205. Solvent-Induced Deuterium Isotope Effects in ^{13}C- and ^{15}N-NMR. Spectra of Enaminones[1])

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Summary

The effect of deuterium on the ^{13}C and ^{15}N chemical shifts of enaminones has been investigated. D/H isotope shifts are reported for neutral and protonated species, *i.e.*, when the isotope is exchanged on the C(2)-, N-, or O-atoms. In cases of slow exchange the isotope shifts were obtained from solutions containing both isotopomers, whereas for fast exchange (acidic solutions) either separate NMR. sample tubes (^{15}N-NMR.) or coaxial tubes (^{13}C-NMR.) were used.

In neutral molecules the isotope effects $\delta_C(D,H)$ are intrinsic in nature. In acidic solutions, the enaminocarbonyl cations formed exhibit $\delta_C(D,H)$- and $\delta_N(D,H)$-values which are discussed in terms of the proton transfer. The mesomeric character of the cations is reflected by characteristic features in the $\delta_C(D,H)$- and $\delta_N(D,H)$-values, which can be ascribed to isotopic perturbation of resonance.

O-Protonation shifts in the ^{15}N-resonance, observed for the first time, are large and positive (+60 to +76 ppm), in contrast to amides, where the effects are of the same sign but an order of magnitude smaller. Both protonation shifts and solvent-induced isotope effects are discussed in connection with the nucleophilic character of the reactive centers in the enaminone synthon.

1. Introduction. – Although isotope effects in NMR. spectroscopy have recently been applied in investigations of various important chemical phenomena such as H-bonding [2–5], conformational equilibria [6] [7] or resonance in carbocations [8] [9] the underlying mechanisms still require systematic studies. The appearance of a positive isotope effect[3]) (high-frequency shift due to the heavier isotope) has attracted attention [11–14], since it is not predicted by the theory of *intrinsic* isotope effects [15] [16]; it is, however, frequently observed in *equilibrium-shift* isotope

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

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[3]) In this and subsequent papers the deuterium isotope effect is defined as $\delta(D,H) = \delta(D) - \delta(H)$ following the convention used in referencing chemical shifts [10].

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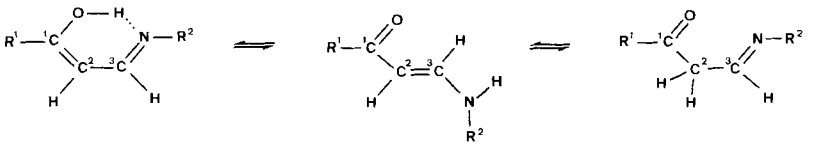
effects [8] [17]. Various isotopic substitutions have been used to follow the mechanism of the phenomenon, as for example $^{13}C/^{12}C$ [12], $^{18}O/^{16}O$ [18–20], $^{37}Cl/^{35}Cl$ [21], and most frequently, $^{2}H/^{1}H$ [2] [3] [6–9] [11] [13] [14]. A novel approach to investigations of C,C-connectivity patterns by means of the observation of ^{13}C-^{13}C double-quantum transitions [22] [23] offers a new possibility for routine measurements of ^{13}C-isotope effects in natural isotope abundance [24].

Since systematic investigations of the solvent-induced isotope effect are less abundant in the literature [25–30], it was the aim of the present work to study this phenomenon in the case of enaminones, especially suitable for this purpose as they possess three sites capable of reacting with a solvent, *i.e.*, the C(2)-, N- and O-atoms. In addition, they potentially exhibit interesting tautomeric properties *(Scheme 1)*.

Scheme 1



The availability of ^{15}N-NMR. spectroscopy and its potential as a structural probe in this class of compounds [1] [31] renders this nucleus particularly attractive for the study of solvent-induced deuterium-isotope effects. The deuteriation on the N- or C(2)-atom permits observation of primarily intrinsic secondary isotope effects induced by σ-bonded isotopes, whereas isotopes H-bonded to the O-atom may induce effects which are of the equilibrium-type and can be propagated over long distances. The latter situation has recently been studied in the case of intermolecular interaction between the carbonyl group in chalcone and trifluoroacetic acid (TFA-*d vs.* TFA) in chloroform solutions [5]. It was found that the observed splittings δ_i in the ^{13}C-NMR. spectra for each C-site in the limit of full complexation are linearly correlated with the parameter Δ_i in *Equation 1*

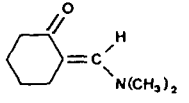
$$\delta_i = (K-1)\Delta_i + K\delta_i(\mathrm{D,H}) \qquad (1)$$

where Δ_i denotes the change in chemical shift between complexed and free ketone, K is the equilibrium isotope-shift constant and $\delta_i(\mathrm{D,H})$ describes the isotope effect depending on the kind of functional group involved.

On the other hand, the regioselective interactions of different solvents with the enaminone pentad, as studied by protonation and D/H isotope exchange, could add to the understanding of the chemical character of such systems.

2. Results and discussion. – 2.1 *Sites of solvent interaction.* In order to introduce deuterium selectively into the three above mentioned positions two types of exchange procedures were used. The results are summarized in *Table 1*. In the first case (types A and B) the enaminones were deuterated *in situ* by D_2O present in deuterated acetone (entries 1 and 2 in *Table 1*). Under these conditions the N-H/D exchange is slow on the NMR. time scale, as evidenced by resolved coupling of the

Table 1. *Solvent-induced deuterium-isotope effects* (δ_C(D,H) [ppm], 30°) *in* ^{13}*C-NMR. spectra of enaminones*[a])

Type	Isotope exchange		Compound	Solvent	Stereo-isomer	δ_C(D,H) C(1)	C(2)	C(3)	Other	
A	N-H→N-D	**1**	$CH_3C^1O-C^2H=C^3H-NHCH_3$	$(CD_3)_2CO$[b])	(*Z,s-Z*)		−0.06	−0.24	N−CH_3;	−0.17
A		**2**	$C_2H_5CO-CH=CH-NHCH_3$	$CDCl_3$[c])	(*Z,s-Z*)	−0.02	−0.05	−0.25	N−CH_3;	−0.16
					(E_{av})	−0.04				
				C_6D_6[c])	(*Z,s-Z*)			−0.25	N−CH_3;	−0.16
A		**3**	$C_2H_5CO-C(CH_3)=CH-NHCH_3$	DMSO[d])	(E_{av})	−0.05	−0.08	−0.21	N−CH_3;	−0.19
									C(2)−CH_3;	−0.05
B	C(2)−H→C(2)−D	**4**	$(i\text{-}C_3H_7)CO-CH=CH-N(C_2H_5)_2$	DMSO[e])	(E_{av})	−0.30		−0.23		
C	(C=O···H→C=O···D / C(2)−H→C(2)−D)	**4**		TFA[f])	(*E,s-Z*)	−0.21	−0.29[g])	−0.28	CH;	−0.12
					(*E,s-E*)	−0.22				
C		**5**	$CH_3CO-CH=CH-N(C_2H_5)_2$	TFA[h])	(*E,s-Z*)	−0.20	−0.28[g])		CH_3;	−0.15
					(*E,s-E*)	−0.19			CH_3;	−0.09
C		**6**	$(t\text{-}C_4H_9)CO-CH=CH-N(CH_3)_2$	TFA[j])	(*E,s-Z*)	−0.11	−0.20[g])	−0.13		
D	C=O···H→C=O···D	**7**		TFA[f])	(*E,s-Z*)	−0.14	−0.09	−0.07		
E	C(2)−H→C(2)−D	**7**		TFA[f])		−0.18	−0.31[k])			

[a]) The δ_C(D,H)-values (±0.02 ppm) express the differences in chemical shifts between the isotopomers containing D- and H-nuclides, respectively; the negative sign denotes a shift to lower frequencies.

[b]) The enaminone was deuterated *in situ* by D_2O present in acetone-d_6 (4.4M solution).

[c]) Deuteration accomplished as in footnote b; after drying and destillation the compound was used for running the spectra in $CDCl_3$ and C_6D_6.

[d]) The spectrum was obtained from a solution of 0.2 g of solute in 1 g DMSO and 1 g of H_2O, deuterated and non-deuterated solvents being used in 10- and 5-mm sample tubes, respectively, T = 50°.

[e]) Deuteration was accomplished as in footnote d; the effect on C(2) was not measured due to broadening of the lines.

[f]) Run in coaxial NMR. tubes; 0.2 g of solute in 2 g of TFA-*d* or TFA in 10- and 5-mm sample tubes, respectively.

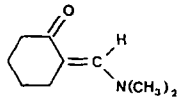
[g]) The C(2)-resonance in a deuterated sample is split into a triplet due to spin coupling with deuterium, ^1J(C(2),D) = 24.5 Hz.

[h]) Spectrum obtained from solutions of 0.2 g of solute in 2.5 g of TFA and 0.5 g of C_6D_6 in coaxial NMR. tubes.

[j]) Spectrum obtained from solutions of 0.15 g of solute in 2.3 g of TFA in coaxial NMR. tubes.

[k]) The C(2)-resonance in the deuterated sample is split into a triplet due to spin coupling with deuterium, ^1J(C(2),D) = 20.5 Hz.

Table 2. *^{13}C-Chemical shifts (δ [ppm]) of the C-atoms in the enaminone skeleton under conditions of O- or C(2)-protonation in (TFA-d)-solution*[a])

	Compound	Protonation site	Isomer	$\delta(^{13}C)$ C(1)	C(2)	C(3)
4	$(i\text{-}C_3H_7)CO-CH=CH-N(C_2H_5)_2$	O–	(*E*,*s*-*Z*) (*E*,*s*-*E*) (*E*$_{av}$)	193.78 196.02 (201.81)	92.57 96.14 (93.03)	162.12 163.90 (150.33)
5	$CH_3CO-CH=CH-N(C_2H_5)_2$[b])	O–	(*E*,*s*-*Z*) (*E*,*s*-*E*) (*E*$_{av}$)	185.12 187.89 (195.12)	95.71 98.19 (96.47)	161.15 163.44 (150.81)
7		O– C(2)–	(*E*,*s*-*Z*) (*E*,*s*-*Z*)	183.09 211.28 (197.43)	105.95 53.94 (104.12)	165.49 180.31 (150.33)
8	$C_2H_5-CO-C(CH_3)=CH-N(CH_3)_2$	C(2)–	(*E*$_{av}$)	211.66 (199.67)	49.71 (105.04)	182.01 (150.86)

[a]) Chemical shift (±0.02 ppm) were obtained from *ca.* 0.9M solutions in TFA-*d* with internal TMS, at 30°; values in brackets give the chemical shifts measured in 0.9M solution in $CDCl_3$ against internal TMS.

[b]) Concentration as in footnote *h* to *Table 1*.

N-methyl group with the proton on the N-atom in the ^{1}H-NMR. spectrum. Hence, both isotopomers can be observed simultaneously in one NMR. tube. Although the enaminones are present as (*E*/*Z*)-mixtures, the isotope effects in the (*E*)-isomers are not observed in compounds **1** and **2** due to broadening of the lines caused by C(3),N-bond rotation. The interference of resonances due to the minor rotamer arising from C(3),N-bond rotation was eliminated in **3** by heating the sample to 50°. The isotope shifts induced by the substitution C(2)–H → C(2)–D (experiment B) were observed in coaxial NMR. tubes using DMSO/H_2O and DMSO-d_6/D_2O as solvents.

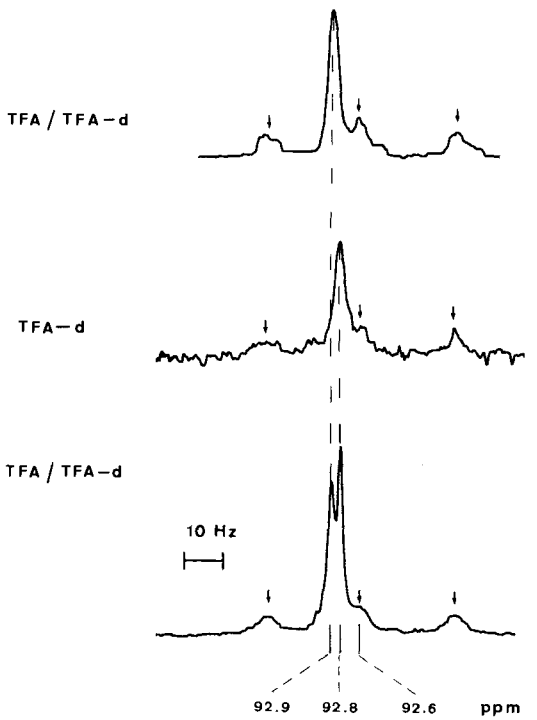
In the second deuteration procedure run in coaxial NMR. tubes (types C, D, E), trifluoroacetic [^{2}H]acid and trifluoroacetic acid (TFA-*d* and TFA) were used as H-bonding and/or protonating agents for tertiary enaminones. In these experiments three different situations were found as shown by ^{13}C-chemical shifts collected in *Table 2*.

In the case of the enaminones **4**, **5** and **6** protonation[4]) occurs on the O-atom as established earlier [32]. Simultaneously, slow exchange of the H-atom on C(2) is observed as shown for compound **4** in the *Figure*.

The bottom trace represents the spectrum taken immediately after dissolving of the base. There are two singlets of non-deuterated C(2)-atoms and a broad triplet due to a C(2)-D group with $^1J(C,D) = 24.5$ Hz. Two of the three resonances are observed in a TFA-*d* solution (center trace). After several hours deuteration is complete and only two signals are recorded in coaxial tubes (upper trace).

In the case of compound **7** (type D and E) (*Tables 1* and *2*) two different cations are present in solution, corresponding to protonation either on the O- or on the C(2)-atom (the latter process was not discussed previously [32]). The assignment of the

[4]) The term 'protonation' is used whenever cation formation is involved, either by reaction with a proton or a deuteron, whereas 'deuteration' is confined to an H/D exchange process.



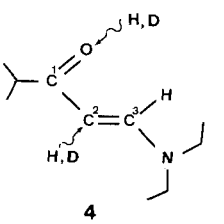


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Figure. *^{13}C-NMR. spectra* (25.2 MHz) *of the C(2)-atom in the enaminone* **4** *obtained with coaxial 10- and 5-mm NMR. sample tubes in (TFA-*d*)- and TFA-solutions, respectively* (The bottom spectrum indicates the situation with partial deuteration on C(2) and shows three resonances assigned to the following species: C=$\overset{+}{O}$H (92.9), C=$\overset{+}{O}$D (92.8) and {C=$\overset{+}{O}$D, C(2)–D} (92.6 ppm, triplet with ^1J(C,D) = 24.5 Hz). The assignments were confirmed by the centre spectrum (5 mm sample tube removed) and the top spectrum (coaxial tubes, complete deuteration on C(2) after several hours)).

protonation sites is straightforward on the basis of the ^{13}C- *(Table 2)* and ^{15}N- *(Table 4)* chemical shifts. C(2)-protonation results in the expected low-frequency shift of the C(2)-atom (53.94 ppm), whereas in the *O*-protonated form of **7** (type D) the C(2)-resonance appears at 105.95 ppm. In the first case the N-chemical shift is characteristic for iminium N-atoms (*ca.* −170 ppm [33]). Noteworthy is the fact that in the C(2)-deuterated form of **7** (type E) (^1J(C(2),D) = 20.5 Hz) the chemical shift of the carbonyl C-atom (211.28 ppm) is very similar as in 2-methylcyclohexanone (210 ppm [34]). Since it is known that the carbonyl resonances undergo strong high-frequency shifts in acidic solutions [35], this observation indicates that the carbonyl group is not H-bonded to another molecule of TFA in the iminium ion of **7**. Besides the C(2)-protonated form one observes the signals of the O-protonated form of enaminone **7**.

In the case of compound **8** only C(2)-protonation is observed as evidenced by ^{13}C- and ^{15}N-chemical shifts.

The ^{15}N-NMR. spectral data for the studied compounds are comprised in *Tables 3* and *4*.

The tables contain the chemical shifts measured in neutral solvents and in (TFA-*d*)-solutions. The differences between the δ-values in these solvents are given as the protonation shifts. The differences between ^{15}N chemical shifts measured in (TFA-*d*)- *vs.* TFA-solutions are cited for several cases as the solvent-induced isotope effects δ_N(D,H).

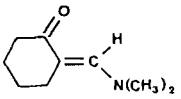
Table 3. *^{15}N-Chemical shifts (δ [ppm]) of tertiary enaminones in neutral solvents and in (TFA-d)-solutions, protonation shifts and solvent-induced isotope effects in TFA-solutions measured at 24°[a])*

Compound	$\delta(^{15}N)$, solv.[b])	Isomer	$\delta(^{15}N)$, TFA-*d*	Proton-ation shift[c])	δ_N (D,H)[d])
5 $CH_3CO-CH=CH-N(C_2H_5)_2$	−271.41; $CDCl_3$ (1.2)	(*E,s-Z*)	−202.97	68.4	+0.04
		(*E,s-E*)	−205.23	66.1	+0.06
9 $C_3H_7CO-CH=CH-N(CH_3)_2$	−302.52; $(CD_3)_2CO$ (6.1)	(*E,s-Z*)	−230.93	71.6	+0.06
		(*E,s-E*)	−233.68	68.8	
4 $(i\text{-}C_3H_7)CO-CH=CH-N(C_2H_5)_2$	−274.43: $(CD_3)_2CO$ (4.5)	(*E,s-Z*)	−202.12	67.8	+0.04
		(*E,s-E*)	−206.57	72.3	+0.05
6 $(t\text{-}C_4H_9)CO-CH=CH-N(CH_3)_2$	−303.71; C_6D_6 (4.9)	(*E,s-Z*)	−227.69	76.0	−0.04
10 $C_6H_5CO-CH=CH-N(CH_3)_2$	−294.87; $(CD_3)_2CO$ (0.9)	(*E,s-Z*)	−228.34	66.7	
11 $CH_3O-C(CH_3)=CH-CH=\overset{\oplus}{N}(CH_3)_2I^{\ominus}$	−225.03; CD_3OD (1.2)				

[a]) Chemical shifts (±0.03 ppm) were measured against external $CH_3{}^{15}NO_2$ in a capillary.
[b]) Numbers in parenthesis denote molar concentrations.
[c]) Parameter denoting the difference between chemical shifts in TFA-*d* and in neutral solvent given in column 3.
[d]) The solvent-induced isotope effect (±0.03 ppm) measured as the difference between chemical shifts obtained in (TFA-*d*)- and TFA-solutions, respectively; (0.2 g of solute in 2.5 g of TFA and 0.5 g of C_6D_6).

The ^{13}C and ^{15}N chemical shift values for tertiary enaminones measured in TFA-solutions provide the possibility of deriving several conclusions concerning the chemical character of the enaminone pentad, exhibited by three nucleophilic centers and their relative affinity to the proton. It is evident from the data in *Tables 2* and *3* that all *C*(2)-unsubstituted enaminones undergo protonation on the O-atom. Simultaneously, as shown in the *Figure*, the H/D-exchange on the C(2)-atom is observed. These two processes can be regarded as the spectral representation

Table 4. *^{15}N-Chemical shifts (δ [ppm]) of C(2)-alkyl-substituted tertiary enaminones measured in neutral solvents and in TFA-d solutions at 24°[a])*

Compound	$\delta(^{15}N)$; solv.	Proton-ation site	$\delta(^{15}N)$, TFA-*d*	Proton-ation shift	δ_N(D,H)[b])
7 	−303.77; $(CD_3)_2CO$ [c])	O−	−226.96[d])	76.8	+0.10
		C(2)−	−173.02	130.8	+0.01
8 $C_2H_5CO-C(CH_3)=CH-N(CH_3)_2$	−312.09; C_6D_6[e])	C(2)−	−176.03[f])	136.1	−0.06
12 $CH_3CO-C(CH_3)=CH-N(CH_3)_2$	−312.74; C_6D_6[e])	C(2)−	−175.48[g])	137.3	

[a]) The chemical shifts (±0.03 ppm) were measured against external $CH_3{}^{15}NO_2$. [b]) Accuracy ±0.03 ppm. [c]) 5.6M Solution. [d]) Same concentration as in footnote f to *Table 1*. [e]) 0.9M Solution. [f]) 0.6M Solution (0.2 g solute in 2.5 g of TFA and 0.5 g of C_6D_6). [g]) 0.7M Solution in neat TFA-*d*.

of an electrophilic vinylic substitution occurring at the C(2)-atom in the *O*-protonated molecule. This also indicates that the C(2)-atom is the prime nucleophilic site in acid-catalyzed electrophilic substitution reactions of the enaminone pentad.

However, the site of protonation strongly depends on the configuration at the C(1),C(2)-bond (*cf. Tables 2* and *4*). The presence of the CH_3-groups in **8** and **12** results in exclusive protonation on C(2) in these derivatives. This is most probably due to breaking of the conjugation between the carbonyl and the double bond as a consequence of steric repulsion between the $COCH_3$ and C(2)-alkyl or C(3)–H groups in (E,s-Z)- and (E,s-E)-forms, respectively. In the cyclic derivative **7** ring constrain prevents breaking of the conjugation and, hence, both O- and C(2)-protonation occurs. In the methyl derivatives **8** and **12** evidence for the conformational change is found in low-frequency ^{15}N-chemical shifts as compared with **6**, **7**, **9**, and **10**. This low-frequency shift has recently been observed in the case of non-planar conformers of enaminones in conditions of frozen rotation about the C(1),C(2) bond and interpreted in terms of increased enamine character of the N-atom [1]. It is clear then that a neutral enaminone system having the spectral characteristic of compounds **8** and **12** should undergo the reactions typical for enamines, *i.e.*, electrophilic attack on C(2). This prediction, supported by the present spectral studies, has been successfully applied in recent synthetic studies of regioselective reactions between quinone and C(2)-alkyl-substituted enaminones [36] [37].

Another conclusion is that in all investigated cases (see *Table 3* and *4*) *O*-protonation of enaminones in TFA-solutions is complete. This is evidenced by the observation of nearly identical ^{15}N-chemical shifts in the O-methylated salt **11** and in enaminones bearing the same alkyl substituents on the N-atom, *e.g.*, compounds **6**, **9** and **10**. This fact and the lack of signals for the spectra of other protonated forms indicate that in the tertiary enaminones studied there is no observable direct protonation on the N-atom or proton exchange between O- and N-atoms in the *O*-protonated molecules. The same conclusion can be derived for the *C*(2)-protonated molecules and it is supported in two different spectral observations. First, the ^{15}N chemical shift is characteristic for an iminium N-atom [33] [38] (see above) and, second, $^1J(C(2),D) = 20.5$ Hz, a value characteristic for alkyl groups and corresponding to $^1J(C,(2),H) = 133.5$ Hz, indicates no reduction which should be observed in the case of proton exchange.

The *O*-protonation shifts for enaminones *(Table 3)* are large and *positive* (+66 to 76 ppm), in contrast to amides where these effects are of the same sign but an order of magnitude smaller [33]. On the other hand, protonation of imines (azines) and enaminones produces iminium salts of related structure ($=\overset{+}{N}H$ and $=\overset{+}{N}<$, respectively). Not unexpectedly, the protonation shifts in this case are of opposite sign, since imines are strongly deshielded whereas enaminones are shielded relative to the iminium salts.

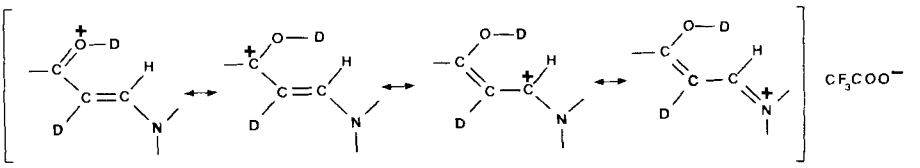
2.2. *Secondary deuterium isotope effects.* After establishing the sites of solvent interaction and H/D-exchange the secondary deuterium isotope effects in the ^{13}C- and ^{15}N-NMR. spectra can be discussed. These data provide new information concerning the characteristics of the phenomenon itself and the tautomeric

equilibrium in the neutral enaminones *(Scheme 1)*. Furthermore, the data may contribute to the understanding of intermolecular interactions between the substrate molecule and solvent in TFA-solution.

Secondary deuterium isotope effects in the ^{13}C-NMR. spectra induced by isotopic exchange on the N-atom in the (*Z*)-isomer of enaminones are intrinsic in nature and, therefore, diminish along the C-chain *(Table 1)*. Slightly higher values were found for one investigated (*E*)-isomer (compound **3**). The effect through two bonds is always larger for an sp^2-C-atom as compared with a corresponding sp^3-hybridized atom (C(3) *vs.* H_3C-N). The introduction of a heavier isotope on C(2) allows for the estimate of intrinsic effects of the deuterium on C(1) and C(3) (**4** in *Table 1*). They are comparable in magnitude with effects through two bonds induced in the N-D isotopomer. These results, along with previously reported spectral data concerning the high energy barrier to (N-H)-proton exchange [39] and ^{15}N-chemical shifts [1], strongly indicate the predominance of the β-amino-enone form *(Scheme 1)* in the investigated secondary enaminones. No evidence was found for other tautomeric forms [4] as for example, isotope effects on the alkyl substituents (R^1) that would indicate the presence of the imino-enol form.

The effects due to an isotope exchange on the O-atom were accomplished by running the ^{13}C-NMR. spectra in coaxial 10- and 5-mm sample tubes or in separate tubes (^{15}N-resonance), each containing one isotopomer. The isotope effects observed on alkyl substituents (R^1) (compare **4** and **5** in *Table 1*) again confirm the proton transfer discussed above on the basis of ^{15}N-chemical shifts. Hence, the species existing in solution is the resonance-stabilized enaminocarbonyl cation *(Scheme 2)*.

Scheme 2



In principle, the observed isotope effect in this case may contain the 'equilibrium' and intrinsic terms. The possible equilibria which can be taken into account are of the intra- or intermolecular-type. Among the former phenomena the (*E*, *s*-*E*) ⇄ (*E*, *s*-*Z*)-conformational process and proton tautomerization between C(2), N- and O-sites can be taken into consideration. Since the conformational process is slow on the NMR. time scale, as evidenced by the appearance of two rotamers in the spectra ((*E*, *s*-*Z*) and (*E*, *s*-*E*), see *Table 3*), and there is no evidence for tautomerization, these processes should not affect the observed isotope shifts. Among the latter, *i.e.*, intermolecular processes, the exchange of a proton between the H-bonded ion pair and the ionic species can be considered (molecular-ionic tautomerization [40]). H-Bonding between the ions is often postulated to appear in aprotic solvents [41–44], but a solvent-separated ion pair is highly favoured in TFA-solution [43], since the CF_3COO^--anion is strongly solvated. The system under study is described

by the latter situation, indicating the presence of enaminocarbonyl cations *not* involved in intermolecular equilibria.

Hence, the most conceivable source of the isotope shifts in this cation is the direct effect of deuterium on vibrational levels of the molecule, *i.e.*, an intrinsic isotope effect. It can easily be deduced from the data in *Table 1* that the isotope shifts in the cations are, in general, similar in magnitude to the ones measured in the ^{13}C-NMR. spectra of the neutral molecules. However, some differences can be figured out, as for example a smaller two-bond isotope effect (compare C(1) in **7** with C(3) in **1** and **2**, *Table 1*) and large four-bond effects for C(3) in **6** and **7**. These differences can be viewed as being derived from the isotopic perturbation of resonance [8] [9] in the mesomeric cation *(Scheme 2)*. In addition to H/D isotope effects on ^{13}C-chemical shifts analogous effects, although smaller and of both signs, are observed in the ^{15}N-resonance (*Tables 3* and *4*). The observed δ_N(D,H)-values are composed of two independent contributions due to the isotope introduced on the O- (and separated by five bonds) and on the C(2)-atom (3 bonds), and these effects may even cancel. Thus, in compound **7** when deuterium is introduced on the O-atom only, the observed δ_N(D,H)-value is the largest measured (+0.1 ppm). These high-frequency isotopic shifts are of considerable interest for the mechanistic interpretation of deuterium isotope effects.

The above isotope shifts observed both in the ^{13}C- and ^{15}N-resonance of the enaminocarbonyl cation could, in principle, be used for the consideration of the relative predominance of oxonium, carbenium and iminium forms in the ground state of a molecule *(Scheme 2)*. However, when interpreting such shifts, one should be aware of the fact that the magnitude of the chemical-shift isotope effect in resonance-stabilized cations depends in a complex way on the relative importance of the contributing resonance structures and on the static chemical shifts in each of them [8]. This analysis was not attempted since the situation in the studied compounds is even more complicated by the fact that two deuterons are introduced into the molecule and each of them can have different influence on the relative importance of the canonical formulae.

In summary it can be concluded that the presented technique of protonation studies coupled with solvent-induced isotope-effect investigations can provide valuable information concerning the chemical character of various reactive centers in a molecule or on intra- and intermolecular processes, fast on the NMR.-time scale. Using this technique spectral characteristics were assigned to the enaminone synthon with respect to regioselectivity towards electrophiles, which is of interest to the synthetic chemist. Further studies of well-defined model systems are necessary to cover the variety of situations in proton-transfer reactions and to gain better understanding of the solvent-induced isotope effect.

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Experimental. – The ^{13}C-NMR. spectra were obtained on a *Varian XL-100-12* spectrometer at 25.2 MHz and 30°. Typical parameters were a spectral width of 5000 Hz, an acquisition time of 3 sec, a 45° pulse angle and 15000 transients. The technique of NMR. measurements in coaxial sample tubes was the same as described elsewhere [5] [26], with TFA-*d* as a lock signal. The assignments of the lines belonging to the solutions in the 10- and 5-mm tubes, respectively, were confirmed by an independent run after removal of the 5-mm sample tube. The agreement between the chemical shifts obtained in both runs was ± 0.005 ppm. The assignment of the lines in experiments with both isotopomers in one sample tube (entries 1 and 2 in *Table 1*) were based on the intensity ratios of the ^{13}C-signals, also known from the integration of the ^{1}H-NMR. spectra, and on the shape of the signals. Isotope effects are expected to be accurate to ± 0.02 ppm. The ^{15}N-NMR. spectra were in most cases obtained from the same solutions as used for the ^{13}C-NMR. spectra and in a 10-mm broad-band probe of a *Varian XL-200* spectrometer at 20.2 MHz and 24°. Chemical shifts were measured against enriched $CH_3{}^{15}NO_2$ contained in a capillary. The pulse sequence INEPT was used for obtaining noise-decoupled spectra with a typical delay time $\tau = 17$ msec, a spectral width of 10000 Hz, 0.6 sec acquisition time, and a pulse sequence delay of 1 sec. The isotope effects in the ^{15}N-NMR. spectra were measured in 10-mm sample tubes, using 2.5 ml of solution, 0.6M in substrate and containing typically 2.5 g of acid and 0.5 g of C_6D_6, in order to provide an internal lock identical for both acids TFA-*d* and TFA. The chemical shifts were measured against the same capillary, the digital resolution being at least 0.03 ppm. All compounds were freshly distilled before use and the trifluoroacetic acid and trifluoroacetic [^{2}H]acid (TFA and TFA-*d*) were kept under anhydrous conditions. The concentrations of the solutions used in experiments leading to isotope-shift determinations were dependent on weighing and are accurate to at least 1%.

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