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^{15}N NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY OF SOME NITROGEN HETEROCYCLES[1a]

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The potential power and utility of ^{15}N NMR spectroscopy in heterocyclic chemistry is illustrated by the natural-abundance high-resolution ^{15}N NMR spectra of representative thiadiazoles and related compounds. The ^{15}N chemical shifts in these compounds were found to range over 250 ppm. The advantages and limitations of the method are discussed.

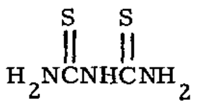
"One of the most confusing oxidation reactions in organic chemistry is the oxidation of thioureas." Thus began a recent report[2] on the structure of Hector's, Dost's and Hugershoff's bases in which it was pointed out that, depending on the substituent groups and reaction conditions, the oxidation of thioureas can give rise to ureas, formamidine disulfides, formamidinesulfinic acids, formamidinesulfonic acids, 1, 2, 4-thiadiazoles and benzothiazole derivatives. As is often the case, the evidence from the usual spectroscopic and chemical techniques was ambiguous, and therefore the structures were finally solved by single-crystal X-ray analysis. But even this ultimate structural tool is not completely satisfying because, although it reveals structures in the solid state, it tells nothing certain about the structure of the same molecules in solution. The object of the present paper is to show the considerable potential of ^{15}N NMR spectroscopy for structural analysis of nitrogen-containing heterocycles in solution.

^{15}N NMR has been very difficult to apply to problems in heterocyclic chemistry because the low natural abundance and low sensitivity of detection of ^{15}N means that it takes 10^{11} times longer to obtain a given signal-to-noise ratio with ^{15}N than with ^{1}H at the same molar concentrations. However, development of wide-bore superconducting solenoids with a high enough degree of field homogenity to permit employing large diameter tubes (20-30 mm) has now made it possible to obtain ^{15}N spectra at the natural abundance level in an almost routine manner.

^{15}N has a negative magnetogyric ratio so ^{15}N atoms with directly bonded hydrogen can, with proton decoupling, experience a maximum negative nuclear Overhauser enhancement (NOE) of -3.93 and thus give an emission signal.[3] If the nitrogen has no directly bonded protons and does not undergo dipolar relaxation induced by nearby protons, its resonance will be a normal absorption peak of the expected intensity. In intermediate situations, where there are competing relaxation processes, noise decoupling can induce a small negative NOE which can completely null the signal. The long relaxation times of many kinds of nitrogen with no attached protons make fast pulsing and collection of transients impossible, so that adequate signal-to-noise ratios are very difficultly attainable in a reasonable length of time.

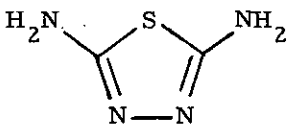
The chemical-shift range over which ordinary organonitrogen compounds are found exceeds 900 ppm, almost 4 times the range for ^{13}C and 90 times the range for ^{1}H. This means small changes in the chemical structure of the molecule can be reflected in large changes in chemical shifts.

Some of the power and the limitations of ^{15}N NMR spectroscopy in heterocyclic chemistry will be illustrated by the spectra of **1** - **6**.



$H_2N\overset{S}{\overset{\|}{C}}NH\overset{S}{\overset{\|}{C}}NH_2$

1



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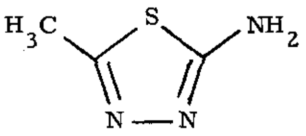

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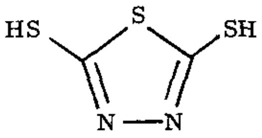

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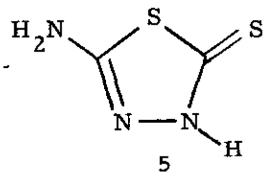

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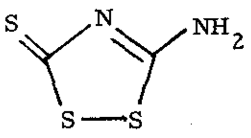

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Experimental Section

Natural-abundance ^{15}N NMR spectra were obtained at 18.25 MHz with a Bruker WH-180 spectrometer using 15 - 20 ml of 1-2 M solutions at 25-mm O.D. sample tubes. A concentric 5-mm tube containing 1.0 M $H^{15}NO_3$ in D_2O provided both lock and reference signals. Chemical shifts are reported with reference to external $H^{15}NO_3$ with positive numbers being upfield. This reference is 6.2 ppm upfield from neat nitromethane. Spectra were obtained with 24 μsec pulses (30° flip angle) with 6- or 7-sec repetition rates.

Dithiobiurea (1). Dithiobiurea was prepared according to the procedure of Chang, et al.[4] The ^{15}N spectra were obtained of a 1 M (saturated) solution in 20 ml of dimethyl sulfoxide (DMSO). An adequate signal-to-noise ratio for the noise-decoupled spectrum was obtained in 10 min while the spectrum without noise decoupling required 80 min.

2, 5-Diamino-1, 3, 4 - thiadiazole (2). This thiadiazole was prepared in 87% yield by hydrogen peroxide oxidation of dithiobiurea according to the procedure of Fromm, et al.[5] The product, recrystallized from water, had mp 197-197.5° (lit.[2] 210°).

2-Amino-5-methyl-1, 3, 4-thiadiazole (3) obtained from the Aldrich Chemical Co. was run as a saturated (~ 1 M) solution in DMSO. With a 7-sec repetition rate, a satisfactory spectrum was obtained in 12.5 hrs.

2, 5-Dimercapto-1, 3, 4-thiadiazole (4) obtained from the Aldrich Chemical Co. was run as a saturated (1.2 M) solution in absolute ethanol. With a 6-sec delay between pulses, 6 hrs was required to obtain the spectrum.

2-Amino-1, 3, 4-thiadiazole-4*H*-5-thione (5) obtained from Aldrich was run as a 2.0 M solution in DMSO containing a small amount of 2-pyrrolidone as a phase reference.[6] With a 6-sec delay between pulses an adequate signal-to-noise ratio was obtained in 5 hrs.

5-Amino-1, 2, 4-dithiazole-3-thione (6) was prepared by the action of hydrochloric acid on ammonium thiocyanate.[7]

Table I. ^{15}N Chemical Shifts[a]

	Chemical Shift			Coupling Constants
Compound	ppm	Nitrogen	Multiplicity	J_{NH}, Hz
1	244.5	3	doublet	105.0
	266.6	1,5	triplet	92 ± 1.8
2	81.7	3,4		
	317.8	2',5'		
3	72.8	3,4	broad	
	312.6	2'		
4	108.0	3,4	broad	
5	110.6	3		
	160.5	4	broad	
	308.7	2'	triplet	
6	–	4		
	264.5	5'		

[a] Shifts in ppm upfield from external 1 M $H^{15}NO_3$ in D_2O.

Results and Discussion

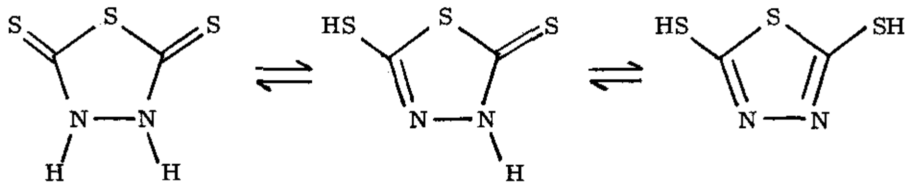
The ^{15}N spectrum of dithiobiurea, **1**, with noise decoupling shows two resonance lines with the upfield line of slightly greater intensity than the downfield line. The spectrum without decoupling is a sharp doublet at 244.5 ppm with J_{NH} = 105.0 Hz and a triplet at 266.6 ppm, J_{NH} = 92 ± 1.8 Hz, so the peaks can easily be assigned to the central nitrogen (low field) and the terminal nitrogens (high field). Because of restricted rotation about the C-N bonds, the terminal hydrogens are not expected to be equivalent, hence the triplet might in fact be found with higher resolution to be a doublet of doublets.

2,5-Diamino-1,3,4-thiadiazole, **2**, after 16 hrs gave a barely perceptible peak at 81.7 ppm attributed to the non-proton carrying nitrogens 3 and 4 and a very intense peak at 317.8 ppm arising from the two equivalent amino groups attached to carbons 2 and 5.

A small broad positive peak, probably two unresolved peaks, at 72.8 ppm in 2-amino-5-methyl-1,3,4-thiadiazole, **3**, is assigned to the two non-equivalent, non-proton-carrying nitrogens 3 and 4 and the intense negative peak at 312.6 ppm in the noise-decoupled spectrum to the amino group attached to C2. Replacement of the amine group in **2** by a methyl group, as in **3**, causes the amino resonance to move downfield by 5 ppm and the ring nitrogen shifts to move downfield by 9 ppm.

The structure of 2,5-dimercapto-1,3,4-thiadiazole, **4**, has been the subject of a number of conflicting reports. The dithione structure, **4a**, has been assigned on the basis of infrared and ultraviolet spectral data.[8]

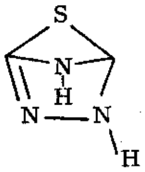
However, the presence of bands at 2600–2550 cm^{-1} in chloroform solution[9] and in the solid state[10] led Katritzky and Lagowski[11] to conclude that 4b was present under these conditions.



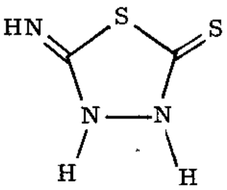
4a 4b 4c

In the present work, the ^{15}N spectrum gave a broad peak at 108 ppm which we interpret as arising from a fairly rapid (on the nmr time scale) tautomerism between forms 4b and 4c with the equilibrium strongly favoring 4c (*cf.* the chemical shift of N3 in 5). Certainly this thiadiazole is not predominantly in form 4a; the ^{15}N chemical shift for 4a should be much more upfield (*cf.* the chemical shifts of dithiobiurea 1a and N4 in 5).

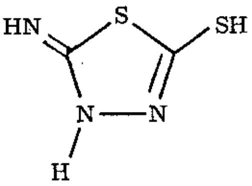
Originally it was suggested[12] that 2-amino-1, 3, 4-thiadiazole-4*H*-5-thione, 5, exists in form 5a. Later speculation centered upon forms 5b and 5c.[13] On the basis of ultraviolet spectra, Petri[14] concluded the compound exists in the thione form 5d. The carbon-sulfur bond lengths determined in a complete X-ray analysis indicate that, in the solid, 5 exists as 5d. The exocyclic carbon-sulfur bond has been assigned 75% double-bond character and the adjacent carbon-nitrogen bond 30% double-bond character.



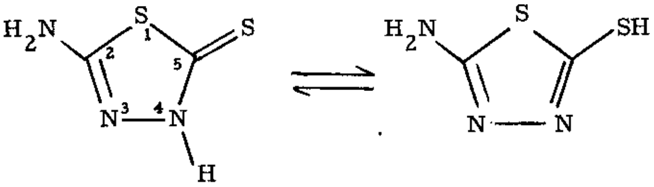
5a



5b



5c



5d 5g

The ^{15}N spectrum provides a great deal of insight into the structure of this compound. The proton-decoupled spectrum, Fig. 1a, consists of a small sharp negative peak at 110.6 ppm which we assign to N3 of 5d. The broad peak at 160.5 ppm arises from N4 and the intense sharp peak at 308.7 ppm to the amino group attached to C2. With the decoupler off, Figure 1b, the 308 ppm peak is a triplet, thus arising from an amino group which means we can definitely rule out 5b and 5c as major contributing forms to the structure of 5. The breadth and the chemical shift of the signal for N4 indicates some degree of tautomerism with 5g. When the decoupler is off, this N4 peak remains a broad singlet.

In a report[16] that heralded the dawn of organic chemistry, Wohler, while still a medical student at Heidelberg, reported in 1821 that treatment of mercuric thiocyanate with hydrochloric acid gave a yellow liquid which,

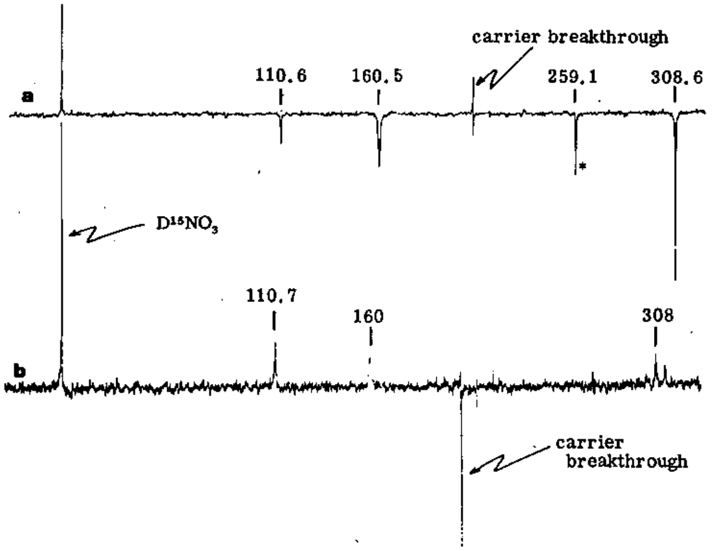
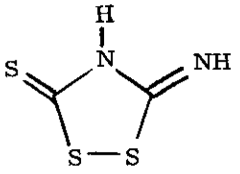
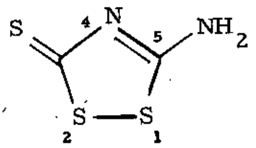


Figure 1. ^{15}N NMR spectrum of 2-amino-1,3,4-thiadiazole-4H-5-thione, 5; (a) proton decoupled (peak marked with * is of 2-pyrrolidone added to act as a phase reference), (b) proton coupled. Shifts in ppm upfield from $D^{15}NO_3$.

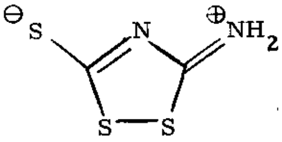
with the evolution of hydrogen cyanide, turned to a yellow solid now known to be 5-amino-1,2,4-dithiazole-3-thione, 6.[16] Liebig synthesized the same solid (and carbon disulfide) by passing hydrogen chloride over molten potassium thiocyanate.[17] Hantzch and Wolvekamp[18] assigned structure 6a but subsequent X-ray[19,20] and infrared spectral analyses[21,22] indicate that the compound exists predominantly in form 6b.



6a



6b



6c

The ^{15}N spectrum of 6 shows just one fairly broad line at 264.5 ppm. The relatively low-field of this amino peak indicates a not inconsiderable contribution from resonance form 6c. A peak for N4 did not appear under the conditions used to obtain this spectrum. If tautomeric form 6a were important we would expect to see N4 in the spectrum.

^{15}N NMR spectroscopy clearly holds promise for providing unique information about the structures of heterocyclic nitrogen compounds in solution. The principal drawbacks to the method at present are the relatively large sample sizes and long times nececessary to acquire spectra. On the other hand, the very large chemical-shift range of ^{15}N serves to distinguish nitrogens in a wide variety of chemical environments.

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