NITROGEN N.M.R. SPECTROSCOPY

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ABSTRACT

Various aspects of nitrogen n.m.r. spectroscopy and its applications to the structural investigations of molecules are discussed. A brief survey of direct and indirect measurements of ^{14}N and ^{15}N n.m.r. spectra is given. Nitrogen chemical shifts and nitrogen coupling constants are presented as a means of differentiation between isomeric or tautomeric structures, structural assignments, and investigation of intermolecular effects in liquids. Potential applications of ^{14}N quadrupolar relaxation data in the study of molecular rotations and electron charge distribution are briefly considered.

INTRODUCTION

The importance of nitrogen atoms in both organic and inorganic compounds makes nitrogen nuclear magnetic resonance an attractive means of insight into molecular structure and electron charge distribution. This branch of molecular spectroscopy, however, is experimentally more difficult than the n.m.r. of other commonly occurring elements, such as hydrogen, fluorine, phosphorus and carbon. The very low magnetic moments of ^{14}N and ^{15}N result in a low sensitivity of detection of their resonance signals. To make things worse, the isotope ^{14}N, largely prevailing in nature, has a non-zero nuclear quadrupole moment, and the quadrupole relaxation mechanism is usually efficient enough to make the n.m.r. signals rather broad, often 50–1000 Hz wide, and sometimes wider still. The other isotopic form, ^{15}N, has a spin of 1/2 and no quadrupole moment, but it is only 0·365 per cent abundant. The negative sign of the gyromagnetic ratio of ^{15}N may seriously impede an application of ^{1}H–^{15}N spin-decoupling for signal enhancement, which is a combined outcome of multiplet collapse and Overhauser effects. The latter are negative for ^{15}N nuclei, and if the contribution of dipole–dipole interactions in the total relaxation rate is less than about 50 per cent then the absolute intensity of the n.m.r. signal decreases, and this may even lead to a fortuitous disappearance of the signal, as can be seen from the following values of intensity gain factors upon proton-decoupling:

$$+1.00 \text{ to } -3.93 \quad \text{for } ^{15}\text{N}$$
$$+1.00 \text{ to } +2.99 \quad \text{for } ^{13}\text{C}$$
$$+1.00 \text{ to } +7.94 \quad \text{for } ^{14}\text{N}$$

For nuclei with positive gyromagnetic ratios at least some gain in intensity may be expected, and the maximum possible enhancement for ^{14}N is quite remarkable, but is seldom, if ever, realized in practice since the quadrupole relaxation mechanism is dominant here.

The characteristics of nitrogen nuclei from the point of view of nuclear magnetic resonance are given in *Table 1*.

Table 1. N.m.r. properties of nitrogen nuclei

	^{14}N	^{15}N
Natural abundance	99.635 %	0.365 %
Spin number	1	1 2
Electric quadrupole moment ($e \times 10^{-24} cm^2$)	1.54×10^{-2}	0
N.m.r. frequency at a field corresponding to a ^1H frequency of 100 MHz	7.225 MHz	10.134 MHz
N.m.r. sensitivity relative to that of a ^1H at the same field	0.00101	0.00194

BRIEF SURVEY OF EXPERIMENTAL METHODS

Direct methods

^{14}N

The main difficulty here lies in low sensitivity and signal overlap. In principle, this may be overcome by the use of sufficiently high magnetic fields, but they are still insufficient even in the most advanced spectrometer systems for the method to be routine. The sensitivity may be increased by a large sample volume or by the spectrum accumulation technique, but there is usually no significant advantage in the pulse and Fourier-transform method over the conventional continuous-wave measurements because of the ^{14}N signal widths. The latter may be reduced by low-viscosity solvents and elevated temperatures (100–200 C). Proton-decoupling has only a marginal utility in ^{14}N n.m.r. measurements by direct methods.

^{15}N

Sensitivity is the most important problem in natural-abundance ^{15}N studies. The spectrum accumulation technique, combined with the pulse method, is of utmost importance here, but even these are barely able to yield usable ^{15}N spectra in commercially aviable spectrometers. A serious disadvantage here is the negative Overhauser effect upon proton-decoupling. Measurements for ^{15}N-enriched samples do not constitute any major problem but suffer from general limitations which may be concerned with the use of labelled compounds.

Indirect methods

Various forms of double- or multiple-resonance techniques may be profit-

ably employed in the spectra of nitrogen-coupled nuclei for the measurements of nitrogen chemical shifts and coupling constants. Such methods may offer a considerable sensitivity gain but are critically dependent upon the coupling, chemical exchange, and quadrupole effects. In general, they involve building a montage of nitrogen spectra from the effects observed in various parts of the spectrum which is actually observed. This is not only time consuming but also results in a lack of general utility. The methods are suitable for ^{15}N-enriched compounds and for ^{14}N studies with the limitations mentioned above. Absolute values of ^{15}N coupling constants, and sometimes those of ^{14}N, are usually measured from multiplet patterns in the spectra of nitrogen-coupled nuclei. The double-resonance technique is helpful in relating nitrogen chemical shifts to a heteronuclear internal standard, such as the proton signal of tetramethylsilane.

NITROGEN CHEMICAL SHIFTS

Chemical shifts of nitrogen nuclei cover an appreciable spectral range of about 900 ppm for most organic and inorganic compounds. There is no measurable isotopic substitution effect on the screening constant so that ^{15}N and ^{14}N shifts may be used interchangeably. The large range of the shifts and the magnitude of structural effects in the spectra do not put stringent requirements on the calibration techniques and referencing procedures. Various standards, internal or external, have so far been employed as references for nitrogen chemical shifts. In the author's opinion which, of course, may be controversial, the following procedures are convenient and reasonable. For precise solvent and concentration effect measurements one may use the internal referencing of nitrogen shifts to a heteronuclear standard, preferably the protons in tetramethylsilane. This may be accomplished either directly, by precise frequency measurements in an internal-lock system, or by double-resonance measurements for an auxiliary homonuclear standard such as $(CH_3)_4N^+$. If the nitrogen chemical shift for the latter is assumed as a reference, then the frequency scale of chemical shifts is recommended where downfield (high-frequency) shifts are taken as being positive. For most applications to structural problems, however, it is convenient to refer the shifts to CH_3NO_2 or the NO_3^- ion, either internally or externally. The two standards may be used interchangeably for most practical purposes. The screening-constant scale, where upfield shifts are positive, is preferable here since the position of the nitrogen resonance signals of the standards is probably not far away from the absolute zero, i.e. the resonance of a bare nitrogen nucleus. We shall use henceforth this scale for nitrogen chemical shifts.

Large chemical shifts in nitrogen n.m.r. are attractive from the point of view of structural investigations of molecules, chemical equilibria, isomerism and tautomeric changes. Rough experimental ranges for nitrogen chemical shifts for a variety of organic compounds are given in *Table 2*.

The following comparison illustrates the potential applicability to a differentiation between isomeric structures.

$R-N=C-N-R$ carbodiimide $c. +280$ ppm		R_2N-CN cyanamide $c. +360$ ppm (NR_2) $c. +190$ (CN)
$R-N=C=O$ isocyanate $c. +350$ ppm	$R-O-CN$ cyanate $c. +200$ ppm	$R-CNO$ fulminate (nitrile N-oxide) $c. +170$ ppm
$R-CN$ nitrile $c. +130$ ppm	$R-NC$ isonitrile $c. +200$ ppm	
$R_2C=N-OR$ oxime $c. +20$ ppm	$R_2C=N(O)R$ nitrone $c. +100$ ppm	$R_3C-N=O$ nitroso compound $c. -400$ ppm
$R-NO_2$ nitro compound $c. 0$ ppm	$R-O-N=O$ nitrite $c. -180$ ppm	
1,3-oxazole $+125$ ppm	1,2-oxazole (isoxazole) -2 ppm	
1,3-thiazole $+56$ ppm	1,2-thiazole (isothiazole) $+80$ ppm	
$R-N=C=S$ isothiocyanate $c. +270$ ppm	$R-S-CN$ thiocyanate $c. +100$ ppm	

Table 2. Approximate nitrogen chemical shifts for organic compounds

Type of compounds	Nitrogen screening constant relative to CH_3NO_2/NO_3^- (ppm)		Type of compounds	Nitrogen screening constant relative to CH_3NO_2/NO_3^- (ppm)	
Nitroso compounds	-480	-540	Azinium ions	$+190$	$+150$
Thionitrites	-350	-420	Cyanamides (CN)	$+200$	$+170$
Nitrites	-180	-210	Guanidines (=NR)	$+210$	$+190$
Nitrosamines (NO)	-150	-180	Isonitriles	$+220$	$+170$
Azo compounds	-130	-170	Cyanates	$+220$	$+190$
Nitroalkanes	0	-40	Thioamides	$+240$	$+200$
Nitroaromatic compounds	$+20$	0	Nitrilium ions	$+250$	$+220$
Nitramines (NO_2)	$+40$	$+10$	Azoles (NR)	$+260$	$+90$
Nitrates, *gem*-polynitroalkanes	$+60$	$+10$	Azides (NNN) , $(RNNN)$	$+270$	$+250$
Azoxy compounds	$+60$	$+40$	Amides, thioureas	$+280$	$+230$
Imines, oximes, furazans, furoxans	$+70$	-30	Amine N-oxides Carbodiimides	$+280$ $+280$	$+250$ $+250$
Nitrones	$+100$	$+80$	Isothiocyanates	$+290$	$+250$
Thiocyanates	$+110$	$+90$	Ureas	$+310$	$+250$
Azines	$+120$	-40	Azides $(RNNN)$	$+320$	$+290$
Nitramines (NR_2)	$+120$	$+90$	Arylamines, hydrazines	$+330$	$+270$
Azides (RNNN)	$+130$	$+110$	Guanidines (NR_2)	$+330$	$+310$
Azoles (N:)	$+140$	-10	Ammonium ions	$+360$	$+300$
Azine N-oxides	$+140$	$+70$	Isocyanates	$+360$	$+320$
Nitriles	$+140$	$+110$	Alkylamines	$+390$	$+300$
Nitrosamines (NR_2)	$+150$	$+120$	Cyanamides (NR_2)	$+390$	$+330$
Fulminates (nitrile N-oxides)	$+180$	$+150$			

Nitrogen-containing molecules, involved in tautomeric equilibria, usually show large differences in their nitrogen chemical shifts, as in the following examples.
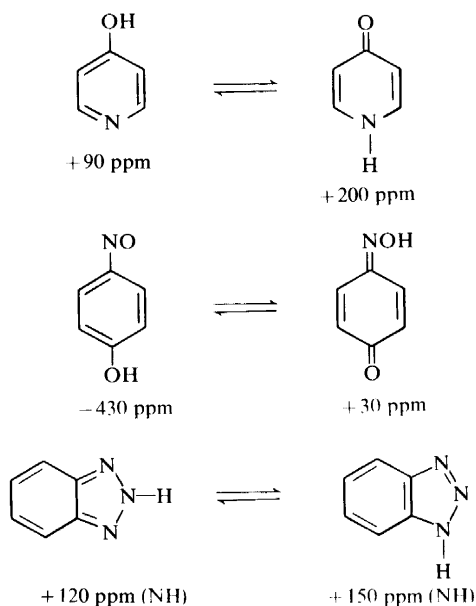
Nitrogen chemical shifts seem to be useful in investigations of electronic structure and structural effects in heteroaromatic ring systems. There seems to be a reasonable correlation of the shifts with the corresponding electron charge densities at nitrogen atoms. In some instances, rather simple additivity rules for the shifts may be found. For six-member ring systems (azines) the following effects of interactions between nitrogen atoms on the nitrogen screening constant are observed :

1,2-interaction	$c. -75$ ppm
1,3-interaction	$c. +20$ ppm
1,4-interaction	$c. -20$ ppm

In many classes of organic compounds, including amines, ammonium ions, isocyanates, isothiocyanates, azides, isonitriles, azinium ions, nitrones and nitroalkanes, where an alkyl group is bonded to a nitrogen atom, downfield shifts of the nitrogen resonance signal are found which follow the sequence CH_3–, CH_2R–, CHR_2–, CR_3– of consecutive replacing hydrogen atoms with alkyl groups, an effect reminiscent of that observed in ^{13}C n.m.r. spectra and known as the beta effect. This may be helpful in distinguishing between various positions of nitrogen-containing substituents in an alkane chain.

A rather simple spectral distinction may be made between the cyano groups in nitriles, cyanates and cyanamides, between the nitro groups in nitroalkanes,

nitramines and covalent nitrates, and also within the amido-type structures, which include amides, thioamides, ureas, thioureas, lactams, etc. There is such a large difference in the nitrogen screening constant between the nitro and the nitroso group that these structural fragments are easily observed in molecules where they occur together, such as in N_2O_3.

$$O=N-NO_2 \qquad \begin{array}{l} -70 \text{ ppm } (NO_2) \\ -300 \text{ ppm } (NO) \end{array}$$

Nitrogen n.m.r. spectroscopy should constitute an important tool for structural investigations of inorganic complexes. It may be particularly useful for the identification of isomeric ligands:

$$(C_2H_5)_4N^+ \ Ag(NCO)_2^- \qquad (C_2H_5)_4N^+ \ Ag(CNO)_2^-$$
$$+344 \text{ ppm } (NCO) \qquad +164 \text{ ppm } (CNO)$$

or the alternative bonding modes of an ambivalent group, such as $NCO.^-$ $NCS.^-$ $ONO.^-$ Nitrogen chemical shifts in nitrogen–sulphur compounds reflect different types of bonding such as S=N–S and S–N(R)–S.

+150 ppm   +355 ppm
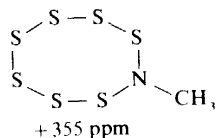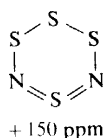
Lanthanide chelates, such as those of dipivaloylmethane (DPM), may be used as chemical shift reagents for nitrogen nuclei. The main application, however, is not to increasing relative chemical shifts but rather to a differentiation between various types of bonding at nitrogen atoms. A good example of this may be found in the spectra of azole ring systems where pyrrole-type nitrogen atoms are characterized by a weak response of their nitrogen shifts to the reagents, whilst pyridine-type nitrogen atoms show large resonance displacements.

		Eu(DPM)$_3$ induced shift(ppm) extrapolated to 1:1 chelate to solute ratio
N-Methylimidazole	(N-CH$_3$)	+80
	(N:)	+1400

Nitrogen chemical shifts in liquids may reflect specific solvent solute interactions which are not easily detected by other methods. Interactions of the lone electron pair at a nitrogen atom with alkyl groups of the solvent are as effective in deshielding the nitrogen nuclei in amines as hydrogen-bond type interactions. Such recognized 'inert' solvents as carbon tetrachloride give rise to similar downfield shifts in amines which suggest complex formation between the amine and the solvent.

NITROGEN COUPLING CONSTANTS

No differences have so far been found between ^{14}N and ^{15}N coupling constants other than those resulting from different gyromagnetic ratios. The relationship is

$$J(^{14}N\text{--}A) = -0.7129\, J(^{15}N\text{--}A)$$

but for theoretical comparisons it is often more convenient to use the reduced coupling constant

$$K_{ij} = 4\pi^2\, J_{ij}/(h\gamma_i\gamma_j)$$

which is, of course, the same for both isotopes in the same bond pattern. Nitrogen–proton couplings are usually measured from proton spectra. There are many structural applications but they may be properly dealt with by proton n.m.r. and only some general trends in the couplings will be discussed here.

Table 3. Examples of nitrogen coupling constants

Compound	J(Hz)	$K \times 10^{-20}\,(cm^{-3})$
N–H coupling:		
Pyrrole-^{15}N	−96.5	+79.3
HCO^{15}NH$_2$	−91.3*	+75.0*
	−86.9†	+71.4†
CH$_3$^{15}NH$_2$	−65.0	+53.4
^{14}NH$_3^+$Br$^-$	+52.8	+60.8
N–C–H coupling:		
HCO^{15}NH$_2$	−14.5	+11.9
CH$_2$=^{15}NOH	−13.9*	+11.4*
	+2.7†	−2.2†
Quinoline-^{15}N	−11.1	+9.1
Pyrrole-^{15}N	−4.5	+3.7
CH$_3$^{15}NH$_2$	−1.0	+0.8
CH$_3$^{14}NC	−2.3	−2.6
CH$_3$^{15}NO$_2$	+2.3	−1.9
N–C–C–H coupling:		
Pyrrole-^{15}N	−5.4	+4.4
Quinoline-^{15}N	−1.4	+1.1
CH$_3$C^{15}N	−1.8	+1.5
(CH$_3$)$_3$C^{14}NC	+2.0	+2.3
[(CH$_3$CH$_2$)$_4$$^{14}N$]$^+$ OH$^-$	+1.8	+2.1

* Coupling to proton *trans* to oxygen atom.
† Coupling to proton *cis* to oxygen atom.

One-bond reduced coupling constants, ^1K(N–H), are invariably positive and larger than long-range constants (*Table 3*). The one-bond coupling increases with increasing s character of the bond and is largest in protonated nitriles. Ketimines are marked exceptions here with anomalously low values of the one-bond NH coupling constant.

	Absolute values of $^1J(^{15}N\text{--}H)$
	(Hz)
Anilinium ion (sp^3)	76.9
Quinolinium ion (sp^2)	96.0
Benzonitrilium ion (sp)	136.0
Diphenylketimine (sp^2)	51.2

Two-bond reduced coupling constants $^2K(N\text{ }C\text{-}H)$ are small (*Table 3*) and may be of either sign. The coupling is particularly small across a tetra-coordinate carbon atom, but is enhanced in the case of a tricoordinate carbon atom.

All three-bond N–C–C–H couplings have positive reduced coupling constants, $^3K(N\text{–}C\text{–}C\text{–}H)$, as can be seen in *Table 3*. If the intervening carbon atoms are saturated, then the coupling is stronger than that across two bonds and has an opposite sign. There seems to be a stereochemical dependence on the three-bond coupling following the Karplus-type curve. If at least one of the intervening carbon atoms is tricoordinate, then the three-bond coupling is influenced by the spatial arrangement of atoms in the multiple-bond system. Similar effects are observed if one of the intervening atoms is N or O.

There are some general trends in the coupling which appear upon proto-nation of the nitrogen lone electron pair. The following algebraic changes are usually found:

$$^1K(NH)\text{—increase}$$
$$^2K(NH)\text{—decrease}$$
$$^3K(NH)\text{—increase}$$

NUCLEAR QUADRUPOLE EFFECTS IN ^{14}N N.M.R.

Quadrupole relaxation may adversely affect the resolution in ^{14}N n.m.r. spectra. However, the resulting signal width provides additional information about the molecular structure and molecular motions in liquids. For ^{14}N nuclei the quadrupole relaxation time, T_q, is dominant in the total relaxation rate. It may be measured from the width of the resonance signals. In general, $1/T_q$ is proportional to the square of the quadrupole coupling constant, $(e^2qQ)^2$ and to a combined function of the asymmetry parameter and correlation times. Since the quadrupolar interaction is large, T_q is quite sensitive to changes in molecular motions. Only rotational motions contribute to the relaxation time. If the rotation is isotropic, it is easy to calculate the correlation time from the equation:

$$\frac{1}{T_q} = \frac{3}{8}\left(\frac{e^2qQ}{\hbar}\right)^2\left(1 + \frac{\eta^2}{3}\right)\tau_q$$

if the values of the quadrupolar coupling constant and the asymmetry parameter η are known from other sources. If the motions are anisotropic, the equation must be modified in terms of the three principal diffusion constants, D_a, D_b and D_c. Various models of molecular rotation in liquids may be tested in this way. Sometimes a reverse procedure is employed, where the quadrupole coupling constants are estimated from experimental T_q values and calculated correlation times. The procedure is not accurate but may be of practical value in specific situations, particularly for molecules of similar size and shape. Nuclear quadrupole coupling constants are a direct measure of electric field gradients at nuclear sites and may provide important information

about electron charge distribution in molecules. The difficulties in the calculation of the constants from T_q may be considerably reduced by the so-called double (or multiple) quadrupolar labelling procedure. This is possible if two or more quadrupolar nuclei are present in a molecule. The highest accuracy is obtained when the other nuclei are placed in such a way that they experience the same motions as the nitrogen nucleus. The known values of the quadrupole coupling constants of the other nuclei make a calculation of the correlation time possible, which may then be used in the estimation of the constant for the nitrogen nucleus.

GENERAL REMARKS

This brief survey constitutes only a rough outline of the scope of investigations and applications of nitrogen n.m.r. spectroscopy. In spite of experimental difficulties, a great deal has already been done in the field of structural correlations of nitrogen chemical shifts, nitrogen coupling constants and relaxation times. For a more detailed discussion the reader is referred to recent monographs and reviews.[1-3]

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