Progress in Nuclear Magnetic Resonance Spectroscopy 46 (2005) 131–155

PROGRESS IN NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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Cryogenically cooled probes—a leap in NMR technology

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Received 20 January 2005

Keywords: NMR (Nuclear Magnetic Resonance); Cryogenic probe technology; Sensitivity; Signal-to-noise ratio

Contents

Abbreviations: 1D, 1-dimensional; 2D, 2-dimensional; 3D, 3-dimensional; ASTM, American Society for Testing and Materials; BPTI, bovine pancreatic trypsine inhibitor; $CDCl_3$, chloroform-d; CD_3CN, acetonitrile-d_3; CD_3OD, methanol-d; i.d., inner diameter; LC, liquid chromatography; MRI, magnetic resonance imaging; MS, mass spectroscopy; NMR, nuclear magnetic resonance; o.d., outer diameter; RDC, residual dipolar coupling; RF, radiofrequency; RP, reverse phase; SAR, structure-activity relationship; S/N, signal-to-noise ratio; SOD, superoxide dismutase; SPE, solid phase extraction; STD, saturation transfer difference; UV, ultra violet.

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0079-6565/$ - see front matter
doi:10.1016/j.pnmrs.2005.03.001

1. Introduction

During the 50 years of NMR, the technology has renewed itself again and again although the basic physical principles remain the same. As technical advances and novel materials boost the performance and stability of NMR spectrometers, the limits of the experiments, sample amounts and measuring time have been shifted beyond what was unthinkable just 10-years-ago. The technology advances in different ways. One is the continuous improvement of the performance of all parts of the NMR instrument. Another one is the occasional development of novel components that notably step up the performance of the NMR instrument and thus, benefit the user in many ways. The cryogenically cooled probes for high-resolution NMR spectroscopy are such an innovation. These enable typically a 3–4-fold enhancement of the detection sensitivity in high-resolution NMR compared to the corresponding conventional probes, enabling measurements of considerably smaller amounts of substances, or within an order of magnitude less time for a fixed sample concentration.

The sensitivity of the NMR-spectrometer is primarily limited by thermal noise in the signal detection pathway. A probe is a sensor positioned in the centre of the magnet containing the coil that is used both to send radiofrequency (RF) pulses to the sample and to detect the NMR-signals returning from the atomic nuclei. In addition to this coil a cryogenically cooled probe, usually, also houses the preamplifier to amplify the detected signal. The sensitivity or signal-to-noise enhancement in the cryogenic probe is accomplished by lowering the temperature of the coil and the preamplifier, thus essentially reducing the thermal noise in the receiver circuitry. The idea of lowering the coil temperature to improve the signal-to-noise ratio of a NMR instrument was initially proposed by Hoult and Richards in 1976 [1]. In 1984, Styles and co-workers [2] described a home-built probe where the receiver coil and the preamplifier were cooled with liquid helium. Cryogenic RF-probe techniques have also been applied to biomedical MRI [3,4]. In the 1990s, commercial products for high-resolution NMR based on the cryogenic probe technology [5] were developed and the first installations of cryogenic triple resonance probes at customer sites were done in 1999. Since then cryogenic probes for high-resolution NMR have been developed for spectrometers with operating frequencies ranging from 400 up to 900 MHz. Today these probes are available for operation with 5 and 3 mm diameter sample tubes and also for LC-NMR and flow injection modes. At present the variety of available configurations comprises probes optimised for ^{1}H- and ^{13}C-detection, and probes for triple resonance involving either ^{15}N or ^{31}P as the third nucleus. The choice of different cryogenic probes is steadily expanding to meet the needs of different NMR applications.

Not only the NMR hardware, but also the NMR methodology has undergone a remarkable development towards increasingly complex and technologically demanding experimental schemes [6,7]. On the one hand, methodological advances pose technical challenges to the instrumentation, on the other hand technological innovation enables progress in the research methods. This reciprocity applies to all parts of a NMR spectrometer, including the magnet construction, probe construction, electronics and the software interface. As a result, the sensitivity, an important criterion of the NMR-instrument, has surged. The ever increasing sensitivity, illustrated in Fig. 1, also reflects the process of continuous innovation during the near four decades of commercial NMR technology. And, by all likelihood we are not near the end of this development.

The scope of the present review is to outline the basic theory and the current state of cryogenic probe technology in high-resolution NMR. In Section 2, we discuss the physical principles that govern the sensitivity of a NMR probe, and in particular the factors that influence the performance of a cryogenic probe. The construction of the necessary hardware, that is, the probe together with the cryogenic cooler, is presented schematically. In Section 3,

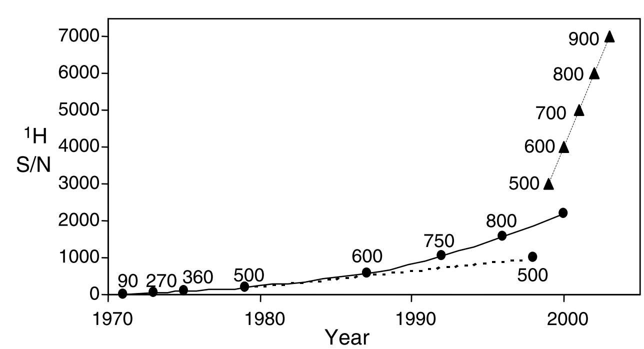

Fig. 1. The specified signal-to-noise ratio of 0.1% ethylbenzene (EB) in $CDCl_3$ for ^{1}H-observe probes plotted as a function of time. The black dots denote the sensitivity of a conventional probe at the launch of a magnet operating at a particular field, and the triangles mark the launches of cryogenic probes at different fields (all data from Bruker BioSpin). The magnetic field (indicated by the ^{1}H operating frequency MHz) is given above the marker. The dashed line indicates the increase in specified sensitivity during two decades for a conventional probe operating at 500 MHz.