Deuterium Isotope Effects on ^{13}C and ^{15}N Nuclear Shielding in Intramolecularly Hydrogen-Bonded Compounds. Investigation of Enamine Derivatives

Poul Erik Hansen,[a] Robert Kawecki,[b] Adam Krowczynski[b] and Lech Kozerski[b]

[a]Institute for Life Sciences and Chemistry, University of Roskilde, DK-4000 Roskilde, Denmark and [b]Institute of Organic Chemistry, Polish Academy of Sciences, PL-00-961 Warszawa, Kasprazaka 44, Poland

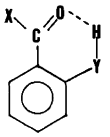
Hansen, P. E., Kawecki, R., Krowczynski, A. and Kozerski, L., 1990. Deuterium Isotope Effects on ^{13}C and ^{15}N Nuclear Shielding in Intramolecularly Hydrogen-Bonded Compounds. Investigation of Enamine Derivatives. – Acta Chemica Scand. 44: 826–832.

Deuterium isotope effects on ^{13}C and ^{15}N nuclear shielding have been investigated in enaminones, enamine esters and nitroenamines. These compounds often exist as a mixture of *E* and *Z* isomers. Deuterium substitution at nitrogen leads to large, two-bond isotope effects at C^1 and to one-bond isotope effects at nitrogen in the *Z* isomer. $^2\Delta C(ND)$ is always larger for the *Z* than for the *E* isomer. For the latter, the change in $^2\Delta C(ND)$ is linked to a change in the C^1–N bond order. The larger isotope effect for the *Z* isomer is caused predominantly by hydrogen bonding. In the *Z* isomer isotope effects can also be observed at the carbonyl carbon. The increase in the magnitude of the isotope effects in the *Z* isomer is only observed for the carbons within the six-membered ring formed by hydrogen bonding. The one-bond isotope effects on nitrogen are larger for the *Z* than for the *E* isomer and thus are again linked to intramolecular hydrogen bonding.

It is also shown that a linear relationship exists between $^2\Delta C(ND)$ and δ_H of NH for both *E* and *Z* isomers.

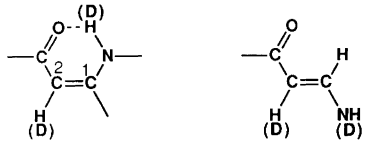
Line-width variations of ^{15}N resonances of ND species are observed. The *Z* isomers show the narrower resonances as a result of hydrogen bonding.

Hydrogen bonding is a structure-determining feature in both organic and biological molecules. Isotope effects on nuclear shielding* have been studied in model systems of type **1AA**, and it has emerged that deuterium isotope effects over two bonds are good indicators of the presence of hydrogen bonds and the strength of these.[1–6] In nitrogen-containing systems isotope effects on ^{15}N nuclear shielding have been studied only infrequently.[7–10] However, isotope effects over one bond, $^1\Delta N(D)$, may be useful as a way of determining hydrogen bonding.[1,9] This feature is particularly important for biomolecules.



1AA

Scheme 1. Intramolecularly hydrogen-bonded aromatic compounds. Y is either O or N, X is either H, C, O or N.

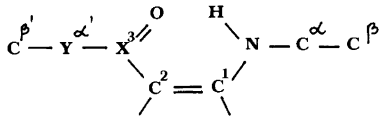


Scheme 2. Isotopomers of deuteriated *E* and *Z* enamines.

Enamines exist in both *E* and *Z* forms (Scheme 2). The enamines studied in this paper include *N*-monosubstituted enaminones, enamine esters and nitro derivatives (Scheme 3). This series of compounds provides a unique opportunity to investigate $^2\Delta C(D)$ and $^1\Delta N(D)$ as a function of hydrogen-bond strength and also to investigate the correlation of δNH vs. two-bond isotope effects. The enamines have been investigated both from a synthetic and an NMR point of view.[7,11–23] ^1H,[13,14,18] ^{13}C[12,15,16] and ^{15}N[7,11,19] NMR spectra have been studied.

Isotope effects over many bonds have been reported in a number of cases.[1–6] One example is the carbonyl carbon of compounds of type **1AA** with deuterium substitution at Y = N, but more distant isotope effects are also observed in conjugated systems.[6] Isotope effects on nuclear shielding are vibrational in origin.[24,26] However, it is not known in detail how these vibrations determine the size of isotope

* Definition. The isotope effects on nuclear shielding are defined at follows: $^n\Delta X^i = \delta X^i(H) - \delta X^i(D)$, where *n* is the number of intervening bonds between the deuterium and the observed nucleus, X^i. A slightly extended version, $^n\Delta X^i(ND)$ or $^n\Delta X^i(CD)$, is used to make it easier to distinguish between deuteriation at nitrogen and at carbon. In this way one can distinguish between, e.g., the two-bond isotope effects at C^1 caused by deuteriation at nitrogen, $^2\Delta C^1(ND)$ and deuteriation at C^2, $^2\Delta C^1(CD)$.



X	Y	
C	C	1–8
C	O	9–11
C	N	12
N	O	13–14
S	C	17–20

Scheme 3. General structure for the enamines studied. *Z* form shown. Many of the compounds are also found in solution as *E* isomers (see Tables 1–3).

effects over more than one bond.[26] The enamines are ideal for investigating such effects. C^1 is part of the conjugated system and part of the six-membered ring, whereas C^α is not (Scheme 2). The ^1H chemical shift of the hydrogen-bond proton has for a long time been used as a measure of the presence of hydrogen bonds.[27] This parameter has a number of disadvantages,[1] but may be used advantageously in series of closely related compounds. A correlation between δ_H and the hydrogen-bond enthalpy has been reported.[27]

Deuteration of linear enaminones leads to deuterium incorporation both at the NH and the C^2 positions as demonstrated in Scheme 2. The latter type provides information about isotope effects, $^1\Delta C(D)$ and $^2\Delta C(D)$, as well as the sparsely investigated $^3\Delta N(CD)$.

Observation of ^{15}N resonances when the nitrogen is deuteriated may be difficult, since the line-widths of the ^{15}N resonances depend on the size of the scalar coupling and the quadrupolar coupling constant of deuterium.[28] The latter depends on hydrogen bonding,[29,30] which may influence the line-width.

Experimental and assignments

Experimental. The liquid enamine esters and enaminones were distilled under vacuum. The deuteriation was accomplished by dissolution of the compounds in an excess of CH_3OD followed by evaporation after some time. The procedure was repeated several times in order to achieve a suitable degree of deuteriation depending on the resonance patterns observed. Owing to slow exchange of the NH and C^2H protons on the NMR timescale it was possible to observe simultaneously all isotopomers (Scheme 2) in the solution.

^1H and ^{13}C NMR spectral data were obtained from $CDCl_3$ solutions (ca. 1 % w/v) with tetramethylsilane as an internal reference on a Bruker AC-250 NMR spectrometer

Table 1. Deuterium isotope effects $^n\Delta C,H(XD)$ (ppm) in the ^1H, ^{13}C and ^{15}N NMR spectra of enaminones and other spectral parameters.[a]

No.	Compound	Isomer	X[a]	$^2\Delta C^1$	$^{1,3}\Delta C^{2\,b}$	$^n\Delta CO$	$^n\Delta C^\beta$	$^2\Delta C^\alpha$	$^3\Delta C^\beta$	$^3\Delta C^1H$	$^4\Delta C^2H$	$^{1,3}\Delta N$	δ(NH)	$^3J(C^1H,NH)$
			N	0.241	0.053	0.035	−0.035	0.106		0.0151	0.0030			
1	$CH_3^{\alpha'}COC^2H{=}C^1HNHC^\alpha(CH_3^\beta)_3$	*Z*-s-*Z*[c]										1.25[d]	10.15	13.2
			C^2	0.082	[e]	−0.035	0.035			0.0004				
			N	0.235	0.054	0.043		0.116		0.0121	0.0036			
2	$(CH_3)_2CHCOCH{=}CHNHC(CH_3)_3$	*Z*-s-*Z*										1.30[d]	10.20	13.2
			C^2	0.077	0.291	0				0.0011				
			N	0.244	0.049	0.052		0.159	0.030	0.0119	0.0006			
3	$(CH_3)_2CHCOCH{=}CHNHC_6H_{11}$[f]	*Z*-s-*Z*										1.28[d]	9.90	12.9
			C^2	0.087	[e]	0				0.0010				
			N	0.244	0.039	0.034		0.161				1.18		
4	$(CH_3)_3CCOCH{=}CHNHCH_3$	*Z*-s-*Z*											9.70	12.5
			C^2	0.069	0.248	0				0.0016		0.12		
		E										0.61[d]	7.30	
		Z-s-*Z*	N	0.272	0.039	0.058	0.036	0.159		0.0243		1.33	9.70	12.2
5	$CH_3CH_2COC(CH_3){=}CHNHCH_2CH_3$													
		E	N	0.104	0.061	0		0.143		0.0045		0.84	4.45	13.3
			N	0.259	0.069	0.052	−0.035	0.104				1.44		
6	$CH_3COCH{=}C(CH_3)NHCH(CH_3)_2$	*Z*-s-*Z*											10.80	
			C^2	0.069	0.312	−0.052[g]	0.052					0.11		
		Z				0.052	−0.035							
7	$CH_3COC(COCH_3){=}CHNHC_6H_5$		N	0.324	0			0.140	0.093	0.0131			12.75	12.5
		E				0								
8	$C_6H_5COCH{=}CHN(CH_3)_2$	*E*	C^2	0.058	0.252	−0.036				0.0061				

[a]The ^{13}C NMR spectra were run in 5 mm sample tubes in $CDCl_3$ solution with internal TMS; positive $^n\Delta C,H(XD)$ shift denotes low frequency shift of a given resonance upon deuteriation. X denotes the nucleus at which deuteriation occurs. [b]$^3\Delta C^2$ is observed when deuteriation occurs at nitrogen, $^1\Delta C^2$ is observed when deuteriation occurs at C^2. [c]Denotes the configuration as seen in Scheme 2. [d]Due to low sensitivity only the total effect of deuteriation at C^2 and N centers can be measured. [e]Not observed owing to low sensitivity. [f]Cyclohexyl. [g]Sign assumed.

Table 2. Deuterium isotope effects $^{n}\Delta C,H(XD)$ (ppm) in the ^{1}H, ^{13}C and ^{15}N spectra of enamino esters, and related spectral parameters.[a]

No.	Compound	Isomer	X	$^{2}\Delta C^{1}$	$^{n}\Delta C^{2}$	$^{n}\Delta CO$	$^{3}\Delta C^{1}CH_{3}$	$^{2}\Delta C^{\alpha}$	$^{3}\Delta C^{1}H$	$^{1,3}\Delta N$	δ(NH)	$^{3}J(C^{1}H,NH)$
9	$C_2H_5OC\overset{2}{O}C(CH_3)=C^{1}HNHCH_3^{\alpha}$	*Z*	N	0.183	[c]	0.035		0.139	0.0086	0.93[b]	7.30	12.77
		E	N	0.095	0.052			0.156	0.0063	0.69	4.60	13.0
10	$C_2H_5OCOCH=C(CH_3)NHCH_3$	*Z*	N	0.165	0.035	0.024	0.087*	0.132		0.97	8.20	
		Z	C^{2}	0.075	0.315	−0.038	0.052*			0.12		
		E	N	0.087	0.056	[c]	0.069*	0.153			5.20	
		E	C^{2}	0.052	[d]	[c]	0.067*					
11	$C_2H_5OCOCH=C(CH_3)NHCH_2C_6H_5$	*Z*	N	0.156	0	0.010	0.069	0.121			9.00	
			C^{2}	0.069	0.261	−0.034	0.035					
12	$(CH_3)_3C^{\alpha}NHCO\overset{2}{C}H=C^{1}HN(CH_3)_2$	*E*	N	0	0.052	0.052[e]		0.121(α′)			5.10	
			C^{2}	0.057	0.278	[c]						

[a]Spectra were measured in $CDCl_3$ solution; a positive value of $^{n}\Delta C,H$ denotes a shift to lower frequency of a given resonance; values marked with asterisk can be interchanged between the *E* and *Z* isomers. [b]Lowering of the temperature leads to a collapse of the triplet structure. [c]Broad signal. [d]Ambiguity in assignment and determination. [e]CON.

Table 3. Deuterium isotope effects $^{n}\Delta C,H(XD)$ (ppm) in ^{1}H and ^{13}C NMR spectra of 2-nitroenamines and their derivatives.

No.	compound	Isomer	X	$^{2}\Delta C^{1}$	$^{3}\Delta C^{2}$	$^{2}\Delta C^{\alpha}$	$^{3}\Delta C^{\beta}$	$^{3}\Delta C^{1}H$	δ(XH)	$^{3}J(C^{1}H,NH)$
13	$NO_2C\overset{2}{(}CH_3)=C^{1}HNH(2'-C_5H_4N)$[a]	*Z*	N	0.253	0	0.096	0.078		10.80	12.1
		E	N	0.138	0	0.115	0.036	0.0035	8.50	13.0
14	$NO_2C\overset{2}{(}CH_3)=C^{1}HNH(2'-C_4H_3N_2)$[a]	*Z*	N	0.215	0	0.076		0.0120	10.70	12.6
		E	N	0.137	0.039	0.091		0.0086	8.7	13.7
15	$HONC\overset{2}{(}CH_3)=C^{1}ONH(2'-C_5H_4N)$[b]	*Z*	O[c]		0.071[d]				13.6	
			N	0.058	0	0.065	0.065		9.4	
16	$HONC\overset{2}{(}CH_3)=C^{1}ONH[2'-(6'-CH_3C_5H_3N)]$[b]	*Z*	O[c]						13.7	
			N	0.070	0	0.058	0.061		9.4	

[a]Measured in saturated dioxane-d_8 solution. [b]Measured in chloroform-*d* solution. [c]Effect of the order of the line-width of the signal. [d]Assignment of the origin of ND or OD effect is ambiguous.

used and routine parameters for acquisition and processing of the the free induction decays were employed as in Ref. 3. The ^{15}N spectra were usually acquired on ca. 60 % v/v solutions in C_6D_6 using 10 mm sample tubes, 25° flip angles, 10 s delays between pulses, 1 s acquisition time and a digital resolution of 1 Hz/point. Twenty hours were required to achieve a sufficient *S/N* ratio for the ND isotopomers. The NH isotopomers, serving as references, appeared more readily. Typical ^{15}N spectra are shown in Figs. 1 and 2. The spectra of species **1** and **2** were recorded on non-spinning samples, using 15° flip angles and 25 s delays between scans to deal effectively with the problem of long relaxation times in these concentrated and non-viscous samples.

The identification of the *E* and *Z* isomers of the nitroenamines, enamine esters and enaminones was easily achieved using NH chemical shifts, which are observed at much higher frequencies for the *Z* isomers than for the *E* isomers (Tables 1–3). Furthermore, for carbonyl compounds the $\delta C^{1}H$ is always found at higher frequences (7.5–7.8 ppm) for the *E* as than for the *Z* form (6.4–6.8 ppm); similarly for 2-nitroenamines, 9.4 and 8.5 ppm, respectively.[17,18]

The appearance of the ^{13}C and ^{15}N spectra is determined by the number of exchangeable protons in the molecule. For the linear compounds (no substituents at C-2) up to four different isotopomers are possible for each isomer leading to a maximum of eight resonances per nucleus as demonstrated in Scheme 2. The resonances for each isotopomer vary in intensity due to their different exchange rates of NH and $C^{2}H$ protons during the deuteriation in CH_3OD.

Results. The two-bond isotope effect is a key parameter. $^{2}\Delta C^{1}(ND)$ of the *Z* isomer is larger than that observed for the *E* isomer of the same compound. A variation is seen for different acceptors (C=O, ROOC and NO_2) with nitro and ketone acceptors giving the largest values (Tables 1–3). The two-bond isotope effects, $^{2}\Delta C^{\alpha}(ND)$, for the two isomers are comparable in magnitude. The nitro derivatives show

the smallest $^2\Delta C^{\alpha}(ND)$ values and the order of two-bond isotope effects is possibly different from that found for $^2\Delta C^1(ND)$. For *Z* isomers $^2\Delta C^1(ND)$ is larger than $^2\Delta C^{\alpha}(ND)$. Isotope effects over three bonds, $^3\Delta C^{\beta}(ND)$, are of the order of 0.03 ppm (Tables 1 and 2) except when the substituent is a phenyl ring as for species **7**, **11** and **13** (Tables 1–3). The larger values found in these compounds are in good agreement with observations for aromatic amines and amides.[31]

Isotope effects, $^n\Delta C{=}O(ND)$, are observed at the C=O carbon of *Z* isomers of the esters and the ketones, but not for the *E* isomers (Tables 1–3). The magnitude of this effect is quite large considering the number of intervening bonds. Similar effects have been observed in aromatic compounds of type **1AA**.[1–5] In particular, the *o*-hydroxy esters show large effects[3] as compared with the enamines esters (Table 2). For alkyl β-thioxocarboxylates[32] the two-bond isotope effect reflects the amount of rotamer that is actually hydrogen bonded and a proportionality is found between $^n\Delta C{=}O(ND)$ and $^2\Delta C^1(ND)$. The correlation is as good for enamines and aromatic compounds.

Some very interesting long-range isotope effects are observed for the β′ carbon, $^{n+1}\Delta C^{\beta'}(ND)$. These effects are negative and of the order of −0.03 ppm. They are only observed in those compounds where the substituent at X is either a methyl or an ethyl group (items **1**, **5** and **6**, Table 1).

Deuteriation of the linear compounds **1–4**, **6**, **8**, **10**, **11** and **12** leads to deuterium incorporation at both the NH and the C^2 position. Several isotope effects can be measured. $^1\Delta C^2(D)$ isotope effects vary considerably (0.248–0.315 ppm) (Tables 1–3). The variation in the one-bond isotope effect is ascribed by Günther *et al.*[33] to a change in hybridization. The values obtained in this study can be compared with values obtained from ethylene (0.273 ppm) and styrenes (0.283, 0.256 and 0.325 ppm for the *trans, cis* and *gem* isotopomers).[33]

The two-bond isotope effects at the carbonyl carbon, $^2\Delta C{=}O(CD)$, are observed in species **1**, **5**, **10** and **11** (Tables 1 and 2). They are negative like those found for acetone[34] and other ketones, esters and aldehydes.[35,36] It appears that these isotope effects are only observed in the esters and the methyl enaminones together with the *E* isomer of **8**.

The ^{15}N resonance of the ND species is a triplet, the center of which is displaced from the NH resonance by the isotope effect, $^1\Delta N(D)$. This is illustrated in Figs. 1 and 2. The one-bond isotope effects are all seen to be positive and larger for the *Z* than for the *E* isomers (Tables 1 and 2). Observation of the ^{15}N resonances of the deuteriated *E* isomers proved to be difficult not only because this is usually the minor isomer in the isomer mixture but also because these resonances in some cases were broad. The ^{15}N resonances of the deuteriated *Z* isomer show only slightly broader resonances than the resonances belonging to the protio isotopomer as seen in Fig. 2. However, lowering of the temperature leads to broad singlets for isomers

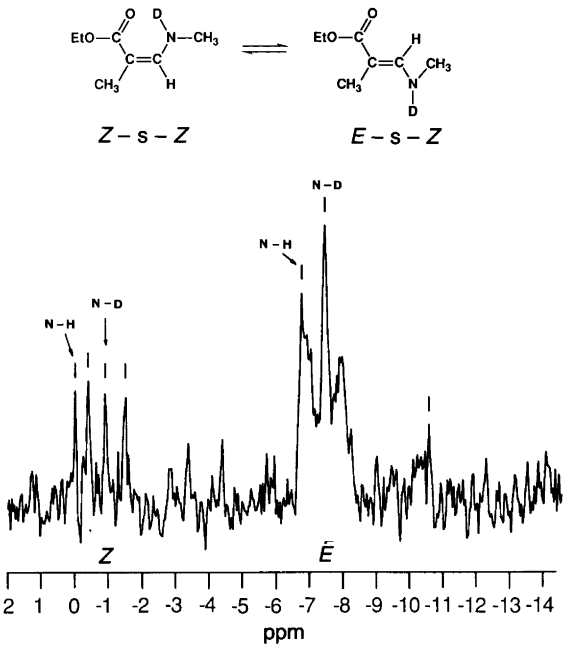


Fig. 1. ^{15}N NMR spectrum of **9** at 300 K (45 % v/v in C_6D_6). Signals at the higher frequency are assigned to the *Z* isomer.

5–9. The one-bond N–D coupling constants were not measured very accurately, but are of the order of $^1J(N,H)/6.5$.[22]

Deuteriation at C^2 makes it possible to measure an isotope effect at nitrogen over three bonds, $^3\Delta N(CD)$. These isotope effects appeared to be quite large, 0.1 ppm (items **4**, **6** and **10** of Tables 1 and 2). Large values for long-range isotope effects on nitrogen were predicted from studies of equilibrium isotope effects on *o*-hydroxy azo compounds.[10]

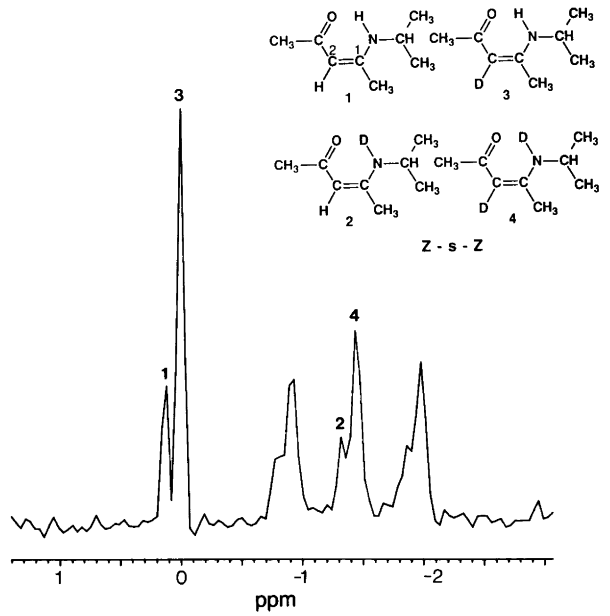


Fig. 2. ^{15}N NMR spectrum of **6** at 300 K (75 % v/v in C_6D_6). The numbers indicate the chemical shifts of the isotopomers **1–4**.

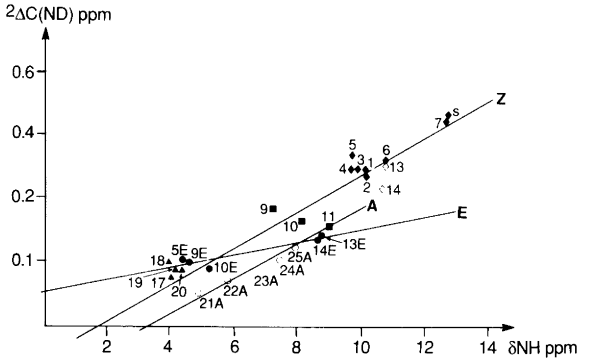


Fig. 3. A plot of two-bond deuterium isotope effects, $^2\Delta C^1(ND)$ vs. ^1H chemical shifts of the NH proton. Points marked **21A–25A** (open circles) are taken from Ref. 6 and are **21A**, aniline; **22A**, methyl 4-aminobenzoate; **23A**, *N*-methyl-4-aminoaniline; **24A**, methyl 2-aminobenzoate and **25A**, *N*-methyl-2-nitroaniline. The point marked *s* is taken from Ref. 8 (enamine derivative marked IV in Ref. 8). The data of the *Z*-enamines from this study are marked as follows: ■ esters; ◆ ketones and ◇ nitro enamines. Included in the graph are also data for β-sulfinyl enamines (▲): **17**, $CH_3CH_2SOC(CH_3)=CHNHC(CH_3)_3$, $^2\Delta$ = 0.076 ppm, δNH = 4.0; **18**, $C_6H_5SOC(CH_3)=CHNHC(CH_3)_3$, $^2\Delta$ = 0.097 ppm, δNH = 3.95; **19**, *p*-$C_6H_4SOC(CH_3)=CHNHCH(CH_3)C_6H_5$, $^2\Delta$ = 0.086 ppm, δNH = 4.18; **20**, $CH_3CH_2SOC(CH_3)=CHNHCH(CH_3)C_6H_5$, $^2\Delta$ = 0.084 ppm, δNH = 4.23.

A plot of $^2\Delta C^1(ND)$ vs. δ(NH) is given in Fig. 3. In the plot are included data from Refs. 6 and 8. A least-squares analysis of the data points corresponding to compounds including an aromatic ring[6] (**21A–25A**) gives a slope of 0.023 and *r* of 0.97 (line A). The *Z* enamines give a similar slope, 0.028 and an *r* value of 0.83, whereas the *E* isomers (filled circles) give a slope of 0.01 and an *r* value of 0.93.

Table 3 includes two rearrangement products of 2-nitroenamines. These were not included in the least-squares analysis. Exchange of the amide protons gives isotope effects of the order of 0.06–0.07 ppm at the carbonyl carbon. These effects are distinctly smaller than found for anilides[31] and so are the effects over two and three bonds on the $C^{1'}$ and $C^{2'}$ carbons.

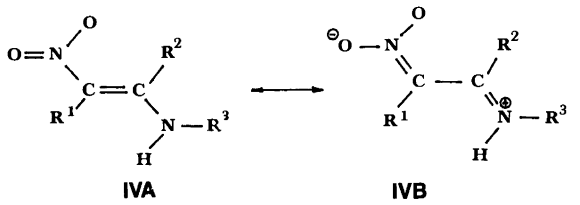
Discussion

The discussion will concentrate mainly on aspects of deuteriation at the nitrogen. The finding that $^2\Delta C^1(ND)$ is larger for the *Z* than for the *E* isomer of the same compound supports the suggestion that hydrogen bonding is responsible for this difference.[2,3] In the *Z* isomer a six-membered hydrogen-bonded ring is formed (Scheme 2). Furthermore, the values of the two-bond isotope effects for the *Z* isomers decrease according to the nature of the acceptor group in the order NO_2 ~ C=O > COOR. The strongest acceptor groups gives the strongest hydrogen bonds and the largest two-bond isotope effects. This is not the case for the two-bond isotope effects observed at the α-carbons for which the isotope effects of the two isomers are comparable in magnitude (Tables 1–3). It is likewise interesting that an isotope effect, $^n\Delta C{=}O(ND)$, is observed at the carbonyl carbon in the *Z* but not in the *E* isomer. It can thus be concluded that the larger isotope effects in the *Z* than in the *E* isomers are related to hydrogen-bonding and confined to the nuclei of the six-membered ring, which are also those in close conjugation. A similar trend may also be observed by inspection of the data given by Reuben[6] on aromatic anilines.

^1H chemical shifts of the NH proton also reflect the hydrogen-bond formation as the chemical shifts move to higher frequencies with increasing isotope effects as seen in Fig. 3. A linear relationship between hydrogen-bond enthalpy and ^1H chemical shifts has been suggested by Schaefer.[27] This has since been extended to cover $^2\Delta C(XD)$.[2] The graph of Fig. 3 shows a linear relationship between the two-bond isotope effect and δNH. The data for the aromatic compounds of Ref. 6 and the enamines fall on almost parallel lines. The displacement of the graph is caused by the slightly different nature of the two types of compounds. The different crossing points with the chemical shift axis demonstrates this fact. Furthermore, the scattering of the data could possibly be ascribed to the fact that the ^1H chemical shifts are slightly concentration dependent. Other factors such as aromatic ring currents may also influence the chemical shifts. Reuben[2,6] corrects for this by substracting the chemical shift value of a reference compound such as the corresponding simple amines or phenols. However, it is not clear why his chemical shifts are referred to amines dissolved in $CDCl_3$, when the isotope effect measurements are performed in dimethyl sulfoxide-d_6.

A logical reference for the *Z* isomer would, in our case, be the *E* isomer. However, the finding that $^1J(H^1, NH)$ is larger for the *E* isomer than for the *Z* isomer suggests that the substituents influence the former more strongly. We hence chose to plot two-bond isotope effects vs. NH chemical shifts without any corrections. Fig. 3 demonstrates that a linear relationship exists, but also that even quite similar compounds like **9**, **10** and **11** may be behave differently. Reuben[6] has discussed substituent effects on the finding that substituted anilines and substituted *N*-methylanilines with intramolecular hydrogen-bonds have different slopes. However, this can, in our opinion, be attributed to the fact that in the former only one of the two NH protons is hydrogen-bonded. Accordingly, this is not really a substituent effect.

Values for the *E* isomers have also been included Fig. 3. These isomers do not form hydrogen bonds, and the values are seen to fall on a separate line with a less steep slope compared with the line for the *Z* isomers. The values for the two-bond isotope effects decrease, as pointed out previously, in the same order for the two isomers. It has been established that the barrier to rotation around the C^1–N bond increases in the same order.[20] It is therefore tempting to relate the larger isotope effects found for the *E* isomers of the nitro enamines to a higher C^1–N bond order in this



IVA IVB

Scheme 4. Resonance structures of nitro enamines.

type of compound. The higher bond order is also expected as shown in structure IVB of Scheme 4. The increased amount of this form also explains the low-field shift of the NH proton. The magnitude of the two-bond isotope effect is therefore related to the double bond character of the C–N bond. A relationship between the magnitude of isotope effects and bond order has previously been found for the isotope effects over two bonds of aromatic compounds.[37] Accordingly, two-bond isotope effects are a way of studying the electron-attracting ability of substituents. Contrary to this explanation variations in isotope effect have been ascribed to solvent effects.[6] It is, however obvious that the chemical shifts are much more sensitive to substituent effects than are the two-bond isotope effects. The findings that the $^2\Delta C^1(ND)$ values for intramolecularly hydrogen-bonded olefins and aromatic compounds show the same dependence on δ_H and that $^2\Delta$ is smaller in the aromatics than in the corresponding olefins (the ratio is 0.55) indicates strongly that the bond order of the C^1–C^2 bond is a determining factor for the magnitude of the two-bond isotope effects and also for the hydrogen-bond strength. The hydrogen-bond-forming acceptor obviously also plays a role. The finding that the acceptor group influences the NH chemical shift of the *E* isomer opens up the possibility that the acceptor group interacts with the donor through the bonds in a push–pull fashion. A prerequisite for formation of a strong intramolecular hydrogen bond seems to be that the acceptor is in conjugation with the double bond and that the double bond has a high double bond character. Both features contribute to an easily polarizable system leading to a strong hydrogen bond and to large isotope effects for the nuclei of the hydrogen-bond ring.

The case discussed above should not be confused with cases in which chemical equilibria are affected by deuteriation and result in equilibrium isotope effects.[1,38] An intriguing case is the cyclic enaminones described by Coppola *et al.*[39] On the basis of observed isotope effects, $^2\Delta C^2(ND) = 0.24$ ppm, $^n\Delta C{=}O(ND) = 0.08$ ppm and the observation of an isotope effect at the carbon *ortho* to the NH group, they suggest a tautomeric equilibrium for six- and seven-membered rings. These results are very similar to those observed in our compounds suggesting that no tautomerism exists in the six- and seven-membered ring compounds. The fact that no isotope effects are observed at the carbonyl carbon[39] of five-membered rings lead the authors to propose a static situation for this type of molecule. Judging from our studies, the affect at the carbonyl carbon is very variable and it seems that all three compounds could be static. However, if a tautomeric situation were indeed present, equilibrium isotope effects should be expected as discussed in Refs. 1, 3, 4 and 38.

Another interesting case is the β-sulfinyl enamines.[17,40] The small magnitude of $^2\Delta C^1(ND)$ observed in this type of compound (see the legend to Fig. 3) suggests that the hydrogen bond is quite weak. This is also supported by the high-field position of the NH proton. This conclusion is at variance with suggestions forwarded in Refs. 22 and 23, and further studies of the solution structure of these enamines are clearly needed.

One-bond isotope effects on ^{15}N nuclear shielding, $^1\Delta N(D)$, are large in simple amides and amines (0.6 ppm).[9] Tables 1 and 2 show that an effect of similar magnitude is observed in the *E* isomers. For the *Z* isomers, a larger value is found and a comparison of $^1\Delta N(D)$ and $^2\Delta C^1(ND)$ shows that they behave in parallel even though they are not exactly proportional. The large one-bond isotope effects are clearly related to hydrogen-bonding. This study thus confirms suggestions based on equilibrium isotope effect studies of *o*-hydroxy azo compounds.[10]

Because of their large magnitudes and the large difference between the values for hydrogen-bonded and non-hydrogen bonded compounds one-bond isotope effects present a way of detecting hydrogen-bond formation in suitable compounds. In particular, proteins and other biomolecules could be investigated as they often contain extensive hydrogen-bond networks and in addition can be biosynthetically enriched, a feature that aids the observation of isotope effects.

The one-bond isotope effects may be difficult to observe in some small molecules because of line broadening of the ^{15}N resonance. The linewidth of an ND nucleus is determined by scalar coupling and the deuterium quadrupolar coupling constant.[28] This decreases markedly upon hydrogen-bond formation[29,30] leading to longer T_1 relaxation times for deuterium.

Conclusions

Intramolecular hydrogen-bonding causes large isotope effects at the C^1 carbon of the *Z* form of enamines but not at the C^α carbon. This is in contrast with the *E* form, in which no six-membered hydrogen-bond ring can be formed. $^2\Delta C^1(ND)$ isotope effects depend on factors that influence the strength of the NH hydrogen bonds. In the enamines, these factors are the electron-donating or -withdrawing ability of the hydrogen-bond forming group at C^2 and the bond order of the double bond. For the *Z* isomer intramolecular hydrogen bonding is the dominant aspect. The same factors determine to a large extent the NH chemical shifts resulting in an approximate linear relationship between $^2\Delta C^1(ND)$ and δNH. The one-bond deuterium isotope effects at nitrogen are also increased considerably by hydrogen bonding, making this a useful parameter for the detection of hydrogen bonds.

Acknowledgements. The authors wish to thank Prof. A. Berg for his kind help, the Danish Natural Science Research Council for at grant supporting L. K. and the Polish Academy of Science for support (Grant No. CPBP 01.13).

References

1. Hansen, P. E. *Ann. Rep. NMR Spectrosc. 15* (1983) 105.
2. Reuben, J. *J. Am. Chem. Soc. 108* (1986) 1735.
3. Hansen, P. E. *Magn. Reson. Chem. 24* (1986) 903.
4. Hansen, P. E. *Acta Chem. Scand., Ser. B 42* (1988) 423.
5. Hansen, P. E. *Prog. NMR Spectrosc. 20* (1988) 207.
6. Reuben, J. *J. Am. Chem. Soc. 109* (1987) 316.
7. Kozerski, L. and von Philipsborn, W. *Helv. Chim. Acta 65* (1982) 2077.
8. Khatipov, S. A., Shapet'ko, N. N., Bogachev, Yu. S. and Andreichikov, Yu. S. *Zh. Fiz. Khim. 59* (1985) 2095.
9. Hansen, P. E. and Lycka, A. *Magn. Reson. Chem. 23* (1985) 973.
10. Lycka, A. and Hansen, P. E. *Org. Magn. Reson 22* (1984) 569.
11. Kozerski, L. and von Philipsborn, W. *Org. Magn. Reson. 17* (1981) 306.
12. Kozerski, L., Kamienska-Trela, K. and Kania, L. *Org. Magn. Reson. 11* (1979) 365.
13. Dabrowski, J. and Kozerski, L. *J. Chem. Soc. B* (1971) 345.
14. Kozerski, L. and Dabrowski, J. *Org. Magn. Reson. 4* (1972) 253.
15. Dabrowski, J., Kamienska-Trela, K. and Kozerski, L. *Org. Magn. Reson. 6* (1974) 499.
16. Kozerski, L. and Dabrowski, J. *Org. Magn. Reson. 5* (1973) 459.
17. Kozerski, L. and Krowczynski, A. *Magn. Reson. Chem. 25* (1987) 46.
18. Osterkamp, D. L. and Taylor, P. *J. Chem. Soc., Perkin Trans. 2* (1985) 1021.
19. Kozerski, L., von Philipsborn, W., Kamienska-Trela, K. and Kania, L. *Helv. Chim. Acta 7* (1983) 2113.
20. Denmark, S. E., Sternberg, J. A. and Luenoend, R. J. *J. Org. Chem. 53* (1988) 1251.
21. Urbanczyk-Lipkowska, Z., Krajewski, J. W., Gluzinski, P. Kozerski, L., Kawecki, R., Anreettil, G. D. and Bocelli, G. *J. Mol. Struct. 35* (1988) 309.
22. Annunziata, R., Cinquini, M., Restelli, A. and Cozzi, F. *J. Chem. Soc., Perkin Trans 1* (1982) 183.
23. Sterling, C. J. M. *J. Chem. Soc.* (1964) 5863.
24. Buckingham, A. D. and Urland, W. *Chem. Rev.* (1975) 113.
25. Jameson, C. J. *Bull. Magn. Reson. 3* (1981) 3.
26. Jameson, C. J. *Chem. Phys. 66* (1977) 4983.
27. Schaefer, T. *J. Phys. Chem. 79* (1975) 1888.
28. Pople, J. A. *Mol. Phys. 1* (1958) 168.
29. Butler, L. G. and Brown, P. L. *J. Am. Chem. Soc. 103* (1981) 6541.
30. Brown, T. L., Butler, L. B., Curtin, D. Y., Hiyama, Y., Paul, I. C. and Wilson, R. B. *J. Am. Chem. Soc. 104* (1982) 1172.
31. Newark, R. A. and Hill, J. R. *J. Magn. Reson. 21* (1976) 1.
32. Duus, F. and Hansen, P. E. *Org. Magn. Reson. 22* (1984) 16.
33. Wesener, J. R., Moskau, D. and Gunther, H. *J. Am. Chem. Soc. 107* (1985) 7307.
34. Maciel, G. E., Ellis, P. D. and Hooper, D. C. *J. Phys. Chem. 71* (1967) 2161.
35. Arrowsmith, C. H. and Kresge, A. J. *J. Am. Chem. Soc. 108* (1986) 7918.
36. Berger, S. and Diehl, B. W. K. *Magn. Reson. Chem. 26* (1988) 327.
37. Martin, R. H., Morau, J. and Defay, N. *Tetrahedron 30* (1974) 179.
38. Siehl, H. U. *Adv. Phys. Org. Chem. 23* (1987) 63.
39. Coppola, G. M., Damon, R., Kahle, A. D. and Shapiro, M. J. *J. Org. Chem. 46* (1981) 1221.
40. Kozerski, L., Kawecki, R. and Hansen, P. E. *In preparation.*

Received January 29, 1990.