficult to take into account and which lead to large negative values of the entropy factor $\Delta S^{\neq}$, are also largely responsible for the "anomalous" values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$.

It has been shown[58,59] by means of special comparative analysis of the temperature variations of the spectrum that under favourable conditions the relative error in the estimation of $\Delta H^{\neq}$ with the aid of approximate formulae is not less than 2–3 kJ mol^{-1}, while ATLS yields an error of the order of 0.6–0.8 kJ mol^{-1}. Under these conditions, the differences between the average values of $\Delta H^{\neq}$ reached 20% (the approximate methods yield unduly low $\Delta H^{\neq}$). The attempts to improve the approximate formulae,[60] including the procedure involving the subdivision of the kinetic range into five intervals instead of the usual three,[61] do not in essence alter the situation. The systematic error factor can be to some extent weakened when the experimental conditions permit the employment of the approximate formulae over the entire kinetic range.[62] The use of these formulae is at present justified only in the region of slow exchange and for the determination of k at the collapse temperature T_C from the ^{13}C NMR spectra, because in the simplest exchange systems, where the one-parameter method is applicable, the line form can be readily calculated on a minicomputer under laboratory conditions.

In the ATLS method the rate constant k is found either by a visual comparison of the calculated spectra and spectra observed at a certain temperature or by resorting to iterative procedures (the method of "digitalisation of the spectra").[63,64]

According to Sandstrom's data,[34] the relative error of the constant k estimated by the spectrum digitalisation method is 5%, i.e. is of the same order of magnitude as in the visual comparison method; in other words, the accuracy of the determination of k by both methods approaches the limit set by the experimental error. However, in the analysis of the exchange in complex spin systems the visual comparison method is sometimes preferable.[65,66] We may note that, when the number of experimental points is sufficient, the method of least squares yields a random error in the estimation of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ comparable to the limit of accuracy under the conditions of a precision experiment.

The optimum conditions of the DNMR experiment are well known.[15,34,46] The importance of conditions such as a slow pass, the absence of phase and amplitude distortions, the monitoring of the resolution over the entire temperature range, etc. is self-evident. Numerous procedures for the measurement of the temperature of the specimen with a high accuracy are known[34] (±0.2–±0.5 K), so that the important problem of the measurement of the specimen temperature can also be excluded from consideration. We may note that in standard DNMR experiments the temperature of the specimen is determined indirectly from the readings of the instruments in the circuit for the electronic stabilisation of the temperature of the heat exchanger stream. Since the temperature calibration is extremely sensitive to the [heat exchanger] flow rate in the region of low temperatures, the readings of the instruments at temperatures below 203 K are as a rule too low, which leads to considerable systematic errors in the determination of $\Delta H^{\neq}$. If an internal NMR thermometer cannot be used for some reason, it is necessary to measure the temperature directly before and after recording each spectrum. The size of the temperature range is undoubtedly important, but, since it is determined solely by the characteristics of the specimen itself, it is necessary to take into account only that the greatest accuracy is achieved for a uniform distribution of experimental points over the temperature range.[34]

The principal source of systematic errors, which is not always subjected to a realistic assessment, is the errors in the determination of the parameters of the spectrum of the exchange partners and the difficulties in the establishment of their temperature variations, which is particularly important in systems involving a complex exchange. This problem is closely intertwined with the general problem of the role of the medium in kinetic experiments and assumes exceptional importance in experiments starting "with the specimen" (mainly in low-temperature studies), because the substance determines both the kinetic range (and hence also the temperature range of the measurements) and the conditions in the medium (these problems have not been reflected in the review literature concerning the solvent effect in NMR spectroscopy[67,68]).

Special difficulties do not arise when it is possible to record a series of spectra in the regions of slow and rapid exchange, since in this case it is possible to obtain not only sufficiently accurate values of δ, J, and $^*T_2$ but also their temperature variations in an analytical form, which are then taken into account in the ATLS. In such cases it is possible to obtain a high accuracy in the determination of the activation parameters: ±0.4–0.08 kJ mol^{-1} for $\Delta H^{\neq}$ and ±0.5–1.0 e.u. for $\Delta S^{\neq}$ [65,66,69] Since it is as a rule difficult to take into account all the sources of systematic errors, it is more reasonable to quote the overall error, which is of the order of ±2 kJ mol^{-1} for $\Delta H^{\neq}$ and ±2.5 e.u. for $\Delta S^{\neq}$ according to the data of Allerhand et al.[57] We may note that it is frequently necessary to introduce the spectroscopic parameters to some extent arbitrarily and one has to postulate just as arbitrarily that their intrinsic (non-exchange) temperature dependence has been maintained over the entire range of the measurements.

The error can therefore prove to be even greater, for example in the solution of dynamic problems in the low-temperature region where experimenters are forced to employ mixtures of solvent which behave differently in different combinations and at a different temperature.[70] The medium effect may become more difficult to take into account when the molecule is non-polar overall but its individual fragments are highly polar. This situation has been observed using specific solvents such as acetone, dimethyl sulphoxide, benzene, and chloroform, which tend to form complexes, hydrogen bonds, etc. (cases where the solvent, for example, chloroform, induces the same reversible changes as the usual intramolecular exchange[71] are not considered here). Such characteristics of the behaviour are to a large extent responsible for the "apparent effects" of the solvent on the activation parameters. It is in fact precisely this factor and not the use of approximate formulae, as believed by Sergeev[15] and Sandstrom,[34] and the simplifcation of the spectrum, as claimed by Ionin et al.,[8] that is responsible for the frequently quoted anomalous values of E_a in dimethylformamide and other amides.[34,52,59,72] Thus use of approximate formulae merely increases the error.[73,74]

From the standpoint of the correctness of the comparative analysis of the activation data obtained in different solvents, particularly for systems with intramolecular non-mutual exchange, the actual dependence of these data on the type of solvent and on the concentration of the test substance in solution is of special interest.

We shall now turn to the results of precision experiments designed to investigate the influence of the solvent on $\Delta H^{\neq}$. The enthalpy of activation for cyclohexane ring inversion is almost independent of the type of solvent (methylcyclohexane, CS_2, hexadeuterioacetone)[75] and varies within the limits ±4 kJ mol^{-1} for acetone (in CCl_4, CH_2Cl_2, and $CDCl_3$ as solvents).[76] In amides and related systems the solvent effects on the enthalpy of activation for rotation about the C–N bond are expressed by a quantity of the order of ±4 kJ mol^{-1};[71,77–80] an appreciable concentration dependence has also not been observed.

For systems with non-mutual exchange, such reliable results are not available. However, one can use data for the influence of the type of solvent on the enthalpy of the conformational equilibrium ΔH_0.[70] For example, the energy difference between the rotational isomers of 1-chloro-2-fluoroethane changes by 1 kcal mol^{-1} on dissolution in cyclohexane, while the corresponding change for *trans*-1,2-dichlorocyclohexane is by 0.89 kcal mol^{-1} [the correction for the temperature dependence of the dielectric constant $\varepsilon(T)$ was not taken into account]. It has been shown[81] that, within the framework of the theory of reactive fields, the correction for the temperature dependence of $\varepsilon(T)$may be neglected in estimating the influence of the solvent on the conformational equilibrium with the aid of NMR: in substituted 1,3,2-dioxaphosphorinanes ΔH_0 varies within the limits 3.5–1 kJ mol^{-1} in a series of solvents—acetonitrile, acetone, methylene chloride, and carbon tetrachloride. Thus the medium factor can be taken into account in the comparative analysis of $\Delta H^{\neq}$, provided that the differences ($\Delta\Delta$) between the different media exceed 4 kJ mol^{-1}. For the free energy of activation, this range of $\Delta\Delta$ values is ±0.3–0.4 kJ mol^{-1} and for $\Delta S^{\neq}$ the $\Delta\Delta$ vary from ±4 to ±5 e.u. The quantities $\pm\Delta\Delta$ lie within a comparison region which can be easily established by analysing the activation data obtained for the same compounds under similar experimental conditions and using similar methods for the interpretation of the spectra (for example, on the basis of the data for cyclohexane quoted above). The same range of $\pm\Delta\Delta$ values has been obtained for the activation parameters determined in standard kinetic NMR experiments.

The discussion of the questions related to the effect of the solvent on activation parameters is outside the framework of the present review. There are numerous publications devoted to this problem.[82–85] It is very likely that in the immediate future, when it will be possible to survey the results of kinetic studies in highly diluted solutions and in the gas phase, the approach to this problem and the existing ideas will undergo radical changes. We may note that the temperature variation of the chemical shifts for reference compounds (tetramethylsiloxane, hexamethyldisiloxane, and benzene)[86–88] does not affect significantly the accuracy of the estimation of the activation data.

The questions concerning the experimental error become particularly important in the study of complex exchange, because here the accuracy is much more significant than in a standard kinetic experiment: insufficiently correct determination of the limits of the probable values of the activation parameters can cause an incorrect treatment of the exchange situation or can lead to the formulation of erroneous ideas about the molecular dynamics of the chemical system investigated.

The intepretation of the activation parameters for chemical exchange is to some extent an independent field of study, but, since these parameters are determined mainly by DNMR, the questions concerning their interpretation are deal with in virtually every serious DNMR study.

Since most of the chemical exchange processes involving polyatomic molecules take place without the participation of the excited levels of the molecule, the transmission coefficient κ in Eqn.(13) is assumed to be 1 or 0.5. The contribution of tunnelling to κ is neglected. This contribution becomes effective for low barriers to interconversions for molecules with few and light atoms.[89]

The constant k is related to the difference between the zero-point energy vibrations in the transition and ground states E_0 by the expression

$$k = \varkappa \frac{k_b T Q^{\neq}}{hQ} \exp(-E_0/RT) , \qquad (15)$$

where $Q^{\neq}$ and Q are the partition functions for the transition and ground states and the relation between E_0 and V (see Figure), which is found with the aid of quantum-chemical calculations of the potential energy surface, is defined by the formula

$$E_0 = V + \sum_i^{\text{trans}} h\nu_i/2 - \sum_j^{\text{gr}} h\nu_j/2 ,$$

where the summation is carried out over the vibrational degrees of freedom for the transition and ground states.

It is assumed that all the vibration frequencies ν_i and ν_j are approximately the same with the exception of the single frequency ν, corresponding to movement along the reaction coordination. The difference between E_0 and V is $6\bar{\nu}$ kJ mol^{-1} ($\bar{\nu}$ is the wavenumber in cm^{-1}) and must be taken into account in the most accurate calculation; when the process is described in terms of torsional vibrations, whose frequencies are much lower, the above difference can be neglected. It follows from Eqn.(15) that

$$\Delta H^{\neq} = E_0 + RT^2 \, \mathrm{d} \ln \frac{Q^{\neq}}{Q} / \mathrm{d}T , \qquad (16)$$

$$\Delta G^{\neq} = E_0 - RT \ln \frac{Q^{\neq}}{Q} , \qquad (17)$$

$$\Delta S^{\neq} = R \ln \frac{Q^{\neq}}{Q} + RT \frac{\mathrm{d}}{\mathrm{d}T} \left(\ln \frac{Q^{\neq}}{Q} \right) . \qquad (18)$$

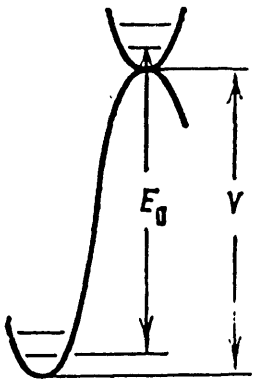


Diagram of the relative vibrational energy levels of the molecule: V = calculated theoretical energy; E_0 = zero-point vibration energy.

It has been suggested that the energy levels of the translational, rotational, and vibrational movements are mutually independent, i.e. $Q = Q_{trans}Q_{rot}Q_{vibr}$. For intramolecular exchange processes, evidently $Q_{trans} = Q_{trans}$ [sic].

(a) The activation enthalpy $\Delta H^{\neq}$. Since, as will be shown below, the ratio $Q^{\neq}_{rot}/Q_{rot}$ is independent of temperature, only the contribution of the vibrational partition functions Q_{vibr} must be taken into account in Eqn.(16). These partition functions differ only by the contribution q_r, which is determined by the degree of freedom of the vibrational movement at a frequency ν_r, which is absent in the transition state. Then

$$\frac{\mathrm{d}}{\mathrm{d}T} \left(\ln \frac{Q^{\neq}}{Q} \right) \simeq \frac{\mathrm{d}}{\mathrm{d}T} \ln \left(\frac{1}{q_r} \right) = \frac{\mathrm{d}}{\mathrm{d}T} \left\{ \ln \left[1 - \exp \left(- \frac{h\nu_r}{k_b T} \right) \right] \right\} ,$$

whence

$$\Delta H^{\neq} = E_0 - R \frac{h\nu_r/k_b}{\exp (h\nu_r/k_b T) - 1} . \qquad (19)$$

Thus $\Delta H^{\neq}$ depends on the temperature, but this dependence is not very pronounced and may be neglected. The difference $\Delta H^{\neq} - E_0$ approaches RT in the limit (at high values of T or at low frequencies ν_r) and can be calculated in principle.

The exceptional value of acurate experimental $\Delta H^{\neq}$ with correctly applied corrections is evident, since only by comparison with the latter is it possible to achieve a reasonable compromise in quantum-chemical calculations on the barriers. This applies both to *ab initio* calculations and to quantum-chemical calculations in terms of semiempirical approximations.[89-91]

The results of calculations have been discussed in the literature.[34,51] Strictly speaking, for comparison with such calculations, it is necessary to have the results of experiments in the gas phase, which, as will be shown below, lead to different values of $\Delta H^{\neq}$.

(b) The activation entropy $\Delta S^{\neq}$. This is a more "dynamic" activation parameter than $\Delta H^{\neq}$, but at the same time it is more difficult to use it for predicting the transition state. However, the view concerning this parameter has become optimistic in recent years. The initial scepticism was caused both by the large errors in the experimental estimates and by the problematic nature of the theoretical calculations of the entropy of the transition state. As a palliative measure, it was suggested that only the statistical contribution to $\Delta S^{\neq}$ be used on the basis of the symmetry properties of the molecule in the ground and transition states. This approach appears entirely convincing, because, subject to the assumptions underlying the estimation of the contribution of vibrational degrees of freedom to $\Delta H^{\neq}$, the contribution of the latter to $\Delta S^{\neq}$ is negligible[34] ($-0.20R-0.03R$). Since the principal moments of inertia of the molecule I_A, I_B, and I_C in the ground and transition states can be assumed to be equal, it follows that the contribution

$$Q_{rot} = \frac{\pi^{1/2}}{\sigma} \left(\frac{8\pi k_b T}{h^2} \right) (I_A I_B I_C)^{1/2}$$

is determined only by the term $\sigma/\sigma^{\neq}$, where σ and $\sigma^{\neq}$ are the group orders of the pure rotations in the ground and transition states. Eqn.(18) can then be written in the form

$$\Delta S^{\neq} = R \ln \sigma/\sigma^{\neq} . \qquad (20)$$

An additional term, namely the entropy of mixing $\Delta S^{\neq}_{mix}$, which takes into account the multiplicity of the degeneracy of the states, must be introduced into this equation:

$$\Delta S^{\neq} = -R \sum_i P_i \ln P_i ,$$

where P_i is the fraction of molecules passing through each transition state.

An alternative approach to the estimation of the statistical contribution to ΔS, consisting in the direct estimation of the number of independent ways in which the barrier can be crossed, is available. A discussion about these questions can be found in the literature.[34,92] However, analysis of a large amount of experimental data leads to the conclusion that this approach does not solve the general problem and furthermore is unjustified even in the simplest case—the description of the inversion of the ring in cyclohexane derivatives,[66] and it is essential to take into account all the contributions to $\Delta S^{\neq}$. However, although the difficulties expected in this procedure are evident, the conclusions reached by Hoffner et al.[66] give rise to a definite optimism. In certain cases it may be useful to discuss the problems in terms of the contributions to the partition functions by the rotational degrees of freedom of the internal rotors; however, this contribution is also insignificant.[34]

The above remarks concerning the corrections to $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and the prospects for the employment of these quantities for the prediction of the transition state apply primarily to systems with the simplest form of the barrier profile under conditions where there are no medium effects. Here the

expected contributions to $\Delta S^{\neq}$ are small, of the order of magnitude of ±2 e.u., and comparable to the contribution of the statistical factor, while the accuracy of the experimental estimate can be raised to ±0.5 e.u. However, this problem has other aspects associated with the interpretation of the $\Delta S^{\neq}$ for a wide variety of compounds which are not merely of theoretical interest. These include the interpretation of the anomalously large positive and negative activation entropies, greatly exceeding their standard experimental error. Qualitatively, these effects have been explained as "entropy effects" of the highly polar interactions: they are caused by the considerable difference between the types of solvation of the molecules in the ground and transition states.[34,82] The sign of $\Delta S^{\neq}$ is determined by the relative polarity of these compounds: the large negative values correspond to molecules with a more polar form of the ground state (of the entire molecule or its individual fragments). It has been suggested that these effects can be used to predict the structure of the transition state.[83]

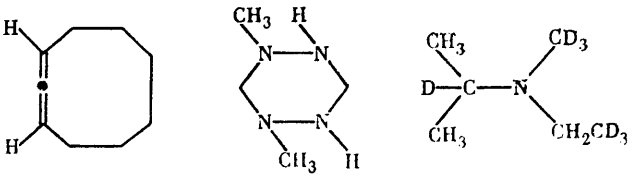
Another manifestation of the effects of this kind is large negative values of $\Delta S^{\neq}$ (up to −20– −30 e.u.), which are typical for tautomeric transformations in cyclic phosphoranes,[93] intramolecular phosphorotropic 1,3-migrations in a series of phosphorylated amidines,[94] and 1,3-sulphenyl migrations in amidine systems.[95] The negative entropies in the first two cases probably reflect the multistage mechanism of the processes described. Clearly, for such systems, theoretical calculations of the $\Delta S^{\neq}$ are hardly feasible in the immediate future. Nevertheless, the prospects for the employment of $\Delta S^{\neq}$ for the prediction of the transition state or at least for the explanation of the experimental results are entirely optimistic, particularly in the case where it is possible to develop reliable semiempirical rules in conjunction with the employment of a correct comparison of data for model compounds.

(c) The free energy of activation $\Delta G^{\neq}$. The high accuracy, the simplicity of the experimental estimation, and the principle of linearity[96,97] have been responsible for the employment of the most varied correlations of this parameter with the properties of the substituents, the medium, etc. in describing intramolecular exchange processes. Certain examples of such correlations have been given by Spaargaren et al.[58] However, we do not consider it necessary to discuss them within the framework of this review. We shall only mention the lack of validity of numerous discussions concerning the activation barriers ($\Delta H^{\neq}$) using free energy of activation data. Such identification is strictly speaking possible when the assumptions underlying the derivation of Eqns. (16)–(20) are valid. Furthermore, when the ATLS has not been carried out with a subsequent estimation of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, the insensitivity of $\Delta G^{\neq}$ to errors in the determination of k and even to the values of k themselves can lead to an incorrect assessment of the exchange situation and hence to errors in the interpretation of different effects influencing the exchange processes. Evidently, in systems with a complex chemical exchange, the use of only the one parameter $\Delta G^{\neq}$ is impermissible.

3. Experimental Studies of Multiparameter Chemical Exchange

We shall consider more fully the studies by the ATLS DNMR method of systems in which a multiparameter exchange is observed and the constant k is determined from the temperature evolution of one group of lines in the spectrum.

In those cases where the processes are separated by a wide temperature range, it is in most cases possible to achieve a separate description of these processes, for example, in terms of the changes in the ^{13}C NMR spectra of cyclonona-1,2-diene (I) in the temperature range 96–263 K.[98]



(I) (II) (III)

The resonance line of the carbon atom in the C–H group, which is a singlet at room temperature, splits into two lines at 123 K with an integral intensity ratio of 2 : 1, of which one, the low-field line, is greatly broadened; on further decrease of temperature, it divides into two lines of equal intensity (at 103 K). These spectral changes correspond to two intramolecular processes: (a) the pseudorotation of the dominant (asymmetric) conformation, which averages out two non-equivalent signals; (b) the interconversion of the type "dominant" form ⇌ minor "symmetrical" conformation, which is responsible for the merging of all the signals into a singlet. Anet and Yavari[98] were able to determine the kinetic parameters of these processes with adequate accuracy.

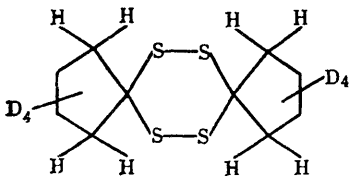
The rates of intramolecular topomerisation have been determined with the aid of the ATLS of the signal of the methylene protons in the ^1H NMR spectra of 1,4-dimethylhexahydro-1,2,4,5-tetrazine (II):[99] the rates of ring inversion and of the inversion of the bond pyramid at the nitrogen atom. Here the changes in the spectrum of the CH_2NH fragment in the temperature range 233–273 K are entirely due to the change in the rate of inversion of the nitrogen atom associated with the intermolecular hydrogen exchange involving the NH groups: the rate constants k were obtained on the assumption that the rate of ring topomerisation is low and does not influence the observed line form. The temperature range of the observed changes in the spectrum as a consequence of the topomerisation of the ring was 253–310 K.

Two intramolecular processes in deuteriated *N*-ethyl-*N*-methylisopropylamine (III) have been investigated:[100] (a) the inversion of the bond pyramid at the nitrogen atom, which is manifested by the exchange broadening of the ^1H NMR signals in the temperature range ~133–152 K, and (b) the rotation about the C–N bond, which contributes to the change in the ^1H NMR line form at 101–124 K. The kinetic parameters of both processes have been estimated on the assumption that the rotation takes place under the conditions of hindered inversion.

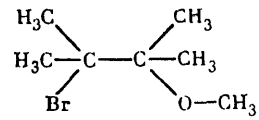
In this case, when the exchange processes responsible for the broadening of the NMR lines are separated by a short temperature range (20–30 K), the task of finding the kinetic parameters may be greatly complicated as a consequence of the uncertainty, noted above, in the determination of the constant k not only in the region of fast exchange but also in the region of slow exchange. If the signals of the "frozen out" forms are characteristic and fairly well separated in terms of the chemical shift scale, then in some cases, for example, when the region of the slow exchange covers a wide temperature range, it is possible to determine the kinetic and activation parameters for exchange processes on the basis of the ATLS of the low-temperature NMR spectrum.

The temperature dependence of the ^1H NMR spectrum of 3,3,6,6-bis(tetradeuteriotetramethylene)-*S*-tetrathiane (IV) has been described in this way[101] within the framework of the chair–twist–chair*–twist*# equilibrium, because the temperature range corresponding to the slow (in terms of the NMR scale) exchange is ~50 K:

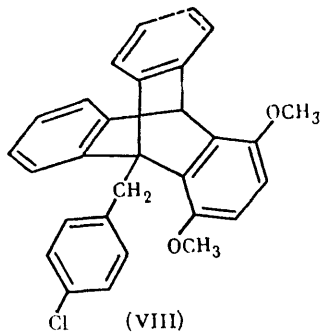
The asterisk denotes inverted structures.



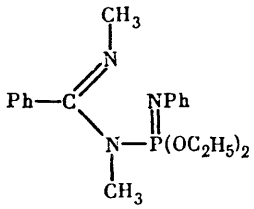
(IV)



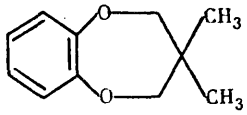
(VII)



(VIII)



(V)



(VI)

The authors showed that the introduction of a rate constant for the direct chair ⇌ chair* or twist ⇌ twist* transitions leads to a deviation of the calculated line form from the experimental form, whence it followed that the energy barriers in these transitions should indeed be higher than for the chair ⇌ twist exchange.

The kinetics of *Z*–*E* isomerisation and phosphorotropic tautomeric processes have been investigated on the same lines[94] for N^1N^2-diethoxy-N^1N^2-dimethyl-*N*-phenyliminophosphonylbenzamidine (V) (in this case the line form is calculated mainly in the region of slow exchange at 418–445 K). In those instances where the NMR spectra of the "frozen out" forms are only slightly separated in terms of the chemical shift scale, the uncertainty in the determination of the constant *k* may prove to be significant over the entire temperature range of the spectroscopic changes and can lead to errors in the determination of the activation parameters. Thus, in a study[102] of 3,3-dimethyl-1,5-benzodioxepan (VI) the ^{1}H NMR spectra of the "frozen out" chair and twist forms were observed at 133 K. The rate constants for the chair–chair and chair–twist transitions in the inversion of compound (VI) were determined by the ATLS method, but the authors[102] do not consider it possible to discuss the energy relations of the processes on the ground of the unreliability of the determination of temperature, the inaccuracy in the determination of the quantities $1/^*T_2$, and also the use over the entire temperature range of postulated relative proportions of the conformers; in the authors view, the anomalously large negative $\Delta S^{\neq}$ (−15 ± 5 e.u.) are a consequence of these errors. We believe that this is caused to a large extent by the erroneous nature of the estimation of the kinetic parameters of the exchange as a result of the uncertainty in the derivation of these parameters, because the changes in the spectrum corresponding to the above processes are manifested in virtually the same temperature range and the authors[102] do not quote alternative calculations of the rate constant which are essential in such cases.

A ^{1}H NMR study of the hindered rotation about the C–C bond in a series of 2-alkoxy-3-halogeno-2,3-dimethylbutenes has been reported.[103] The singlet due to the methyl groups (CH_3^*), observed in the spectrum of compound (VII) at room temperature splits into three lines at 162.5 K: an intense singlet and two lines with equal integral intensities, the ratio of the integral intensity of the first line to the sum of the other two being 43 : 57. This change in the signal of the methyl groups is caused by the decrease of the rate of rotation about the C–C bond when the rotational process can be regarded as exchange between the *trans*- and *gauche*-forms (a) and between two *gauche*-forms (b). Using the ATLS, the authors point out that it is impossible to differentiate the temperature dependence of the rate of the second process, because the theoretical line forms obtained with and without allowance for k_b do not reveal a significant difference (the spectra for $k_b = 0$ and $k_a = k_b$ were calculated) and are close to the observed line forms.

A study[104] of the hindered rotation about the C–C bond in 9-(*p*-chlorobenzyl)-1,4-dimethoxytriptycene (VIII) is instructive in this connection. At a low temperature (~246 K) the ^{1}H NMR signals of the methylene protons consist of an AB quartet and a singlet, due to the *d*-, *l*-, and *meso*-forms respectively. An increase of temperature leads to the merging of these signals into a singlet. It has been shown that, for different selections of the rate constant k_1 and k_2 for the *meso* ⇌ *d*(*l*) and *d* ⇌ *l* exchange processes respectively, the calculated line form agrees with the observed line form and the ranges of the constants k_1 or k_2 in which this occurs are comparable to the true values of k_1 or k_2. The authors[104] formulated the problem of the estimation of the kinetic parameters of exchange processes having similar rates and responsible for the exchange-induced broadening of a single group of NMR lines, but do not propose a solution. The solution of a similar problem for mutually independent processes has been described.[105] The uncertainty in the estimates of k_1 and k_2 (for two independent processes) can be expressed graphically by a family of $\ln k_1 - \ln k_2$ "iso-F" curves, along which the theoretical line form agrees with the experimental line form at a specific temperature when different sets of k_1 and k_2 are used. In order to find the solution, a series of straight lines intersecting the "iso-F" curves are drawn and the points of intersection are transferred to $\ln k_1 - T^{-1}$ and $\ln k_2 - T^1$ plots. A unique solution, corresponding to a real process, is found from the minimum standard deviation of the linear relations found in this way between $\ln k_1$ and $\ln k_2$ and temperature.

The examples examined are distinguished by the simplicity of the exchange situation, because the exchange mechanism is known. However, there are many systems in which there is a possibility of different versions of the exchange process and the choice of an unambiguous solution is an extremely complex problem, which probable cannot always be solved by the ATLS DNMR method. It can be solved fairly rigorously for the simplest case where the intramolecular exchange is characterised by a single rate constant and it remains only to find an alternative exchange mechanism. This problem has

been discussed in detail in a review,[30] where it is shown that in such cases agreement between the calculated and experimental line forms over the entire temperature range is a criterion of the reliability of the selected model. However, it is not always possible to predict the ways in which the exchange mechanisms can increase in complexity or to describe quantitatively this kind of chemical exchange in cases where an increase in its complexity has been established experimentally.

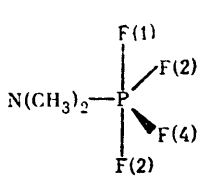
On the basis of the analysis of numerous experimental data and our own studies, we propose three criteria for the reliability of the description of complex chemical exchange, whose employment makes it possible to avoid errors in the interpretation of DNMR data:[106]

1. agreement between the calculated and observed NMR line forms over the entire temperature range;
2. the linearity of the temperature variation of the rate constants for the processes;
3. agreement between the activation parameters obtained as a result of the analysis of multiparameter exchange with the analogous values for systems where the particular process is unique.

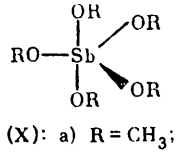
Examples which logically reflect the application of these criteria with increasing complexity of the exchange situation are presented below. One of the first studies of this kind was that of Saunders (see Steigel[30]), who investigated the degenerate shift of the methyl group in the heptamethylbenzenium ion. Two possible versions of the exchange were considered: in one case the methyl group passes to a neighbouring position (the 1,2-shift), whereas in the other the shift is random. Depending on the pathway followed in the shift, two versions of the transitional structure are also possible. Analysis of the ^{1}H NMR line form made it possible to give preference to the first exchange mechanism. The problem of the intramolecular exchange of the $CuP(C_2H_5)_3$ group in the $C_5H_5CuP(C_2H_5)_3$ molecule, in which the group either shifts to a neighbouring position or there is exchange between the 1- and 3-positions, has been solved analogously.[30,107] The calculated line forms for these exchange mechanisms differ appreciably; comparison with experiment has shown that the exchange proceeds via the 1,2-shift mechanism.

Processes leading to the averaging of the ^{1}H NMR spectra of *O*-acyl-3,7-dibenzyltropolones have been identified.[108] The ATLS method enabled the authors[108] to identify, together with the acyltropic tautomerism, two conformational transitions, namely the rotation of the acyloxy-group about the troponyl–O bond and the rotation of the acyl group in the acyloxy-fragment.

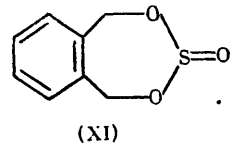
In the study of intramolecular dynamic processes in the phosphorane $PF_4N(CH_3)_2$ (IX),[30,109] it proved possible to distinguish two mechanisms of the rearrangement: the one-pair and two-pair ligand exchange processes in the pseudorotation of the bonds, i.e. the 1–4, 1–3, 2–3, and 2–4 or (1–3)(2–4) and (1–4)(2–3) ligand exchange processes. Analysis of the ^{31}P NMR line form permitted the unambiguous selection of the second type of rearrangement:



(IX)



(X): a) $R = CH_3$; b) $R = CH(CH_3)_2$

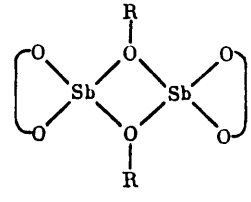


(XI)

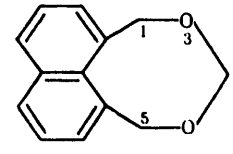
The possible mechanisms of the exchange in the dimeric structure of pentamethoxyantimony (Xa) have been examined.[110] It has been established that the mechanism according to which there is exchange between the dimeric structures (dissociation and formation of bridge bonds) operates and that, simultaneously with the rupture of the bridge bonds, the configuration of the bonds at the Sb atom changes, both processes being characterised by different rate constants.

The determination of the components of the conformational equilibrium using DNMR can be illustrated in relation to the analysis of the line form in the spectrum of the methylene protons of phthalyl sulphite (XI). The form of the low-temperature spectra indicates the appearance in solution of two forms[111,112] (two AB quartets). The "chair-a" conformation (with the axial position of the S=O bond) predominates. Additional arguments in favour of the second, "twist" conformation were obtained on the basis of the ATLS, because the exchange mechanism in which the low-field and high-field lines of the two AB quartets are averaged out corresponds to the real process. If the alternative "chair-e" conformation were realised, the mechanism would have corresponded to the averaging out of the high-field signal of the dominant form with the low-field form and conversely.

The use of the ATLS made it possible to establish for the first time that, as a result of the dynamic processes manifested in the ^{1}H NMR spectra, in the cyclic compounds of tricoordinate antimony the bond pyramid undergoes a change in its configuration.[113,114] It has been established that the monomeric form in the "chair-a" conformation and the dimeric form (XII) exist in solution and that exchange between them in fact reflects the evolution of the line form in the NMR spectra.



(XII)



(XIII)

In the examples quoted the first of the proposed criteria for the description of intramolecular chemical exchange processes in terms of DNMR was applied. Fundamental information about the validity of the description can be extracted from the analysis of the temperature dependence of the rate constant for the process described. When a suitable mathematical model of the real exchange mechanism is used, this dependence should be linear in terms of a plot of $\ln(k/T)$ against $1/T$ and, since changes in line form are observed over a narrow temperature range (~50 K), it should also be linear in terms of a plot of $\ln k$ against $1/T$. This approach is based on the high accuracy of the estimation of the activation parameters reached in the ATLS method.

A study of the molecular dynamics of 2,4-dioxa-3,5-dihydro-1*H*-cyclo-octa[*de*]naphthalene (XIII) showed[115] that calculation of the ^{1}H NMR line form for the methylene groups in the 1(5)- and 3-positions on the assumption of mutual conformational exchange led to its agreement with the experimental line form over the entire temperature range for both groups of protons. However, the differences between the values of k at the same temperature for the above groups of protons greatly exceeded the experimental error and the dependence of $\ln k$ on $1/T$ could not be fitted by a straight line. Analysis of the variation of the non-equivalence of the chemical shifts of the methylene protons at C(1) [C(5)]

in 3-*t*-butyl-2,4-dioxa-3,5-dihydro-1*H*-cyclo-octa[*de*]naphthalene (XIV) made it possible to establish that the change in the line form for compound (XIII) is caused by the chair–chair exchange in the presence of rapid chair–boat exchange. Calculation of the line form corresponding to this exchange mechanism, using the spectroscopic parameters of the "chair" and "boat" forms of compound (XIV) yielded a satisfactory linear temperature variation of the rate of the chair–chair transition for compound (XIII).

This principle was also used in the solution of the previously discussed problem of the separation of the contributions of the exchange processes occurring at similar rates and responsible for the exchange-induced broadening of one group of NMR lines.[105]

Using the same procedures, the "synchronous" nature of the rotation of a pair of rings in the collective internal rotation of the three aromatic rings in the triaryl derivatives of arsenic and phosphorus has been demonstrated[116] on the basis of the ATLS of the ^{19}F DNMR spectrum.

Finally there is a possibility of the situation where the changes in the NMR spectra are caused by processes whose spectroscopic assignment gives rise to no doubts and the $\ln(k/T)-1/T$ relation is linear. In this case it is necessary to employ a third criterion.

Thus, in the study quoted above,[99] identical activation energies were obtained for both processes and, on the basis of a comparison of this quantity with the literature data for similar processes, the authors concluded that their rates are limited by the inversion of the bond pyramid at the nitrogen atom. Olekhnovich et al.,[108] who noted the auxiliary role of the conformational transformations in acylotropic tautomerism, were guided by the same principle.

In the study quoted above,[110] approximately equal values of $\Delta H^{\neq}$ were obtained for the exchange of the dimer–dimer type involving compound (Xa) and for the pseudorotation of its bonds (~76 kJ mol^{-1}); the latter cannot be accounted for in terms of the ideas concerning the energy relations of the pseudorotation of the bonds of the pentacoordinate P, As, and Sb atoms, although the spectral changes in the case under consideration are consistent with the pseudorotation process. The study of the NMR for the monomeric compound (Xb) showed[110] that the barrier to the pseudorotation of the Sb^{V} bonds does not exceed 20 kJ mol^{-1}. The activation parameters for compound (Xa) were interpreted within the framework of ideas concerning the rate-limiting stages in the processes.

By virtue of the improvement in the computational procedures and in the apparatus, one can probably expect in the immediate years ahead a considerable progress in the study of systems with complex chemical exchange.

III. SPECIAL METHODS

1. The ATLS of Nuclei Other than ^{1}H

The exchange-induced broadening effects in the resonance absorption spectra of various nuclei with a spin of 1/2 (^{19}F, ^{13}C, ^{31}P, and ^{15}N) are described by the same equations as in the ^{1}H spectroscopy (the presence of a quadrupole moment in nuclei with a spin greater than 1/2 and their greater spin multiplicity make relaxation methods preferable to ATLS). The ^{19}F and ^{1}H NMR spectroscopic methods have similar sensitivities and the methods of the kinetic investigations using these nuclei differ little. The employment of the ATLS of the NMR spectra of the remaining nuclei has many features in common, which involve the sensitivity and the time scale of the method as well as the procedure used to record the spectra, which, considered together, distinguish the DNMR spectroscopy involving these nuclei from ^{1}H DNMR.

In the course of its rapid development, ^{13}C DNMR spectroscopy has already passed the inevitable period involving comparison with the scope of ^{1}H DNMR. Its advantages and, equally, its limitations and experimental difficulties have been demonstrated in relation to extensive experimental data,[27,29,34,117–119] which cannot be discussed within the framework of this review. We shall only touch upon some of the most important methodological aspects.

It is known that the range of the ^{13}C chemical shift (in p.p.m.) is ~20 times greater than that of the ^{1}H NMR shifts (or ~5 times greater in terms of frequency units). The range of the measurable rate constants therefore increases by a factor of 25 towards higher rates and collapse is reached at higher temperatures. However, one should note that, within the limits of a single structural fragment, an increase in the shift scale may not in fact occur.[113,120] In other cases the difference between the ^{13}C chemical shifts for the exchanging positions is so great that the advantage of a more extended time scale is transformed into a disadvantage of the method;[121] the region of the collapse and of the intermediate exchange occupies such a wide spectral range that the broadened spectral line merges with the base line. For "moderate" barriers (~40–60 kJ mol^{-1}), this region covers a wide temperature range and none of the regions of the rapid or slow exchange can be reached, which can lead to an erroneous interpretation of the spectrum.

In dynamic ^{13}C NMR with broad-band ^{1}H decoupling the exchange situation is relatively simple—it involves as a rule a two-sided exchange in a system of uncoupled spins, which has in fact led to numerous kinetic studies using ^{13}C NMR spectroscopy. However, serious experimental problems have been encountered, which must be taken into account in selecting the research methods. In the main they are associated with the low sensitivity of ^{13}C NMR spectroscopy and relaxation processes.

Special difficulties do not arise in studies with liquid specimens or with highly concentrated solutions. Here it is comparatively simple to attain a satisfactory signal-to-noise ratio in the region of the intermediate exchange in order to be able to employ the ATLS (naturally for moderate degrees of nonequivalence of the chemical shifts, amounting to ~200 Hz). However, it is usually necessary to work with dilute solutions, which requires a large number of accumulations. The time taken to record a single spectrum is so prolonged that the recording of a high quality spectrum in the region of intermediate exchange rates and collapse becomes extremely problematical, since it becomes essential to ensure a long-term stability of temperature and of its measurement.

This time factor becomes especially important in low-temperature measurements in solutions of sparingly soluble crystalline substances: after prolonged exposure to low temperatures, the substance crystallises. The measurement of temperature in the ^{13}C NMR method becomes very important in the recording of spectra with broad-band suppression of the ^{1}H signal, because the interaction of the microwave frequency radiation with a polar solvent leads to additional heating of the specimen (the degree of heating is proportional to the polarity of the solvent). For this reason, in those cases where a quantitative treatment of the temperature dependence of the ^{13}C NMR spectra is necessary, it is desirable to employ a ^{13}C NMR thermometer. The use of wide bulbs in order to increase the sensitivity creates certain difficulties in the measurement of temperature as a consequence of the high temperature gradient in the specimen (2 K cm^{-1}).

The relaxation processes are directly reflected in the accuracy of the determination of k from the exchange-induced broadening of the spectra. The point is that even in a single

exchange pair the relaxation times T_1 and the nuclear Overhauser effect (NOE) differ. This is clearly manifested in the region of a slow exchange, where the integral line intensities are inconsistent with the number of exchanging spins. An accurate analysis of the line form presupposes the knowledge of the temperature variation of T_1, which is not feasible owing to the chemical exchange effects.

Since the line width in the ^{13}C NMR spectra is just as small as in the ^{1}H NMR spectra, in kinetic studies it is very important to ensure the highest possible resolution determined by the capacity of the minicomputer. Such resolution is specified by the condition[34,122] $\Delta\nu = 2w/N$, where w is the width of the spectrum in the given frequency range and N the number of selected points on the descending component of the induction signal(DIS) (their uniform distribution on the DIS curve is assumed), i.e. $\Delta\nu$ is the distance between two points in the frequency range. Consequently the uncertainty in the determination of the line width is $2\Delta\nu$. Since the number N is limited by the capacity of the minicomputer, an improvement of the potential resolution is achieved by reducing w (in order to avoid the convolution of the spectrum, it is necessary to adjust the frequency range). For example, a resolution of 1.2 Hz is attained in the presence of 8192 points on the DIS curve for a width of the spectrum of 5000 Hz.[27] Since the error in the determination of the width of the exchange and non-exchange lines is ±1.2 Hz, for an exchange-induced broadening less than 10 Hz the constants k will be found with large errors. Another limiting factor and source of errors is the line broadening as a consequence of the residual splitting arising as the power of the microwave frequency field of the broad-band decoupling diminishes (the power is reduced in order to diminish the heating of the specimen).

It is easily seen that the ATLS method appplied to ^{13}C DNMR encounters serious difficulties and is justified only in those cases where the exchange problem cannot be solved by ^{1}H DNMR either due to the complexity of the spectra (for example, in the case of exchange in a five-spin or even more complex systems) or because the chemical exchange process itself cannot be observed.

We shall not dwell on well-known examples illustrating the inapplicability of ^{13}C DNMR spectroscopy to the study of certain types of chemical exchange, which can readily be identified by ^{1}H DNMR methods. We shall merely draw attention to the fact that the combined employment of both methods can be exceptionally useful in the analysis of systems with complex chemical exchange. The point is that in ^{13}C NMR spectroscopy one observes fairly frequently several exchange pairs simultaneously and the exchange processes can be manifested in different pairs. On the other hand, the same process can be reflected in different ways in the ^{1}H and ^{13}C NMR spectra, which makes it possible to avoid the uncertainty discussed previously. This approach has been illustrated by Sandstrom and Sjostrand.[123]

The ^{15}N NMR time scale is of the same order of magnitude (in terms of frequency units) as the ^{13}C NMR spectroscopic scale, but the sensitivity of ^{15}N spectroscopy is lower by two orders of magnitude than that of ^{13}C NMR. Kinetic studies on specimens with the natural abundance of the ^{15}N isotope therefore involve even greater difficulties. There has been only one investigation[124] of the hindered rotation about the C–N bond in L-arginine using ATLS. There have been more investigations using relaxation methods.[125] A number of studies have been carried out with the aid of the ATLS of the ^{15}N NMR spectra of enriched specimens, but these studies have been mainly devoted to intramolecular and intermolecular hydrogen exchange processes.[126–130].

The ^{31}P NMR time scale in frequency units is somewhat narrower than in carbon spectroscopy (by a factor of ~1.5), but, since the sensitivity of the ^{31}P NMR method is somewhat lower than that of ^{1}H NMR (by a factor of ~20), the difficulties are associated mainly with the relaxation processes when broad-band $^{31}P-\{^{1}H\}$ decoupling is used. There have been few studies carried out using ATLS. The intramolecular rearrangements in which the chemical shift of the signal due to the phosphorus nucleus remains unchanged but the line form is altered by virtue of the transposition of the spins linked to the ^{31}P nucleus are perhaps of greatest methodological interest.[109] Kinetic experiments under the conditions of selective $^{31}P-\{^{1}H\}$ decoupling will probably yield much information.

2. Kinetic Studies under Extreme Conditions. Gases. Liquids at High Pressures

Theoretical calculations of the activation and equilibrium parameters of chemical exchange are usually carried out for isolated molecules and until recently the calculated data have been compared with the results of studies in solutions. However, even the early ^{1}H DNMR data for the gas phase showed how incorrect is such a comparison.[131,132] There is no doubt that these experiments cannot be performed for every substance, but the exceptional value of experimental data of this kind has stimulated studies on these lines and their number has appreciably increased in recent years.

The main requirements which must be met by the given substance is a fairly high barrier to intramolecular transformations and volatility. A low concentration of the test substance is a very serious but not insurmountable obstacle in the experiments. Another cause of the reduced sensitivity is the broadening of the lines in the spectra for the gas phase owing to the low times T_1, because the mechanism of the spin–rotational relaxation in gases is more effective than in liquids.

The experimental technique has already been discussed.[132, 136] The Table presents the results of kinetic studies for the ATLS of the ^{1}H DNMR spectra for classical types of chemical exchange. On the basis of the very few data available, one can merely make general remarks. The temperature of the collapse with transition to the gas phase as well as the values of $\Delta H^{\neq}$ and k for different compounds vary in different ways. The times T_2 depend markedly on the pressure (the temperature and pressure dependences of the static parameters δ and J had been determined earlier and have been the subject of other investigations—see, for example, Raynes and Chadburn[138] and Bernstein[139]).

Interesting data have been obtained for the phase dependence of the rate constant and activation parameters for ring inversion in cyclohexane.[135,136] Assuming that the internal pressures in gaseous and liquid CS_2 at 298 K are respectively 0 and 3714 atm, while the difference between the values of $\Delta G^{\neq}$ in the gas phase and in the CS_2 solution is 370 cal mol^{-1}, then the activation volume is $\Delta V^{\neq} = -4$ cm^3 mol^{-1} [$\Delta V^{\neq} = (\partial G^{\neq}/\partial p)_T$]. This result is correlated with data obtained recently in the kinetic studies on cyclohexane ring inversion in various solvents at a variable pressure.[74] When the pressure is varied from 1 to 5000 atm, the $\Delta V^{\neq}$ vary from −5.0 cm^3 mol^{-1} (in acetone) to −1.5 cm^3 mol^{-1} (in $C_6D_{11}CD_3$), which is also consistent with the results of a study in which data for *NN*-dimethylacetamide were discussed.[140]

These experiments showed that, in the absence of strong electrostatic interactions, the activation parameters depend greatly on the state of aggregation. Few studies of this kind have been made. Experiments at a high pressure using shift reagents have been reported.[141] Data obtained in NMR studies of the influence of pressure on chemical kinetics[142] and molecular conformations[143,144] are available. The experimental technique is specific and has been discussed in the original communications.

Activation data for chemical exchange in liquid and gas phases.

Compound	Type of process	Conditions	T_c, K	$\Delta G^{\neq}$, kJ mol^{-1}	$\Delta H^{\neq}$, kJ mol^{-1}	$\Delta S^{\neq}$, e.u.	Refs.
NN-Dimethylnitrosamine	hindered rotation	pure liquid	456	97.4	—	—	[34, 131]
NN-Dimethylnitrosamine	hindered rotation	gas	431	88.4	—	—	[34, 131]
Aziridine	inversion of nitrogen	in CCl_4	298	72.7	76.1±2.0	−6.2±1.4	[132]
Aziridine	inversion of nitrogen	in decalin	298	71.5±3.0	63.9±1.6	+2.7±2.0	[132]
Aziridine	inversion of nitrogen	gas	338	72.0±0.2	63.5±2.6	−6.2±1.3	[132]
NN-Dimethylthioformamide	hindered rotation	pure liquid	473	106.6	—	—	[34, 133]
NN-Dimethylthioformamide	hindered rotation	gas	420	94.1	—	—	[34, 133]
NN-Dimethylacetamide	hindered rotation	in CCl_4	298	72.3	—	—	[77]
NN-Dimethylacetamide	hindered rotation	gas	305	65.5±0.4	—	—	[134]
NN-Dimethyltrifluoro-acetamide	hindered rotation	10% in CCl_4	—	74.4±1.6*	73.6±2.5	−0.6±2.0	[137]
NN-Dimethyltrifluoro-acetamide	hindered rotation	gas	—	68.5±2.0	67.3±2.0	−1.1±0.3	[137]
Cyclohexane	ring inversion	10% in CS_2	—	42.6	45.1	+2.8	[135, 136]
Cyclohexane	ring inversion	1% in CS_2	—	42.2	43.0	+0.6	[135, 136]
Cyclohexane	ring inversion	gas (333 kPa)	—	43.4	50.4	+5.7	[135, 136]

*Here and below in the Table the determinations were made at 298 K.

3. Special Methods

Fairly numerous methods, supplementing or modifying the classical ATLS method, are known. Many of these have been used since the beginning of intensive investigations of DNMR and are well known. They include the isotope tracer method,[15,34,145] the employment of lanthanide shift reagents,[34,146,147] and the direct stereomutation method (the equilibration method) proposed by Mannschreck[148] and developed in subsequent studies[149,150] (for a discussion, see Sergeev[15] and Sandstrom[34]). Studies of the internal movements of molecules dissolved in nematic media are of special interest. They are based on the high sensitivity of the spectra of partly oriented molecules to chemical exchange processes, which average out certain direct dipole–dipole interaction constants. Their energy barriers can be estimated quantitatively, provided that the intramolecular movement and the rotation of the molecules as a whole in the liquid crystal mesophase matrix are independent. The method involves also other assumptions and limitations, but it is nevertheless extremely attractive because it makes it possible to obtain activation parameters which cannot be determined by other procedures (low barriers, barriers in systems where there are no suitable NMR labels for investigation by standard methods).

A detailed discussion of this method, which is in essence a component of NMR investigations in the mesophase, may be found in the article of Emsley and Lindon.[151] We may note certain publications in recent years devoted to the study of ring inversion in S-trioxan,[152] the pseudorotation in cyclopentane,[153] and internal rotation in alkylamides in a polystyrene matrix.[154]

When spectrometers operating at markedly different frequencies ν_0 are available, it appears very attractive to make use of the simplicity and relatively high accuracy of the determination of k at T_c from a relation of the type $k = \pi\Delta\nu/2^{1/2}$ for mutual exchange, where $\Delta\nu$ is the limiting line separation. Since $\Delta\nu$ depends on ν_0, it follows that T_c also depends on ν_0 (in amides T_c changes by 3 K when the frequency is altered from 60 to 220 MHz). This method is believed[155] to guarantee a high accuracy of the estimation of $\Delta H^{\neq}$ and $\Delta S^{\neq}$. In individual instances this is probably valid, but one should note that the accuracy of the recording of collapse is low and is in fact lower the greater the rigour with which the condition governing the applicability of this formula is fulfilled. The collapse temperature T_c is determined to within 2 K and the presence of 3–4 points over a narrow range cannot ensure a high accuracy of the interpretation of an equation of type (12). However, the main deficiency of the method is the unjustifiably large consumption of apparatus time: in essence, it is necessary to carry out the entire kinetic experiment, from slow exchange to collapse, on several spectrometers, because, the occurrence of collapse must be determined very accurately. There is no doubt that in many cases it is essential to use the same NMR thermometer.

Major difficulties arise in the use of formulae for mutual exchange which relate k in the vicinity of collapse to the spectroscopic parameters and which include the working frequency ν_0 as the variable parameter.[156] The above methods have not found extensive application probably for this very reason. The use of the effect of the "concertina chemical shifts", arising when a train of four pulses with phase rotation by 90° is employed, appears more attractive.[122] In media of low viscosity, where there is no dipole–dipole broadening, the duration of the pulses can be regulated in such a way that the chemical shift scale varies from 0 to 1, while the indirect spin–spine coupling constants remain unaltered. This technique, which has become available in recent years, can prove extremely useful in the analysis of exchange in complex spin systems and in systems with multiparameter exchange (and naturally when the above methods with variation of ν_0 are employed).

The method involving a rapid change of the medium[157] has been proposed for the investigation of hindered rotation in molecules which cannot be heated owing to their thermal instability. It is applicable in the presence of fairly high energy barriers when the equilibrium depends markedly on the solvent polarity and the equilibration time is long enough to record the NMR spectra. The experimental technique is fairly simple: the test substance is rapidly mixed with the solvent with a markedly different polarity and the attainment of a new equilibrium at a certain temperature is then observed. The scope of the method has been illustrated in relation to the study of the hindered rotation about the C–C bond in 9-(2-methoxy-1-naphthyl)-9-fluorol.

A high accuracy of the estimation of $\Delta H^{\neq}$, to within 3 kJ mol^{-1}, was attained. The limitations of the method are self-evident: the usual problems involving the employment of mixed solvents and the inconsistency of the observed heights of the barriers with the quantities obtained in non-polar solvents remain. It is easily seen that the method is similar to the direct stereomutation method already mentioned.

4. Relaxation Methods

Standard selective relaxation methods make it possible to obtain the same information about chemical exchange processes as DNMR is a stationary regime, but their application in the region of intermediate rates of exchange is less preferable, mainly due to the high errors in the determination of the rate constant k. In the regions of slow and rapid exchange, which are limiting as regards the ATLS, the relaxation methods yield more accurate values of k.

Methods involving the use of relaxation processes, which can yield data inaccessible by the ATLS method, are known. One of these involves the measurement of the relaxation time T_1 in a rotating coordinate system.[34,158] The nuclear spin system is acted upon by a 90° microwave pulse with an amplitude B_1 along the x axis. At the instant when the precessing (with a frequency $\nu_1 = \gamma B_1/2\pi$) vector with a magnetisation M is aligned rigorously along the y axis, the phase of the pulse is altered by 90° and it is applied along the y axis. Since the vectors B_1 and M are now parallel, the vector M is maintained along the y axis. This entails an exponential decrease of the length of the vector M with a characteristic time T_1. In the simplest case of a two-sided exchange we have

$$(T_{1\rho}^{-1})_{exch} = T_{1\rho}^{-1} - T_1^{-1} = \frac{\pi^2 k \cdot \Delta\nu^2}{k^2 + 4\pi^2 \nu_1^2} .$$

This relation is valid subject to the conditions $\Delta\nu^2/k \ll 1$ and $\Delta\nu \ll \nu_1 \ll \nu_0$. The method makes it possible to measure rates in the range 10^3–10^6 s^{-1} and to determine $\Delta\nu$, which is impossible in direct experiments in this range of rates.

In another method, proposed by Hoffman and Forsen[24] and known as the "saturation transfer method", the direct NOE is used in systems with slow chemical exchange. A procedure based on the cross-relaxation NOE has also been developed.[160,161] The idea of the saturation transfer method is simple and has been described in a number of communications;[15,24,162] when nuclei in a position r are acted upon by an additional saturating microwave frequency field, the line intensity corresponding to the nuclear transitions in the position s changes provided that the nuclei are interchanged between these positions. The method is useful in studies of complex chemical exchange, but its application is restricted; the spectral lines corresponding to these positions must be sufficiently remote from one another to avoid the occurrence of beats associated with the two microwave frequencies employed. This difficulty can be readily overcome in ^{13}C NMR spectroscopy (an additional pulse generator is required for this purpose). The method permits the measurement of rate constants smaller by 2–3 orders of magnitude than in ATLS. Questions concerning its use with allowance for the possibilities of modern experimental techniques have been discussed in a number of communications.[163–165]

Kinetic studies employed 2-D spectroscopy, which in many cases constitute an alternative to the saturation transfer method, have been developed in recent years.[166–171] They will probably prove effective in the study of multiparameter exchange but hitherto they have mainly aroused much publicity and have been of a comparative character.

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DNMR, which is at present based on a highly sophisticated experimental technique, is undoubtedly a powerful method for the investigation of stereodynamics, tautomeric transformations, and other chemical exchange processes. In many cases its extensive possibilities make it possible to overcome difficulties in the study of systems with complex exchange. However, this does not resolve the general problem of the uncertainty arising in the use of ATLS and much effort is essential in this field to search for effective methods of analysis of the temperature variations of the NMR spectra.

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