NMR — from chemistry to medicine

Tony Ferrige and John Lindon review the rapid advances that have taken NMR spectrometers from the chemical to the medical laboratory

BEFORE the commercial advent of nuclear magnetic resonance spectroscopy (NMR), about 10-12 years ago, NMR spectroscopy appeared to have found its niche. Spectrometers were being used in both academic and industrial chemical laboratories to study relatively simple molecules whilst the large biological molecules were considered too complex for the technique. Since then, however, the widespread introduction of NMR systems using Fourier transform techniques has led to an explosion in the applications of NMR. Due largely to simultaneous improvements in the two main elements of the NMR system — the data acquisition technology and the data processing techniques — NMR can now be used to study biochemistry, physiology and medicine.

NMR relies on the interaction between magnetically sensitive nuclei which are exposed to both a strong magnetic field and a pulsed radio frequency. Almost all elements have a magnetically active isotope which can be observed by NMR. The most readily detected, and hence the most frequently studied, is the proton, ^{1}H, but other less sensitive, although commonly used, nuclei include ^{31}P, ^{13}C, ^{15}N and ^{17}O. It is the development of more sensitive techniques coupled to advances in data analysis to reduce the background noise associated with biological molecules which has made the analysis of whole organs or even live animals now possible.

Technical advances

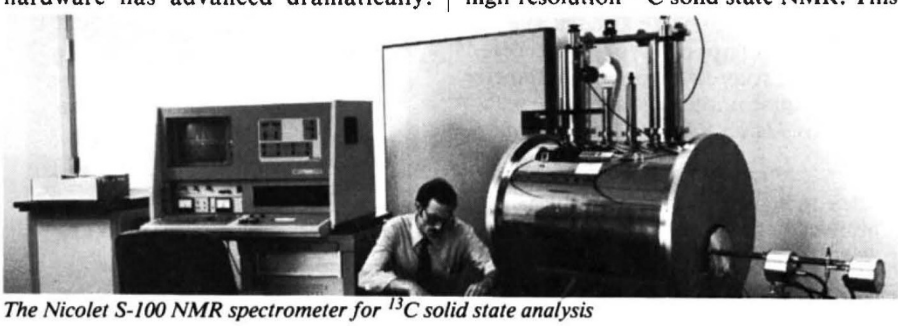
On the technological front, helium-cooled superconducting magnets are now commonplace. These boost the magnetic field obtained from the equivalent of 100 MHz for ^{1}H which is produced by a conventional iron magnet to a commercial limit of 500 MHz achievable with a superconducting magnet.

On the data analysis front, computing hardware has advanced dramatically. Multi-tasking virtual memory computers coupled to array processors now perform Fourier transforms in a few milliseconds, and whereas before data acquisition and analysis had to be carried out separately, they can now be run concurrently. Previously, analysis required a minicomputer, but there is a growing trend for these to be replaced by microcomputers with an array processor option. Programs are increasingly written in high-level languages so that they can be modified by the user, and automatic processing routines, such as spectrum phasing, are being introduced.

Specific advances

In conjunction with these non-specific technical advances which have had an indirect impact on NMR, the technique has benefitted enormously from improvements in specific areas. The development of multiple pulse sequences has allowed even the most complex spectra to be simplified so that large biological molecules can be studied. Similarly, the advent of fast 15 and 16 bit analog to digital converters, as compared to the conventional 12 bit models, has increased the amount of data which can be processed and, coupled to the use of good non-spinning resolution solenoid magnets, has opened the door for on-line HPLC-NMR using flow cells. This was previously impossible because of the strong masking signal derived from the chromatography solvent. The development of high-resolution non-spinning techniques, facilitated by the high power superconducting magnets, has eliminated the spinning side-bands which formally confounded the interpretation of quantitative ^{1}H measurements.

Perhaps the most important development however, has been the extension of NMR techniques to the solid state through high-resolution ^{13}C solid state NMR. This technique, the result of extensive collaboration between industry and university, is now available commercially. It uses a special pulse sequence which transfers the high ^{1}H sensitivity to the ^{13}C nuclei whilst removing ^{1}H-^{13}C interactions. This high sensitivity coupled to a high sample spinning rate (about 250,000 r.p.m.) at a very precise angle (54° 44′) relative to the magnetic field yields narrow signals which gives the technique further gains in sensitivity. The resulting sharp spectra compare with those obtained from solutions and allow the extraction of information on molecular conformation and interactions.



The Nicolet S-100 NMR spectrometer for ^{13}C solid state analysis

Biological applications

Using these new techniques and the vastly improved multi-dimensional data display options provided by commercial colour raster visual display units, NMR is now used to extract information on molecular conformation and interactions including transport through cell walls and tissues.

NMR has now entered the biological and medical laboratories, where it is used to study both isolated tissues and whole limbs or organs. It is used to predict the viability of human kidneys prior to transplantation and to trace the metabolism of labelled substrates or the effect of drugs on metabolism. For the study of organs and limbs within whole animals a new technique, topical magnetic resonance, has been developed which uses field gradients and complex pulse sequences to obtain spectra, usually ^{31}P, by focusing in on any organ in the body. For humans, special magnets with bores of 20–60 cm (compared to a conventional 49–110 mm) have been designed to accommodate whole limbs. Other related systems which measure proton density and relaxation times are now commercially available for use in tumour and cancer detection.

NMR is cheaper now in real terms than at any other time, both in cost per Hertz and in the number of experiments that can be done on even standard instruments. As the past decade has seen the demise of non-Fourier systems so the next decade should see the further expansion of the applications as field strengths, and hence frequencies, increase allowing alternative detection methods. □

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