Translated from *Uspekhi Khimii*, **55**, 743-768 (1986) U.D.C. 541.124+543.422.25

The Application of High Resolution Nuclear Magnetic Resonance in the Study of Fast Non-equilibrium Reactions

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Literature data concerning the use of high resolution NMR in the study of the mechanisms of fast non-equilibrium chemical reactions are examined and surveyed. Attention is concentrated on the methods and techniques of flow experiments in which stationary and pulsed Fourier-transform NMR is used. The possibilities and prospects for the development of these methods are analysed.
The bibliography includes 139 references.

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I. INTRODUCTION

The greatest advances in the study of fast reactions by high resolution NMR have been made in the investigation of equilibrium processes with the aid of the dynamic magnetic resonance methods,[1-4] the saturation transfer effect,[5-8] and two-dimensional NMR.[9,10] On the other hand, the study of non-equilibrium processes, including irreversible chemical reactions, has been limited to very slow reactions with characteristic times $t_{1/2}$ in excess of 100 s.[11-14] This limitation was associated primarily with the lack of special methods for the measurement and treatment of high resolution NMR spectra for non-equilibrium reaction mixtures. At the same time there is no doubt about the likely usefulness of the application of NMR in the determination of the structures of relatively unstable intermediates in fast† chemical reactions and the determination of independent kinetic information.

The increase of the working frequency of spectrometers and the introduction of pulsed methods of recording[15] greatly increased the sensitivity and speed of NMR spectroscopy, which extended its functional possibilities for the study of rapid non-equilibrium chemical reactions in solution. The application of NMR in this field makes it possible to obtain qualitative and quantitative information about the composition of a non-equilibrium reaction mixture 0.05 s after the start of the reaction and hence permits an expansion by 3–4 orders of magnitude of the range in which it can be employed.

The large amount of information derivable from NMR spectra is one of the main factors responsible for the vigorous development of NMR methods for the rapid recording of short-lived intermediates in non-equilibrium chemical reactions. At the same time, the relatively low sensitivity of NMR prevents its being a competitor, in the determination of kinetic information, of the UV, IR, and EPR spectroscopic methods widely used for such purposes.[16-18] However, here too there has been definite progress as a result of the improvement of the methods of the kinetic NMR measurements and the development of fundamentally new methods for the determination of kinetic data.

The aim of the present review is the analysis of the methods and characteristics of the employment of NMR in the study of fast non-equilibrium reactions in solution. Two main factors are considered: the method whereby the initial non-equilibrium state of the specimen is established in the measuring cell of the NMR spectrometer and the actual NMR recording of the attainment of equilibrium in the test system. The first studies of the use of NMR in the investigation of fast irreversible reactions dealt with the effects of chemically induced nuclear polarisation (CINP),[19] electrolysis,[20] and radiolysis.[21] In order to generate the initial non-equilibrium state, appropriate exciting devices were used. However, among the special methods for the investigation of fast reactions in solution,[22] flow methods, in which equilibrium is perturbed as a result of the chemical reactions, have come to be most widely employed.[23] In most investigations the recording of the attainment of equilibrium is to some extent associated with the measurement of a high-resolution NMR spectrum in a flowing liquid. We shall therefore deal with the characteristic features of the use of an NMR spectrometer as the detecting device in flow methods for the study of fast reactions.

II. FLOW METHODS AND NUCLEAR MAGNETIC RESONANCE IN A FLOWING LIQUID

The flow methods for the study of fast chemical reactions in solution are based on the rapid and effective mixing of the initial reactants at the mixing point and the recording of the changes in the NMR parameters as a function of time at the point where the receiving coil of the spectrometer sensor is located.

In virtually all the known studies two commonest and simplest methods have been used in one form or another, namely the continuous and stopped flow methods. The choice of one of them is associated primarily with the amount of the solution of the initial reactants available and the speed with which the observation can be made. The first of the methods is based on the establishment of a stationary composition of the reaction mixture at the recording point as a result of the uniform flow of the specimen through the spectrometer sensor and makes it possible to record the spectrum under the usual conditions. The NMR spectrum obtained in this way corresponds to the time necessary for the transport of reaction mixture after the start of the

†In ^{1}H NMR, the term "fast" reaction should be understood as implying reactions occurring at room temperature with half-lives $t_{1/2} < 30$ s.

reaction (τ_{tr}), which is unambiguously defined by two parameters of the flow system—the flow rate of the reaction mixture v and the distance between the mixing and recording points l:

$$\tau_{tr} = \frac{l}{v} \quad . \tag{1}$$

When the stopped flow method is used, the amount of reactants consumed is much smaller. In this case, a selected section of the spectrum "varying" with time is rapidly scanned after the rapid arrest of the flow of the reaction mixture.

The theoretical principles of NMR in a flowing liquid, which have been described in a monograph,[24] reduce to the following: the flow of the specimen in the sensor along the y axis does not entail any frequency distortions in the NMR spectrum and is expressed by a decrease of the effective (observed) spin–lattice (T_1^*) and spin–spin (T_2^*) relaxation times. As early as 1951, an increase of the amplitude of the NMR signal was noted[25] under the conditions of a uniform movement of the liquid compared with a stationary specimen. This effect was explained[26] by the acceleration of the spin–lattice relaxation of the volume-average magnetisation of the nuclei, which takes place as a result of the flow into the sensor of the liquid with a uniform magnetisation. It was concluded that the signal amplitude in the flow sensor corresponds to the effective spin–lattice relaxation time T_1^*, which is related to the natural time T_1 by the expression

$$\frac{1}{T_1^*} = \frac{1}{T_1} + \frac{1}{\tau} \, , \tag{2}$$

where τ is the time during which a proportion 1/e of the depolarised nuclei is replaced by polarised nuclei as a result of the flow of liquid in the resonance zone (e is the base of natural logarithms).

At the same time an analogous decrease of the effective spin–spin relaxation time T_2^* was observed:

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{\tau} \quad . \tag{3}$$

This entails a broadening of the spectral lines. Owing to this broadening, Bloom and Shoolery[27] were unable to increase the sensitivity of high-resolution NMR spectrometers with the aid of a flow sensor and a varying working substance. Their attempt was based on the possibility of using higher powers of the microwave frequency field H_1 by reducing T_1^* and T_2^* in the flowing liquid while maintaining the value of the saturation factor z:

$$z = 1 + (\gamma H_1)^2 T_1^* T_2^* \, .$$

Another feature of the use of flow NMR which is of practical importance is the difficulty of ensuring the necessary equilibrium magnetisation of the liquid. Whereas for a usual specimen the equilibrium magnetisation M_0 is attained by placing it for a time in the field of the spectrometer magnet H_0, for a flowing specimen it can be achieved as a result of its being passed beforehand through a special polariser, since the time during which the specimen flows through the sensor is insufficient for the establishment of the equilibrium magnetisation. The polariser is usually placed in the space between the poles of the spectrometer magnet and, when no free space is available for this purpose, the flowing specimen is polarised with the aid of an additional polarising magnet having a field strength H_0^{pol}.[24]

The initial parameters in the calculation of the geometry of the polarisation coils are the spin–lattice relaxation time of the ith transition investigated (T_1^i) and the flow rate of the specimen. For a multispin system, the residence time of the flowing specimen in the polariser t_p is chosen from the condition

$$t_p \geqslant 5 T_1^{max} \, , \tag{4}$$

where T_1^{max} is the maximum spin–lattice relaxation time among all the values of T_1^i. When condition (4) holds, the Boltzmann distribution in the flow system is established to the extent of 98% and the phenomenon of nuclear magnetic resonance can be observed in it. Depending on the ratio of the reaction half-life and the value of $5T_1^{max}$, the preliminary magnetisation of the reaction mixture can be achieved both before and after mixing the initial reactants. For very short spin–lattice relaxation times, the role of the polariser can therefore be fulfilled by the section between the mixing and recording points located within the gap of the spectrometer magnet.

If the condition $H_0^{pol} > H_0$ holds when a second polarising magnet is used to polarise the flowing specimen, then an increase of the sensitivity of the spectrometer is achieved together with the magnetisation of the specimen. For sufficiently short times taken for the transport of the test specimen from the polarising magnet to the spectrometer magnet, the effective equilibrium magnetisation $M_0^{eff}(t)$ remains greater than the value of M_0 which can be attained in the uniform spectrometer field H_0. The disadvantage of this method of increasing sensitivity is that the amplification factor K depends on the relaxation times of different nuclei T_1^i:[24]

$$K = \frac{M_0^{eff}(t)}{M_0} = \frac{M_0^{tot} \exp(-t/T_1^i)}{M_0} = K_0 \exp(-t/T_1^i) \, ,$$

which should distort the true ratio of the signal intensities in the NMR spectrum of the reaction mixture. However, since there is no need for a high uniformity of the field of the more powerful polarising magnet, these methods for the polarisation of the flowing specimen can be preferable in some cases.

Another approach to the establishment of the preliminary magnetisation in the flowing specimen consists in the artificial shortening of the spin–relaxation time of the nuclei with the aid of paramagnetic additives. However, this entails the simultaneous shortening of the corresponding spin–spin relaxation times, which leads to the broadening of the spectral lines to hundreds of gauss.[28] This disadvantage has been eliminated in a recently proposed method.[29] Owing to the interaction of the flowing liquid with the free radicals adsorbed on the solid substrate, the time necesssary for the polarisation of the specimen in the field of the spectrometer magnet is shortened in zone A (Fig.1) by several orders of magnitude. It becomes comparable to the residence time of the flowing specimen in zone A. In the region B, the influence of paramagnetic centres on the width of the lines is to a large extent weakened owing to the effective filtration of the adsorbent on a glass filter. The necessary conditions for the use of free radicals in this procedure are their chemical inertness, the ease of filtration of the adsorbent, and the constancy of the concentrations in zone A. According to the authors,[29] the use of paramagnetic relaxants leads to the prospect that ^{13}C NMR experiments, which have longer spin–lattice relaxation times, may become possible.

The overall requirements which must be met by the method and technique of any flow experiments are well known.[22] These are primarily the necessity for the rapid and effective mixing of the reactants, the establishment of the laminar flow of the reaction mixture in the continuous flow method, and the rapid arrest of the flow in the stopped flow method. The main characteristic of the efficiency of the apparatus in

flow measurements is the experimental dead time τ_0—the minimum time after the start of the reaction necessary to record any physical quantity. For the continuous and stopped flow methods, it includes the reactant mixing time τ_{mix} and the time required for transport to the recording point τ_{tr}, while for the stopped flow method there is in addition the time necessary to stop the flow (τ_{st}).

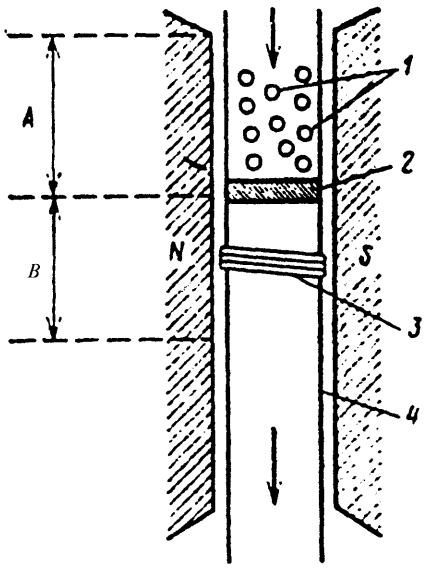


Figure 1. Artificial reduction of the magnetisation time of a flowing specimen by introducing stable paramagnetic centres into the recording channel in NMR flow experiments:[29] *1*) free radicals adsorbed on a solid substrate; *2*) glass filter; *3*) receiving coil; *4*) recording channel; *A*) preliminary polarisation region; *B*) recording region.

The mixing chambers developed previously for the UV, IR, and EPR methods[17,30,31] makes it possible to mix almost completely two solutions of the reactants over a period of ~10^{-3} s; the flow of the reaction mixture can be arrested with the aid of a removable syringe and electromagnetic valves over a period of $(1-5) \times 10^{-3}$ s.[32] These values are much shorter than those which are really necessary when an NMR spectrometer is used as the recording device, for which the dead time is limited by the transport time, amounting usually to $(50-100) \times 10^{-3}$ s. The principal elements of the flow technique—the mixing chamber and the syringe system for the injection of reactants and the arrest of the flow—have been almost wholly taken from analogous studies employing IR, UV, and EPR spectroscopy.[33,34]

When NMR is used in the continuous flow method, the dead time can be shortened mainly by reducing the transport time τ_{tr}, which can be achieved, according to Eqn.(1), either by increasing the flow rate or by reducing the distance between the mixing and recording points. However, the increase of flow rate entails the shortening of the residence time of the spin state in the region of the receiving coil and, according to Eqn.(3), the broadening of the spectral lines. The decrease of the distance between the reactant mixing point and the spectrum recording point is therefore the most suitable procedure for shortening the dead time. In the stopped flow method the use of high rates of transport (under the conditions of an effective arrest of the flow) does not introduce additional distortions into the NMR spectrum and the experimental dead time can be reduced to several milliseconds.[35]

Since there are two fundamentally different methods of recording NMR spectra—stationary and pulsed, it is useful to divide all the published communications concerning the application of NMR in the study of fast irreversible reactions into two groups and to consider for each examples of the practical employment of the continuous and stopped flow methods. Special mention should be made of the difference between the speeds at which information can be secured by the above two methods of NMR measurements. Thus usually 4–5 min is required to record a spectrum 10 p.p.m. wide in the stationary regime of the operation of the NMR spectrometer, while the counting of the free induction signals in the same spectral region under a pulsed regime takes only 4 s. From the point of view of speed, the continuous flow method is more suitable for stationary NMR spectroscopy despite the considerable consumption of the initial reactants, while the stopped flow method is more suitable for pulsed Fourier-transform NMR.

III. STATIONARY NUCLEAR MAGNETIC RESONANCE

When stationary NMR is used, the following conditions governing the passage of resonance lines must be maintained:[36]

$$\frac{d\nu}{dt} \ll (\Delta\nu_{1/2})^2,$$

where $\Delta\nu_{1/2}$ is the spectral line half-width. The time taken to record a single NMR signal should then be ~2–3 s, which determines the minimum possible scanning period in the stopped flow method. An increase in the rate of scanning distorts the signal both due to transient processes and as a result of the progressive saturation of the spin system.[37] The stopped flow method is therefore convenient for the study of the kinetics of chemical reactions whose half-life is more than 5–10 s. Since only a very narrow section of the overall NMR spectrum of the reaction mixture is recorded in this instance, the stopped flow method yields very little information from the standpoint of the determination of the structure of the intermediates. Even for comparatively slow reactions ($t_{1/2} > 5$ s) one therefore as a rule records initially the total spectrum of the reaction mixture with the aid of the continuous flow method in which the signal intensities are independent of time. The structure of the intermediates and the reaction pathways are inferred from the interpretation of the resulting spectrum and the process kinetics are then studied by the stopped flow method.

The kinetic data for the lifespans of the shortest-lived intermediates ($t_{1/2} \cong 0.1-1$ s) can be obtained only by the continuous flow method involving the variation of two independent parameters which determine the transport time in Eqn.(1). For intermediate values of $t_{1/2}$, the time variation of the concentration is found from data obtained by both methods.

1. The Continuous Flow Method

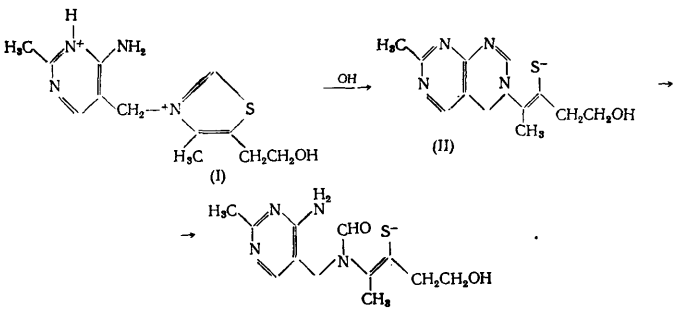
The possibility of using high resolution NMR in the study of fast irreversible reactions by the continuous flow method was first reported by Schaumberg,[38] who was not only the first to propose the preliminary magnetisation of the initial

reactants in the gap of the spectrometer magnet but also initiated a series of the most promising directions in the development of the technique and methods of NMR flow experiments, many of which have now been successfully realised. For example, the idea of using the saturation transfer effect[39] in the study of the mechanisms for irreversible chemical reactions whose half-life is comparable to the spin–lattice relaxation time is due to him. This method is based on the transfer in the course of reaction of the magnetisation defect of one or several nuclear spins; this magnetisation defect arises as a result of the inversion or saturation of the equilibrium magnetisation in the spin system of one of the reactants directed before mixing.

The experimental realisation of this method with the aid of a stationary spectrometer in the broad-band version as a method of inverting the magnetisation of one of the reactants has been achieved by Fife et al.[40], who used the rapid adiabatic passage through the resonance conditions by the specimen[41] in the non-uniform section of the magnetic field whose strength was $0.7H_0$. This method, called "electronic isotope substitution", might have permitted, in its selective version, the selective observation at any stage of the given reaction of the transformations occurring in a non-equilibrium reaction mixture. However, the creation of selective magnetisation defects in a flowing liquid must take place in the uniform section of a magnetic field H_0 and, owing to the finite residence time of the spin system in this region, in the continuous flow method this entails the overcoming of a series of technical problems,[24] which restricts the application of this method to stationary NMR. On the other hand, Fourier-transform NMR methods, which have appeared in recent years and which are based on multipulse trains,[42,43] are more convenient for the generation of a microwave frequency label in the spin system of one of the reactants and for the recording of its transfer in the course of an irreversible chemical reaction.[44–46]

The wide-scale experimental employment of NMR in a flowing liquid for the investigation of fast irreversible reactions began in connection with the discovery of the phenomenon of chemically induced nuclear polarisation (CINP) and the possibility of investigating radical reactions by NMR.[47] In 1967 Bargon et al.[19] first recorded in a flowing liquid the polarised signals of benzene—the diamagnetic product of a radical reaction initiated by photolysis. This so-called "Bargon" tube[46] played a major role in these experiments,[19,48,49] making it much simpler to carry them out because its use shortens the transport time (as a consequence of the use of a thin capilliary) and simplifies the removal of the spent reaction mixture (Fig. 2). The radical reaction is initiated outside the spectrometer magnet and the polarised products are then transferred via a connecting tube to the NMR sensor in order to record the spectrum.

A simpler modification of the Bargon tube has been used[51] to detect the unstable thiol form (II) formed in the reaction of the thiazole (I) with KOH:



A vacuum pump ensured the removal of the spent reaction mixture from the rotating tube at a flow rate of 3 ml min^{-1}. The authors[51] obtained the complete NMR spectra of the reaction mixture, corresponding to its composition 5 s after mixing the reactants.

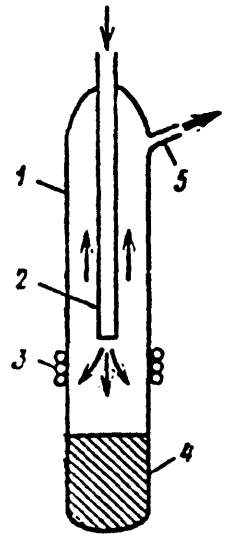
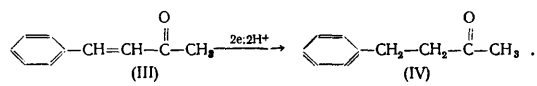


Figure 2. Bargon tube:[50] *1*) rotating bulb; *2*) capillary for the rapid injection of the reaction mixture into the recording region; *3*) receiving coil of spectrometer; *4*) Teflon insert for the optimisation of the recording volume; *5*) aperture for the removal of the reaction mixture.

An analogous technique has been used[20] in the study of the electrochemical reduction of the unsaturated ketone (III):



The NMR spectra of the electrolysis product (IV) were measured at a flow rate of 0.4 ml min^{-1} and a current in the range 0–5 mA.

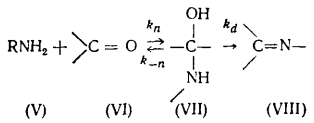
Lawler and Halfon[52] used a second additional magnet for the preliminary polarisation of the nuclei in the test system and investigated the dependence of the CINP effect on the field strength of this magnet in the photolysis of di-t-butyl ketone; the maximum flow rate did not exceed 4 ml min^{-1}.

The experimental dead time achieved with the aid of the Bargon tube was several seconds, which was quite sufficient for the solution of the problems formulated in the above investigations. A further shortening of the dead time within the framework of the given technique is difficult owing to the necessity for the effective preliminary polarisation of the n;uclei and the difficulty of ensuring the rotation of the specimen at high flow rates.[53] These disadvantages have been eliminated in a study,[54] where, by abandoning the rotation of the specimen, it was possible to raise the flow rate of the reaction mixture to 60 ml min^{-1}#.[55] The equilibrium magnetisation was attained with the initial

#A further increase of the flow rate led to excessive (more than 5 Hz) broadening of the lines in the NMR spectrum.[54]

reactants flowing through two polarisation coils placed between the sensor and the pole tips of the spectrometer magnet; the reactants were mixed in a Teflon mixer, which was fixed over the inlet opening to the sensor and was rigidly connected to the recording channel. Two pairs of tangentially disposed inlet openings (d_{in} = 0.36 mm) into the high pressure mixing chamber ensured the rapid and effective mixing of the reactants. In order to reduce the time required for the transport from the sensor, the device ensuring the rotation of the specimen under the standard conditions of the operation of the spectrometer was removed and the mixing chamber was thereby brought as close as possible to the recording point; in addition, the diameter of the recording channel outside the region of the receiving coils was reduced to 2.5 mm.

With the aid of this technique, Fife, Cocivera, and co-workers carried out and published about 30 studies, some of which have been discussed in a review.[56] The studies[57-63] of the mechanisms of the reactions involving the nucleophilic addition of nitrogen-containing bases (V) to the carbonyl group (VI) are based on the measurement of strong-field NMR spectra of the signals due to the methyl protons of the aminocarbinol fragment (VII):



(V) (VI) (VII) (VIII)

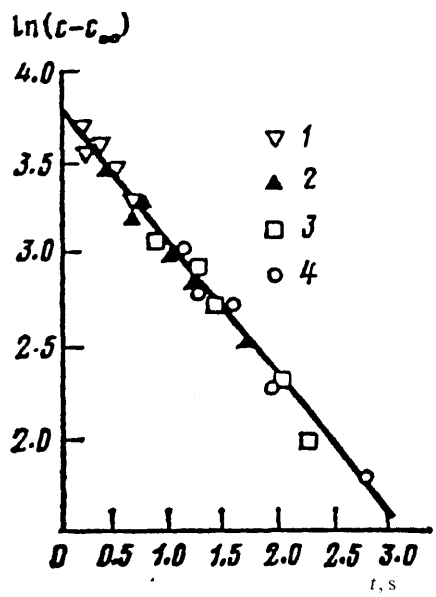
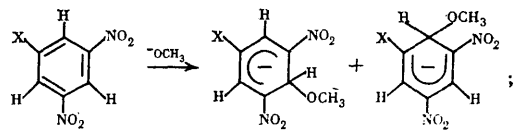


Figure 3. Dependence of $\ln(c - c_\infty)$ on t, where c is the concentration of compound (X); distance between the mixing and recording points (cm):[65] *1*) 4; *2*) 5; *3*) 6; *4*) 7.

The authors were able to observe individual signals due to form (VII) only in the study of the interacton of acetaldehyde with hydroxylamine.[61] Owing to the reversibility of the first stage, in the remaining cases the spectrum showed the signals of the corresponding protons of the initial form (VI) and the intermediate form (VII) averaged by the rapid exchange (VI) ⇌ (VII). A standard approach, based on the determination of the half-width of the line averaged by the rapid exchange and of its position in the spectrum, was used to estimate the rate constants for the forward and reverse reactions (k_n and k_{-n}) in these cases.

Thus the application of the continuous flow method extended the applicability of dynamic NMR in the study of the reversible stages of non-equilibrium reactions. The additional broadening of the lines associated with the movement of the reaction mixture [see Eqn.(3)] in these experiments was taken into account by introducing into the reaction mixture inert line form standards—t-butyl-alcohol[58] or methyl alcohol.[57] The position of the line of the standard molecule in the spectrum served simultaneously as the reference point for the reckoning of the chemical shift. The absorption lines of the solvents H_2O, CH_3OH, and DMSO were used as stabilisation signals. In the study of Cocivera and Effio,[57] the mixing chamber with six inlet openings was placed within the tube (5 mm) in the immediate vicinity of the receiving coil of the spectrometer sensor, which made it possible to reduce by a factor of 3 the transport time without increasing the flow rate of the reaction mixture.

Other studies by the same investigators[55,64,65] were devoted to the nucleophilic aromatic substitution reactions. The method is based on the direct recording of the thermodynamically unstable product (X) and the experimental determination of its lifespan as a function of the structural characteristics of the substrate (IX):

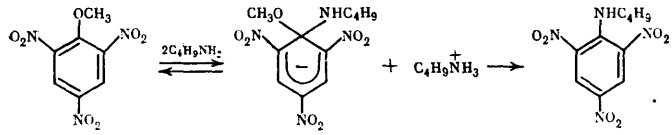


(IX) (X) (XI)

X = CN, CF_3, $COOCH_3$, $COOCH_2CH_3$, $COOCH(CH_3)_2$, $COOC(CH_3)_3$.

Fife et al.[65] demonstrated the possibility of using the continuous flow method to determine the kinetic parameters of fast reactions by varying the flow rate or the distance between the mixing and recording points. Such measurements yield a set of overlapping results for different experiments (Fig. 3) and ensure the determination of reliable kinetic data.

Yet another important methodological feature of the studies by this group of workers was the involvement in NMR flow measurements of the procedure for the study of the irreversible reactions in which the reaction mixture is cooled.[66-71] This makes it possible, on the one hand, to move the system to the range of reaction rates convenient for study and to detect in the reaction mixture the intermediates which are absent at room temperature and, on the other hand, it permits a wider employment of the more economical stopped flow method. The separate temperature control of the recording region and of the initial reactants has been employed in a number of studies.[61-66] The recording channel was cooled by means of a standard gas thermostatic control system, while the initial reactants were cooled by passing them through a liquid thermostat.[66-74] The temperature of the reaction mixture was measured before and after the experiment with the aid of methanol as the NMR temperature standard. Such a cooling system permits a reduction of the temperature to −40 °C and a qualitative study of the composition of the reaction mixture under these conditions Thus the interaction of 2,4,6-trinitroanisole (XII) with n-butylamine has been investigated:[66-68]



(XII) (XIII)

At −40 °C the maximum concentration of the intermediate (XIII) is observed 1 s after the start of the reaction (Fig. 4).

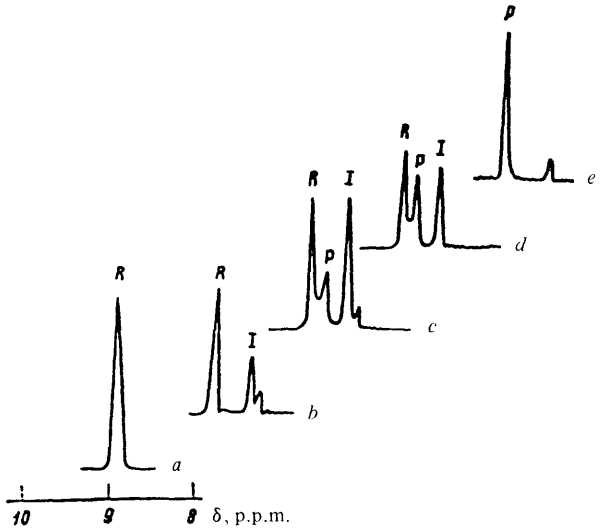


Figure 4. Section of the ^{1}H NMR spectrum of a mixture of 2,4,6-trinitroanisole (XII) with n-butylamine at −40 °C obtained by the continuous flow method before (*a*) and at different times after mixing the reactants [*b*) 0.44 s; *c*) 0.98 s; *d*) 1.5 s; *e*) 30 s];[67] *R*, *I* and *P* are the absorption signals of the ring protons of the initial reactant, the intermediate, and the reaction product respectively.

The main disadvantage of the cooling method considered is the separate thermostatic control and the separate measurement of the temperatures of the initial reactants and of the recording region and also the existence under these conditions of a non-thermostatted section, including the mixing chamber. The above disadvantages§ can lead to considerable errors in the determination of the exact reaction temperature and to technical difficulties in its measurement during the flow experiment. Ultimately an appreciable scatter and poor reproducibility of the kinetic parameters of the reaction are observed.

§ Account should also be taken of the contribution to the error of the kinetic results introduced by the temperature gradient along the length of the recording channel, which is characteristic of the usual procedure for NMR measurements over a wide range of temperatures. The temperature drop along the length of the recording section of the reaction mixture can reach several degrees.[75]

It is known that the best results can be obtained when the entire measuring cell and the components of the flow system are simultaneously temperature-controlled in a liquid thermostat.[76] However, in the case of NMR the measuring cell is the sensor whose standard design precludes this procedure for the thermostatting of the flowing specimen. The above problem has been solved with the aid of a closed liquid thermostatic system[77,78] for the entire flow apparatus, which made it possible not only to improve greatly the quality of the thermostatic control of the flowing specimen and the accuracy of the determination of the temperature in the course of the reaction but also to eliminate the need for the employment of secondary NMR temperature standards.[79,80]

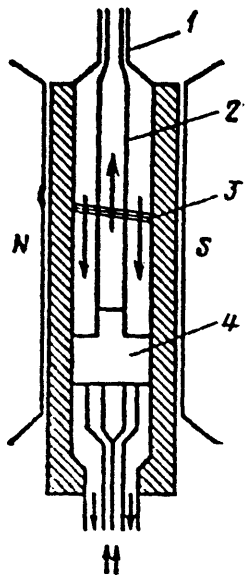


Figure 5. Liquid type thermostatic system in NMR flow experiments:[79] *1*) external circuit of the cryostat; *2*) recording channel; *3*) receiving coil of spectrometer; *4*) mixing chamber.

In the working regime two opposed streams are generated in the region of the receiving coil (Fig. 5): the stream of the reaction mixture within tube *2* which is 5 mm in diameter and the stream of the thermostatting liquid in the cylinder with an annular cross-section formed by the coaxially arranged glass tubes 12 and 5 mm in diameter. The mixing chamber *4*, located within the NMR sensor in direct vicinity to the receiving coil *3*, consists of a truncated cylinder and does not interfere with the circulation of the thermostatting stream. The disposition of all the elements of the flow system, including the initial reactants, within the outer circuit *1* of the cryostat ensures a high accuracy of the thermostatic control of the reaction mixture (±0.1 °C) in the temperature range from −40° to +60 °C. The influence of the absorption signals of the thermostatting liquid (H_2O, CH_3OH) on the spectrum of the reaction mixture is weakened owing to its incomplete magnetisation in the magnet gap[24] and the broadening associated with the decrease of its effective spin–lattice relaxation time T_2^* [see Eqn. (3)]. This influence can be fully eliminated, for example, by introducing

paramagnetic additives.[28] The liquid thermostatic system for the flow apparatus was used in the study of the mechanism of the reactions of 1,3-diketones with hydrazines[81–83] and demonstrated the high reproducibility of the results of the kinetic measurements.

2. The Stopped Flow Method

The determination of data on the structures of the intermediates in irreversible chemical reactions by the continuous flow method is the first stage in the study of their mechanisms. The next stage consists of the study of the kinetics of the interconversions of the intermediates. If their half-lives are not less than 5 s, then kinetic data can be obtained with the aid of the stopped flow method by the rapid scanning of the selected section of the spectrum immediately after arresting the flow of the reaction mixture.

In order to achieve the rapid arrest of the flow in the stopped flow method, one usually employs a system with a third receiving syringe (Fig. 6). A microswitch ensures the disconnection of the reversible motor which moves the plungers of the supplying syringes. The time taken to arrest the flow by this method is usually ~1 s and permits the first recording to be made 2–3 s after the start of the reaction. The position of the microswitch can be varied within specific intervals within the limits of the amplitude of the movement of the plunger of the receiving syringe, which enables one to carry out repeated kinetic measurements under identical conditions.

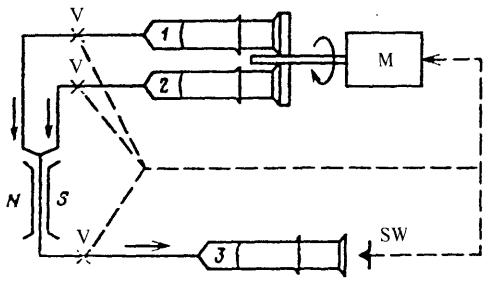
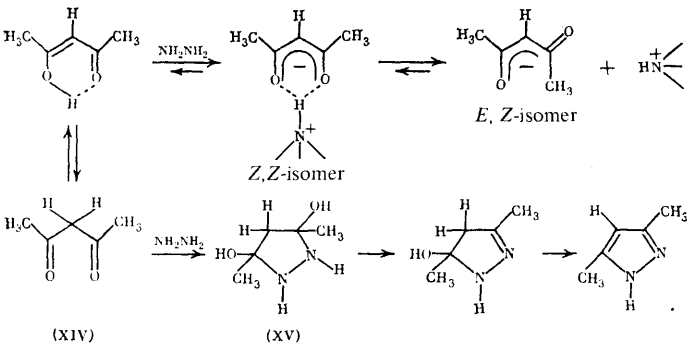


Figure 6. Schematic illustration of the apparatus for the stopped flow method: *1*) and *2*) supplying syringes; *3*) receiving syringe; SW = microswitch; V = electromagnetic valves; M = reversible motor.

The concentrations are usually determined from the integral[81–83] or peak[57–63] intensities of the corresponding signals in the NMR spectra. In carrying out the measurements, one must take into account the possibility of a synchronous increase of the intensities of all the signals during the reaction owing to the time variation of the dielectric constant of the reaction mixture.¶ The influence of this effect can be eliminated either by adding an inert signal intensity standard to the reaction mixture[58] or by calculating the relative signal intensities of all the components of the reaction mixture at each instant.[82,83]

The technique used in the cooling and thermostatting of the reaction mixture in the stopped flow method does not differ fundamentally in any way from that described for the continuous flow method.[67,79] The factors limiting the low-temperature measurements may be only the high freezing point of the solvent and the poor solubility of the individual components of the reaction mixture. The low temperature in the stopped flow method has been used[82] to demonstrate the higher reactivity of the keto-form of acetylacetone (XIV) compared with the enolic form in the reaction with hydrazine:



In methanol at −70 °C the attainment of the keto–enol equilibrium for acetylacetone is greatly retarded and the rapid formation of the dihydroxypyrazolidine intermediate (XV) from the keto-form can be observed immediately after mixing with hydrazine, while the enol form participates in the establishment of equilibrium between the hydrazinium salt having the *Z*, *Z*-configuration and the free anion with the *E*, *Z*-configuration.

The examples of the use of stationary NMR spectroscopy for the study of irreversible reactions discussed above show that the dead time of 0.05 s attained in the continuous flow regime[70] is apparently close to the limit for this method of measurement and further development of these procedures will take place to an increasing extent as a result of the wide-scale application of low-temperature measurements. This will permit the measurement of the NMR spectra of unstable intermediates in rapid non-equilibrium reactions which are inaccessible to investigation at room temperature even by the stopped flow method and will lead to the wider use of the more economical stopped flow method for kinetic measurements.

IV. PULSED FOURIER-TRANSFORM NUCLEAR MAGNETIC RESONANCE

The main advantage of the pulsed Fourier-transform NMR is the simultaneous interaction of the microwave frequency pulse with all the spins of the non-equivalent nuclei, which makes it possible to accumulate in the study of rapid non-equilibrium reactions the free induction signals (FIS) at each point on the kinetic plot and hence to reduce the concentrations of the initial reactants in measurements involving the ^{1}H nuclei and also leads to the prospect of being able to employ ^{31}P, ^{27}Al, ^{13}C, etc. NMR in the study of the compositions of non-equilibrium reaction mixtures.

¶This leads to the breakdown of the orthogonality of the polarisation of the microwave frequency fields of the receiving and transmitting coils which entails the leakage of the power of the transmitter to the input device of the receiver and a change in the regime governing its operation and hence to an identical distortion of the absolute intensities of all the signals in the spectrum.

The principal limitation in the wide-scale use of pulsed NMR in the study of rapid reactions is determined by the data access time, which for a spectral width of 8 p.p.m. is ~4 s and actually determines the minimum time interval between the recordings of the spectra in kinetic measurements. The artificial decrease of this interval by reducing the number of memory cells leads to the corresponding impairment of the quality of the spectra[15] but does allow one to reduce the scanning period in the stopped flow method to 0.1–0.2 s.[84]

1. The Continuous Flow Method

A characteristic feature of the pulsed regime in the operation of spectrometers is the difficulty, in principle, of obtaining the FIS from the flowing liquid.[85] After the application of the microwave frequency pulse, the signal is weakened owing to the continuous removal at a rate v of the "excited" volume of the reaction mixture from the receiving coil. The increase of the rate of decay of the transverse component of the magnetisation (M_{xy}) in the time region corresponds to the widening of the absorption signals in the spectral region. In the present case this broadening is a complex function of the flow rate v, because the intensity of the recorded FIS diminishes as $1/l^2$ with the distance l between the receiving coil and the excited volume.[24]

This problem can apparently be partly solved by employing a sensor with the receiving and transmitting coils separated by a specific distance which depends on the rate v. In order to eliminate completely the influence of the flow of the specimen on the line width, it is necessary to remove the receiving circuit during the recording of the FIS along the y axis at a rate v in the same direction, which presents significant difficulties.

Virtually no studies involving the use of Fourier-transform spectrometers in the continuous flow method have been described in the literature. In order to maintain a high concentration of a cell suspension in a state of equilibrium in studies of unstable biological objects by ^{31}P NMR, the suspension was supplied continuously into the measuring region. In the accumulation of the FIS the access time was in this case reduced artificially to 0.2 s, which made it possible to avoid the distortion of the spectrum for a flow rate of the specimen of 5–10 ml min^{-1}.

One should also note the publications which appeared recently concerning the use of a flow-type Fourier-transform NMR spectrometer as the detecting device in liquid chromatography.[88–92] In terms of the technical and methodological problems solved in the above studies, they are closely related to the problems considered in this Section.

The conditions in the recording of ^{1}H NMR spectra in quantitative measurements with the aid of a flow-type Fourier-transform spectrometer operating under accumulation conditions have been examined.[88] It has been found that, in order to eliminate the influence of various apparatus distortions in quantitative NMR flow measurements, it is best to introduce an intensity standard. It can be introduced either into the solvent before the mixing of the reactants or into the reaction mixture via the mixing chamber immediately before the recording.

The effect of the nuclear relaxation time T_1 on the measured signal intensity ratios in the spectrum was examined in the same study. It is inconvenient to eliminate this effect by increasing the arrest time between the pulses owing to the increase of the overall duration of the experiment. The requirement for the complete restoration of the Boltzmann equilibrium in the spin system is therefore not usually met. The use of the Bloch equation for the description of the equilibrium component of the magnetisation after a series of pulses,[93] which is a complex function of the spin–lattice relaxation time T_1, greatly simplified the analysis of the expression for the spectral density. It was concluded[88] that, in NMR flow measurements with pulsed recording of the composition of the reaction mixture, the accuracy of the quantitative measurements increases with decrease of the recording volume and with increase of the flow rate. Fig.7 illustrates the dependence of the effective spin–lattice relaxation times T_1^* on the residence time τ of the spins in the recording region [see Eqn.(2)]. Evidently the lower the value of τ, the smaller the difference between the values of T_1^* for nuclear spins with different natural spin–lattice relaxation times T_1^i. The decrease of the effective spin–lattice relaxation times T_1^* with the simultaneous equalisation for different nuclei in a flowing specimen has been used recently to increase the relative sensitivity of the recording of slowly relaxing quaternary carbon atoms in ^{13}C NMR spectra.[94]

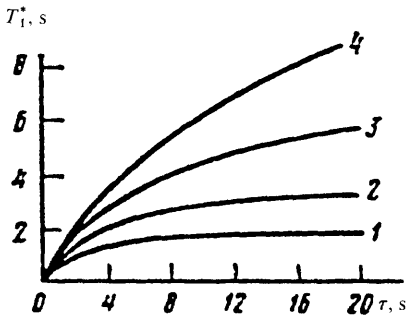


Figure 7. Dependence of T_1^* on the residence time of the spin system in the recording region; natural spin–lattice relaxation times T_1(s):[88] *1*) 2; *2*) 4; *3*) 8; *4*) 16.

Thus the continuous flow method in the pulsed mode of operation of the spectrometer has no advantages over other NMR methods for the investigation of non-equilibrium reactions as regards the decrease of the experimental dead time, because it can be used only for very low flow rates of the reaction mixture ($\leq$1 ml min^{-1}) for which the distortions in the NMR spectrum due to the movement of the specimen can be neglected.

2. The Stopped Flow Method

An example of the employment of the pulsed Fourier-transform NMR for detection in the stopped flow method is provided by the studies of Grimaldy, Sykes, and co-workers who justified theoretically as early as 1972 [95] and later demonstrated in practice[96] the advantages of the pulsed methods for the study of rapid reactions compared with stationary NMR spectroscopy.[97,98] The simple application of the Fourier-transform NMR proposed by these workers consists in the successive recording of the NMR spectra of the non-equilibrium reaction mixture investigated within the limits of the inequality

$$n(\mathrm{AT} + \mathrm{TT} + \mathrm{PD}) \leqslant t_{1/2} \qquad (5)$$

where n is the number of spectra recorded during the reaction time, AT the data access time, TT the time required for the Fourier transformation or for the transfer of the FIS to the memory device, and PD the delay period needed to restore the Boltzmann equilibrium ($AT + PD \geq 5T_1$). It follows from Eqn.(5) that, in order to increase n, it is necessary to reduce the times AT, TT, and PD. This is associated with additional distortions in the NMR spectrum. The PD time can be reduced to zero and for very short spin–lattice relaxation times ($T_1 \leq 0.1$ s) this does not introduce appreciable distortions into the final spectrum. The TT time can be reduced to 0.1 s by employing high-speed computers. The situation is different as regards the AT time, whose reduction to 0.1 s entails a broadening of the spectral lines to 5–10 Hz.[97]

Thus the method examined makes it possible to investigate reactions with half-lives up to 0.5 s and to reduce the dead time in experiments of this kind to 0.1 s. The method has been applied in a number of studies.[99–103] In an investigation of the kinetics of the base-catalysed deuterium exchange reaction between [D_4] methanol and the nitromethane anion (XVI), i.e.

$$CH_3NO_2 + [OCD_3]^- \xrightarrow{\text{fast}} [CH_2NO_2]^-,$$
$$[CH_2NO_2]^- + 2CD_3OD \xrightarrow{\text{slow}} [CD_2NO_2]^- + 2CD_3OH,$$
(XVI)

its slow second stage was recorded using pulsed NMR;[100] the microwave frequency pulses were repeated at 1.1 s intervals (Fig. 8). In order to increase the speed of recording, a spectral width of 1.2 kHz was used; time taken to transfer each FIS to the disc memory was 0.03 s.

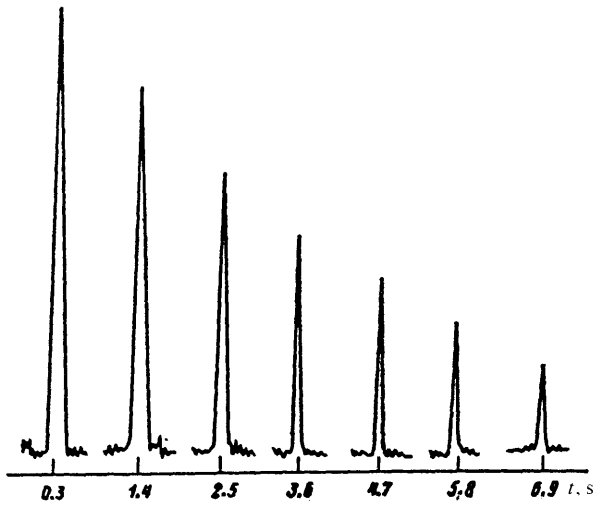


Figure 8. Decrease of the intensity of the signal of the nitromethane anion (XVI) (δ = 5.74 p.p.m.) during deuterium exchange with [D_4]methanol at 295 K.[100]

Another example of the effective use of this technique is provided by a study[102] of the hydrolysis of aluminium(III) by the method involving the ^{27}Al NMR of the reaction mixture; a single line is then present in the spectrum, which greatly facilitates the task of increasing the speed of recording such a spectrum. This enabled the authors[102] not only to obtain 20 points on the kinetic curve during 30 s but also to accumulate 20 FIS per second for each point.

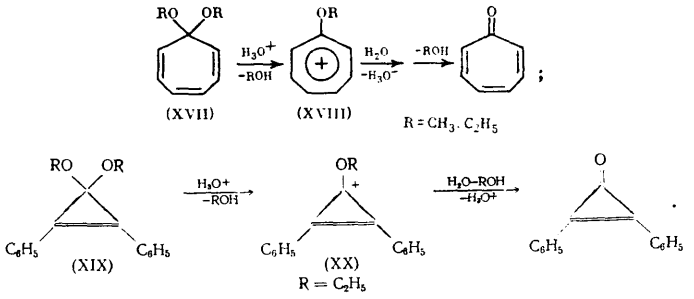
The question of the possibility of accumulating FIS in kinetic measurements has been examined in two investigations[95,105] and it has been concluded that the accumulation of several FIS at a single time point is legitimate only in the study of reactions proceeding in accordance with a first-order kinetic equation For reactions of higher order, the data must be accessed without accumulation. This problem plays a significant role in the employment of Fourier-transform ^{13}C NMR for kinetic measurements.[106–109] The difficulty of the quantitative analysis based on ^{13}C NMR spectra is associated with the influence of the spin–lattice relaxation time T_1 and the nuclear Overhauser effect on the peak intensities of the lines. In order to eliminate these influences on the recorded ^{13}C NMR spectrum of the non-equilibrium reaction mixture, it has been suggested[109] that longer delays be employed between the microwave pulses and that specific relaxation additives be introduced to shorten the time T_1, while in another study[108] the possibility of using special pulse trains for the same purpose has been discussed. However, as a rule, these procedures reduce the signal to noise ratio. For this reason, the differences between the spin–lattice relaxation times and Overhauser coefficients for individual atoms are usually ignored and the changes in signal intensities during the reaction are estimated with the aid of an intensity standard introduced into the reaction mixture.[106]

The technique used to mix the reactants in pulsed NMR flow methods differs little from that in the analogous devices employed in stationary NMR.[110,111] The synchronisation of the instant at which the microwave frequency pulse is triggered and the instant when the reaction mixture is transferred from the mixing chamber to the recording point requires special attention in the stopped flow method. A modern pulse Fourier-transform NMR spectrometer, which is equipped with a minicomputer, makes it possible to achieve readily not only the synchronisation of the start of the experiment but also one can program the entire experimental procedure.[13,84,99–104,110,112,113]

In order to shorten the dead time and to achieve the rapid arrest of the flow of the reaction mixture, various piston devices have been used.[84,99–103,110,113] In the first instant, local inhomogeneities in the composition of the reaction mixture can arise in the region of the receiving coil and can lead to additional broadening of the spectral lines in the first spectrum. Provision must be made for delays of 0.1 to 0.2 s to eliminate this effect before the first pulse of the kinetic series.

We believe that in many respects the apparatus and experimental methods proposed by McGarrity and co-workers[84,110] are optimal. By combining the mixing and recording points into one and using a novel mixing device, the authors[84] were able to achieve a reduction of the dead time to 0.04 s with effective stirring of the initial reactants directly in the rotating tube (Fig. 9). The preliminary polarisation of the initial reactants, one of which is in the tube and the other in the supplying capillary, is achieved naturally in the gap of the NMR spectrometer magnet. The problem of the temperature control of the recording region is solved simultaneously, which makes it possible to increase appreciably the accuracy of the kinetic measurements in conjunction with high reproducibility of the experimental conditions. To demonstrate the possibilities of this method, the authors repeated the study of the reaction of methylamine with trinitroanisole, which had been carried out earlier with the aid of stationary NMR in a flowing liquid.[67] The results and conclusions reached in this comparative investigation agreed fully with the available data, but the amount of initial

reactants consumed for this purpose was smaller by 2–3 orders of magnitude. Another example of the employment of this technique† is the direct detection of the unstable oxocarbonium ions (XVIII) and (XX) formed in the acid hydrolysis of the corresponding ketals (XVII) and (XIX):



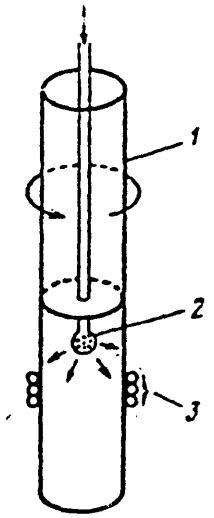


Figure 9. Apparatus for the rapid mixing of the initial reactants proposed by McGarrity et al.[84]: *1*) rotating bulb 5 mm in diameter; *2*) mixing device; *3*) recording region.

The tropylium ion (XVIII) proved to be sufficiently stable to detect it in an aqueous medium. On the other hand, the measurement of the ^1H NMR spectrum of the less stable intermediate (XX) required the use of the 1:1 D_2O–$(CD_3)_2CO$ mixed solvent; the lifespan of the intermediate in the reaction mixture was then 0.4 s.

The possibilities of the "rapid injection" method in securing quantitative kinetic information have been demonstrated[84] in the determination of the rate of hydrolysis of trimethyloxonium tetrafluoroborate (XXI):

$$\underset{\text{(XXI)}}{(CH_3)_3O^+BF_4^-} + 2H_2O \xrightarrow{k} CH_3OH + (CH_3)_2O + H_3O^+ + BF_4^- .$$

The kinetic relation (6) was obtained[84] on the basis of six kinetic experiments in each of which eight spectra were measured (Fig. 10):

$$\ln\left(\frac{[XXI]_t}{([XXI]+[CH_3OH])_t}\cdot\frac{([XXI]+[CH_3OH])_{t_0}}{[XXI]_{t_0}}\right) = -k(t-t_0) . \quad (6)$$

The instant when the first spectrum was recorded in each of the six kinetic experiments was adopted as the initial time t_0 in Eqn. (6). If the instant of mixing of the reactants were adopted as t_0, then, although the slope of each of the kinetic curves would be unaltered, the scatter of the points around the resulting straight line would depend on the efficiency of the mixing of the reactants in each experiment. As a result of the above choice of the time t_0 and the adjustment for consistency of the integral intensities of all the components of the reaction mixture at each instant, the error of the determination of the hydrolysis rate constant was less than 1%. Thus the above example shows that NMR can be used successfully for exact kinetic measurements.

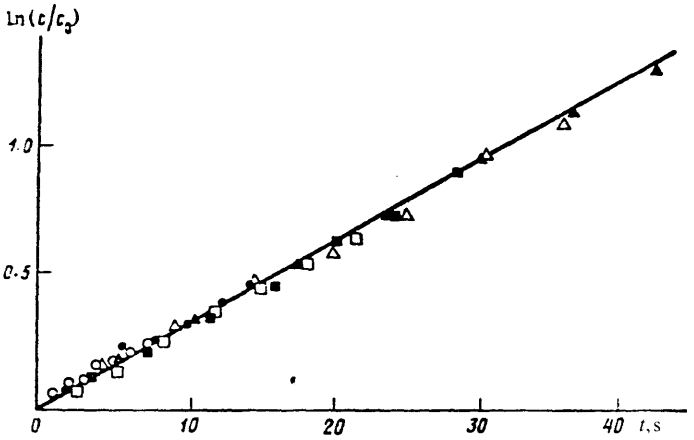
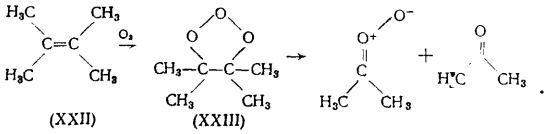


Figure 10. Kinetics of the hydrolysis of compound (XXI) in the 16:1 D_2O–[D_3]nitromethane mixed solvent at 23.4 °C; the points obtained in each of six independent measurements are designated by different symbols.[84]

The stability of the unstable intermediates in the reaction of tetramethylethylene (XXII) with ozone in [D_2]dichloromethane has been investigated by the rapid injection method:[110]



The use of low temperatures with a simultaneous reduction of the dead time of the kinetic measurements to 0.02 s and of the data access time to 0.1 s enabled the authors[110] to obtain half-reaction times of 4,4,5,5-tetramethyl-1,2,3-trioxolan (XXIII) in the temperature range from −80° to −100 °C and to estimate the thermodynamic parameters of its decomposition reaction. Even at −80 °C, where the half-reaction time is only 0.15 s, 11 spectra of the reaction mixture can be obtained for the construction of the kinetic curve. The error of the determination of $t_{1/2}$ does not then exceed 10%. The decrease of the temperature to −100 °C and the corresponding increase of $t_{1/2}$ to 3.2 s make it possible to increase the data access time and 25 virtually undistorted

†The technique of the NMR flow measurements was called by the authors the "rapid injection" method.[84]

NMR spectra of the reaction mixture can be obtained during the kinetic experiment (the error of the determination of $t_{1/2}$ at −100 °C is less than 2%).

The above study[110] was carried out on a spectrometer with a working frequency of 360 MHz and a superconducting magnet, which enabled the authors to reduce greatly the concentration of the initial reactants and to obtain qualitative ^{1}H NMR spectra of 0.005 M solutions of the reaction mixture without the accumulation of the FIS.

Another promising aspect of studies of the kinetics of fast reactions by Fourier-transform NMR is the development of a dynamic resonance theory for non-equilibrium processes. In 1979 a group of investigators under the leadership of Ernst solved the problem of the influence of fast (comparable to the data time) non-equilibrium changes occurring in the spin system and the behaviour of the magnetisation vector.[113] They examined in a general form the non-normalised density operator $\sigma_j = [A_j]\rho_j$, where ρ_j is the normalised density operator and $[A_j]$ the concentration of the molecules A_j, which depends on time under the conditions of an irreversible chemical reaction. Consequently the equation of motion for σ_j is

$$\frac{d\sigma_j}{dt} = [A_j]\frac{d\rho_j}{dt} + \frac{d[A_j]}{dt}\rho_j \ .$$

Its solution for the line shape function S_t has been obtained[113] for the simplest case of a first-order reaction. Analysis of the expression for S_t permits the conclusion that the occurrence of rapid irreversible processes in the spin system does not lead to new spectral transitions compared with the equilibrium case. However, these processes are responsible for the broadening of the absorption lines of the initial reactants; the spectral lines of the product are not broadened, but they do undergo a phase distortion.

The fact that the amplitude and phase changes in the spectrum of the non-equilibrium mixture are analytically related to the reaction rate constant k virtually leads to a new application of pulsed Fourier-transform NMR—the study by the method involving the total line shape analysis of the kinetics of irreversible chemical reactions whose half-lives are comparable to the data access time.

An an example, Fig. 11 illustrates the theoretical variation of the spectrum for the simplest case of a single-stage transition in a one–spin system $A \overset{k}{\rightarrow} B$ as a function of the rate constant k. The greatest changes in the spectrum of a non-equilibrium reaction mixture take place for comparable values of k and of the difference between the chemical shifts of the initial reactant and the final product, while the character of the phase distortions of the line shape for the product is determined by the relative positions of the absorption signals for the initial and final states. Consequently the sign of the phase distortions of the NMR signal of the product is a criterion of the region in which the corresponding signal of the initial reactant is located relative to it.

Fig. 12 presents the theoretical spectra for a one-stage reaction of a two-spin system, $AB \overset{k}{\rightarrow} CD$, for different values of the rate constant k. These spectra were constructed subject to the following condition: as a result of the reaction, A is converted into C and B is converted into D; $\nu_A > \nu_C$ and $\nu_B < \nu_D$ and the phase distortions therefore have the opposite signs.

To demonstrate the possibilities of this new kinetic method, its authors selected the base hydrolysis of methyl formate (XXIV):

$$\underset{\text{(XXIV)}}{HCOOCH_3} + Na^+OD^- \xrightarrow[D_2O]{k_2} HCOO^-Na^+ + CH_3OD.$$

In the presence of an excess of NaOD, this reaction proceeds in accordance with a pseudofirstorder equation and the second-order reaction rate constant k_2 can be obtained from the expression $k_1 = k_2[O\bar{D}]$. The kinetic isotope effect, obtained from a comparison of the experimental and theoretical spectra of the reaction mixture (a mixture of a 0.15 M solution of lithium formate and a 0.63 M solution of NaOD) in H_2O and D_2O, is

$$k_2(H_2O)/k_2(D_2O) = 0.64 \pm 0.08 .$$

This value is comparable to the familiar literature data (0.75).[114] The dead time in these measurements was $(3-5) \times 10^{-3}$ s and the number of repetitions of the experiments in order to accumulate the FIS ranged from

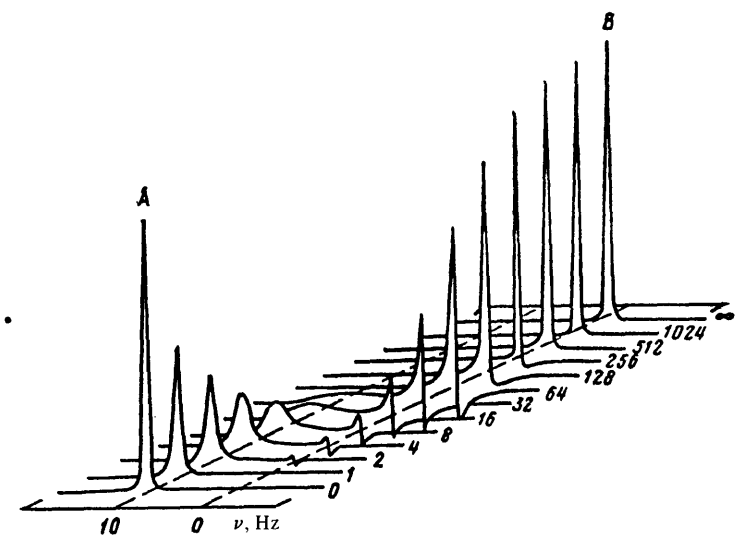


Figure 11. Theoretical dependence of the line shape for a single-stage reaction of a one-spin system for different rate constants k;[113] the numerals opposite each spectrum denote the values of k (Hz) ($\nu_A - \nu_B = 10$ Hz).

40 to 100. In order to reduce τ_0, the volume of the recording medium was artificially diminished and in the determination of the temperature of the reaction mixture a correction, taking into account the temperature rise (it did not exceed 3 °C when the accuracy of the thermostatic control of the recording region was to within 1 °C), was applied.

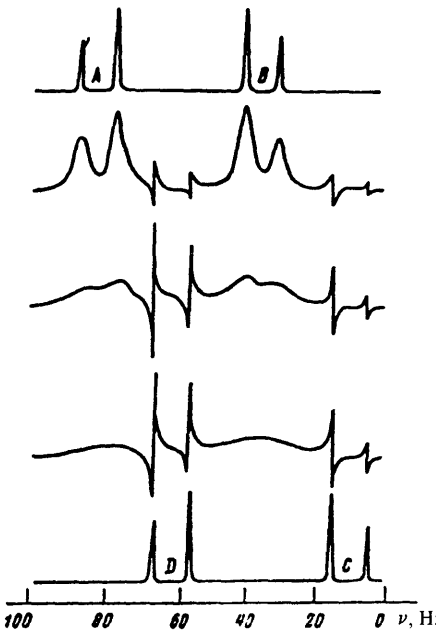


Figure 12. Theoretical variation of the line shape for a single-stage reaction of a two-spin system for different rate constants k(Hz):[113] *1)* 0; *2)* 10; *3)* 30; *4)* 50; *5)* ∞ (ν_A = 80 Hz, ν_B = 35 Hz, ν_C = 10 Hz, ν_D = 60 Hz, J_{AB} = 10 Hz, J_{CD} = 10 Hz).

The use of the method involving the total analysis of the line shape in order to obtain kinetic data for non-equilibrium chemical reactions[113] is so far limited to first-order reactions for which it is possible to obtain explicit analytical relations between the line shape in the NMR spectrum and the rate constant k. For higher-order reactions, numerical integration is required, which greatly complicates the construction and interpretation of the theoretical spectra.

The Fourier-transform NMR has been used for the first time[44–46] to study non-equilibrium chemical reactions with the aid of the saturation transfer effect, which has been applied previously only in the study of equilibrium reactions.[5,39] This selective magnetisation defect, which the authors[44–46] called the "microwave frequency label", is generated with the aid of a homonuclear decoupler by saturating the signals of specific atoms in the initial reactant directly before measuring the ^{1}H NMR spectrum of the reaction mixture. The method involving the microwave probing of chemical reactions under specific conditions[46] makes it possible to trace, by employing NMR spectra, the path followed by the labelled atom in the course of the reversible reaction from the initial reactant to the product. The transfer of the label can be recorded by comparing the signal of intensities in the NMR spectra obtained with saturation and in the absence of saturation of specific signals from the initial reactant.

Fig. 13 illustrates the ^{1}H NMR spectra of the reaction mixture of allyltriethylstannane (XXV) and bromotrichloromethane obtained under different conditions in the course of the photochemical reaction

$$(C_2H_5)_3Sn\overset{1}{C}H_2—\overset{2}{C}H=\overset{3}{C}H_2 + BrCCl_3 \xrightarrow{h\nu}$$

(XXV)

$$\xrightarrow{h\nu} CCl_3\overset{1'}{C}H_2—\overset{2'}{C}H=\overset{3'}{C}H_2 + (C_2H_5)_3SnBr\,.$$

(XXVI)

[the numerals 1, 2, 3, and 1′, 2′, and 3′ denote isotypical groups of atoms the reactant (XXV) and the product (XXVI), whose signals are indicated in the NMR spectra in Fig. 13*a*].

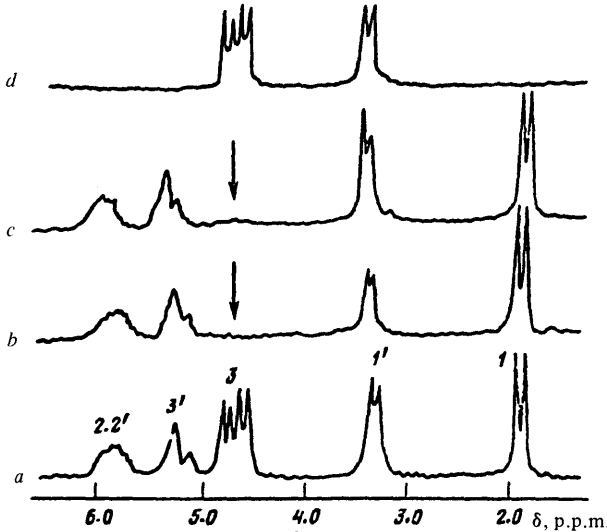


Figure 13. A section of the ^{1}H NMR spectrum obtained in the course of the photochemical reaction of compound (XXV) with bromotrichloromethane in [D_{12}]cyclohexane under different conditions: *a*) reaction mixture without microwave frequency saturation of signals (the numerals denote the line assignment); *b*) and *c*) with saturation of the signals in the 3-position in compound (XXV) (the arrow indicates the position of the saturating field); spectra *b* and *c* were obtained with and without irradiation of the specimen by light respectively;[44] *d*) as for spectrum *b* but obtained with the aid of a selective pulse train[46] (evolution time ~1 s).

The fact that the saturation of signal 3 from the initial reactant (XXV) leads to a decrease (by 30–40%) of the intensity of signal 1′ from the product (XXVI) (Fig. 13*b*) compared with the intensity of this signal in the spectrum obtained without irradiating the specimen with light (Fig. 13*c*), while saturation of signal 1 from the reactant (XXV) entails a decrease of the intensity of signal 3′ from the product (XXVI) demonstrates unambiguously the occurrence of the 3 → 1′ and 1 → 3′ transitions in this reaction.[44,45]

The main deficiency of this method for the recording of the microwave frequency label is that the saturation transfer effect is observed against the background of the signal from the part of the product whose magnetisation has already returned to the state of equilibrium. In order to eliminate this disadvantage, an effective method involving the artificial isolation of the signals due to labelled atoms in the NMR spectrum of the reaction mixture has been proposed.[46]

This is achieved by the selective separation of the magnetisation vectors of the "labelled" and all the remaining atoms of the initial reactant during the preparatory period of the pulse train containing two in-phase microwave frequency pulses (broad-band and selective). Fig. 13*d* illustrates the spectrum of the reaction mixture obtained as a result of the effect of such a pulse sequence in the case of the selective isolation of signals associated with the generation of a microwave frequency label in the atomic group 3 of the initial reactant (XXV). The spectrum consists of only two signals (3 and 1'), which demonstrates the occurrence of the corresponding reaction transition.[46]

In connection with the employment of Fourier-transform NMR in the study of non-equilibrium reactions, it is essential to examine also the problems associated with the use for this purpose of NMR involving "rare" nuclei. Despite the difficulties due to the low sensitivity of these methods, ^{13}C,[80,106,115-117] ^{31}P,[86,87,118] and even ^{15}N [119] NMR has been used in recent years to obtain qualitative information about the structure of unstable intermediates in a whole series of chemical and biochemical reactions. Such investigations merit attention, because they provide an idea about the character of the experimental difficulties arising when they are carried out. In assessing the methodological advantages of these studies, it is necessary to take into account the fact that the very concept of a "fast reaction" has a different significance for each of the above nuclei#. In the determination of the experimental dead time τ_0 in the stopped flow method, it is therefore necessary to take into account in addition the total FIS accumulation time in order to obtain an acceptable signal to noise ratio, which is to a first approximation§ inversely proportional to the square of the natural abundance of the isotope employed.

The frequent repetition of the entire procedure for the generation of the FIS in the non-equilibrium reaction mixture and for the accumulation of such signals must be regarded as the simplest and most effective method whereby the dead time in such experiments can be reduced,[113,120] which naturally requires an appropriate increase in the amount of the initial reactants. It is even more difficult to extract quantitative (or semiquantitative) kinetic information from NMR involving "rare" nuclei, because here one must take into account the influence of the relaxation effects on the peak intensities of the NMR signals. These problems have been discussed in detail in a number of studies[106,108,109,121] of the use of ^{13}C NMR for the recording of CINP effects. To save time, it is recommended that an external computer be used in kinetic measurements either for the simple storage of FIS corresponding to different time points on the same kinetic relation[101,110] or for their summation at a single time point for each of the frequently repeated kinetic experiments.[113,120]

#According to the definition given by Caldin,[22] the term "fast reaction" in relation to a given method of measurement should be understood as one which cannot be investigated under normal conditions and by means of a standard experimental technique.

§Here no account is taken of other parameters of the spin system and the NMR spectrometer which determine the resulting signal to noise ratio.

V. CONCLUSION

The examples of the use of high-resolution NMR in the study of the mechanisms of fast irreversible reactions examined above indicate a vigorous development of mainly the flow methods and methods for the recording of CINP effects in which a non-equilibrium initial state is generated respectively as a result of the rapid mixing of the initial reactants and a photochemical reaction. The simple apparatus developed for these purposes, based on the use of NMR in a flowing liquid, makes it possible to obtain not only the spectral NMR characteristics of the relatively unstable intermediates with lifespans up to 0.02 s [110] but also quantitative data concerning the kinetics of their reactions. The relative error of the kinetic measurements can be reduced to 1% [84] and the chemical shift[14] or the spin–spin interaction constant[96] can serve as a time-dependent physical quantity together with the integral (or peak) signal intensity. Although kinetic data obtained with the aid of NMR are less accurate than the analogous results of the kinetic studies using the more sensitive UV, IR, and EPR spectroscopic methods, they can prove extremely useful in those cases where the intermediates do not contain chromophoric groups or unpaired electrons.

A characteristic feature of the development of NMR methods for the study of fast reactions is at the present time the tendency towards a wider employment of the stopped flow method with pulsed Fourier-transform recording of the spectra. This can be explained both by the economy of the method from the standpoint of the consumption of the reactants and the possibility of programming the experiment and by the increased sensitivity owing to the accumulation of the FIS, which permit, on the one hand, studies involving ^1H nuclei in more dilute solutions and, on the other, the use on a wider scale of measurements involving the ^{13}C, ^{31}P, ^{27}Al, ^{15}N, etc., nuclei. Fig. 14 presents the dead times τ_0 attained with the aid of various ^1H NMR methods. It is noteworthy that $\tau_0 \cong (3-5) \times 10^{-3}$ s has been obtained by the Fourier-transform NMR under stopped flow conditions, such times being characteristic of the flow technique involving UV and IR spectroscopic analysis of the composition of the non-equilibrium reaction mixture, while the scope of the continuous flow method with stationary recording of the spectrum has been virtually exhausted and is restricted to $\tau_0 \cong 0.05$ s.

Another trend involves the use of methods with rapid NMR measurements at low temperatures. This permits a considerable extension of the range of irreversible reactions susceptible to study. Thus a decrease of the temperature of the reaction mixture to −90 °C expands the NMR time scale by approximately 8 orders of magnitude: by 4 orders of magnitude owing to the rapid measurement and by a further 4 orders of magnitude as a result of the decrease of temperature. The technical difficulties which arise in the development of the low-temperature NMR flow technique are associated primarily with the requirement for the effective temperature control of the measuring channel taking into account the possibility of the self-heating of the reaction mixture in the course of an exothermic reaction or heating due to the pulsed irradiation in the sensor of the Fourier-transform spectrometer.[77] These problems have been solved most successfully in the "rapid injection" method,[84,110] which permits kinetic measurements at temperatures up to −100 °C.

A study[122] involving the use of the NMR spectrometer as the recording device in a non-isothermal method[123] for the investigation of fast reactions is of interest from the standpoint of the employment of low temperatures and the economy in the consumption of the initial reactants. This method

consists in recording the changes in the NMR parameters of a non-equilibrium reaction mixture in the course of a linear temperature variation.[124] Analysis of this relation permits the calculation of the activation energy for first- or second-order reactions tending to equilibrium on the basis of a single kinetic experiment.

The extension of methods for the study of fast equilibrium reactions such as the total line shape analysis (TLSA) and the saturation transfer effect (STE) to the non-equilibrium case leads to new possibilities for the measurement of kinetic parameters and the study of mechanisms of irreversible reactions with half-lives comparable respectively to the data access time of the Fourier-transform spectrometer and the spin–lattice relaxation time of a selectively polarised nucleus.[45,46] The microwave frequency probing method has already found a practical application in the study of the mechanism of photochemical reactions.[44–46] However, its unique possibilities in meeting specific requirements[46] can be used in the study of a wider range of organic reactions.

The creation in the system of a non-equilibrium initial state with subsequent observation of its transition to the initial or new equilibrium state constitutes a general method for the investigation of both equilibrium and non-equilibrium chemical reactions.[125] For this reason, experimental methods and techniques for the NMR recording of fast irreversible transitions induced by chemical reactions, which have been examined in this review, can be useful in the study of both irreversible and irreversible chemical reactions in combination with other familiar methods for disturbing the equilibrium such as temperature,[126] or pressure jump[22] methods etc. The absence of NMR studies of this kind is associated in many respects with experimental difficulties in the creation of a sharp temperature or pressure drop in the standard NMR sensor. Nevertheless, it is to be expected that in the immediate future these relaxation methods will develop, for example, on the basis of sensors with wide temperature and pressure ranges, which have already been devised (for the solution of other problems).[127–131]

The problem of the low sensitivity of NMR involving "rare" nuclei, which prevents their wide-scale employment in the study of non-equilibrium reactions, has been partly solved with the aid of multipulse methods for the transfer of polarisation between atoms coupled by the spin–spin interaction which have been developed in recent years.[132] These methods for the artificial increase of the sensitivity and the corresponding shortening of the accumulation time of the NMR spectra involving "rare" nuclei have already found applications in the study of non-equilibrium biochemical reactions associated with the metabolism of living organisms.[133] The possibility of obtaining high-quality ^{31}P,[135–137] ^{13}C,[117,138] and ^{19}F [139] NMR spectra in soft tissues in the course of several minutes with the aid of surface coils[134] has given rise to wide possibilities for medical diagnostics with the aid of NMR and studies in this field merit separate consideration.

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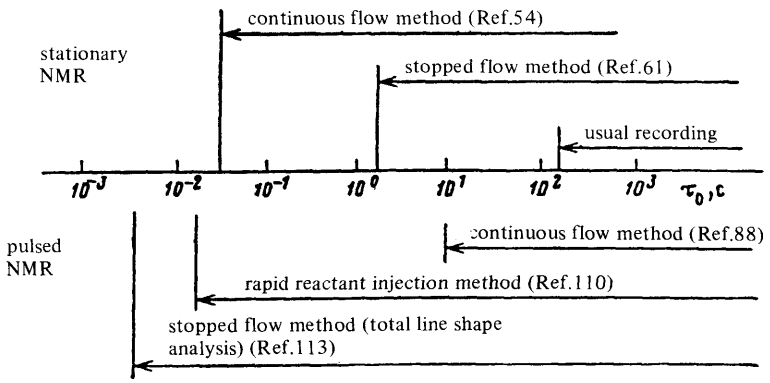


Figure 14. Experimental dead times τ_0 in various NMR methods for the study of fast non-equilibrium chemical reactions.

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