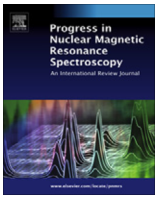
Progress in Nuclear Magnetic Resonance Spectroscopy 59 (2011) 295–318

Contents lists available at ScienceDirect

Progress in Nuclear Magnetic Resonance Spectroscopy

journal homepage: www.elsevier.com/locate/pnmrs



Direct detection of nitrogen-14 in solid-state NMR spectroscopy

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ARTICLE INFO

Article history:
Received 10 February 2011
Accepted 7 April 2011
Available online 20 April 2011

Keywords:
Solid-state ^{14}N NMR
Integer spin
First-order quadrupolar interaction
Ultra-wideline
Magic angle spinning
Overtone spectroscopy

Contents

Abbreviations: A-β, amyloid-β; ADRF, adiabatic demagnetization in the rotating frame; C_{16}TAB, *n*-hexadecyltrimethylammonium bromide; CP, cross polarization; CS, chemical shift; CSA, chemical shift anisotropy; CW, continuous wave; DANTE, delays alternating with nutation for tailored excitation; DAPT, dipolar assisted polarization transfer; DAS, dynamic angle spinning; DDAB, didodecyldimethylammonium bromide; DEISM, direct enhancement of integer spin magnetization; DFT, density functional theory; DIPOTSHIFT, dipolar overtone shift; DISQUO, dipolar splittings, quadrupolar offset; DMPC, dimyristoyl phosphatidylcholine; DPPC, dipalmitoyl phosphatidylcholine; EFG, electric field gradient; EPC, egg yolk phosphatidylcholine; EXPRESS, exchange program for relaxing spin systems; FID, free induction decay; FOQI, first-order quadrupolar interaction; HMT, hexamethylenetetramine; LC, liquid crystal; MAS, magic angle spinning; NAV, *N*-acetylvaline; ORR, overtone rotary recoupling; PISEMA, polarization inversion spin exchange at magic angle; QCPMG, quadrupolar Carr Purcell Meiboom Gill; RF, radio frequency; RotIsseRIe, reorientation-induced redistribution of isochromats; *S/N*, signal to noise ratio; SLF, separated local field; SOQI, second-order quadrupolar interaction; STARS, spectrum analysis for rotating solids; STEAMER, slow turning for echo amplitude modulation and echo reduction; WURST, wideband, uniform rate, smooth truncation; XRD, X-ray diffraction.

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doi:10.1016/j.pnmrs.2011.04.001

1. Introduction

Nitrogen is the seventh most abundant element in our solar system and is of the utmost importance in chemistry, biology and materials science. It is therefore unfortunate that both NMR-active isotopes of nitrogen have rather unfavorable NMR properties (Table 1). ^{15}N is a spin-1/2 nucleus and thus can be studied with relatively high resolution even in the solid state, but it suffers from a low natural abundance (0.37%), which translates to a poor sensitivity. While this trait allows for the useful possibility of selective labeling, isotopic enrichment can be difficult and expensive, and there are far fewer ^{15}N NMR studies reported than for ^{13}C, which has both a higher natural abundance (1.07%) and gyromagnetic ratio, making it several orders of magnitude more receptive. While the number of published ^{15}N NMR papers is disproportionately small relative to the importance of nitrogen, studies utilizing the 99.6% natural abundance ^{14}N isotope are even scarcer. The difficulty of ^{14}N NMR stems from two main factors. First, the nucleus has a very low gyromagnetic ratio ($\gamma_N = 1.934 \times 10^7$ rad T^{-1} s^{-1}), meaning that it is inherently less sensitive than other nuclei (having a receptivity of 0.001 relative to ^{1}H), and also suffers from equipment-related issues such as acoustic ringing and limited radio frequency (RF) pulse powers. Secondly, and more importantly, it is a spin-1 nucleus, and while its electric quadrupole moment is not particularly large ($Q = 20.44$ mbarn), both of its Zeeman transitions experience significant perturbations due to the quadrupolar interaction (see Section 2). This interaction will be present for all but the most spherically-symmetric nitrogen environments, resulting in rapid relaxation in solution and significant heterogeneous broadening of spectral lineshapes in the solid state. Ideally, the quadrupolar nature of ^{14}N should be considered as an advantage, as it potentially allows the retrieval of structural and dynamic information that could not be accessed with ^{15}N, but, pragmatically, it is more often a hindrance, prohibiting (or at least making extremely difficult) the use of standard NMR experiments, and reducing the overall sensitivity and spectral resolution.

The combination of the importance of nitrogen and the high natural abundance of ^{14}N has spurred much effort to develop solid-state NMR techniques that can make use of this isotope in the characterization of materials. Notably, the last few years have seen the establishment of a variety of methods for the indirect detection of ^{14}N using more amenable nuclei such as ^{1}H or ^{13}C, offering a route to heteronuclear correlation experiments that can provide both structural and dynamic information with a potentially very high resolution. These techniques have recently been reviewed by Cavadini [1]. The purpose of this article is to provide a summary of solid-state NMR techniques that detect the signal *directly* from the ^{14}N nuclei. A wide range of approaches have been proposed and utilized, with each method offering unique advantages and limitations in terms of the systems that can be studied and the information that can be extracted. The article will concentrate on a qualitative description of the techniques, with the aim of highlighting the numerous, diverse and interesting ways in which the ^{14}N nucleus can be exploited. In the following section, a minimal amount of theory is presented in order to provide a basic understanding of the effects of the most common NMR interactions on solid-state ^{14}N spectra.

2. Interactions and definitions

Being a spin-1 nucleus, ^{14}N has three energy levels which are split by the Zeeman interaction in the presence of an external magnetic field B_0, giving rise to two single-quantum transitions and one double-quantum transition. In the majority of cases, the secular approximation can be applied and the various interactions experienced by the nucleus can be considered as perturbations to the Zeeman transition energies. In such cases, only the single-quantum transitions, $+1 \leftrightarrow 0$ and $0 \leftrightarrow -1$, are observed. Whilst there are situations when this approximation breaks down and the axis of quantization is tilted away from B_0, a treatment of this has been provided elsewhere (see, for example, references in Section 6), and most of the experiments described in this article may be sufficiently understood using the straightforward perturbation approach. Fig. 1 shows schematically the perturbations caused by the most common interactions experienced by the ^{14}N nucleus. To further simplify the discussion throughout this article, these perturbations are described as frequencies (ν, in units of Hz) rather than energies, allowing for a direct comparison with the spectral features to which they give rise.

The Zeeman splitting results in two single-quantum (or fundamental) transitions whose frequencies are given by:

$$\nu_0 = \frac{\gamma_N B_0}{2\pi} \tag{1}$$

In the absence of other interactions, this frequency is identical for both transitions, and the NMR spectrum will feature a single resonance line at ν_0 (the Larmor frequency). In most instances, however, an electric field gradient (EFG) will exist at the nitrogen site and thus the quadrupolar interaction will be present. The ^{14}N EFG can be described as a traceless, symmetric, second-rank tensor quantity and is conventionally reported using two parameters, the quadrupolar coupling constant C_Q (in Hz) and the asymmetry parameter η_Q (dimensionless, and ranging between 0 and 1):

$$C_Q = \frac{eQV_{33}}{h}; \tag{2}$$

$$\eta_Q = \frac{V_{11} - V_{22}}{V_{33}}, \tag{3}$$

where e is the charge of the electron, Q is the ^{14}N quadrupole moment, h is the Planck constant and V_{nn} are the principal components of the EFG tensor in its diagonalized form, ordered such that $|V_{33}| \geq |V_{22}| \geq |V_{11}|$. The orientation of this tensor with respect to B_0 is specified by the polar angles θ and φ.

The description of the quadrupolar interaction derived from perturbation theory involves an expansion in terms of increasing order, each of which can be considered separately. While third-order effects can play an important role in indirectly-detected ^{14}N experiments [1], in most cases only the first- and second-order quadrupolar interactions (FOQI and SOQI) need to be considered. The first-order quadrupolar perturbation to the single-quantum ^{14}N transition frequencies is given by:

$$\nu_Q^{(1)} = \frac{3}{8} C_Q (3\cos^2\theta - 1 + \eta_Q \sin^2\theta \cos 2\varphi). \tag{4}$$

The FOQI is directly proportional to C_Q, and is usually the dominant perturbing interaction in solid-state ^{14}N NMR. The C_Q is

Table 1
Properties of the two NMR-active isotopes of nitrogen.

	Spin number, I	Natural abundance (%)	Frequency, ν_0 (MHz) (^{1}H = 100 MHz)	Gyromagnetic ratio, γ (10^7 rad T^{-1} S^{-1})	Quadrupole moment, Q (mbarn)	Receptivity (^{1}H = 1.0)
^{14}N	1	99.632	7.226	1.934	20.44	1.0×10^{-3}
^{15}N	1/2	0.368	10.137	−2.713	0	3.8×10^{-6}