208. ^{15}N-NMR Study of Activated Enamines[1])

Structural Dependence of δ (^{15}N) and ^nJ (N, H) in Primary, Secondary and Tertiary Enamino-Ketones, Esters and Amides

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Summary

The pulse sequence INEPT was used to obtain proton-coupled ^{15}N-NMR spectra in natural isotope abundance for enamines substituted in 2-position with electron-withdrawing groups.

The chemical shifts and coupling constants are discussed in terms of their relationship to structural features such as multiple *N*-alkyl substitution, double-bond configuration, H-bonding, N-lone-pair delocalization within the conjugated system, and steric effects.

It is concluded that ^{15}N chemical shifts are a sensitive probe for local structural modifications at the N-atom and conformational changes in a remote part of a conjugated molecule, while one-bond N, H-coupling essentially reflects N-hybridization and subtle local geometric distortions. Stereospecific three-bond N, H spin coupling to olefinic protons (4.0 ± 0.2 Hz) has been found a characteristic feature of (*Z*)-isomers in all investigated compounds, whereas two-bond coupling to olefinic protons (^2J (N, H) = 0.5 to 5 Hz) is observed in (*E*)-isomers. The sensitivity to solvents and steric properties of remote substituents renders geminal coupling a useful probe for studying electronic effects in the C–N bond.

1. Introduction. – Owing to the potential of ^{15}N-NMR in the study of structure and chemical properties of various classes of organic compounds [2–4] ^{15}N-parameters of activated enamines, considered as important synthetic intermediates in general and pharmaceutical synthesis [5–7], are of considerable interest. In this respect, relatively few data exist in the literature for the present class of compounds [3] [4] [8–11].

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[1]) ^{15}N-NMR Spectroscopy, Part XI; Part X: [1].

[2]) On leave to the Institute of Organic Chemistry, University of Zurich, 1981–1982.

In our laboratories, interests in ^{15}N-NMR parameters are directed towards revealing their significance as a structural probe in various open-chain and cyclic conjugated systems. Thus, it was recently shown [9–11] that ^{15}N chemical shifts in enaminones are especially sensitive to the extent of n-π conjugation and, hence, dependent upon conformational changes in remote parts of a molecule.

Since the application of INEPT pulse sequences [12] allows for routine measurements of ^{15}N-spectral parameters in natural isotope abundance, in moderate substrate concentrations and during a reasonable instrumental time the δ- and ^nJ-parameters obtained from proton-coupled spectra of activated enamines can be discussed in terms of the elctronic and stereochemical environment of an N-atom. The present paper deals with the effects on N-shielding and N,H-coupling constants exerted by electronegative β-substitution of the enamine system, molecular stereochemistry, H-bonding and solvents.

2. Results and Discussion. – 2.1. *Chemical Shifts, Coupling Constants and Stereochemical Assignments.* The experimental data for the compounds studied (**1–31**) are collected in *Tables 1–4*.

Table 1. *^{15}N Chemical Shifts (δ (^{15}N) [ppm]) and Coupling Constants (^nJ (^{15}N,H) [Hz]) of Primary Enaminones*[a])

	Compound	Solvent		Isomer[b])	δ (^{15}N)	$\Delta\delta_{Z}^{Ec}$)	^1J (^{15}N,H)	^3J (^{15}N,*H*–C(2)
1	$C_2H_5\overset{1}{C}O-\overset{2}{C}H=\overset{3}{C}H-NH_2$	C_6D_6	(1.9)[d])	(*Z*, s-*cis*)	−289.6	−10.4	92.9	3.9
				E_{av}	−300.0			
2	*i*-$C_3H_7CO-CH=CH-NH_2$	C_6D_6	(15.1)	(*Z*, s-*cis*)	−290.5		92.5	4.1
		C_4D_8O[e])	(10.0)	(*Z*, s-*cis*)	−287.5	−10.3		
				E_{av}	−297.8			
3	*t*-$C_4H_9CO-CH=CH-NH_2$	C_6D_6	(3.7)	(*Z*, s-*cis*)[f])	−289.8	−10.2	92.7	4.0
				E_{av}	−300.0			
4	$C_6H_5CO-CH=CH-NH_2$	C_4D_8O	(0.5)	(*Z*, s-*cis*)	−287.8	−12.3	92.5	4.0
				E_{av}	−300.1			
5	$CH_3CO-C(CH_3)=C(CH_3)-NH_2$	C_6D_6	(4.7)	(*Z*, s-*cis*)	−274.4		88.8	
6	$(CH_3CO)_2C=CH-NH_2$	$CDCl_3$	(1.0)	(*Z*)/(*E*)	−273.0		92.7	

[a]) Chemical shifts (± 0.1 ppm) are given using external $CH_3{}^{15}NO_2$ in a coaxial capillary as reference. Couplin constants were determined under non-decoupling conditions.

[b]) Stereochemical assignments refer to the C(2)=C(3) bond and the C(1)–C(2) bond.

[c]) Parameter denoting the difference between the chemical shifts in (*E*)- and (*Z*)-isomers.

[d]) Molar concentration.

[e]) C_4D_8O = (D_8)THF.

[f]) ^2J (N,*H*–C(3)) = 1.7 Hz was found in this case, whereas broadening of the lines due to unresolvabl ^2J (N,*H*–C(3)) was observed for other aliphatic derivatives.

In *Table 1* spectral parameters are cited for primary enaminones with different substituents in 2-position of the enamine system. In the solvents used, the concentration of the (*E*)-isomer is of the order of 10%, as evaluated from ^{1}H-NMR spectra and hence, no attempts were made to measure proton-coupled ^{15}N-NMR spectra of this isomer. In (*Z*)-isomers, one-bond coupling ^1J (N,H) of 93–94 Hz and three-bond coupling ^3J (N,C(2)–H) of about 4 Hz were found. While in other alkyl derivatives the lines were only broadened due to small two-bond coupling a larger value of this coupling, ^2J (N,C(3)–H) = 1.7 Hz found in the *tert*-butyl compound **3** allowed for unambiguous assignment of the couplings by selective irradiation of the C(3)–H proton

resonance. It was also found that $^1J(N,H)$ is identical for both protons of an NH_2-group. This information is deduced from a proton-coupled single-pulse ^{15}N-NMR experiment (upper trace in *Fig. 1*) showing a symmetrical triplet-type signal and confirmed in the INEPT spectrum (lower trace in *Fig. 1*) where the central signal is fully cancelled [12a, b].

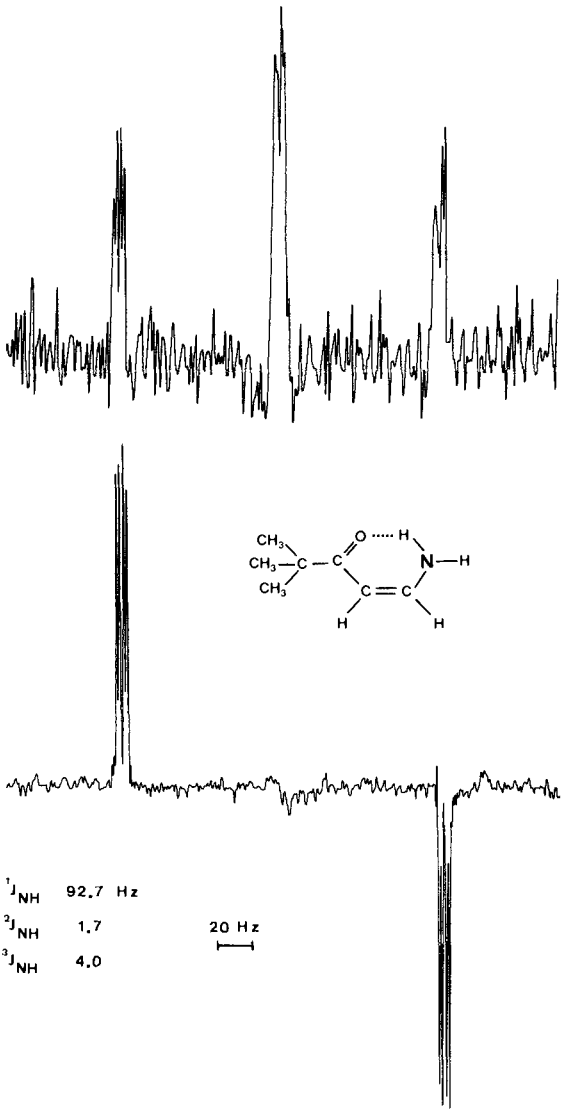
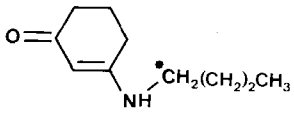


Fig. 1. *Single-pulse* (upper trace) *and INEPT* (lower trace) *^{15}N-NMR fully proton-coupled spectra of* **3** ((*Z*, s-*cis*)-form; 3.7 M solution in C_6D_6; recorded at 20.28 MHz and 23°). Experimental conditions: upper spectrum, sweep width 2000 Hz, 1 s acquisition time, 45° pulse width, 2.6 s pulse delay, measuring time 10 h; lower spectrum, sweep width 10,000 Hz, 5.5 ms pulse delay, 0.8 s acquisition time, 1 s pulse sequence delay, measuring time 1.9 h.

Table 2. *^{15}N Chemical Shifts (δ (^{15}N) [ppm]) and Coupling Constants (^nJ (^{15}N,H) [Hz]) of Secondary Enaminones*[a])

	Compound	Solvent		Isomer	δ (^{15}N)	$\Delta\delta^{E}_{Z}$	^1J (^{15}N,H)	^2J (^{15}N,H–C(3))	^3J (^{15}N,H–C(2))	Other	
7	$CH_3\overset{1}{C}O-\overset{2}{C}H=\overset{3}{C}H-NHCH_3$[b])	CD_2Cl_2	(5.0)[c])	(*Z*, s-*cis*)	−281.7	− 6.7	91.4		4.0		
				(*E*, s-*cis*)	−288.4		91.8				
				(*E*, s-*trans*)	−291.0		94.3				
8	$C_2H_5CO-CH=CH-NHCH_3$	C_6D_6	(4.5)	(*Z*, s-*cis*)	−286.4	− 9.6	92.2		4.1		
				E_{av}	−296.0						
9	*i*-$C_3H_7CO-CH=CH-NHCH_3$[d])	C_4D_8O	(7.8)	(*Z*, s-*cis*)	−286.1	−10.0	92.1	0.8	4.2		
				E_{av}	−296.1		93.7				
10	*t*-$C_4H_9CO-CH=CH-NHCH_3$[e])	C_6D_6	(10.0)	(*Z*, s-*cis*)	−286.5	− 8.4	92.4	0.6	4.2	^2J (N,CH_3)	1.4
				(*E*, s-*cis*)	−294.9		95.5				
11	*i*-$C_3H_7CO-CH=CH-NHt-C_4H_9$	$CDCl_3$	(1.7)	(*Z*, s-*cis*)	−247.3		89.4		3.8		
		C_6D_6	(1.7)	(*Z*, s-*cis*)	−250.5		89.7		3.9		
12		$CDCl_3$	(1.8)	(*E*, s-*trans*)	−274.2		91.5				
13	$CH_3CO-CH=C(CH_3)-NHCH(CH_3)_2$	$CDCl_3$	(7.0)	(*Z*, s-*cis*)	−249.2		88.5				
		C_6D_6[f])	(5.5)	(*Z*, s-*cis*)	−253.0		88.4		1.8	^3J (N,CH_3)	1.8
14	$C_2H_5CO-C(CH_3)=CH-NHCH_3$	CD_2Cl_2	(6.7)	(*Z*, s-*cis*)	−291.5	−11.6	92.4				
				E_{av}	−303.1		91.6	1.7		^3J (N,CH_3)	3.0
15	$C_2H_5CO-C(CH_3)=CH-NHCH_2CH_3$	CD_2Cl_2	(4.4)	(*Z*, s-*cis*)	−273.5	−12.5	91.5				
				E_{av}	−286.0		90.4	0.6			
16	$(CH_3CO)_2-C=CH-NHCH_3$	$CDCl_3$	(2.4)	(*Z*)/(*E*)	−268.0		91.7				
17	$(CH_3CO)_2-C=CH-NHC_6H_5$	$CDCl_3$	(0.6)	(*Z*)/(*E*)	−249.2		93.1			^3J (N,H_o)	2.1[g])

[a]) The chemical shifts were measured against external $CH_3{}^{15}NO_2$ in a coaxial capillary at 24°, unless otherwise indicated, under conditions of broad-band proton decoupling. The coupling constants were measured using low-power selective decoupling of the protons marked with * in the structure and were corrected for reduction (see *Exper. Part*).

[b]) The chemical shifts were measured at −60° without external standard, values based on a carrier frequency as in [9]; the coupling constants measured at the same temperature.

[c]) Molar concentration.

[d]) The chemical shift measured at 0°; the coupling constants measured at 24° in the same solution.

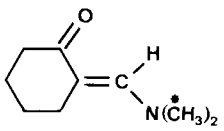
[e]) The chemical shift determined at 10°; the coupling constants measured at 24° in the same solution.

[f]) The isopropyl-CH_3-protons were irradiated yielding two *quint.* with equal spacing between the lines. Since ^2J (N,H) contributed to the line width of each line (half-width *ca.* 1 Hz), it is assumed that remaining three-bond couplings with C(3)–CH_3 and H–C(2) protons are equal.

[g]) The coupling to *ortho*-protons in the aromatic ring.

Spin coupling of the N-atom to the two protons can be accidentally the same, however, this is not observed in secondary enaminones although the differences for the two stereochemical situations *(Scheme 1, Table 2)* are small. More probably, the equivalence of both couplings is the result of an exchange due to rotation about the C(3)–N bond.

Table 3. *^{15}N Chemical Shifts* (δ (^{15}N) [ppm]) *and Coupling Constants* (^{n}J (N,H) [Hz]) *of Tertiary Enaminones*[a])

	Compound	Solvent		Isomer	δ (^{15}N)	^{2}J (^{15}N,*H*–C(3))	^{3}J (^{15}N,*H*–C(2))
18	$HCO-\overset{1}{C}H=\overset{2}{C}H-\overset{3}{N}(\overset{*}{C}H_3)_2$	C_6D_6	(2.5)[b])	(*E*, s-*trans*)	−294.1	2.4	
		$(CD_3)_2CO$	(2.5)		−293.3	1.7	
		CD_3OD	(2.5)		−283.5	2.9	
19	$C_3H_7CO-CH=CH-N(\overset{*}{C}H_3)_2$	C_6D_6	(5.0)	E_{av}	−303.6	2.8[c])	
		$(CD_3)_2CO$	(4.6)		−302.2	3.0	
		CD_3OD	(3.8)		−282.4	2.8	
20	$C_6H_5CO-CH=CH-N(\overset{*}{C}H_3)_2$	CD_3OD	(1.5)	E_{av}	−284.9	1.8	
21	t-$C_4H_9CO-CH=CH-N(\overset{*}{C}H_3)_2$	C_6D_6	(1.2)	(*E*, s-*cis*)	−303.7[d])	4.0	0.9
	t-$C_4H_9CO-CD=CH-N(\overset{*}{C}H_3)_2$	[e])		(*E*, s-*cis*)	−227.7	3.1	
22		C_6D_6	(2.8)	(*E*, s-*cis*)	−304.0	2.4	
		$(CD_3)_2CO$	(2.3)		−303.8	5.2	
		CD_3OD	(2.7)		−290.7	2.2	
23	$CH_3CO-C(CH_3)=CH-N(\overset{*}{C}H_3)_2$	C_6D_6	(1.7)	E_{av}	−312.6	2.3	
24	$C_2H_5CO-C(CH_3)=CH-N(\overset{*}{C}H_3)_2$	C_6D_6	(1.6)	E_{av}	−311.3	2.5	

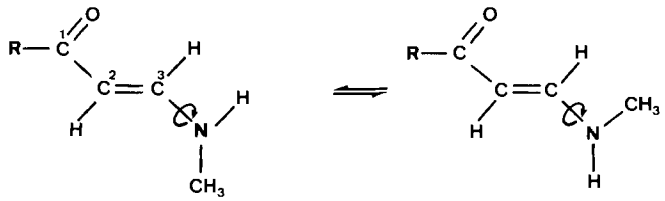
[a]) The chemical shifts and coupling constants were measured under conditions specified in *Footnote a* to *Table 2*.
[b]) As in *Footnote d* to *Table 1*.
[c]) Assignment of geminal coupling confirmed by deuteration at C(2).
[d]) Measured in 5 M solution [9].
[e]) The cited values are determined in CF_3COOD-solution (0.2 g of base in 1.5 g CF_3COOD and 0.5 g C_6D_6) after the deuteration at C(2) was completed.

The ^{15}N-spectral parameters measured in secondary enaminones are collected in *Table 2*. The assignments of ^{15}N chemical shifts in both isomers are based on the recently published result [9] that internally H-bonded (*Z*)-isomers are deshielded by 7 to 12 ppm with respect to the (*E*)-isomers (1–10 M solutions in common solvents). An additional feature used in identifying the signals of the (*E*)-isomer was their broadening due to intermediate rates (at 200 MHz) of rotation at the C(3)–N bond giving rise to the (s-*cis*/s-*trans*)-isomerism *(Scheme 1)*, in analogy to that observed for the amide bond [13].

The s-*cis*-isomer is predominant in C(2)-unsubstituted (*E*)-enamines (as evidenced by vicinal coupling to the N–H proton observed in the C(3)–*H* resonance) while s-*trans*-forms appear more favourable in C(2)-alkyl-substituted compounds (**14**, **15**, **26**) due to partial release of steric strain caused by interaction between C(2)- and *N*-alkyl groups in the former isomer.

The characteristic broadening, however, was the main obstacle in fully characterizing the (*E*)-isomers in secondary enaminones since small long-range couplings could

Scheme 1



s(C, N)-*cis* s(C, N)-*trans*

not be read accurately from the exchange-broadened resonances. Increasing the temperature of an experiment introduces the uncertainty in the one-bond N,H spin coupling measurement due to possible acceleration of N–H proton exchange, while lowering of the temperature produces broadening due to slowing down rotation about the C(1)–C(2) bond.

The information concerning long-range coupling in (*E*)-isomers was gathered then from ^{15}N-NMR spectra of tertiary enaminones *(Table 3)* where C(3)–N bond rotation does not affect the ^{15}N-resonances, and coupling to N–CH_3-protons is eliminated from the spectra by low-power selective irradiation. In the case of secondary enamines selective irradiation constitutes also a sensitive assignment method in cases where chemical shifts of both isomers are very close and, hence, cannot be unambiguously assigned because solvent effects may be of comparable magnitude. In *Fig. 2* this technique is exemplified for the case of the enamine-N-atom in the enamino-amide **30**. The spectral data concerning the amide-N-atom in **30** are given in *Table 4* where data for other enamino-amides and esters are also listed.

As shown in *Fig. 2* it is possible, even in the case where lines from both isomers overlap, to read long-range couplings due to the fact that sharp resonances are obtained only for the isomer in which the *N*–CH_3-group is irradiated. Hence, four strong lines in the central signal of the lower spectrum are assigned to the (*Z*)-isomer and two weaker left-side lines of this signal to the (*E*)-isomer, as seen from the upper spectrum. It is also worth noting that the intensity argument which is often important in assigning the isomers in ^{1}H-NMR spectra may not be valid in ^{15}N-NMR spectra, since line intensities depend strongly on the relaxation time of the proton used for the INEPT experiment. Assignments of the long-range couplings with olefinic protons in (*E*)- and (*Z*)-isomers were confirmed in several instances by selective irradiation as in **3** or by specific deuteration at the C(2)-atom (compounds **19**, **21** and **28**) [11]. Furthermore, the solvent dependence of ^2J(N,H)-values in (*E*)-isomers was examined for three compounds, two of which having fixed conformations at the C(1)–C(2) bond (*E*, s-*trans* and *E*, s-*cis*) in **18** [14] and **22**, respectively *(Table 3)*. Finally, it should be noted that although selective decoupling was used throughout this work to eliminate the two-bond N,H-coupling with *N*–CH_3-protons ($\approx$ 1.5 Hz, as found in this work and in [13]), the overlap of simultaneously occurring small couplings, in the case of longer aliphatic chains on N- or alkyl-substituted double bonds, broadens the signals so that only limited information can be obtained, as for example in **12** *(Table 2)*. Hence, not all possible coupling constants were determined because of line broadening due to exchange or signal overlap and, in several cases, due to their small values as compared with line width ($\approx$ 0.5 Hz).

Table 4. *^{15}N Chemical Shifts (δ (^{15}N) [ppm]) and Coupling Constants (^{n}J (^{15}N, H) [Hz]) of Enamino Esters and Enamino Amides*[a])

	Compound	Solvent	Isomer	δ (^{15}N)	$\Delta\delta_Z^E$	^1J (^{15}N, H)	^2J (^{15}N, H–C(3))	^3J (^{15}N, H–C(2))	Other	
25	$C_2H_5O\overset{1}{C}O-\overset{2}{C}H=\overset{3}{C}H-NHC\overset{*}{H}_3$	$CDCl_3$ (1.9)[b])	(*Z*, s-*cis*)	−296.9	−8.1	92.4	1.3	4.1		
			E_{av}	−305.0		93.0				
26	$C_2H_5OCO-C(CH_3)=CH-NHC\overset{*}{H}_3$	CD_2Cl_2 (4.4)	(*Z*, s-*cis*)	−302.3	−7.8	91.6	1.4		^4J (N, CH_3)	0.6
			E_{av}	−310.1		90.0	2.2		^4J (N, CH_3)	0.4
27	$C_2H_5OCO-CH=C(CH_3)-NHC\overset{*}{H}_2C_6H_5$	$CDCl_3$ (2.7)	(*Z*, s-*cis*)	−278.1		90.9		2.7	^3J (N, CH_3)	2.0
		C_6D_6 (1.0)	(*Z*, s-*cis*)	−283.7		92.6		3.4	^3J (N, CH_3)	1.8
28	$(C\overset{*}{H}_3)_2NCO-CH=CH-N(C\overset{*}{H}_3)_2$[c])	C_6D_6 (2.2)		−312.8			4.6			−295.5
			(*E*, s-*cis*)						δ (NCO)	
	$(CH_3)_2NCO-CD=CH-N(C\overset{*}{H}_3)_2$	CD_3OD (0.9)		−305.2			3.0			−289.3
									δ (NCO)	−251.2
29	t-$C_4\overset{*}{H}_9NHCO-CH=CH-N(C\overset{*}{H}_3)_2$[d])	$CDCl_3$ (1.3)	(*E*, s-*cis*)	−314.2			3.1		^1J (N, H)	89.3
30	$(C_2H_5)_2NCO-CH=CH-NHC\overset{*}{H}_3$	C_6D_6 (3.3)	(*Z*, s-*cis*)	−302.1		91.7	1.5	3.9		−262.2
					−4.3				δ (NCO)[e])	
			(*E*, s-*cis*)	−306.4		94.8	3.8	1.8		−263.2
31	$(i\text{-}C_3H_7)_2NCO-CH=CH-NHC\overset{*}{H}_3$	C_6D_6 (1.3)	(*Z*, s-*cis*)	−302.9	−4.1	91.6	1.5	3.8	δ (NCO)[f])	−248.2
			(*E*, s-*cis*)	−307.0		94.8	3.4	1.8		−249.9

[a]) The chemical shifts and coupling constants were measured under conditions specified in *Footnote a* to *Table 2*.

[b]) As in *Footnote d* to *Table 1*.

[c]) No INEPT spectrum was obtained after irradiation of *N*-CH_3-groups in the amide moiety indicating absence of resolvable coupling of the amide-N-atom to olefinic protons.

[d]) Irradiation of t-C_4H_9-group was performed to obtain one-bond coupling; no coupling to olefinic protons was observed as in *c*.

[e]) Obtained from 4.2 M solution in $CDCl_3$; assignment based on intensity argument.

[f]) Assignment as in *e*.

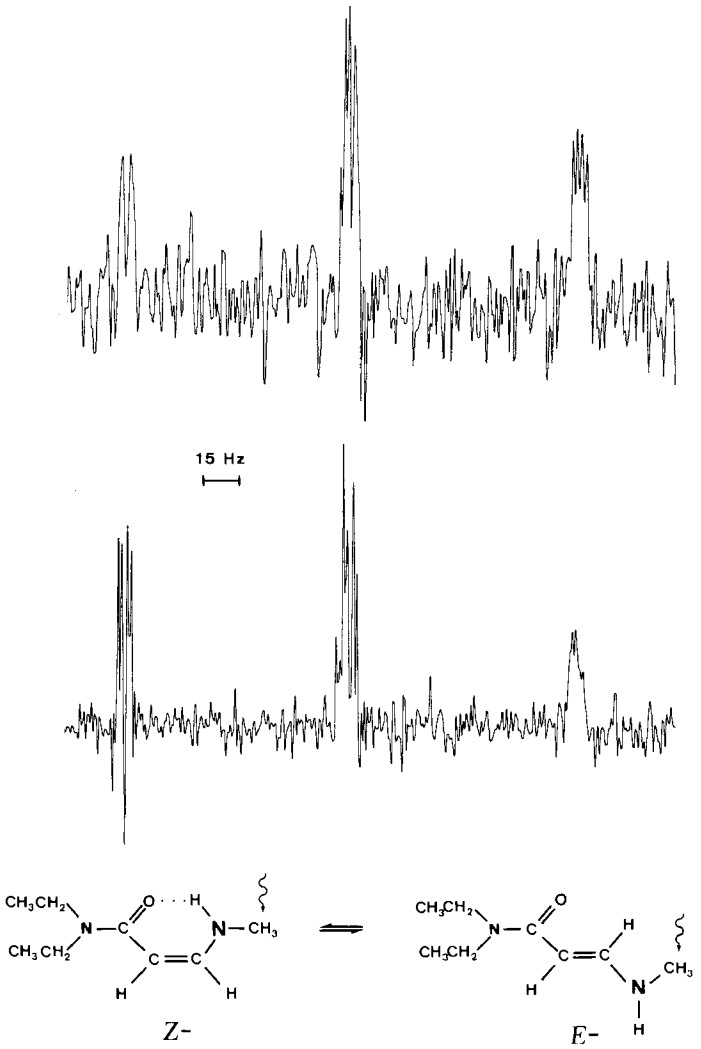


Fig. 2. *^{15}N-NMR proton-coupled INEPT spectra of the enamine N-atom in a mixture of (*E*)/(*Z*)-isomers of* **30** (3.3 M solution in C_6D_6) *under conditions of selective low-power irradiation of the N–CH_3-group in the (*Z*)-isomer* (lower spectrum, $\delta(CH_3) = 2.70$ ppm) *and in the (*E*)-isomer* (upper spectrum, $\delta(CH_3) = 2.87$ ppm). Experimental conditions: spectral width 10,000 Hz, 0.8 s acquisition time, 5.6 ms delay time, 0.8 s pulse-sequence delay time, $\gamma H_2 = 20$ Hz, 5,000 and 1,000 transients in lower and upper spectrum, corresponding to measuring times of 2.2 h and 45 min, respectively.

In the unsubstituted secondary enaminones studied (*Z*, s-*cis*)-conformations predominate in cases where intramolecular H-bonding is involved [15]. In (*E*)-isomers the fast-exchange mixture of (*E*, s-*cis*)- and (*E*, s-*trans*)-conformations is usually observed [16], this fact being denoted in the tables by the symbol E_{av}, but (*E*, s-*cis*)-conformations prevail when bulky alkyl substituents are attached to carbonyl [17] leading ultimately to a predominance of the (*E*, s-*cis*)-form with a *tert*-butyl substituent (*e.g.*, **21**).

The nonplanar character of (*E*, s-*trans*)-conformations and the conformational assignment of three ^{15}N-resonances appearing in secondary enaminones in the limit of slow rotation about the C(1)–C(2) bond have recently been described [9]. The (*E*)-isomers of C(2)-alkyl substituted enaminones exhibit a mixture of conformers [14]; both of them may suffer from steric repulsions which can be the cause of low-frequency shifts in the ^{15}N-resonance as compared with C(2)-unsubstituted derivatives [11]. The same conclusions can be applied to the composition found in enamino-esters or amides as recently confirmed by the studies of electronic spectra of the latter derivatives [18].

2.2. *Influence of Intra- and Intermolecular Environment on N-Shielding.* Enamines have been subject of a few ^{15}N-NMR studies [10] [19] [20] and their parameters reviewed in recent accounts [3] [4] on ^{15}N-NMR spectroscopy. The present study of chemical shift data for over 30 activated enamines, many of them as (*E*/*Z*)-isomer pairs detectable on the NMR time scale, supplies new information concerning the influence exerted on N-shielding by *N*-alkyl substitution, H-bonding or long-range effects from the stereochemical and electronic character of substituents at C(2).

The data presented in *Table 5* illustrate three important effects on N-shielding in primary, secondary and tertiary activated enamines, *i.e.*, increasing $N-CH_3$-substitution, change of configuration and H-bonding. While the first two effects are given explicitly as $\Delta\delta^{NRR'}_{NH_2}$- and $\Delta\delta^{E}_{Z}$-values, the latter phenomenon is underlying both former effects. It is easily seen that CH_3-substitution in primary enamines results in a high-frequency shift in both isomers but it is twice as large and opposite in direction when going from secondary to tertiary amine derivatives. Although there is still no ready explanation for the α-substituent effect in ^{15}N-NMR spectroscopy [3] [4], the support to qualitatively account for possible contributions in the observed effects is supplied by the data reported for structurally related amides. It was found in ^{14}N-NMR spectra of primary and secondary amides studied in $CHCl_3$-solutions [21] that CH_3-substitution causes a high-frequency shift in the sequence primary → secondary, but the opposite effect was recently observed in the same compounds studied as neat liquids in ^{15}N-NMR spectra [13] [22] [23]. Strong intermolecular association of an H-bond type is usually postulated in several recent studies of amides bearing N–H protons [22] [24] [25]. With respect to that *ca.* 10-ppm low-frequency shifts were found when diluting various amides in H_2O [22] indicating that H-bond formation results in shifts to higher

Table 5. *The Effects of* N–CH_3*-substitution* ($\Delta\delta^{NRR'}_{NH_2}$ [ppm]) *and Change of Configuration* ($\Delta\delta^{E}_{Z}$ [ppm]) *on N-Shielding in Enamines*[a])

$\Delta\delta^{E}_{Z}$[b])	$\Delta\delta^{NHCH_3}_{NH_2}$ (*Z*)	$\Delta\delta^{NHCH_3}_{NH_2}$ (*E*)	Structural change	$\Delta\delta^{E}_{Z}$[c])	$\Delta\delta^{N(CH_3)_2}_{NHCH_3}$	Structural change
−10.4	+3.2	+4.0	(**1** → **8**; C_6D_6)	− 9.6	−7.6	(**8** → **19**; C_6D_6)
−10.3	+1.4	+1.7	(**2** → **9**; C_4D_8O)	− 8.4	−8.8	(**10** → **21**; C_6D_6)
−10.2	+3.3	+5.1	(**3** → **10**; C_6D_6)	−11.6	−8.2	(**14** → **24**; $CDCl_2 \rightarrow C_6D_6$)
	+5.0		(**6** → **16**; $CDCl_3$)	−11.6	−9.5	(**14** → **23**; $CDCl_2 \rightarrow C_6D_6$)
				− 4.3	−6.4	(**30** → **28**; C_6D_6)
				− 4.1	−5.8	(**31** → **28**; C_6D_6)

[a]) All values are in ppm (± 0.1); positive sign denotes deshielding. The compound numbers and solvent change are indicated in brackets.

[b]) Values refer to the change of configuration in the primary enamines **1**, **2** and **3**, respectively.

[c]) Values refer to the change of configuration in secondary enamines.

frequencies. On the other hand, the structural change leading to decreased ability to form H-bonds, for example N–CH_3-substitution, should contain in its spectral effect a contribution similar to that produced by dilution. In view of these results deshielding effects on N–CH_3-substitution in primary enamines originate from at least three counterbalancing factors, *i.e.*, the 'true' CH_3-substitution effect which can be reasonably assumed to cause deshielding, the change in ability to form an H-bond and, in addition, a possible contribution from the change of N-hybridization. Solvent effects and H-bonding are likely to dominate the observed $\Delta\delta_{NH_2}^{NRR'}$-values since the smallest positive effects in both isomers were found for compounds **2** and **9** studied in a more polar solvent (THF) in highly concentrated solutions (*ca.* 9 M, *Table 5*). Furthermore, consecutive N–CH_3-substitution leading to tertiary enamines *(Table 5)* results, on average, in a 7.7-ppm low-frequency shift in (*E*)-isomers, apparently reflecting the lack of association of tertiary enamines with respect to secondary ones. In addition, diminution of the intrinsic N-alkyl substitution effect on multiple substitution can be assumed similarly to what is observed in the ^{13}C-resonance.

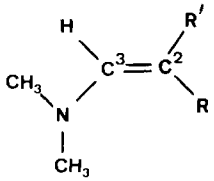
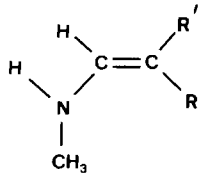
The (*Z*) → (*E*)-isomerization *(Table 5)* results in most cases in 10-ppm low-frequency shifts and shows solvent dependence as described recently [9]. Although the changes in geometry and different ability of the lone-pair delocalization in both isomers can certainly be taken into account, again breaking of the intramolecular H-bond in the (*Z*)-isomer may be considered as the dominant shielding contribution. This view is supported by the fact that a much weaker H-bond in (*Z*)-isomers of the enaminoamides **30** and **31**, with respect to the ones formed in enamino-ketones as evidenced by the low-frequency shift of the N–H proton by *ca.* 1.5 ppm, in **30** *vs.* **7**, **8**, results in a smaller shielding effect (*ca.* 4 ppm) induced by (*Z*) → (*E*)-isomerization in the ^{15}N-resonance.

High sensitivity of the N-shielding to the degree of N-lone-pair delocalization along the amide bond has been postulated [21] [23] [26] [27] and δ (N)-values were correlated with activation energies of rotation about the C–N bond [3] [23]. In addition, steric effects of bulky N-substituents were considered to be involved [28]. Our present results show that the lone-pair delocalization effect can be very large in similar systems with extended conjugation even when electron-withdrawing groups are attached to C(2). These effects are summarized in *Table 6*.

Replacement of the C(2)–CH_3-group by electron-withdrawing substituents produces high-frequency shifts spanning *ca.* 50 ppm within the −325 to −270 ppm region for mono- and dialkyl-substituted N-atoms. Some intuitively predicted dependences are clearly seen. Strong electron acceptors like NO_2, CHO when coplanar with the C=C bond (**18**) [17] [14] or double substitution by carbonyl groups in **16** result in strongest deshielding effects. On the other hand, substitution with the weaker electron-withdrawing ester or amide group in **25**, **28** and **29** gives high-frequency shifts *ca.* 17 ppm smaller than in the aldehyde **18**.

Long-range conformational effects on N-shielding, revealed recently in this classes of compounds by variable temperature [9] and protonation [11] studies for C(2), C(3)-unsubstituted and C(2)-alkyl substituted enaminones, respectively, are confirmed here by a larger data base. The low-frequency shift of the (*E*, s-*trans*)-isomer (**7**, *Table 2*), explained in terms of non-planarity of the double bonds leading to reduced conjugation [9], is also reflected in a series of enaminones with increasing substituent volume at

Table 6. *Effect of C(2)-Substituents* (R') *on N-Shielding*[a]) ($\Delta\delta^{R'}_{CH_3}$) *in Enamines*

Substitution $CH_3 \rightarrow R'$		Compound R	Compound R'	Reference shielding	$\Delta\delta^{R'}_{CH_3}$
		H	CH_3	−350.8[b])	[c])
		CH_3	CH_3		−0.4[d])
		H	C_6H_5		+26.8[b])
	18	H	HCO		+55.2
		H	CH_3CO		+52.3[b])
	19	H	C_3H_7CO		+48.3
	21	H	t-C_4H_9CO		+47.1
	23	CH_3	CH_3CO		+38.2
	24	CH_3	C_2H_5CO		+39.5
	28	H	$(CH_3)_2NCO$		+38.0
	29	H	t-C_4H_9NHCO		+36.6
		H	NO_2		+66.6[e])
		H	CH_3	−343.1	[f])
	16	CH_3CO	CH_3CO		+75.1
	25	H	C_2H_5OCO		+38.1
	26	CH_3	C_2H_5OCO		+33.0
	30	H	$(C_2H_5)_2NCO$		+36.7
	31	H	$(i\text{-}C_3H_7)_2NCO$		+36.1

[a]) All values are in ppm; positive sign denotes deshielding.
[b]) From [3], p. 119 and [19]; neat liquid.
[c]) The values below refer to the (*E*)-isomers.
[d]) From [3], p. 119 and [10].
[e]) Present work; $\delta(^{15}N) = -284.2$ ppm from external CH_3NO_2 in 2.3 M solution in $CDCl_3$.
[f]) As in *c;* the reference shielding was calculated using the mean value of $\Delta\delta^{N(CH_3)2}_{NHCH_3}$ from *Table 5* as the increment for N–CH_3-substitution in the (*E*)-isomer and reference shielding −350.8 ppm.

the carbonyl group (H, CH_3, C_3H_7, t-C_4H_9, *Table 6*). Thus, a larger high-frequency shift in the case of the planar (*E*, s-*trans*)-conformation of **18** [14] is observed than in the case of ketones which contain non-planar (*E*, s-*trans*)-isomer and (*E*, s-*cis*)-isomer, both of them contributing to the low-frequency shift (*cf.* **7** in *Table 2*).

The alkyl substitution in C(2)-position leading to steric repulsions in both (*E*)-forms [11] (see text above) is reflected by low-frequency shifts seen in several pairs where the C(2)-unsubstituted compound is compared with the C(2)-alkyl substituted one, *e.g.*, **8** and **14** in *Table 2;* **19** and **23**, **24** *(Table 3);* as well as **25** and **26** in *Table 4*. The reason for the low-frequency shift is looked upon as a breaking of conjugation between the double bonds as a result of steric repulsion between the alkyl groups on C(2) and at the carbonyl group in the (*E*, s-*cis*)-conformer or between the alkyl substituent at the carbonyl group and C(3)–H in the (*E*, s-*trans*)-conformer [11]. Alternatively, pushing out of the plane of conjugation of the $N(CH_3)_2$-group can be considered, however, this is less likely in view of the ^{15}N chemical shifts for **14** and **15** and **22–24** which are characteristic for enaminones but not for amines, and because of the observation of iminium salts for **22–24** in ^{15}N-NMR spectra [11] expected for enamines upon C(2)-protonation.

The solvent effect, even in non-polar solvents used throughout the work, has considerable influence on absolute values of chemical shifts and trends are seen in agreement

with theoretical considerations [29]. However, since both intra- and intermolecular H-bonds are involved and concentrations are relatively high, detailed dilution studies are required to allow a quantitative discussion of the solvent dependence of ^{15}N chemical shifts.

2.3. *$^{15}N,H$ Spin Coupling Constants in Activated Enamines.* Information concerning $^{15}N,H$ spin coupling constants in enamines has been acquired up to now from studies on ^{15}N-labelled compounds [3]. Some values of one-bond and long-range spin-coupling constants are available for primary [30] and secondary enamines [31–33] bearing *N*-alkyl substituents, and for secondary ones with *N*-phenyl substituents [3] [34] [35].

The significance of one-bond $^{15}N,H$-coupling constants rests upon their use as a probe for monitoring intermolecular exchange [36] [37], studies of H-bonding [3] [4] [31] [33] [38] and interaction with solvents of different properties [29] [38]. With respect to these problems the study of ^{15}N-labelled enaminones [30] [31] [39] and dynamic ^1H-NMR results on enaminones [15] revealed the stability of the N–H proton towards exchange in the temperature range between −20° and +40° in aprotic solvents. The exchange of the N–H proton in enaminones is greatly accelerated in basic or acidic conditions and in protic solvents [15].

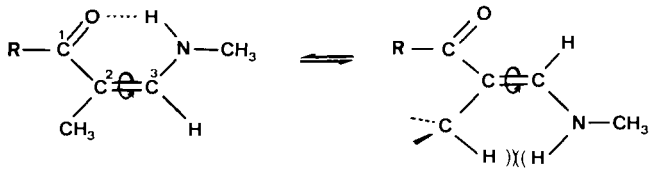
Several structural relationships concerning one-bond N,H spin couplings can be discerned in this class of compounds by comparison with structurally related amides. Thus, it is evident from *Tables 1, 2* and *4* that $^1J(N,H)$ in the studied enamines range from 88 to 95 Hz and fall within the range observed for amides [3] [4] [13] [40] despite the fact that the bond order of the amide bond is much higher [41] than the C(3)–N bond in enaminones as judged from very different activation parameters to the hindered rotation, and ^{15}N chemical shifts [10] [19] [23]. Since planar sp^2-hybridized geometry is assumed in both cases, this factor seems to be of major importance, with the effective nuclear charge on the N-atom playing a minor role.

Another feature which relates both classes of compounds, concerns a similar orientational dependence of $^1J(N,H)$ as established in amides [3] [13] [40]. It is universally observed that coupling to the proton in *cis*-position to a double bond (*i.e.*, C=O, in amides), corresponding to the s-*trans*-isomer in enaminones (see *Scheme 1*) is smaller than coupling to the proton in *trans*-position. This dependence is observed in our work in all cases where (*E*)/(*Z*)-pairs are available of C(2)-alkyl-unsubstituted derivatives.

In contrast to all C(2)-unsubstituted (*E*)/(*Z*)-pairs in the three investigated cases **14**, **15** and **26** characterized by C(2)-alkyl substitution, one-bond coupling is smaller in the (*E*)-isomer despite the fact that in both (*E*)- and (*Z*)-isomers conformation at the C(3)–N bond is maintained *(cf. Scheme 2)*.

As a result of the isomerization process about the C(2)=C(3) bond, the entire H–C(3)–NH–CH_3 fragment is turned from a nearly strain free (*Z*)-isomer having attractive C=O · · · H–N interaction to the (*E*)-isomer where C–H ↔ H–N repulsive interactions, well-known in ^{13}C-NMR spectroscopy as the γ-compression effect, exist *(Scheme 2)*. This change results in a decrease of the $^1J(N,H)$-values in the (*E*)-isomer whereas the values found in the (*Z*)-isomer are similar to those in other internally H-bonded compounds (compare (*Z*, s-*cis*)-form of **14**, **15**, **26** with **1–4**, **8**, **9**, **25**, **30**, and **31**). Although there is no ready theoretical explanation for this behaviour, nevertheless the known dependence of one-bond $^{13}C,H$ spin couplings on internuclear angle bending [42] can be invoked, since several other trends observed in this class of compounds

Scheme 2



and in amides seem to support this view. It is known from ^{13}C-NMR studies that an increase of the internuclear angle C–^{13}C–H results in a decrease of one-bond ^{13}C,H spin coupling. Similarly, opening of the angle C(3)–N–H in the (*E*)-isomer *(Scheme 2)* due to steric repulsion may lead to a change in interorbital angles on the N-atom giving rise to the observed decrease in spin coupling. Not unexpectedly then, the same trend, *i.e.*, decrease of ^1J-values, is found with enlargement of *N*-alkyl substituents in **11**, **12**, **13**, **15** and **27**, where the ^1J(N,H)-values are smaller than in the same stereoisomers of corresponding *N*–CH_3-compounds, *e.g.*, in **8**, **9** and **10**. CH_3-substitution on the C(3)-atom results in further decrease in spin coupling, as observed in **11** *vs.* **13**. In view of the above results these changes can be attributed to sterically induced in-plane angle distortions within the fragment H–C(3)–N–CH_3 in the (*Z*)-isomer (see *Scheme 2*). Accordingly, the difference between N,H-couplings in (*E*)- and (*Z*)-isomers of C(2)-alkyl-unsubstituted compounds can be regarded as reflecting subtle changes in steric interactions localized around the N-atom in both stereochemical situations depicted in *Scheme 1*. In support of these considerations a systematic decrease of ^1J(N,H)-values is observed in sterically overcrowded *cis*-isomers of amides with increasing volume of *N*-alkyl substituents [13] [40], the dependence of the effect on angular distortion being reflected in INDO calculations [40]. Furthermore, the present data seem to indicate that the difference between spin coupling in both isomers does not originate from H-bonding of the N–H proton in the (*Z*, s-*cis*)-conformation. This is confirmed by the fact that ^1J(N,H)-values in (*Z*, s-*cis*)-conformations of **7**–**10**, **25**, **30**, and **31** are nearly the same (91.4 to 92.4 Hz) although the strength of intramolecular H-bonding is different in enamino-ketones, esters and amides (*cf.* discussion above). It is also interesting to note that no definite solvent dependence of one-bond spin coupling can be discerned, this surprising result [29] being in accord with the behaviour of N,H-coupling in amides [40].

The above features and the lack of sensitivity of ^1J(N,H)-values to long-range conformational effects in enaminones allow the conclusion that this parameter essentially reflects N-hybridization and subtle local geometrical distortions.

Few systematic studies of long-range n-bond N,H coupling in enaminones have been carried out so far [3], most of the theoretical approaches being directed towards correlation between ^3J(N,H)-values and dihedral angle φ in peptides [43–46] or stereospecific dependence of ^2J(N,H) on the lone-pair orientation [3] [47]. Since the present results are concerned with substituted alkenes it is worth to discuss long-range N,H-couplings in view of the structural dependences found for corresponding C,H-couplings which have already been thoroughly investigated for a wide range of mono, di- and tri-substituted alkenes [48–50].

In general, if reduced couplings ^nK(N,H) and ^nK(C,H) are compared, coupling interactions lead to much the same K-values for both nuclei, hence, observed ^2J- and ^3J-values for the N,H-system are nearly 2.5 times smaller. This can be exemplified by comparison of $^3J(CH_3,H)$ in (*Z*)-isomers of a α,β-unsaturated aldehydes [50] with ^3J(N,H) in the present work. The attachment of electronegative substituents (R–CO) at the terminal C-atom of the coupling pathway N–C(3)=C(2)–H is apparently responsible for the large $^3J^t/^3J^c$-ratio [50] which in the present work is of the order of 2.2 in cases where comparison of both couplings in (*Z*)/(*E*)-pairs was possible, as for example in **30**, **31**.

A stereospecific coupling constant $^3J^t(N,H) = 4.0 \pm 0.2$ Hz in the (*Z*)-isomers is a characteristic feature which can be used for structural assignments. The only exception was found in compounds **13** and **27** where CH_3-substitution at the C(3)-atom reduces the value of this coupling. The reason for this reduction may be found in the angle distortions discussed above for the effect of alkyl substitution at the C(3)-atom on one-bond N,H-coupling.

Another interesting feature of long-range two- and three-bond coupling with olefinic protons is a reversal of their magnitude in (*Z*)-isomers and (*E*)-isomers, respectively. Interestingly, the two couplings appear simultaneously only in benzene solution and in cases where a bulky substituent is attached to the terminal C-atom of a coupling pathway, *i.e.*, to the C(2)-atom as in **3**, **9**, **10**, **21**, **30**, and **31**. Clearly then, the solvent and long-range conformational effects have meaningful influence on a coupling mechanism. However, this appears to be true only for geminal coupling constants, since in all compounds studied in (*Z*)-form vicinal couplings are apparently independent of the solvent nature and concentration, or the kind of substituent at the carbonyl function (see *Tables 1, 2* and *4*). On the other hand, geminal couplings change in the range of 0.6 to 5.2 Hz and show a complex dependence on solvent (as in **18**, **19**, **22**) and stereochemical properties of substituents on the C(2)-atom. This may render them a valuable probe for structural elucidations of a local environment around the N-atom provided the sign can be determined in the experiment. Observed dependencies of the two-bond N,H-coupling may be taken as indicative that the charge distribution along the C(3)–N bond plays an essential role in the geminal-coupling pathway similarly to what is observed for geminal couplings in imines after lone-pair protonation [3] [47]. In support, results of earlier studies of enaminones can be cited which indicate that specific interaction of solvents with enaminones [14] and stereochemical properties of C(2)-substituents influence the charge distribution along the C(3)–N bond as reflected in $\Delta G^{\neq}$-values of hindered rotation about this bond [17].

In conclusion, it can be stated that unlike the one-bond coupling constant, long-range two- and three-bond N,H-coupling constants with olefinic protons not only reflect the local structural environment at the N-atom, but can also be used to characterize stereochemical features of the whole molecule. In the case of geminal couplings, it may prove useful in characterizing the electronic properties of the C(3)–N bond.

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Experimental. – The ^{15}N-NMR spectra were run on a *Varian XL-200* spectrometer, operating at 20.28-MHz frequency, at 24° using a 10-mm broadband probe. The chemical shifts were referenced against external CH_3NO_2 contained in a capillary, and no susceptibility correction was applied. The pulse sequence INEPT with refocusing pulses was utilized to obtain fully proton-decoupled spectra with the following typical parameters, a spectral width of 10,000 Hz, pulse delay time $\tau = 2.8$ ms for primary and secondary N-atoms, or $\tau = 83$ ms for tertiary N-atoms, 0.6 s acquisition time and a pulse sequence delay of 1 s. Under these conditions, and with sample concentrations given in the *Tables*, less than ½ h was required to get decoupled N-resonances with a sufficient signal/noise ratio. Proton-coupled spectra were typically obtained as non-refocused multiplets (see *Fig. 1*) using 2000-Hz sweep width, the same pulse conditions as above, no decoupling power for primary N-atoms and selective low-power irradiation of *N*-alkyl groups in the case of secondary and tertiary enamines. The irradiating power γH_2 was typically of the order of 30 to 80 Hz. In all cases cited in *Tables 2–4*, the coupling constants are corrected for reduction using *Pachler's* equation [51] with the assumption that $\gamma H_2 \gg 1/2\,|J_o - J_r|$. The error in ^1J(N,H)-values is ± 0.5 Hz and ± 0.2 Hz for long-range coupling constants.

Primary, secondary and tertiary enaminones were prepared as described earlier [17]. The enamino-esters **25**, **26** were obtained from the appropriate esters in a *Claisen* condensation below r.t. with excess of HCOOEt. The ester **27** was prepared by condensation of the β-ketoester and amine in presence of TsOH. The preparation of enamino-amides was described in [18].

N–H exchange due to moisture or acid was avoided by fresh distillation of the liquid samples and confirmed by the observation of well-resolved couplings of the N–H proton to N-alkyl and olefinic protons on a low-frequency spectrometer (90 MHz), since at 200 MHz the signals of the (*E*)-isomer are, in several cases, broadened due to an intermediate rate of rotation about the C(3)–N bond in secondary enaminones. In some cases, drying of the solution over Na_2SO_4 was sufficient to slow down the exchange of the N–H-proton, this being the critical condition for obtaining an INEPT spectrum using this proton.

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