an enormous paf would be required to effect simple proton removal. A possible alternative route is the conversion of the carbonyl compound to the protonated Schiff base.

$$R_2C{=}O + RNH_2 + H^+ \rightleftharpoons R_2C{=}\overset{+}{N}HR + H_2O$$

Such species do indeed have reactive methylene groups,[37] and can be present in reasonable concentrations in neutral solution. Further work is needed to determine the importance of this alternative form of activation.

(37) (a) M. L. Bender and A. Williams, *J. Am. Chem. Soc.*, **88**, 2502 (1966); (b) G. E. Lienhard and T. C. Wang, *ibid.*, **90**, 3781 (1968); (c) M. Roseman, personal communication; (d) J. Hine, *Acc. Chem. Res.*, **11**, 1 (1978).

Flow and Stopped-Flow Nuclear Magnetic Resonance Investigations of Intermediates in Chemical Reactions

COLIN A. FYFE,* MICHAEL COCIVERA, and SADRUDIN W. H. DAMJI

Guelph-Waterloo Centre for Graduate Work in Chemistry, Guelph Campus, Department of Chemistry, University of Guelph, Guelph, Ontario, Canada

Received July 27, 1977

The investigation of reaction intermediates has played an important role for many years in the elucidation of the mechanisms of chemical reactions. In the earliest work, investigation of intermediate species depended upon their isolation from the reaction mixture and was thus limited to relatively stable, long-lived species. With the advent of spectroscopic techniques, it became possible to investigate these intermediate species in situ during the reaction.

Various spectroscopic techniques have been used, but UV–visible spectroscopy has become by far the most widely used in these investigations in both flow and stopped-flow experiments.[1] The main advantage of UV–visible spectroscopy is its extreme sensitivity, which permits the use of low concentrations of substrates (10^{-4}–10^{-6} M) which gives relatively ideal solutions and in many instances considerably lowers the rate of reaction. Ultraviolet–visible spectroscopy has, however, the disadvantage of being a relatively nondiagnostic technique so that often accurate kinetic measurements may be made on transient species but little information obtained as to their structures.

High-resolution nuclear magnetic resonance spectroscopy is relatively insensitive and much more concentrated solutions ($\sim 10^{-1}$ M) must be used, but its great diagnostic character has made it the most widely used spectroscopic technique for structure determinations, especially in organic and organometallic systems.[2] NMR has also been used to study very slow chemical reactions ($t_{1/2} \gtrsim 3$–5 min) by measurement of changes in peak areas as the reaction proceeds, and much work has been done in the study of fast exchange reactions in systems at equilibrium by the study of line-shape changes.[3]

Until recently, however, NMR has not been utilized in flow or stopped-flow experiments, possibly due to concern over the relatively long relaxation times commonly found for magnetic nuclei.[4] Recently, techniques and equipment have been developed which make it possible easily and simply to use high-resolution NMR in both flow and stopped-flow experiments. These enable kinetic measurements to be made in the range 50 ms–5 min and thus cover a range of reaction times previously inaccessible to NMR investigation. They also provide an excellent diagnostic tool for the identification of transient intermediate species and in this context usefully complement UV–visible spectroscopy. The techniques to be described all utilize commercial spectrometers available to most chemists. It is hoped that this Account will encourage their wider use.

Flow Nuclear Magnetic Resonance Spectroscopy

The characteristic properties of nuclear magnetic resonance in flowing liquids have been known for some time[5] and are well described.[5,6] The signal amplitude depends on the length of time the sample has been in the magnetic field, and there is broadening of the signals due to a reduction in the effective T_2 of the sample by the flow.[5] There is a corresponding decrease in T_1 which allows more power to be applied before saturation occurs.

The apparatus developed and used in our laboratory for continuous flow NMR measurements is shown in

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Colin A. Fyfe is Professor of Chemistry at the University of Guelph. He received both B.Sc. and Ph.D. degrees from the University of St. Andrews, Queen's College, Dundee, Scotland, and spent 2 years as a Killam Fellow at the University of British Columbia. His research interests are in the investigation of reaction mechanisms, detection of transient intermediates by flow NMR, and the investigation of the dynamic structures of solids by solid-state NMR.

Michael Cocivera is Professor of Chemistry at Guelph. He studied at Carnegie Institute of Technology for his B.S. degree. Following graduate work at UCLA, where he received his Ph.D. in 1963, he was on the staff of Bell Telephone Laboratories until moving to Guelph in 1969. His research concerns the application of flow NMR to chemical reactions and the study of CIDNP processes.

Sadrudin W. H. Damji is on the faculty of Pearson College, Victoria, B.C., Canada. He received his Ph.D. from the University of Guelph in 1976 under the direction of Dr. Fyfe.

(1) C. N. R. Rao, "Ultra-Violet and Visible Spectroscopy: Chemical Applications", 2nd ed, Butterworths, London, 1967.

(2) N. F. Chamberlain, "The Practice of NMR Spectroscopy", Plenum Press, New York, N.Y., 1974.

(3) "Dynamic Nuclear Magnetic Resonance Spectroscopy", L. M. Jackman and F. A. Cotton, Ed., Academic Press, New York, N.Y., 1975.

(4) Characteristically these range from 1 to 30 s.

(5) A. I. Zhernovoi and G. D. Laytshev, "Nuclear Magnetic Resonance in a Flowing Liquid", Consultants Bureau, New York, N.Y., 1965.

(6) D. W. Jones and T. F. Child, *Adv. Magn. Reson.*, **8**, 123 (1976).

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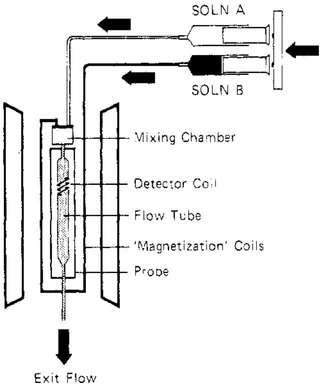


Figure 1. Schematic diagram of the general arrangement used for the measurement of flow NMR spectra (adapted from ref 7 and 8).

Scheme I

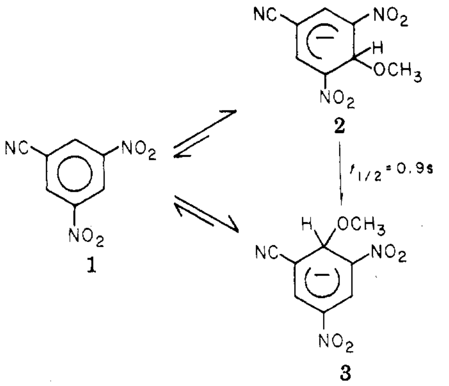


Figure 1.[7,8] (An alternate design by Bargon will be referred to subsequently.) An important feature of the apparatus in Figure 1 is the use of two coils in which the reactant solutions are equilibrated in the magnetic field for a time much longer than T_1, the spin–lattice relaxation time of the nuclei. The solutions are flowed continuously from these through a high-pressure mixing chamber and through the transmitter–receiver coils of the probe where the spectrum of the flowing, chemically reacting system is measured. At a constant flow rate, the solution will have a constant composition at the receiver coils, and thus the spectrum obtained is exactly analogous to the conventional high-resolution spectrum except that the flow tube is not spinning.

The performance of the equipment is illustrated in Figure 2. This shows spectra obtained during the reaction of 3,5-dinitrocyanobenzene (1) with base[9,10] (Scheme I). The top spectrum shows the ring proton absorptions of 3,5-dinitrocyanobenzene and illustrates that good high-resolution spectra can be obtained even with a nonspinning sample tube. The intermediate spectra in Figure 2 were obtained at the flow rates indicated after the reaction of 1 with methoxide ion. Besides the three resonances of equal intensity assigned to the ring protons of the thermodynamically stable complex 3, there are two other signals in the ratio of 2:1 which can be assigned to the thermodynamically less stable isomer 2. The relative intensities of the latter increase with increasing flow rate, reaching the limiting situation indicated in the 50 mL/min spectrum. When the flow is stopped and the spectrum quickly scanned, only the signals due to 3 are observed (lowest spectrum). Thus the spectra of the kinetically formed mixture of 2 and 3 could not have been obtained at all by conventional means.

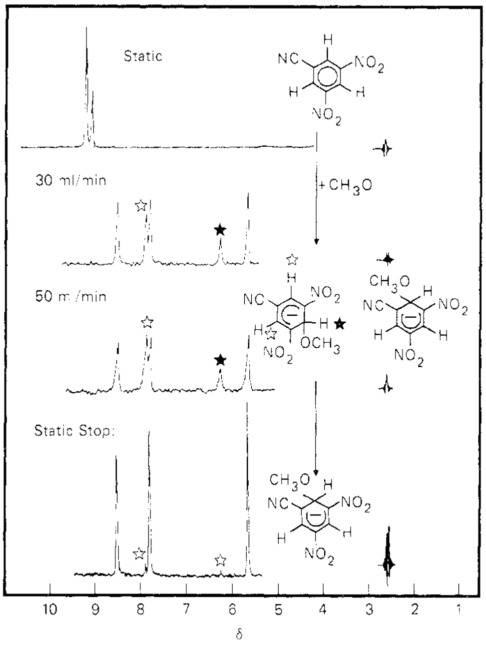
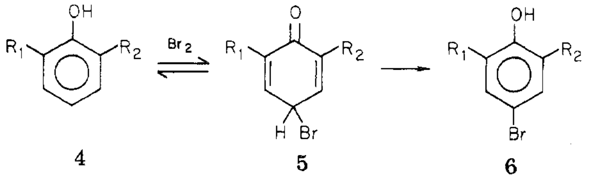


Figure 2. Representative ^{1}H NMR spectra recorded at 100 MHz, showing the ring proton absorptions of 3,5-dinitrocyanobenzene alone (top spectrum) and during its reaction with 1 equiv of methoxide ion (in 87.5% Me$_2$SO/12.5% MeOH) under the conditions of flow rate indicated (from ref 10).

Scheme II



$t_{1/2}$ = 0.12 s, $R_1 = R_2 = CH_3$

As can be seen from Figure 1, there are two parameters that can be varied in this type of system to obtain kinetic data on very fast reactions in flowing systems.[10] First, the flow rate may be varied for a fixed distance (and, therefore, volume) between the mixing chamber and the receiver coil and spectral measurements made. Secondly, this distance may be varied and these measurements repeated by varying the flow rate at each distance. Permutation of these two variables yields a set of data which should be self-consistent and yield an accurate description of the kinetics of the system. The half-life of species 2 is found to be 0.94 s at 30 °C. Its spectrum could not have been obtained at all by conventional techniques.

Use of a continuous flow cell which utilizes a capillary feed from the mixing chamber to the point of observation reduces the minimum time between mixing and observation to ~20 ms and makes possible the observation of even shorter lived species.[11] Thus, it has

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(7) S. W. H. Damji, Ph.D. Thesis, University of Guelph, 1975.

(8) C. A. Fyfe, M. Cocivera, T. A. Hostetter, D. Sproat, and J. O'Brien, *J. Magn. Reson.*, **23**, 377 (1976).

(9) C. A. Fyfe, M. Cocivera, and S. W. H. Damji, *Chem. Commun.*, 743 (1973).

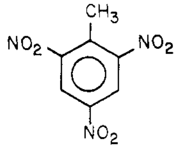
(10) C. A. Fyfe, M. Cocivera, and S. W. H. Damji, *J. Am. Chem. Soc.*, **97**, 5707 (1975).

(11) C. A. Fyfe and L. Van Veen, Jr., *J. Am. Chem. Soc.*, **99**, 3366 (1977).

been possible to characterize the cyclohexadienone intermediates formed in the reaction of 2,6-disubstituted phenols 4 with bromine in aqueous acetic acid (Scheme II; $R_1 = R_2 =$ *tert*-butyl; $R_1 = R_2 =$ *sec*-butyl; $R_1 = R_2 =$ isopropyl; $R_1 = R_2 =$ methyl; $R_1 =$ *tert*-butyl, $R_2 =$ methyl; and $R_1 =$ *tert*-butyl, $R_2 =$ H). As the steric interactions of the two groups in the 2 and 6 positions are reduced, the rate of the second step in the reaction increases and the lifetime of the intermediate becomes shorter. Even under the optimum conditions of solvent composition and temperature, many of these are of the order of $t_{1/2} = 100$ ms and can still be accurately measured using this equipment (e.g., $R_1 = R_2 = CH_3$; $t_{1/2} = 0.12$ s, 0 °C, 85% HOAc).[11]

Although kinetic parameters can be obtained from NMR measurements, these are best determined by UV–visible spectroscopy. An excellent combination of the two techniques utilizes NMR for the identification of transient species and assignment of their UV–visible spectra. Ultraviolet–visible spectroscopy is then used to obtain accurate kinetic data in dilute, more ideal solutions. This can be achieved by using very short path length UV–visible cells and recording the UV–visible spectra of the solutions under the same conditions as those used for the NMR measurements.[10] Comparison of the two sets of data allows the unambiguous assignment of the UV spectra of the transient species, even if several are present. Thus in the reaction of **1** with methoxide ion above (Scheme I), the UV spectrum immediately on mixing the two reactants shows two absorptions at 505 and 555 nm which eventually yielded a single major peak at 500 nm with a shoulder. The initial spectrum had previously been assigned to **2**, and the final spectrum to **3**, whereas the direct comparison of the NMR and UV data reveals that in fact **2** and **3** show single absorptions in the visible region at 550 and 500 nm, respectively.

A similar identification of short-lived species and assignment of their UV–visible spectra have been made in the reaction of 2,4,6-trinitrotoluene (**7**) with base,[12] a reaction for which a whole variety of species had been postulated to be formed from UV measurements. Using the flow NMR system,[12] we were able to determine that in 87.5% Me_2SO/12.5% MeOH the reaction of equimolar quantities of **7** and methoxide ion yields first the complex **8** in a very fast reaction and the anion **9** in a second slower reaction. The conversion to **9** is not 100% efficient and radical ions are present in the mixture which destroy the spectra of other neutral products which appear more slowly. If a twofold or higher excess of base is used in the same solvent mixture, the only species observed is the dianion **10** which is stable to further reaction.[12] In mixtures containing a larger proportion of methanol, all three species, **8**–**10**, are present and the relationships between them can be deduced. More importantly, by means of the techniques indicated above, the UV–visible spectra of all three species can be unambiguously assigned. It should now be possible to investigate these reactions in detail in ideal solutions.



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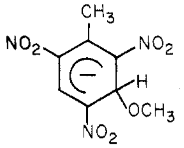

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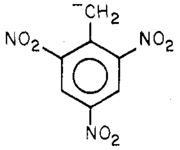
$t_{1/2} \simeq 25$ s



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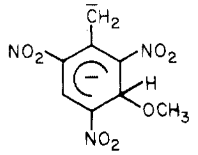

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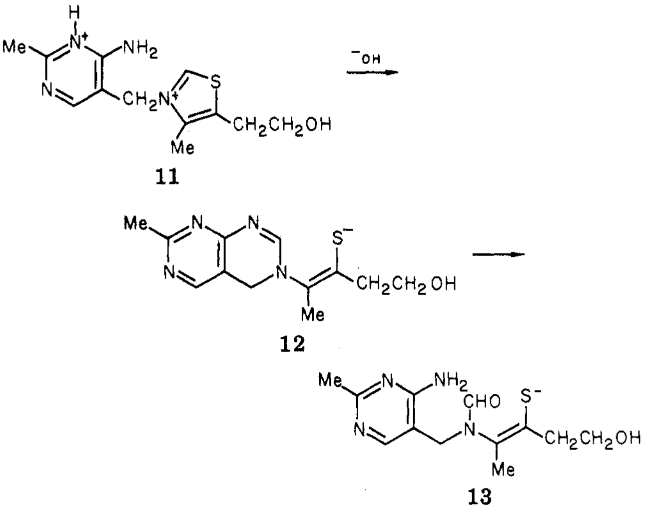
Scheme III



A similar situation exists in the action of nucleophiles on pyridinium ions. Isomerization of the intermediate initially formed by attack in the 2 position to the thermodynamically stable 4-isomer can be followed by NMR, and the UV–visible absorption spectra of both species can be assigned.[7]

Continuous flow NMR has also been used by Asahi and Mizuta[13] who investigated various designs of flow cell. Their final system was similar to that of Bargon and, although the flow rate was limited to 3 cm^3/min, they were able, in the reaction of thiamine with hydroxide ion, to detect the yellow thiol form **12** alone some 5 s after mixing before its slow conversion to the colorless thiol form **13** (Scheme III). Conventional NMR techniques had previously detected only a mixture of **12** and **13**.

In some cases, the transient species under investigation have no chromophoric group and NMR will yield information which cannot be obtained by other techniques. In the reaction of nitrogen nucleophiles with carbonyl compounds, kinetic evidence obtained from measurements on the reactants and products strongly supports the existence of an intermediate carbinolamine. Since they are transparent in the UV–visible spectral region, no direct measurements could be made on species of this type.

In the reaction of hydroxylamine with acetaldehyde the flow NMR technique makes it possible to identify directly this intermediate species (**14**) and to measure its rate of decomposition and the rate of formation of both the syn and anti oximes **15** and **16**.[14] The rate of formation of the syn oxime is slower than the trans

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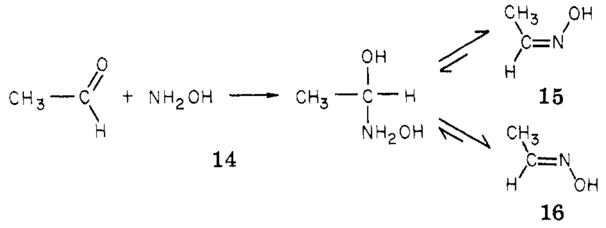
(12) C. A. Fyfe, C. D. Malkiewich, S. W. H. Damji, and A. R. Norris, *J. Am. Chem. Soc.*, 98, 6983 (1976).

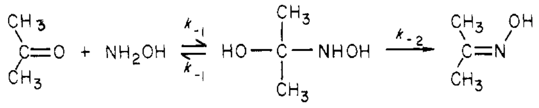
(13) Y. Asahi and E. Mizuta, *Talanta*, 19, 567 (1972).

(14) M. Cocivera, C. A. Fyfe, A. Effio, S. P. Vaish, and H. E. Chen, *J. Am. Chem. Soc.*, 98, 1573 (1976).

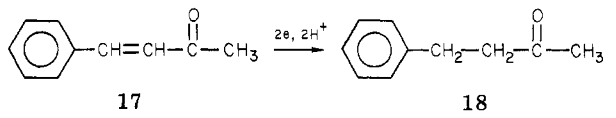
Scheme IV



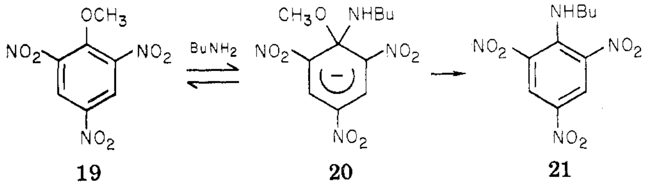
Scheme V



Scheme VI



Scheme VII



max concn at 1 s (−40 °C)

oxime. In addition, there is an equilibrium established between the two oximes. Because the concentrations of all species could be monitored simultaneously, most of the rate constants in Scheme IV could be determined. In this work, as in the previous example involving the pyridinium ions, the reaction is slow enough for the flow to be stopped and the appropriate spectral region to be quickly and repeatedly scanned. The measurements are similar to those by the stopped-flow technique described in the next section.

In the above instance it was not possible to determine the rate of the first, very fast addition step forming the tetrahedral intermediate. However, in the case of the addition of hydroxylamine to acetone in aqueous solution, the flowing spectrum shows a narrow signal due to the CH_3 protons of a small amount of oxime and a broad signal due to the coalescence of the signal from the acetone and that from the intermediate.[15] By relating the line width of this signal to the rate constant for the addition step, we were able to determine all the kinetic parameters in Scheme V.

Equipment of this type also makes possible the observation of transient effects as well as species. An early application of the flow technique to the observation of CIDNP was the work of Lehnig and Fisher who, in studying the photolysis of aroyl peroxides, used a system that enabled the photolysis to be carried out in the fringes of the magnetic field and the solution flowed into the probe for spectral measurement.[16] The sample was delivered into a closed 5-mm NMR tube, flowed continually and removed by an overflow arrangement at the open top of the tube. This type of flow arrangement is described in detail by Bargon.[17] In this design the solution enters into a standard NMR tube, closed at the bottom, and is continually removed by an aspirator via a second capilliary set above the receiver coils. The main advantage of this type of arrangement is that the NMR tube can still be spun and better resolution obtained. The main disadvantage is that the flow rates obtainable are relatively low compared to the "straight-through" technique.

This flow-cell design of Bargon[17] has been used by Lawler and Halfon[18] who also employed a second magnet of variable (lower) field strength in which the sample could be polarized and irradiated prior to flowing into the probe for measurement. Their purpose was to investigate quantitatively the field-strength dependence of the CIDNP effect in the photolysis of di-*tert*-butyl ketone. The maximum flow rate used was 4 cm^3/min.

Measurements may also be made on this type of system using the straight-through flow-cell design. Thus, while only a small CIDNP effect was observed in the oxidation of isopropyl alcohol by $TiCl_3$ plus H_2O_2 when the spectrum was measured by the conventional technique of quickly mixing the reactants outside the probe, transferring them into the probe (~5 s), and recording the spectrum as quickly as possible, very large effects were observed when the reaction was carried out with use of the flow system. The data obtained, in conjunction with ESR data, enable the mechanism of the reaction to be deduced.[19] Recent additional applications of the flow NMR technique in CIDNP studies have been the investigations by Trifunac and coworkers[20,21] of the polarization effects induced by pulse radiolysis.

The versatility of the continuous flow technique and the breadth of its possible applications are illustrated by the work of Richards and Evans[22] who designed a flow cell, again with a spinning tube and relatively low flow rates, which incorporated an electrolysis cell. The electrolysis cell consisted of a cation exchange membrane with a porous bed electrode packed inside through which the solutions flow and a concentric coil of platinum wire wound on the outside which served as the counter electrode. They monitored the formation of 1-phenyl-3-butanone (**18**) formed by the two-electron reduction of **17** (Scheme VI).

It is probable that other, quite different applications of continuous flow will be found in areas where the diagnostic character of NMR could not to date be fully exploited.

One recent development in our laboratory, of general importance in flow NMR studies, has been the use of very low temperatures.[23] An important feature of working at low temperatures is that T_1 in general is considerably shortened, and thus the sample needs a

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(15) M. Cocivera and A. Effio, *Chem. Commun.*, 393 (1976).

(16) M. Lehnig and H. Fischer, *Z. Naturforsch.*, *A*, **24**, 1771 (1969).

(17) (a) J. Bargon, German Patent 2004973 (1972); (b) *Chem. Abstr.*, **76**, 92940b (1972).

(18) R. G. Lawler and Halfon, *Rev. Sci. Instrum.*, **45**, 84 (1974).

(19) M. Cocivera, C. A. Fyfe, S. P. Vaish, and H. E. Chen, *J. Am. Chem. Soc.*, **96**, 1611 (1974).

(20) A. D. Trifunac, K. W. Johnson, and R. H. Lowers, *J. Am. Chem. Soc.*, **98**, 6067 (1976).

(21) A. D. Trifunac and D. J. Nelson, *J. Am. Chem. Soc.*, **99**, 1945 (1977).

(22) J. A. Richards and D. H. Evans, *Anal. Chem.*, **47**, 964 (1975).

(23) (a) C. A. Fyfe, S. W. H. Damji, and A. Koll, unpublished results; (b) C. A. Fyfe, C. D. Malkiewich, S. W. H. Damji, A. Koll, and P. A. Forte, *Can. J. Chem.*, **55**, 1468 (1977); (c) C. A. Fyfe, C. D. Malkiewich, S. W. H. Damji, A. Koll, and P. A. Forte, *J. Chem. Soc.*, *Chem. Commun.*, 335 (1977).

much shorter time to become magnetized in the field before reaction, with considerable practical simplification in the system design. Moreover, there is the expected decrease in reaction rates. Thus at -40 °C it is possible to identify the intermediate complex **20** directly on the substitution pathway of 2,4,6-trinitroanisole (**19**) with *n*-butylamine (Scheme VII).[23a,c] The concentration of the intermediate is at a maximum after 1 s, even at these low temperatures, and the spectra could only be obtained using flow techniques. Similar observations have been made of the intermediate complex during the reaction of 1-ethoxy-2,4-dinitronaphthalene with *n*-butylamine.[23b,c]

Another development in our laboratory which is applicable to both flow and stopped-flow work is that it has been found possible to "label" one of the reactant streams by signal inversion prior to mixing ("*electronic isotopic substitution*").[24] By this means, the fate of these nuclei in the conversion to product may be traced just as in a classical isotopic substitution experiment, without recourse to chemical substitution. In a preliminary experiment to illustrate the potential of the technique, a solution containing naphthalene was mixed with one containing phenol and the NMR spectrum of the mixture recorded using the continuous flow system. When the phenol solution was subjected to an "adiabatic rapid passage" prior to entering the mixing chamber, its absorptions in the spectrum of the mixture were clearly inverted. In the future it may be possible to label each individual nucleus in either reactant, something which is not always practical in chemical isotopic substitution.

Stopped-Flow Nuclear Magnetic Resonance

Simultaneous with the development of the flow NMR techniques described above, other groups of workers have developed stopped-flow applications of NMR. The earliest of these were true NMR analogues of the UV–visible stopped-flow measurements at a single fixed frequency. A single line in the NMR spectrum is chosen and by continuously monitoring the height of this peak after stopping the flow, a kinetic trace is obtained. Thus Sudmeier and Pesek[25] used the ^{35}Cl resonance of a 1.5 M NaCl solution to investigate the reactions of mercury(II)–bovine serum albumin (BSA) with various ligands. The line width of the ^{35}Cl resonance depends markedly on whether the BSA is free or bound to mercury. Thus the progress of the displacement of mercury by various ligands could be studied by mixing the solutions, introducing them into the receiver coil, and monitoring the change in line width of the ^{35}Cl resonance by measurement of the height at a single fixed frequency.

A basically identical (in principle) experiment was carried out by Sykes and co-workers[26] who studied the broadening of the solvent water resonance after reaction of $Ni(NH_3)(H_2O)_5^{2+}$ with aqueous nitric acid. In a later, more sophisticated, biological application, the conformational changes induced in concanavalin A by the binding of Mn^{2+}, Ca^{2+}, and α-methyl D-mannoside were studied by measurement of the associated changes in the H_2O resonance of the solvent.[27]

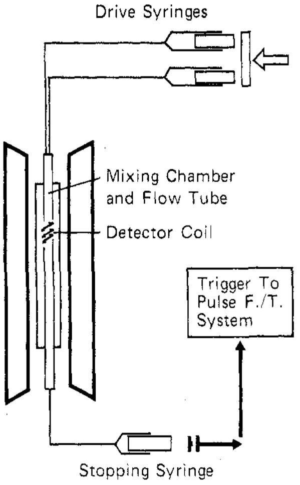

Figure 3. Schematic diagram of the general arrangement used for the measurement of stopped-flow NMR spectra (adapted from ref 26 and 29).

The basic drawback in the application of this technique to the investigation of reaction intermediates (although it will without doubt find applications in areas related to the examples above) is that for transient species, the frequency at which the measurements must be made is not known. To obtain this information one must know the spectrum of the transient species.

However, the development of equipment for stopped-flow experiments has coincided with another important advance in NMR, namely, the availability of commercial pulse Fourier-transform spectrometers[28] which enable a single "scan" of a spectrum to be taken in about 2 s. The main application of these has been in signal enhancement by spectral accumulation but they also provide a method for moderately fast periodic sampling of the spectrum of a chemically reacting solution, and this has been exploited by several groups of workers. A typical design, due to Sykes[29] (Figure 3), is similar to that used for single-frequency stopped-flow measurements. The reactant solutions are quickly introduced into the probe, the flow is stopped, and a series of spectra is quickly recorded as the system reacts. There are limitations on how quickly the first spectrum can be taken (the accumulation of each spectrum takes 1–2 s) and on how quickly the procedure can be repeated (unreliable relative peak areas will result if this is done too quickly). The method is best suited to reactions of half-life > 10 s or so, but it is an easily implemented technique using commercially available equipment which uses relatively small quantities of material, an important consideration in many circumstances.

The technique has been used by Grimaldi and Sykes to study the α-chymotrypsin-catalyzed hydrolysis of *tert*-butyl-L-phenylalanine.[30] They also discuss in some detail the capabilities of this technique. An alternate system in which small quantities of the reactant solutions are delivered into a spinning standard NMR

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(24) C. A. Fyfe, W. E. Sanford, and C. N. Yannoni, *J. Am. Chem. Soc.*, **98**, 7101 (1976).

(25) J. L. Sudmeier and J. J. Pesek, *Inorg. Chem.*, **10**, 860 (1971).

(26) J. J. Grimaldi, Sr., J. Baldo, C. McMurray, and B. D. Sykes, *J. Am. Chem. Soc.*, **94**, 7641 (1972).

(27) J. J. Grimaldi, Jr., and B. D. Sykes, *J. Biol. Chem.*, **250**, 1618 (1975).

(28) T. C. Farrar and E. D. Becker, "Pulse and Fourier Transform NMR; Introduction to Theory and Methods", Academic Press, New York, N.Y., 1971.

(29) J. J. Grimaldi, Jr., and B. D. Sykes, *Rev. Sci. Instrum.*, **46**, 1201 (1975).

(30) J. J. Grimaldi, Jr., and B. D. Sykes, *J. Am. Chem. Soc.*, **97**, 273 (1975).

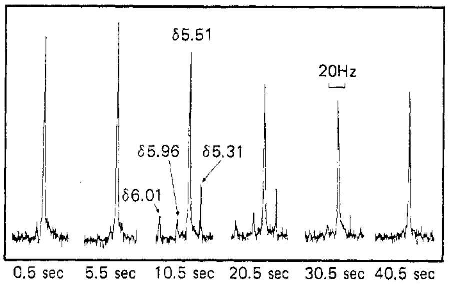
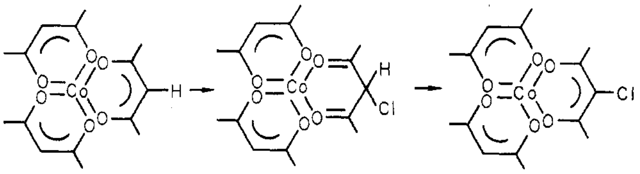


Figure 4. Parts of the ^1H NMR spectra obtained at 5-s time intervals during the course of reaction 8 at 295 K in $CDCl_3$: $[Co(acacH)_3] = [NClS] = 0.15$ mol L^{-1}. The signals at δ 5.31, 5.96, and 6.01 are assigned to the proton on the chlorinated sp^3 hybrid carbon atom and to the other two methine protons in the two unchlorinated ligands, respectively, in intermediate **23** (adapted from ref 33).

Scheme VIII



22 **23** **24**

tube has been used by Moore and co-workers[31] and by Robinson and Rosenfeld,[32] who investigated the moderately fast (~30 s) reaction between tetracyanoethylene and *N*,*N*-dimethylaniline in CH_3OD.[32] Previous kinetic analyses by UV-visible spectroscopy had clearly indicated the existence of a colorless intermediate, and one species had been isolated from solution and investigated by NMR, but no in situ investigations had previously been made. The interpretation of the spectra must still be made in terms of model compounds, but even if the intermediates had not been colorless, the superior diagnostic character of NMR is evident.

Moore and co-workers[33] have applied their design of stopped-flow equipment[31] to the reaction of excess tris(pentane-2,4-dionato)cobalt(III) $[Co(acacH)_3]$ (**22**) with *N*-chlorosuccinimide in $CDCl_3$. In earlier studies by UV-visible spectroscopy, no evidence of a transient intermediate was found, but the stopped-flow NMR spectra (Figure 4) clearly indicate the presence of such a species, tentatively assigned structure **23** (Scheme VIII). These authors have also investigated the hydrogen-deuterium exchange between methanol-d_4 and the nitromethane anion and the rate of solvent exchange between $Al(Me_2SO)^{3+}$ and Me_2SO-d_6.[34]

Conclusions—Future Developments

The advantage of continuous-flow NMR measurements is that they provide good spectra of reliable relative intensities for species of very short lifetime. Their main disadvantage lies in the large quantities of material currently needed. Stopped-flow measurements are restricted to somewhat longer lived species but have the distinct advantage of needing much smaller quantities of material, an important consideration in many situations.

However, there is no reason why pulse Fourier-transform or correlation[35] NMR spectroscopy cannot be applied to continuously flowing liquids[36] (hence decreasing the time the liquid must be kept flowing). If these are implemented, relatively small quantities of material will be needed for the flow measurements. In fact, the two types of measurement could be incorporated in a single piece of apparatus if FT or correlation NMR techniques were used for spectral measurement, and the complementary nature of flow and stopped-flow measurements could be exploited.

In all measurements, when the transient species show UV-visible absorptions, the best approach will be to characterize these species by NMR, to unambiguously assign their UV-visible absorption spectra, and then to carry out the detailed kinetic investigations on the system by UV-visible spectroscopy in dilute, ideal solutions.

As illustrated above, the techniques of flow and stopped-flow NMR have already found considerable application in the investigation of reaction mechanisms. They are simple and inexpensive to implement and may be expected to find a rapidly growing clientele in the immediate future. Further, as the use of very low temperatures is further developed, direct observation of less and less stable intermediates, hitherto only postulated, may be reasonably expected.

The authors acknowledge the National Research Council of Canada for grants in aid of research (C.A.F., M.C.) and the Canadian Commonwealth Scholarship and Fellowship Administration for the award of a Commonwealth Scholarship (S.W.H.D.). Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This article was written while one of us (C.A.F.) was a Visiting Foreign Scientist at the IBM Research Laboratory, San Jose, and he thanks them for these facilities.

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(31) D. A. Couch, O. W. Howarth, and P. Moore, *J. Phys. E*, 8, 831 (1975).

(32) M. J. T. Robinson and S. M. Rosenfeld, *Tetrahedron Lett.*, 1431 (1975).

(33) D. A. Couch, O. W. Howarth, and P. Moore, *Chem. Commun.*, 822 (1975).

(34) A. J. Brown, D. A. Couch, O. W. Howarth, and P. Moore, *J. Magn. Reson.*, **21**, 503 (1976).

(35) J. Dadok and R. F. Sprecher, *J. Magn. Reson.*, **13**, 243 (1974).

(36) C. A. Fyfe and S. W. H. Damji, unpublished results.