146. ^{15}N-NMR Spectra of Azoles with Two Heteroatoms[1])

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Summary

The ^{15}N-NMR spectra of azoles, with natural isotope abundance, have been measured under different experimental conditions, and chemical shifts are reported for imidazoles, pyrazoles, oxazoles, isoxazoles, thiazoles, and isothiazoles. General trends of substituent effects in this heterocyclic series are discussed based on the data of 67 substituted azoles, dihydro- and tetrahydroazoles. ^{15}N, ^{1}H spin-coupling constants have been determined from spectra obtained by [^{1}H]→ ^{15}N polarization-transfer experiments, *i.e.* an application of INEPT and DEPT pulse sequences. Two-bond and three-bond coupling constants are fully assigned and are discussed in terms of the specific pathways in azoles. The potential of structural applications of the new data is illustrated for isomeric nitro-imidazoles and highly-substituted pyrazoles, and in the case of ring-chain tautomerism of 2-substituted tetrahydro-oxazoles.

Introduction. – Azoles, *i.e.* five-membered heterocycles with one or more N-atoms, constitute important structural units in natural products and are of considerable interest in pharmaceutical chemistry. The synthesis of substituted azoles often results in the formation of structural isomers (constitutional isomers and stereoisomers) which may be differentiated only with difficulty. Yet recognition becomes important on theoretical grounds as well as for practical purposes. Thus azoles are important building blocks for biologically active molecules, *e.g.*, pyrazolyl ketones are antihypertensives and tranquilizers [2a] and 5-nitroimidazoles are broad-spectrum antiprotozoics [2b]. We have shown previously that ^{13}C-NMR spectroscopy, in particular proton-coupled ^{13}C-NMR spectra, are a powerful aid in the structure determination of thiazolidinones and dihydrothiazinones [3]. Since ^{15}N-NMR became available as a new spectroscopic source, the chemical shift and spin-coupling parameters of this nucleus may provide additional structural information. Earlier work on the ^{14}N-resonance of aza-heterocycles [4] yielded mainly

[1]) ^{15}N-NMR Spectroscopy, Part X. For Part IX see [1].

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chemical-shift information, and application was handicapped by unfavorable linewidth and, consequently, limited sensitivity and accuracy. Nevertheless, the potential of structural applications became apparent in several contributions, *e.g.* [5] [6]. More recently, shielding and spin-coupling information became available on azoles from NMR studies using the ^{15}N-isotope both in enriched and natural isotope abundance. In particular, the pyrrole [7], imidazole [8] and pyrazole [9] systems were studied. However, some of the chemical-shift information was still obtained on ^{15}N-labelled substrates, either by direct observation of the isotope or by indirect ^{1}H-$\{^{15}N\}$ double-resonance experiments.

With the advent of multinuclear pulsed spectroscopy and high-sensitivity probe heads ^{15}N-NMR can be routinely performed at natural isotope abundance. Furthermore, application of $[^{1}H] \rightarrow {}^{15}N$ polarization-transfer experiments, *e.g.* INEPT, DEPT, or SPT pulse experiments, leads to a facile disclosure of ^{15}N-NMR parameters in heterocycles, *i.e.*, shielding values and ^{15}N, ^{1}H spin-coupling constants [10]. The latter are of particular importance for the study of constitutional and stereoisomers in heterocyclic chemistry. In this contribution we report on the ^{15}N chemical shifts and ^{15}N, ^{1}H-coupling constants of imidazoles, oxazoles, thiazoles, and the corresponding 1,2-isomers. In addition, chemical shifts are presented for some dihydro- and tetrahydroazoles.

2. Results and Discussion. – 2.1. *Chemical Shifts.* The ^{15}N-NMR spectra were recorded under different conditions. First, chemical shift data were obtained from $(CD_3)_2SO$- or $CDCl_3$-solutions in 20-mm sample tubes at 10.1 MHz using inverse-gated proton-decoupling. To allow for faster spin-lattice relaxation (T_1^{-1}), these solutions were 0.05 M in $Cr(acac)_3$. Under such conditions the chemical shift effect of the relaxation reagents is minimized ($\pm$ 1–2 ppm) [11]. On the other hand, proton-coupled ^{15}N-NMR spectra were measured in the same solvents without relaxation reagent, in 10-mm sample tubes at 20.2 MHz, with the aid of the INEPT pulse sequence [10a, b]. In some cases, selective ^{1}H-irradiation was applied during acquisition of the free induction decay to simplify the ^{15}N-signal, and to allow for an assignment of the ^{15}N, ^{1}H-coupling constants. *Figure 1* illustrates typical examples for fully proton-coupled and selectively decoupled INEPT spectra as obtained with 5-methylisoxazoles (**33**). A satisfactory spectrum may be measured within an hour or less on 50–100 mg of sample dissolved in 1 ml solvent. For applications of the DEPT pulse sequence see *Sect. 2.2.*

2.1.1. *Imidazoles.* The chemical-shift data for substituted imidazoles are collected in *Table 1.* The shielding values for the parent compound **1** showing fast proton exchange (in $CDCl_3$: -172.4; in $(CD_3)_2SO$: -169.0 ppm) are in very good agreement with literature data (in $CHCl_3$: -172.6 [4c] [8c], in $(CD_3)_2SO$: -168 ± 1 ppm [8b]). It should be noted that we quote chemical shifts to *lower* frequency from the nitromethane reference with a *negative* sign [11]. The individual N-resonances can be observed in *N*-substituted derivatives, *i.e.* 1-methyl- and 1-acetylimidazole. For the latter, no data have been reported yet. Whereas there is a large deshielding effect for N(1) in the acetyl derivative **6** ($\Delta\delta = +50$ ppm), N(3) is deshielded by only +10 ppm when compared with 1-methylimidazole (**4**). Small shielding effects on the N-atom are observed for C-methyl substitution, *i.e.*, -1.8 ppm in 2-methyl-

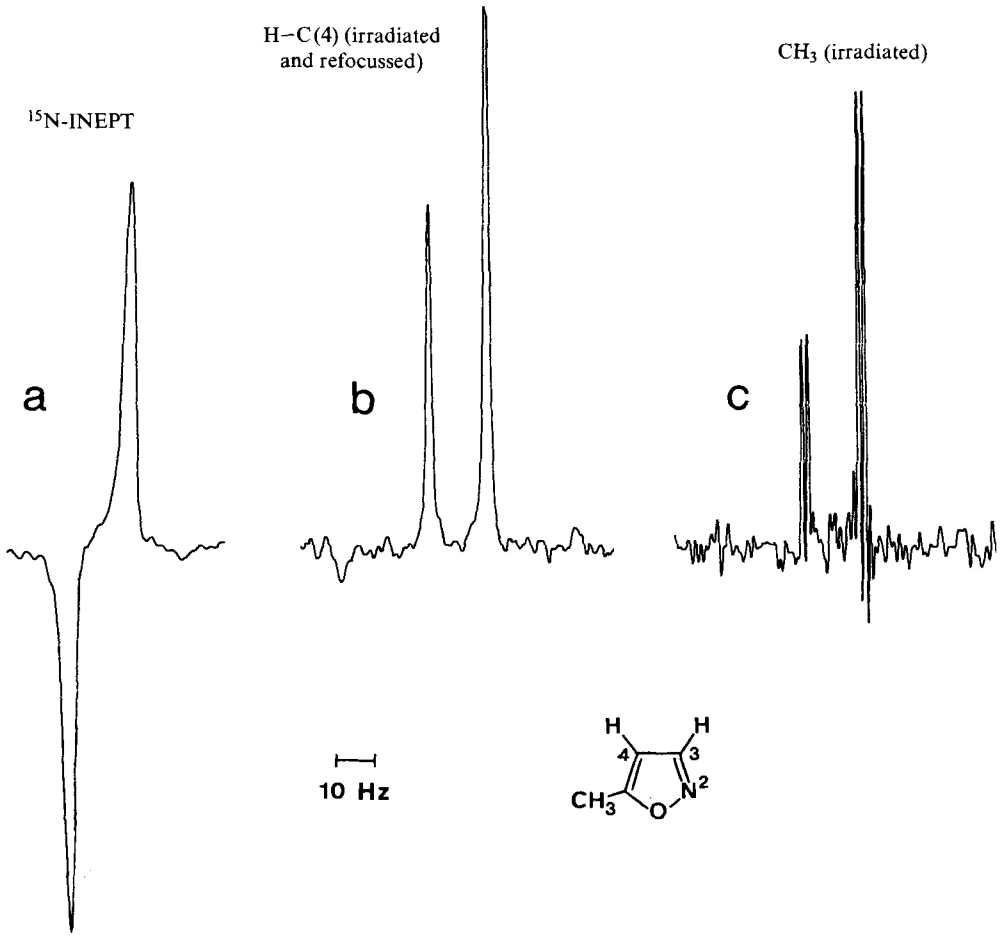


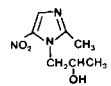
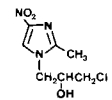
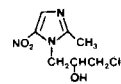
Fig. 1. *^{15}N-INEPT-NMR spectra of 5-methylisoxazole* (**33**) ($(CD_3)_2SO$, 20.2 MHz). a) Fully proton-coupled; b) refocussed and selectively irradiated at the H–C(4) resonance; c) refocussed and selectively irradiated at the CH_3-resonance.

imidazole (**2**). In the nonsymmetrical 5-methyl derivative **3** the effect of the CH_3-substituent is -0.4 ppm for N(1) and $+5.4$ ppm for N(3). Although the ratio of the non-equivalent tautomers is not known these data indicate a deshielding effect from a CH_3-group *via* a (formal) C–N single bond in the heterocyclic system, as observed in aliphatic systems [12].

The nitroimidazoles were of particular interest to us. In the course of extensive synthetic studies in this series (*cf.* [13] and further references cited therein), an unambiguous structural assignment of 4-nitro- and 5-nitroimidazoles became important. Whereas ^{1}H-NMR spectra were used for characterization, proton-coupled ^{13}C-NMR spectra so far offered the best method for the differentiation of the isomers. This, however, should also be possible by N-NMR spectra.

Table 1. *^{15}N Chemical Shifts*[a]) *of Imidazoles*

Compound	Solvent	N(1)	N(3)	NO_2
1 	$(CD_3)_2SO$	−169.0	−169.0	
		−168±1	−168±1[b])	
	$CDCl_3$	−172.4	−172.4	
		−172.6	−172.6[c])	
2 	$(CD_3)_2SO$	−171.6	−171.6	
	$CDCl_3$	−174.2	−174.2	
3 	$(CD_3)_2SO$	−172.8	−163.9	
	$CDCl_3$	−172.8	−167.0	
	TFA	−213.2	−209.0	
4 	$(CD_3)_2SO$	−219.2	−119.1	
	$CDCl_3$	−221.7	−124.1	
5 	$(CD_3)_2SO$	−223.2	−121.5	
	$CDCl_3$	−225.0	−127.3	
6 	$(CD_3)_2SO$	−170.0	−110.3	
	$CDCl_3$	−171.9	−113.9	
7 	$(CD_3)_2SO$/			
	$(CH_3)_2CO$ (3:1)	−205.6	−128.9	−17.4
	$(CD_3)_2SO$	−202±5	–	−16±2[d])
8 	$(CD_3)_2SO$	−205.8	−133.2	−17.0
9 	$(CD_3)_2SO$	−208.5	−127.7	−18.0
10 	$(CD_3)_2SO$	−219.4	–[c])	−25
	$CDCl_3$	−222.3	–	−26

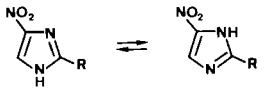
Compound	Solvent	N(1)	N(3)	NO_2
11 	$(CD_3)_2SO$	−210.3	−130.2	[e])
12 	$(CD_3)_2SO$	−224.1	−121.0	[e])
13 	$(CD_3)_2SO$	−203.3	−132.0	[e])
14 	$(CD_3)_2SO$	−216.4	−120.5	[e])
15 	$(CD_3)_2SO$	−205.7	−131.7	[e])
16 	$(CD_3)_2SO$	−218.7	−120.4	[e])

[a]) δ[ppm] relative to external, neat CH_3NO_2. [b]) From [8b]. [c]) From [4c] [8c]. [d]) From [7b]. [e]) Not measured.

No ^{15}N-NMR data were available yet for nitroimidazoles, and the ^{14}N chemical shifts are incomplete. In particular, only one of the ring N-atoms could be observed [7b]. From ^{15}N-NMR spectra the three ^{15}N-resonances can be clearly identified and assigned (with increasing frequency) to the >N–, –N= and $-NO_2$ groups, respectively.

Introduction of a NO_2-group into the 4-position of imidazole leads to two possible tautomeric structures **7a** and **7b**, but it was shown by UV evidence [14] and ^{13}C-NMR data [7b] that in solution isomers **7a** and **8a**, respectively, predominate in the cases of 4(5)-nitroimidazole (**7**) and 2-methyl-4(5)-nitroimidazole (**8**). A comparison of the ^{15}N chemical shifts of **7** and 1-methyl-4-nitroimidazole (**9**) shows close agreement which supports the predominance of tautomer **7a**.

Scheme 1



7a R = H **7b**

8a R = CH_3 **8b**

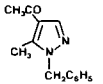
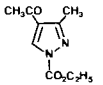
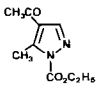
4-nitro- and 5-nitroimidazoles are most easily differentiated by the chemical shifts of the NO_2-group (-18 ± 1 ppm and -25 ± 1 ppm, respectively)[3]). Corresponding effects for the shielding values of the NO_2-group have also been observed in the ^{15}N-NMR spectra of nitropyrroles [7b]. Also the ring N-atoms exhibit clearly defined chemical shift ranges in the two isomeric series. In the 5-nitroimidazoles the observed δ(N)-values are (220 ± 4) ppm for N(1) and (120 ± 1) ppm for N(3) and these data are not significantly different from the parent compounds **4** and **5**. In the 4-nitro series, however, the N(1)-resonance is deshielded ((207 ± 3) ppm) whereas increased shielding is observed for the N(3)-resonance (130 ± 3 ppm). These data illustrate that the NO_2-group in 4-position is more effectively conjugated with the imidazole ring system.

2.1.2. *Pyrazoles.* The ^{15}N-NMR studies in this series were motivated by an intention to differentiate the isomeric *N*-benzyl and *N*-ethoxycarbonylpyrazoles **21/22** and **23/24**, respectively. The spectra of *N*-unsubstituted pyrazoles, including the parent compound **17**, are strongly solvent-dependent. Whereas in $CHCl_3$ in N–H exchange is fast on the ^{15}N-NMR time scale leading to an averaged signal at -134.0 ppm in $CDCl_3$ (in $CHCl_3$: -134.7 [9a], $(CD_3)_2SO$ as a solvent is slowing down the process due to H-bonding and permits the observation of separate signals for the triligant –N< and biligant –N= atoms at -173.1 and -79.8 ppm, respectively [9a] *(Table 2)*. CH_3-Substitution in 3-position (**18**) leads to averaged ^{15}N-shifts in both $CHCl_3$- and $(CD_3)_2SO$-solution and the observed values in $(CD_3)_2SO$-solution are *low*-frequency shifted (-7 to -15 ppm) relative to the calculated averaged ^{15}N-shift of pyrazole in the same solvent ($\bar{\delta}=-126.5$ ppm).

[3]) The $\delta(NO_2)$-values are sensitive to small amounts of H_2O in $(CD_3)_2SO$ causing a shift to higher frequencies.

Table 2. *^{15}N Chemical Shifts*[a]) *of Pyrazoles*

Compound	Solvent	N(1)	N(2)
17 	$(CD_3)_2SO$	−173.1	−79.8[b])
	$CDCl_3$	−134.0	−134.0
	$CHCl_3$	−134.7	−134.7[b])
	TFA	−188.2	−188.2
18 	$CDCl_3$	−133.4	−138.3
	$(CD_3)_2SO$	−133.4[c])	−141.9[c])
	TFA	−195.6	−192.5
	HCl + DCl (2:1)	−190.4	−186.3
19 	$CHCl_3$	−180.8	−76.5[b])
20 	$(CD_3)_2SO$	−108.5	−84.6 −56.9 (NO_2)
	$CDCl_3$	−109.1	−86.1 −59.0 (NO_2)
21 	$(CD_3)_2SO$	−168.9	−72.9
	$CDCl_3$	−173.1	−75.7

Compound	Solvent	N(1)	N(2)
22 	$(CD_3)_2SO$	−163.2	−75.5
	$CDCl_3$	−167.0	−91.4
23 	$(CD_3)_2SO$	−166.7	−78.9
	$CDCl_3$	−167.9	−83.2
24 	$(CD_3)_2SO$	−159.2	−76.0
	$CDCl_3$	−159.9	−80.6

[a]) δ [ppm] relative to external, neat CH_3NO_2. [b]) From [9a]. [c]) Assignment from [9a].

For the $CHCl_3$-solution the CH_3-substituent effects are considerably smaller (−4 to +1 ppm). The assignment of the two similar chemical-shift values in **18** was reported by *Roberts et al.* [9a] and is based upon spin coupling of N(1) with the ring protons. The large value (14 Hz), reported for $J(1,5)$ indicates that it has to be assigned to a −N=C−H pathway (*cf. Sect. 2.2.1)*. This would lead to the conclusion that the equilibrium for 3-methylpyrazole lies on the side of the N(2)-H tautomer.

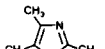
The other pyrazoles listed in *Table 2* are *N*-substituted derivatives, allowing observation of the individual shielding values of the two pyrazole N-atoms. A comparison of the data of 1-methylimidazole (**4**) and 1-methylpyrazole (**19**) shows that the two types of N-atoms (−N< and −N=) are deshielded by ≈40 and ≈50 ppm, respectively, in the pyrazoles.

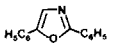
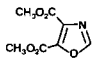
The spectra of the *N*-benzyl derivatives **21** and **22** and of the N-ethoxycarbonyl derivatives **23** and **24** were taken using the INEPT [^{1}H]→ ^{15}N polarization technique (see *Sect. 2.2*), and the assignments within each pair of isomers result from an interpretation of the ^{15}N, ^{1}H-coupling constants, *cf. Sect. 2.2.3.* Introduction of the acetyl group into the 4-position of the pyrazole causes a considerable deshielding of the triligant N-resonance, whereas the imine resonance is little affected, thus indicating mesomeric interaction of the N(1)-atom with the carbonyl group (*i.e.*, a vinylogous amide structure). Further deshielding of the tertiary N-atom is observed in the *N*-ethoxycarbonyl derivatives **23** and **24**, and in particular in 1-nitropyrazole (**20**).

2.1.3. *Oxazoles and Isoxazoles.* The oxazole system has found little attention yet from the side of N-NMR spectroscopy. Only ^{14}N chemical shifts have been reported for the parent compound **25** (−124 ppm, CCl_4) and benzoxazole [15]. The ^{15}N-resonance in oxazole (**25**) (−126.6 ppm, $CDCl_3$) lies close to the value for 1-methylimidazole (**4**) (δ(N−3) = −124.1 ppm) which suggests similar electronic environments for the azole N-atom in both systems, this being confirmed by calculated electron densities, *cf.* [4a], p. 208f. The ^{15}N chemical shifts of oxazole (**25**) and 2,4,5-trimethyloxazole (**26**) in different solvents are given in *Table 3* and, together with the above mentioned ^{14}N-data, suggest a typical resonance range of −122 to −126 ppm for alkyl-substituted oxazoles. Alkyl substitution in 2-position is expected to lead to shielding of the N-atom, as already observed in 1,2-dimethylimidazole (**5**) (δ(N−3): −127.3 ppm). Shielding of the N-atom by alkyl-substitution in 2-position is also evident in 4,5-dihydrooxazoles (**47**–**49**) *(cf. Table 5).* On the other hand, CH_3-substitution in 4-position induces *de*shielding effects on the N(3)-atom (**52** and **53** *vs.* **48**), as already observed in imidazoles. As a result of both effects the chemical shift of N(3) in **26** is only little affected. Phenyl substitution as well as alkoxycarbonyl groups in 4- or 5-position (compounds **27**–**31**) have only small deshielding effects on the oxazole ^{15}N-resonance. The oxazoles were investigated also with the intention to obtain ^{15}N, ^{1}H-coupling constants from INEPT spectra, and the corresponding results will be discussed in *Sect. 2.2.* Furthermore, ^{15}N-NMR data on 4,5-dihydrooxazoles are presented in *Table 5* and discussed in *Sect. 2.1.5.*

Isoxazoles have scarcely been studied by direct observation of the ^{15}N-resonance [17]. The parent compound **32** shows a highly deshielded resonance at +0.6 ppm ($CDCl_3$) which is slightly shifted to higher frequencies in $(CD_3)_2SO$ (+2.2 ppm).

Table 3. *^{15}N Chemical Shifts*[a]) *of Oxazoles and Isoxazoles*

Compound		Solvent	N(3)
25		$(CD_3)_2SO$	−123.7
		$CDCl_3$	−126.6
		CCl_4	−124 ± 1[b])
26		$(CD_3)_2SO$	−121.9
		$CDCl_3$	−126.2
		TFA	−194.9
27	 R = $C_6H_4CN(p)$	$(CD_3)_2SO$	−118.9
			−122.0 (CN)
28	 R = $C_6H_4NO_2(p)$	$(CD_3)_2SO$	−117.7
29	 R = $C_6H_4CF_3(p)$	$(CD_3)_2SO$	−118.4

Compound		Solvent	N(3)
30		$(CD_3)_2SO$	−122.0
31		$(CD_3)_2SO$	−119.2
		$CDCl_3$	−119.6
32		$(CD_3)_2SO$	+2.2
		$CDCl_3$	+0.6
33		$(CD_3)_2SO$	+0.1
		$CDCl_3$	−2.4
34		$(CD_3)_2SO$	−9.2
		$CDCl_3$	−12.0

[a]) δ [ppm] relative to external, neat CH_3NO_2. [b]) From [15].

Earlier measurements of the ^{14}N-resonance have resulted in a chemical shift range from -4 to $+6$ ppm depending on solvent [4a-c]. CH_3-substitution in 3-position leads to shielding of the ^{15}N-resonance (**34** *vs.* **33**) by 9 ppm in $(CD_3)_2SO$ and 10 ppm in $CDCl_3$. Similar shielding effects have been observed in imidazoles and pyrazoles.

2.1.4. *Thiazoles and Isothiazoles.* N-NMR data have so far only been reported for three thiazoles, the parent compound **35** (^{14}N-NMR: [15] [16]; ^{15}N-NMR: [17], 2-formylthiazole (**40**) (^{15}N-NMR): [18], and benzothiazole (^{14}N-NMR): [15] [16]).

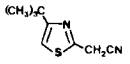
Our results on thiazole (**35**) (-58.0 ppm, *Table 4*) measured in $(CD_3)_2SO$-solution (0.9 M) agree well with the ^{14}N- and ^{15}N-data on the neat liquid (-58 ± 1 ppm). In $CDCl_3$-solution, the thiazole resonance appears to be more shielded, -62.2 ppm (≈ 1.3 M, 0.05 M in $Cr(acac)_3$, 10.1 MHz), and -62.0 ppm (1.3 M, no relaxation reagent, 20.2 MHz). Alkyl substitution (compound **36**), again causes only small effects whereas the thiazole resonance becomes more shielded by C_6H_5-, NH_2- or SR-groups in 2-position *(Table 4)*, the +M effect of the substituents probably being responsible for the increased shielding. A formyl group in 2-position, on the other hand, causes deshielding of the ^{15}N-resonance.

The chemical shift of protonated thiazole has been measured in trifluoroacetic acid (TFA) and in aqueous HCl, and the protonation shifts relative to **35** in $(CD_3)_2SO$ (-57.8 ppm) amount to -116 ppm and -111 ppm, respectively. These values closely correspond to the protonation shift for pyridine (-118 ppm [19] and indicate that there is no considerable stabilisation of the imonium ion by the S-atom. Such a mesomeric interaction is expected to lead to a decrease in the positive charge at the N-atom and, hence, to a decrease in the protonation shift, as observed for 1-methylimidazole (-75 ppm [8b]; -73 ppm [8d]).

The ^{15}N-resonance of isothiazole (**41**) (-81.76 ppm, 90% in acetone) [18] is shielded by about 25 ppm relative to thiazole, in contrast to isoxazole (**32**) which is strongly deshielded relative to oxazole (**25**) ($\Delta\delta \approx +125$ ppm). Three substituted isothiazoles have been included into *Table 4* and they exhibit a resonance range of (86 ± 4) ppm. Thus, isothiazoles have chemical shifts which are typical for imino N-atoms (see *Sect. 2.1.5*).

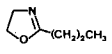
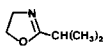
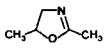
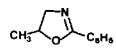
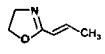
2.1.5. *4,5-Dihydro-derivatives.* To our knowledge ^{15}N- (or ^{14}N-) NMR spectra of 4,5-dihydro-derivatives of imidazoles, oxazoles and thiazoles have not yet been reported. The spectra of 2-methyl-4,5-dihydroimidazole (**45**) and 2-ethyl-4,5-dihydroimidazole (**46**) *(Table 5)* in different solvents show single lines due to rapid proton transfer between the two non-equivalent N-atoms. The shielding value is considerably higher (-263 to -267 ppm) than the averaged chemical shift calculated for amine and imine structures (≈ -200 ppm), illustrating the increased basicity of the amidine system. 4,5-Dihydroimidazoles (imidazolines) are also by about 100 ppm more shielded than the corresponding imidazoles. In contrast, the N-atom in 4,5-dihydrothiazoles appears to be only about 20 ppm more shielded than in thiazoles (*e.g.*, **62** *vs.* **35**, $(CD_3)_2SO$). The chemical shift of **62** (-79.3 ppm) is typical for an imine-N-atom and again illustrates that the S-atom shows only weak interaction with the imine system. The O-atom exhibits a stronger interaction with the imine group, as evidenced by the shielding values (in $(CD_3)_2SO$) of 4,5-dihydrooxazoles (-155 to -165 ppm). As in the imidazole series the increased shielding

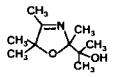
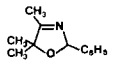
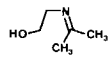
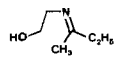
Table 4. *^{15}N Chemical Shifts*[a]) *of Thiazoles and Isothiazoles*

Compound	Solvent	N(3)
35 	neat	−57.2[b])
	$(CD_3)_2SO$	−58.0
	D_2O/H_2O	−73.0
	$CDCl_3$	−62.2[c])
		−62.0[d])
36 	$(CD_3)_2SO$	−55.9
		−130.4 (CN)
37 	$(CD_3)_2SO$	−66.4
	$CDCl_3$	−76.8
38 	$(CD_3)_2SO$	−63.9
39 	$(CD_3)_2SO$	−129.9
		−309.6 (NH_2)
40 	90% in $(CD_3)_2CO$	−38.14[e])
41 	90% in $(CD_3)_2CO$	−81.76[e])
	Et_2O	−82[f])
42 	$(CD_3)_2SO$	−81.8
	$CDCl_3$	−87.0
43 	$(CD_3)_2SO$	−86.6
	$CDCl_3$	−90.6
44 	$(CD_3)_2SO$	−89.6

[a]) δ[ppm] relative to external, neat CH_3NO_2. [b]) From [17]. [c]) 1.3 M with 0.05 M $Cr(acac)_3$, at 10.1 MHz. [d]) 1.3 M, no relaxation reagent, at 20.2 MHz using the DEPT pulse sequence. [e]) From [18]. [f]) From [15].

Table 5. *^{15}N Chemical Shifts*[a]) *of Dihydro- and Tetrahydroazoles*

Compound	Solvent	δ(N)
45 	$(CD_3)_2SO$	−263.4
	$(CH_3)_2CO$	−265.3
46 	$CDCl_3$	−267.1
47 	$(CD_3)_2SO$	−154.5
48 	neat	−162.6
	$(CD_3)_2SO$	−161.9
	$CDCl_3$	−166.6
49 	neat	−164.7
	$(CD_3)_2SO$	−164.0
	$CDCl_3$	−167.6
50 	neat	−164.5
	$(CD_3)_2SO$	−163.3
	$CDCl_3$	−168.9
51 	neat	−166.4
	$(CD_3)_2SO$	−164.9
	$CDCl_3$	−171.4
52 	$(CD_3)_2SO$	−147.1
53 	$(CD_3)_2SO$	−134.8
	$CDCl_3$	−139.3
54 	neat	−163.2
	$(CD_3)_2SO$	−162.3
	$CDCl_3$	−167.7
55 	neat	−161.6
	$(CD_3)_2SO$	−160.2
	$CDCl_3$	−166.9
56 	$(CD_3)_2SO$	−146.2
57 	neat	−161.8
	$(CD_3)_2SO$	−161.0
	$CDCl_3$	−167.4
58 	$(CD_3)_2SO$	−157.6

Compound	Solvent	δ(N)
59 	neat	−172.6
	$(CD_3)_2SO$	−170.7
	$CDCl_3$	−176.5
60 	$(CD_3)_2SO$	−66.6
	$CDCl_3$	−75.0
61 	$(CD_3)_2SO$	−73.3
	$CDCl_3$	−75.2
62 	$(CD_3)_2SO$	−79.3
	$CDCl_3$	−87.9
63 	$(CD_3)_2SO$	−342.8
64 	$(CD_3)_2SO$	−322.7
65 	$(CD_3)_2SO$	−327.0
	$CDCl_3$	−324.5
66a 	neat	−305.4
	$(CD_3)_2SO$	−315.8
	$CDCl_3$	−313.7
66b 	neat	−74.5
	$(CD_3)_2SO$	−69.3
	$CDCl_3$	−76.4
67a 	neat	−319.4
	$(CD_3)_2SO$	−319.5
	$CDCl_3$	−318.4
67b 	neat	−73.5
	$(CD_3)_2SO$	−70.8
	$CDCl_3$	−74?

[a]) δ [ppm] relative to external, neat CH_3NO_2.

of the imine-N-atom must be attributed to the +M effect of the heteroatom in the dihydro derivatives. This also follows clearly from a comparison of the δ(N)-values of 2-methyl-4,5-dihydrooxazole (**48**) and the 2,5-dihydrooxazoles **20** and **61**, the latter being deshielded by ≈90 ppm.

A variety of substituted oxazolines was studied to evaluate the substituent effects on ^{15}N-shielding (*i.e.*, **48** *vs.* **47**: −7.4 ppm ($(CD_3)_2SO$). CH_3-substitution in 4-position, however, results in a deshielding effect of +12 to +15 ppm, *i.e.*, a typical β-substituent effect (**52/48**; **53/52**; **56/55**). Substituents in 2-position acting as π-donors cause variable shielding effects on the ^{15}N-resonance, such as phenyl (**55**) (−6 ppm), propenyl (**58**) (−3 ppm) and cyclopropyl (**59**) (−16 ppm).

Three tetrahydroazoles are included in *Table 5*. The ^{15}N chemical shifts (in $(CD_3)_2SO$) of 1,3-dimethylimidazolidine (**63**) (−342.8 ppm), 3-methyloxazolidine (**64**) (−322.7 ppm) and thiazolidine (**65**) (−327.0 ppm) are typical for tertiary amines and may be compared with the value reported for 1-methylpyrrolidine (−340.2 ppm, in benzene, [20]). 2,2-Dialkyltetrahydrooxazoles exist as mixture of the cyclic and open-chain (*Schiff*-base) forms *(cf. Sect. 2.2.3)*.

2.2. *^{15}N, ^{1}H-Coupling Constants.* The hitherto available information on ^{15}N, ^{1}H spin-coupling in five-membered azaheterocycles is scarce and originates to a large extent from ^{1}H-NMR spectra of ^{15}N-labelled substrates. Thus, two-bond (^{2}J) and three-bond (^{3}J) coupling constants have been reported for pyrrole and substituted pyrroles [7] [11] [21], imidazole [8d] and histidine [8d] [22], and pyrazole [23]. Furthermore, thiazole [24], isothiazole [18] and isoxazole [25] have been studied. No data are as yet available on oxazoles.

For these coupling constants it is essential that they can be obtained from non-labelled substrates to be useful for structural assignments. More recently, therefore, [^{1}H]→^{15}N polarization-transfer experiments (INEPT [10a] [10b], DEPT [26], SPT [10c] [18]) have been used successfully to measure N,H-coupling constants in azaheterocycles, by direct observation of the ^{15}N-resonances. In the following we discuss N,H-coupling constants obtained by the INEPT and DEPT techniques on selected representatives of the present series of azoles. Some structural applications of these data will be given in *Sect. 2.2.3*.

2.2.1. *Two-bond N,H-Coupling Constants* (^{2}J(N,H)). The typical range for this interaction in azoles is (−)3 to (−)15 Hz[4]) whereby biligant N-atoms (=N−) exhibit larger values (9–11 Hz in **4**) than triligant >N− atoms (5–8 Hz in **4**) *(Table 6)*. The largest coupling constants are observed across a formal double-bond Y−N=CH−X (10–14 Hz), and these data are of considerable diagnostic value in assignments of ^{15}N-resonances and structures *(cf. Sect. 2.2.3)*. Such large values are, however, only observed if the C−H bond is in *cis*-orientation to the lone pair of the N-atom (*cf.* [11] p. 194 and [4c] p. 114), a condition which is fulfilled for the biligant (=N−) but not for the triligant N-atom (−N<). The magnitude of this coupling is not greatly affected by the nature of the substituent X and by the substitution on the N-atom (Y), *i.e.*, typical values in oxazoles, isoxazoles and isothiazoles are 13–15 Hz. These rather large constants constitute a convenient

[4]) The sign of ^{2}J(N,H) is attributed in analogy to the results on 1-methylimidazole (**4**) [8d]. In the following, only abs. values of ^{n}J(N,H) are given.

Table 6. *$^{15}N,^{1}H$-Coupling Constants (J, ±0.3 Hz) of Imidazoles*

Compound		Solvent	N(1)			N(3)			Other
			$^2J(1,2)$	$^2J(1,5)$	$^3J(1,4)$	$^2J(3,2)$	$^2J(3,4)$	$^3J(3,5)$	
4		H_2O	−7.6[a]	−5.5	−3.5	−10.8	−9.0	−1.7	N(1),CH_3 −1.6
		$(CD_3)_2SO$	8.1	4.7	3.4		[b]		
5		$(CD_3)_2SO$		[b]		–	10.0	1.0	
6		$(CD_3)_2SO$	8.2	4.1	4.1	11.5	10.0	1.6	
9		$(CD_3)_2SO$	7.8	3.3	–	12.4	–	1.5	N(1),CH_3 1.7 NO_2,H(5) 1.5
12		$(CD_3)_2SO$	–	–	1.8	–	9.5	–	N(1),CH_3(1) 1.8 N(1),CH_3(2) 2.0 N(3),CH_3(2) 2.5 NO_2,H(4) 2.8

[a]) From [8d]; ±0.2 Hz, for the signs see discussion of these authors. Our data are given in absolute values. [b]) Not determined.

Table 7. *$^{15}N,^{1}H$ Coupling Constants [J, ±0.3 Hz] of Oxazoles and Thiazoles*

Compound		Solvent	$^2J(3,2)$	$^2J(3,4)$	$^3J(3,5)$
25		$(CD_3)_2SO$[a])	13.4	10.4	1.2
27	 R = $C_6H_4CN(p)$	$(CD_3)_2SO$	13.4	9.9	–
31		$(CD_3)_2SO$	13.7	–	–
		$CDCl_3$	13.7	–	–
47		$(CD_3)_2SO$	14.6	–[b])	–[b])
35		$CDCl_3$	10.5	10.5	2.2
		CS_2	−10.56[c])	−10.6	−1.97
40		90% in $(CD_3)_2CO$	–	−10.53[d])	−1.93

[a]) Measured at 40.6 MHz on a *WM-400* instrument. [b]) Not determined. [c]) From [24]. [d]) From [18].

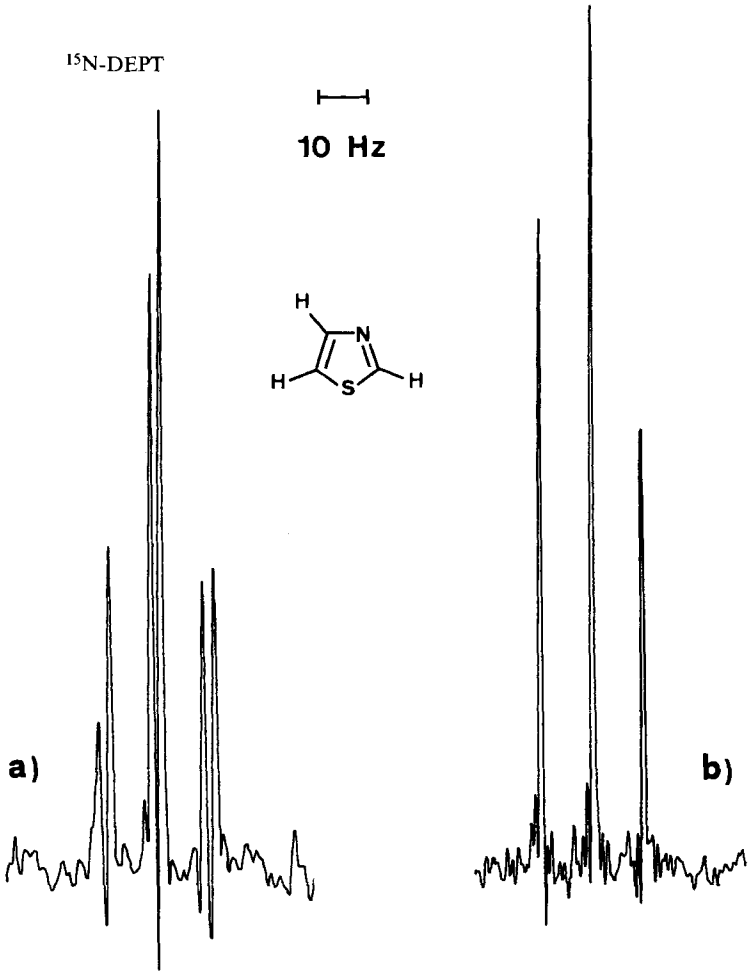


Fig. 2. *^{15}N-DEPT-NMR spectra of thiazole* (**35**) ($CDCl_3$, 20.2 MHz). a) Fully proton-coupled; b) with selective irradiation of the H–C(5)-resonance

monitor-coupling for polarization transfer in INEPT pulse sequences since it allows for short delay times $\frac{1}{4} \cdot J(N,H)$ of the order of 15 to 20 ms.

π-Electron delocalization leads to a decrease of $^2J(N,H)$ across the formal double bond and to an increase of this coupling across the formal single bond. Thus, whereas $^2J(3,2)$ in 4,5-dihydrooxazole (**47**) is 14.6 Hz, the value decreases to 13.4 Hz in oxazole (**25**) *(Table 7)*. The corresponding data for thiazole (**35**) and 1-methylimidazole (**4**) are 10.5 and 10.8 Hz, respectively. In thiazole, $^2J(3,2)$ and $^2J(3,4)$ have the same values (10.5 Hz) which is in agreement with extensive π-electron delocalization in this heterocycle [27]. The proton-coupled spectrum of thiazole is illustrated in *Figure 2*. Two-bond coupling of the triligant N-atom in the imidazoles may be compared to the data reported for pyrrole [11] (4.3 to

5.4 Hz, solvent-dependent). In fact, $J(1,5)$ in the imidazoles **4** and **6** lie in the same range; $J(1,2)$ shows slightly higher values (7–8 Hz), which must be due to the N(3)-substituent on C(2). Two-bond N,H-coupling across a C–N single bond is usually very small, and corresponding values are observed for the N(1)–CH_3 coupling (≤ 2 Hz).

2.2.2. *Three-bond N,H-Coupling Constants* (^3J(N,H). Coupling constants across three bonds between a N-atom and a ring proton in azoles lie between 1.5 and 10.5 Hz. The values for the biligant =N– atom are always small (<2.5 Hz), irrespective of the type of azole. The vicinal coupling of the triligant N-atom in imidazoles and pyrazoles shows a wider range of values. Thus, $^3J(1,4)$ in **4** and **6** is 3.5 and 4.1 Hz, respectively, whereas the corresponding value in 1-phenylpyrazole was reported to be 6.0 Hz [9b] and 1-nitropyrazole (**20**) yields 7.4 Hz *(Table 8)*. This increase in ^3J(N,H) is caused by the *N*-substituents (N(2) and NO_2) on the terminal atom of the N(1)–C(5)=C(4)–H coupling pathway, and finds a parallel in the dependence of vicinal C,H-coupling on the electronegativity of the substituents on the C-atom leading to a similar increase in J(C,H) [28]. In the pyrazoles **22** and **24** also $^3J(1,3)$ across the *transoid* N(1)–N(2)–C(3)–H pathway exhibits large values (9–10 Hz) which are of the same magnitude as the geminal N,H-coupling constants in azoles. Here, the corresponding coupling constant in 1-nitropyrazole (**20**) can serve as a reference value (10.3 Hz). Vicinal coupling between ring N-atoms and C-methyl protons are invariably small (1.5–3 Hz), and the values agree with those recently reported for alkyl-substituted pyrazoles from ^{1}H-NMR of ^{15}N-labelled substrates [29].

2.2.3. *Structural Applications.* We wish to exemplify in this section the usefulness of ^{15}N-NMR spectroscopy in differentiating between structural isomers.

Nitroimidazoles. It is well known that 5-nitroimidazoles (*e.g.,* 1-methyl-5-nitroimidazole (**10**), 1,2-dimethyl-5-nitroimidazole (**12**), 1-(2-hydroxypropyl)-2-methyl-5-nitroimidazole (**14**), 1-(3-chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole (**16**) are potent antiprotozoics, while their 4-nitro isomers are not [2b] [30]. The synthesis of the former is achieved by either of the routes (a) and (b) *(Scheme 2)* and often leads to the formation of the latter as significant by-products [2b]. We have reviewed earlier the methods available for their differentiation and shown the usefulness of ^{13}C-NMR spectroscopy in this respect [13].

In *Sect. 2.1.1,* we have seen that the chemical shifts of N(1), N(3) and of the NO_2-group in the isomeric pairs of nitro-imidazoles serve to characterize them.

Scheme 2

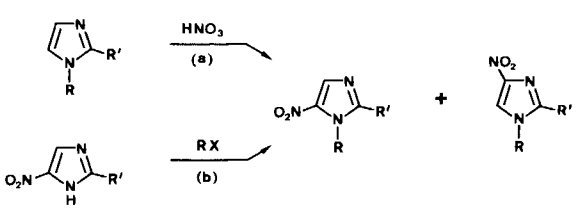
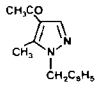
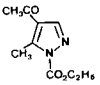
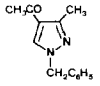
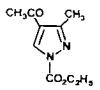


Table 8. *$^{15}N,^{1}H$ Coupling Constants*[a]) [*J*, ±0.3 Hz] *of Pyrazoles, Isoxazoles and Isothiazoles*

Compound		Solvent	*J*(1,3)	*J*(1,4)	*J*(1,5)	*J*(2,3)	*J*(2,4)	*J*(2,5)
20		$(CD_3)_2SO$	10.3	7.4	3.1	13.5	≤1	≤1
22		$(CD_3)_2SO$	10.5[b])	–	–	12.0[b])	–	–
24		$(CD_3)_2SO$	9.0	–	–	13.7	–	–
21		$(CD_3)_2SO$	–	–	3.6	–	–	[c])
23		$(CD_3)_2SO$	–	–	3.4	–	–	1.9
32		$(CD_3)_2SO$[d]) $CDCl_3$[e])	– –	– –	– –	14.7 14.4	1.6 1.8	<1 –
33		$(CD_3)_2SO$	–	–	–	14.4	1.4	–
34		$CDCl_3$	–	–	–	–	1.3	– 3.0 [J(2,C(3)CH_3)]
41		$(CD_3)_2CO$	–	–	–	−14.20[f])	−1.86	+1.32
42		$(CD_3)_2SO$	–	–	–	14.4	–	1.3
43		$(CD_3)_2SO$	–	–	–	14.5	2.2	–
44		$(CD_3)_2SO$	–	–	–	–	–	1.5

[a]) Determined in some cases by use of selective irradiation of either CH_3 or CH_2 protons. [b]) Error limits ±0.5 Hz. [c]) Not determined. [d]) Measured at 40.6 MHz on a *WM-400* instrument. [e]) From [25]. [f]) From [18].

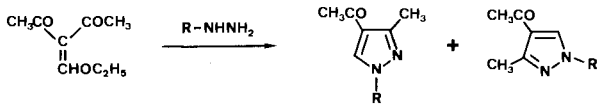
From *Table 6* it can be recognized that ^{2}J(N(3),H–C(4)) serves to strengthen these deductions. Thus in **4** and **5** ^{2}J(3,4) is 9–10 Hz, while ^{3}J(3,5) is 1–1.7 Hz. Accordingly, in the 4-nitroimidazole **9**, lacking the H-atom on C(4), the N(3),H(4)-

coupling is not seen, but in the 5-nitroimidazole **12** N(3) is coupled strongly (9.5 Hz) to the H-atom on C(4).

Pyrazoles. Isomeric acetylpyrazoles serving as precursors for biologically active substances [2a] are formed by the reaction of monosubstituted hydrazines with 3-(ethoxymethylene)-2,4-pentanedione *(Scheme 3)*. The ratio of the products depends upon the nature of R. ^{13}C-NMR spectroscopy has been used to distinguish between the isomers [13a]. ^{15}N-NMR spectroscopy can also be utilized with advantage as we discuss below.

The chemical shifts of N(1) in **22** in $(CD_3)_2SO$ (−163.2) and **24** (−159.2) are different from those in **21** (−168.9) and in **23** (−166.7) due to the deshielding effect of the β-CH_3-group (5–8 ppm) *(cf. Sect. 2.1.1)*. More significantly, as would be expected, **22** and **24** show for N(2) large geminal coupling constants $^2J(2,3)$ of 12.0 and 13.7 Hz respectively, which are lacking for **21** and **23** *(Table 8)*.

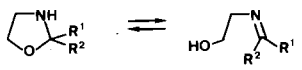
Scheme 3



21.23 **22.24**

Oxazolidines. Oxazolidines can be expected to show ring-chain tautomerism as shown in *Scheme 4*. ^{15}N-NMR spectroscopy serves as a unique tool to demonstrate this equilibrium. Thus, 2-dimethyloxazolidine (as neat liquid, in $CDCl_3$- or $(CD_3)_2SO$-solutions) shows two signals, one in the low-frequency region (−305 to

Scheme 4



66a $R^1 = R^2 = CH_3$ **66b**

67a $R^1 = C_2H_5$, $R^2 = CH_3$ **67b**

−316 ppm) for the cyclic structure **66a** with the basic, triligant N-atom, and a second high-frequency signal typical for a biligant imine-N-atom (−69 to 76 ppm) *(Table 5)*. Analogous results are obtained for 2-ethyl-2-methyloxazolidine (**67a** ⇌ **67b**). These observations are in agreement with the conclusions which we have drawn from ^{1}H- and ^{13}C-NMR-spectra. In $CDCl_3$-solution the cyclic species **66a** and **67a** predominate. For further studies on this tautomeric system *cf.* [31].

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Experimental. – 1. *Origin of Compounds.* The following compounds are of commercial origin and their purity was checked by ^{1}H- or ^{13}C-NMR prior to the ^{15}N-NMR measurements: *Fluka AG*, **1–6**, **17**, **18**, **32**, **35**, **39**, **62**, **65**. *EGA Chemie*, **7**, **8**, **26**, **33**, **53**. The substituted oxazoles **27–29** and the thiazoles **36–38** were kindly supplied by *Schering AG*, Berlin. The nitroimidazoles **9–16** are known [2a]. They were resynthesized at *Hindustan Ciba-Geigy Ltd.* and their properties studied extensively [13]. The pyrazoles **21–24** have also been reported [13a]. The isothiazoles **42** and **43** are commercially available, while **44** was synthesized [13b]. The syntheses and characterization of the following compounds are described under the respective references; prior to the ^{15}N-NMR measurements the samples were checked by ^{1}H- or ^{13}C-NMR: **20** [32], **25**, **31** [33], **30** [34], **45**, **46** [35], **47** [36], **48–59** [37], **60** [38], **61** [39], **63** [40], **64** [41], **66**, **67** [42].

2. *Instrumental.* ^{15}N chemical-shift determinations were made on a *Varian XL-100-15* spectrometer at 10.1 MHz or on a *Varian XL-200* at 20.3 MHz. In the first case, a homebuilt probe head [43] for 20-mm o.d. sample tubes was used, in the latter 10-mm fixed-frequency or broad-band probes were applied. Probe temperatures were *ca.* 35° under inverse-gated proton-noise decoupling condition *(XL-100)* and 23° *(XL-200)*. ^{15}N,^{1}H spin-coupling constants were determined on the *XL-200* instrument with the aid of the polarization-transfer pulse sequences INEPT [10a] or DEPT [26], using in some cases selective proton irradiation during the acquisition period. The proton-coupled spectra also served for chemical shift determinations. The samples were dissolved in $CDCl_3$ (dried over Al_2O_3) or $(CD_3)_2SO$ (kept anh. over molecular sieves). Typical concentrations were 150–200 mg/ml but in the INEPT or DEPT experiments, concentrations were in some cases as low as 50–100 mg/ml. All chemical shift determinations were performed relative to neat nitromethane contained in a capillary. The solutions in $(CD_3)_2SO$ and $CDCl_3$ used on the *XL-100* spectrometer (20-mm tubes) contained 70–100 mg (<0.05 M) of $Cr(acac)_3$ to shorten T_1 relaxation times in single-pulse experiments, whereas all measurements at 20.3 MHz *(XL-200)* were performed without relaxation reagent. Chemical shifts determined on the two instruments, therefore, exhibit small deviations which are due to a) a temperature difference of *ca.* 10°, b) the presence or absence of Cr^{3+}, c) concentration differences, and d) the necessity for susceptibility corrections for the two different alignments of the field and the sample including the external reference. Shift measurements on the same sample on the two different instruments have shown in several cases that the observed δ(N)-values, without susceptibility correction, do not deviate by more than 1–2 ppm, whereby the data obtained in the conventional iron magnet are shielded relative to values from the superconducting magnet. Estimation of the susceptibility correction [44] for the two sample/field alignments amounts to -0.6 ppm for the *XL-100* and to $+1.2$ ppm for the *XL-200*, assuming a $\Delta\chi = \chi(CH_3NO_2) - \chi(\text{sample})$ of ≈ 20 emu/mol. For the above reasons, the reproducibility of the tabulated uncorrected δ(N)-values is ± 1 ppm; for an example measured under two different conditions see thiazole (**35**).

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