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Alternative Protonation Centres in the Molecule of 1-(*N*-Methylimino)-2-(*N,N*-disubstituted)aminobut-2-ene

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The formation of enammonium salts by protonation of azomethine derivatives of *N,N*-disubstituted α-aminocrotonaldehydes, their easy *E,Z*-isomerisation and subsequent transformation to the corresponding immonium salts has been found for the first time.

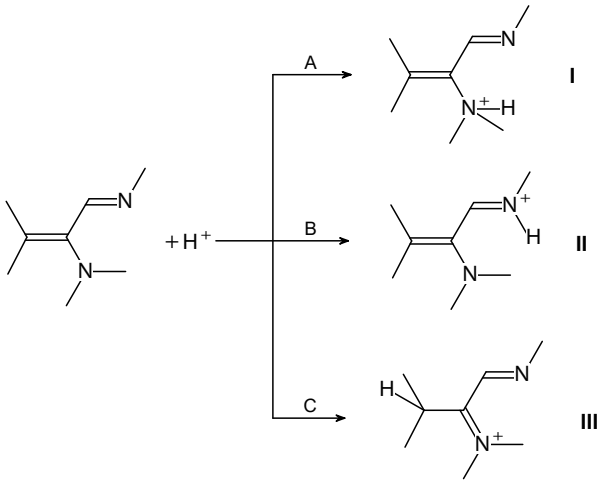
The controversial problem of alternative reactive centres constantly attracts the attention of investigators. Azomethine derivatives of *N*, *N*-disubstituted α-aminoenals **1** are ambident conjugated systems possessing three nucleophilic centres. Protonation is one of the simplest processes which allows evaluation of the reactivity of such systems, particularly their affinity towards electrophilic reagents.

Previously we have shown[1,2] that *N*, *N*-disubstituted α-aminoenals protonate regiospecifically on the nitrogen atom. In contrast to the investigations of Matsushita,[3,4] we are the first to isolate and describe enammonium salts which do not transform into the corresponding immonium salt.

Here we would like to report preliminary results of a study of the reaction of 1-(*N*-methylimino)-2-(*N*, *N*-disubstituted)-aminobut-2-enes **1** with strong carboxylic acids.

The non-coordinative interaction of protected amino and azomethine groups in the molecule of imine **1** assumes *a priori* possible protonation of any nucleophilic centres: nitrogen

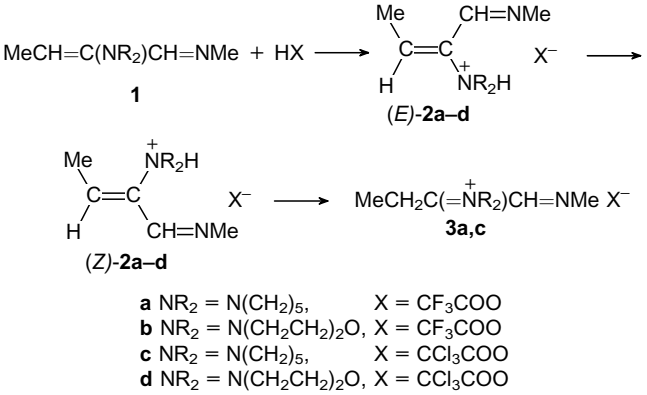
atom of the amino group (route A), nitrogen atom of the azomethine group (route B) and carbon atom at the position 3 (route C) (Scheme 1).



Scheme 1

By means of NMR spectroscopy we found the following succession of steps for the reaction of α-piperidino- and α-morpholinocrotonaldehyde *N*-methylazomethines with trifluoro- and trichloroacetic acid (Scheme 2).

The ^{1}H NMR spectra of trifluoro- and trichloroacetates of α-piperidino- and α-morpholinocrotonaldehyde *N*-methylazomethines formed at −20 °C testify to the existence of a non-equimolar mixture of geometrical isomers of enammonium salt **2** (Table 1). This is confirmed by the preservation of the *C*-methyl group doublets and the olefin proton quartets and by their downfield shift compared with the initial base **1**. The largest shift is observed with the signals of olefin and azomethine protons (1.02–1.85 and 0.55–0.91 ppm, respectively), the downfield shift of *N*-methyl protons being as low as 0.15–0.30 ppm. The formation of a *C*-protonated structure of type **III** is easily excluded by the absence of any ethyl group resonance. At the same time, the chemical shift of the NMe signal (3.5–3.7 ppm instead of 4.5 ppm for $\overset{+}{N}$Me [6]) excludes the assignment of structure **II** to this product. A substantial downfield shift of β-olefin carbon (30 ppm) with simultaneous upfield shift of the imine methyl carbon (10 ppm) in the ^{13}C NMR spectrum provides additional strong evidence for amine nitrogen protonation.



Scheme 2

The principal change in the conjugation of the C=C–C=N chain, after protonation, leads to a reduction in the nature of the C=C double bond. Thus, increasing the temperature to −10 °C changes the *Z*- and *E*-isomer ratio of enammonium salt **2b,d** from 4:1 to 1:1. This facile *E,Z*-isomerisation is also typical of the enammonium salts of *N,N*-disubstituted α-amino-α,β-unsaturated aldehydes.[2] In addition, this agrees with the observation of the lowering of the C=C energy barrier under the influence of polar substituents linked to the formal double bond, which proceeds through a transition state characteristic of acrylic systems.[7]

Further behaviour of the enammonium salts **2a–d** is dependent on the nature of substituted amino group. There are no changes in the proton spectra of a solution of enammonium salts **2b,d** even after a day at room temperature. In contrast, the signals of the *C*-protonated forms **3a,c** appear in ^{1}H NMR spectra from **2a,c** after a short period at −10 °C. The intensity of these signals increases with time. The structure of the hydrolysis product EtC(O)CH=NMe is not supported by ^{1}H NMR spectroscopy. So, the chemical shift of the α-protons of the

Table 1 ^{1}H NMR spectra of azomethines **1** and their salts.

Compound[a]	Isomer[b]	Chemical shift, δ (ppm) ($CDCl_3$/HMDS)					
		Me	CH= or CH_2 (for **3**)	CH=N	amine moiety		
					NMe	α-CH_2	β(β,γ)-CH_2
1	*Z*	1.80d	5.49q	7.66q	3.33d	2.92m	1.53m
(NR_2 = Pp)	*E*	1.82d	5.18q	8.06q	3.42d	2.70m	
1	*Z*	1.87d	5.65q	7.67q	3.32d	3.04m	3.71m
(NR_2 = Mp)	*E*	1.85d	5.23q	8.11q	3.44d	2.82m	
2a	*Z*	2.09d	6.79q	8.72q	3.57d	2.75m	1.56m
2a	*E*	2.17d	6.70q	8.28q	3.52d	2.89m	
2b	*Z*	2.21d	6.87q	8.72q	3.58d	2.99m	3.79m
2b	*E*	2.12d	6.67q	8.22q	3.51d	2.72m	
2c	*Z*	2.23d	7.03q	8.97q	3.72d	3.03m	1.64m
2c	*E*		6.86q	8.39q	3.63d		
2d	*Z*	2.24d	6.97q	8.89q	3.70d	2.83m	3.91m
2d	*E*	2.16d	6.68q	8.40q	3.63d	3.10m	
3a	–	1.20t	3.08q	8.52q	3.72d	4.15m	1.93m
3c	–	1.25t	3.12q (mask.)	8.70q	3.73d	4.22m	1.96m

[a] Pp – piperidine, Mp – morpholine. [b] The assignment of *E*- and *Z*-isomers is achieved by a comparison of experimental δ(CH=) values with those calculated by the increment equation.[5] The determination of *E,Z*-configurations of the *N*-protonated structure is carried out on the assumption that the predominant isomer of the enammonium salt which is formed immediately after addition of acid has the same configuration as the major isomer of the initial base.

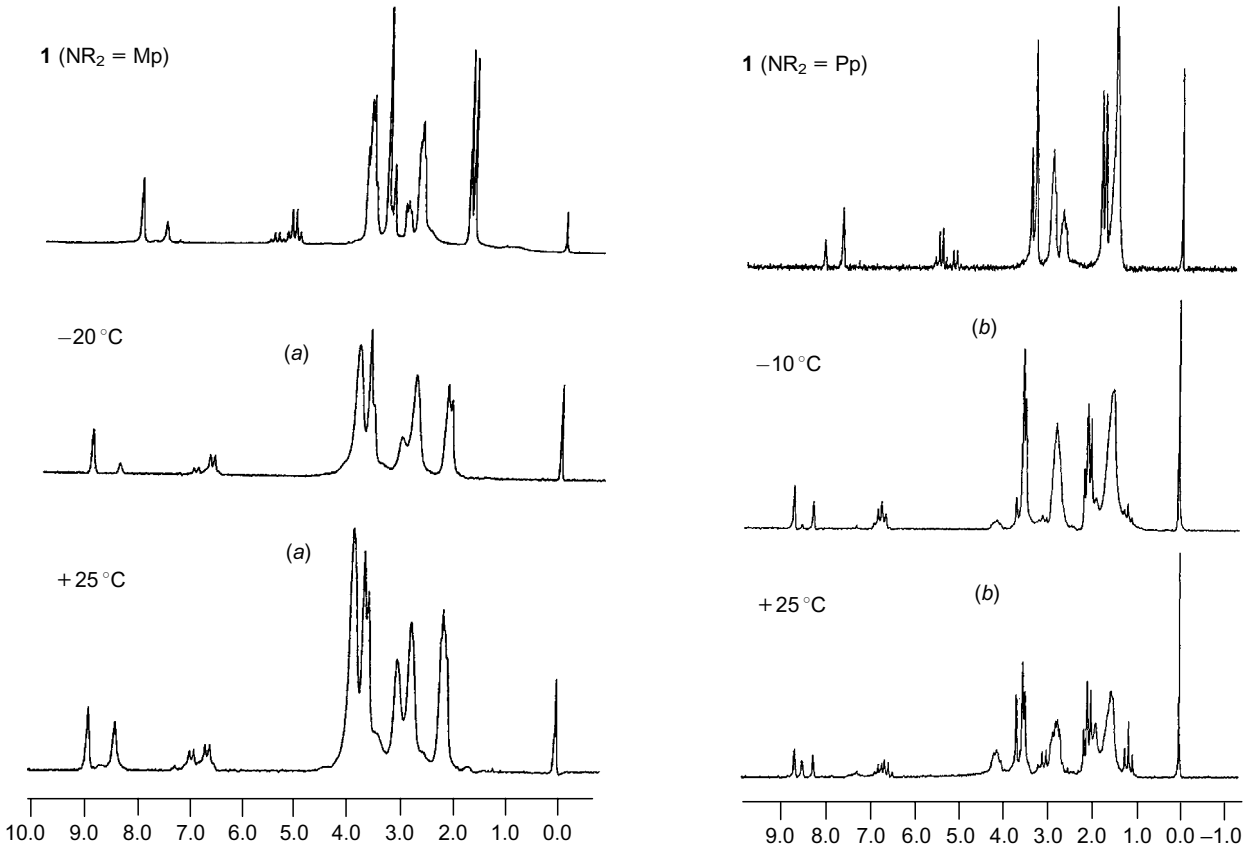


Fig. 1 ^{1}H NMR ($CDCl_3$/HMDS) monitoring of the reaction of (*a*) 1-(*N*-methylimino)-2-morpholinobut-2-ene with trichloroacetic acid; (*b*) 1-(*N*-methylimino)-2-piperidinobut-2-ene with trichloroacetic acid.

piperidine ring of the enammonium salt resonate at 4.20 ppm[8,9] while for piperidine trifluoroacetate this value is 3.03 ppm. The reaction dynamics are illustrated in Fig. 1.

Thus, the action of strong carboxylic acids on azomethine derivatives of *N,N*-disubstituted α-aminoenals **1** leads to the enammonium salt **2** which first undergoes *E,Z*-isomerisation followed by transformation in the case of piperidine derivative to the immonium salt **3** which exists in equilibrium with the enammonium structure **2**. Such stability of the enammonium salt can be explained by the C=C bond–azomethine group conjugation which occurs after the nitrogen electron pair is eliminated from conjugation with the C=C bond by protonation. However, the electron-withdrawing ability of the azomethine group is smaller than that of the aldehyde group. This results in the C_β-atom in the molecule of initial base **1** bearing a higher partial negative charge δ– than in the molecule of the carbonyl analogue. The decrease in the δ– value on the β-carbon atom in the molecule of azomethine **1** (NR_2 = Mp) can be attributed to a higher inductive effect of the diethyl ether group [$(CH_2CH_2)_2O$ $\sigma^* = +0.67$] compared to the pentamethylene group [$(CH_2)_5$ $\sigma^* = -0.18$].[11] Thus, in contrast to the enammonium salts of α-aminoenals, the enammonium salts of azomethines **2** possessing a highly basic amine fragment are able to undergo *N,C*-isomerisation to form the immonium salt **3**. We will discuss in more detail this transformation in the next paper.

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