

Spectral Study of the Reaction of Functionally Substituted Enehydrazides with Proton Donors

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Abstract—Reactions of new enehydrazides, *N,N'*-dimethyl-*N*-vinylpropenohydrazide and *N,N'*-dimethyl-*N*-vinylbenzohydrazide with chloroform, phenol, and hydrogen chloride in carbon tetrachloride were studied by IR spectroscopy. In the first two cases, molecular complexes are formed between the hydrazide and proton donor. The reaction of *N,N'*-dimethyl-*N*-vinylpropenohydrazide with HCl results in formation of dihydropyrazole derivative which exists as a tautomeric mixture of the major lactam and minor lactim forms. *N,N'*-dimethyl-*N*-vinylbenzohydrazide reacts with hydrogen chloride to give protonated form in which proton is localized on the amino nitrogen atom. The structure of the initial compounds and the products was analyzed in terms of AM1 quantum-chemical calculations.

Interest in new functionally substituted hydrazine derivatives, specifically in enehydrazines and enehydrazides, is explained by their high biological activity (which is responsible for their application in medicine) and the ability to undergo tautomeric and conformational transformations [1–5]. Some transformations of enehydrazines (provided that they have an appropriate structure) are not typical of common hydrazines, and they involve both nitrogen atoms simultaneously [2]. Although enehydrazines may be regarded as aza analogs of extensively studied enamines, the similarity in stereochemical behavior of enamines and enehydrazines is sometimes difficult to reveal since the latter have been studied poorly.

The most typical transformation of enehydrazines is cyclization to pyrroles or their fused analogs, which is accompanied by loss of one nitrogen atom. As a rule, such processes occur on heating or (in the presence of acids) even in the cold [2]. Acetylation of arylhydrazones [6] gives acyl derivatives of enehydrazines, which are converted into indoles on treatment with dilute acids or alkalis. Another important property of enehydrazines is enehydrazine–hydrazone tautomerism, which is formally analogous to keto–enol or imine–enamine tautomerism; however, there

are strong differences due to specific electronic structure of the enehydrazino group [1, 2, 4, 5, 7, 8].

It is also known that, despite the presence of several basic centers, enehydrazines are protonated at -70°C at the carbon atom (like enamines) to give hydrazone salts which were isolated in the crystalline state [9]. However, N-protonated species were not detected by spectral methods though the results of enehydrazine transformations in the presence of acids clearly indicate the existence of such forms. Presumably, the basicity of the nitrogen atoms is strongly reduced or the concentration of N-protonated species is very small.

In the recent years, increased number of studies were published, where the stereochemistry of hydrazine derivatives was examined by both experimental [1, 4, 10] and theoretical [11] methods. In the present work we studied by IR spectroscopy reactions with proton donors of new enehydrazides possessing unsaturated functional groups of different polarities: *N,N'*-dimethyl-*N*-vinylpropenohydrazide (**I**) and *N,N'*-dimethyl-*N*-vinylbenzohydrazide (**II**). As proton donors we used chloroform ($\text{p}K_{\text{a}} = 15$), phenol ($\text{p}K_{\text{a}} = 9.95$) in carbon tetrachloride, and dry hydrogen chloride ($\text{p}K_{\text{a}} = 7$) in carbon tetrachloride. We also

analyzed the electronic and steric structure of the initial compounds and products of their transformations in terms of the AM1 quantum-chemical method.

The IR spectra of dilute solutions of compounds **I** and **II** in carbon tetrachloride contain the following absorption bands, cm^{-1} : $\nu(\text{C-H})$ 3030–3120, $\nu(\text{C=O})$ 1660–1670, $\nu(\text{C=C})$ 1635–1615, $\nu(\text{C-N})$ 1315–1305, $\nu(\text{N-N})$ 1060, and $\omega(\text{CH=CH}_2)$ 960–970. This pattern is consistent with the enehydrazide structure [2, 12, 13]. The carbonyl and hydrazine groups each give a single band, though both hydrazides and enone systems in solution can exist as different conformers or their equilibrium mixtures (*Z* and *E* conformers) due to some degrees of freedom and restricted rotation about formally single bonds in conjugated systems, specifically about the amide C–N bond [2, 11]. The carbonyl absorption frequency is unexpectedly low, as compared to the frequency region 1680–1700 cm^{-1} typical of related hydrazides and enones [12–14].

Heating of solutions of enehydrazides **I** and **II** in decane to 130°C leads to appearance of a high-frequency $\nu(\text{C=O})$ band at 1680 cm^{-1} and increase in its intensity. By contrast, the amide $\nu(\text{C-N})$ band shifts to lower frequencies. The absence of concentration dependence of the carbonyl absorption frequency and intensity and similarity in the variation of the $\nu(\text{C=O})$, $\nu(\text{=CH})$, and $\omega(\text{=CH})$ bands with rise in temperature suggest that the corresponding fragments are involved in intramolecular hydrogen bond like $\text{C=O}\cdots\text{H-C=}$, which undergoes rupture as the temperature rises.

A different pattern of spectral changes is observed in a proton-donor solvent (chloroform) at room temperature: in addition to the main carbonyl absorption band at 1660 cm^{-1} , a low-frequency component appears at 1650 cm^{-1} . Simultaneously, the frequency and intensity of the $\nu(\text{C-N})$ band considerably increase (to 1330 cm^{-1}). These data indicate formation of a new, though weak, intermolecular hydrogen bond between the carbonyl group and proton-donor solvent and partial rupture of the intramolecular H-bond.

In the IR spectra of solutions of enehydrazines **I** and **II** in carbon tetrachloride in the presence of phenol we observed a new low-frequency carbonyl band at 1650 cm^{-1} and a broad band with two maxima at 3340 and 3430 cm^{-1} which belongs to associated hydroxy group of phenol. With excess phenol, the low-frequency absorption band at 1650 cm^{-1} predominates in the carbonyl region. The observed spectral changes unambiguously indicate formation of intermolecular hydrogen bond between the ene-

hydrazide and phenol and complete rupture of the intramolecular hydrogen bond.

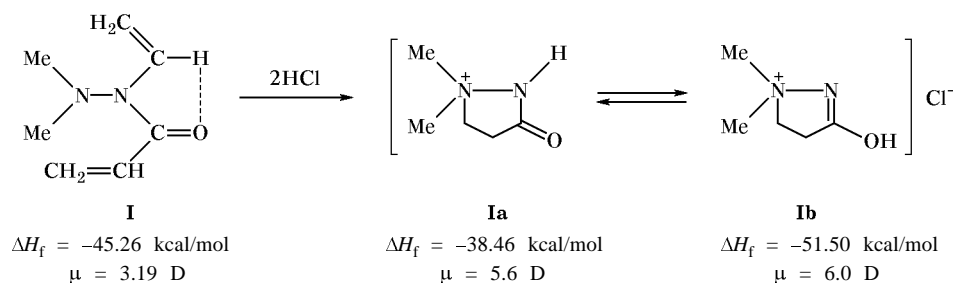
On the basis of the set of spectral shifts of the stretching vibration frequency of free phenolic OH group, which characterize complex formation with various bases [15], we can conclude that the observed shifts $\Delta\nu_{\text{OH}} = 262$ and ~ 400 cm^{-1} correspond to a 1:2 molecular complex with $\text{C=O}\cdots\text{H-O}$ and $\text{N}\cdots\text{H-O}$ intermolecular hydrogen bonds.

Radically different transformations occur in the reaction of enehydrazides **I** and **II** with dry hydrogen chloride in CCl_4 solution. When a solution of **I** in carbon tetrachloride was purged with dry HCl for 2 to 20 min, bands belonging to the vinyl group disappeared from the spectrum. Simultaneously, new bands at 1720 [$\nu(\text{C=O})$] and 3370 cm^{-1} [$\nu(\text{NH})$] and a series of characteristic bands at 1080, 1250, and 1360 cm^{-1} appeared, and their intensity sharply increased. This pattern should be interpreted as rupture of C=C bonds and formation of five-membered ring [16] with a secondary amide (lactam) group (the above frequencies are typical of a fixed *cis*-O=C–N–H moiety). In addition, strong amide II (1520 cm^{-1}) and amide III bands (1290 cm^{-1}) appear [12, 16], which are lacking in the spectrum of the initial enehydrazide. The bands at 2800 [$\nu(\text{N}^+\text{CH}_3)$], 1410 [$\delta(\text{N}^+\text{CH}_3)$], and 908 cm^{-1} [$\nu(\text{N}^+\text{-N})$] [16, 17] can be assigned with certainty to protonated form in which the positive charge is localized on the terminal nitrogen atom of the hydrazine fragment. The possibility for protonation of the N^α atom is ruled out, for in this case the $\nu(\text{N}^+\text{-H})$ frequency should be 3000 cm^{-1} or lower, as was shown for homoconjugated NH groups [18].

Elimination of the *N*-vinyl group from enehydrazide **I** by the action of HCl yields 1,1-dimethyl-4,5-dihydropyrazolinium-3-oxide (**Ia**) which is the major tautomer. However, the presence of minor tautomer **Ib** in solution cannot be excluded: in the IR spectrum we observed absorption at 1570 cm^{-1} due to endocyclic C=N bond [16]. Thus the product gives rise to lactam–lactim tautomerism (Scheme 1).

The geometric structure of initial compounds **I** and **II** was calculated for a large set of possible conformations with account taken of rotation about the C–N, C–C_{arom}, and N–N bonds. The most favorable conformers were selected on the basis of the lowest heats of formation, which correspond to *cis*-orientation of the hydrazine fragment with respect to the double bond. Schemes 1 and 2 give the structures, enthalpies of formation, and dipole moments of the predominant conformers of enehydrazides **I** and **II** and products of their transformations. It should be noted

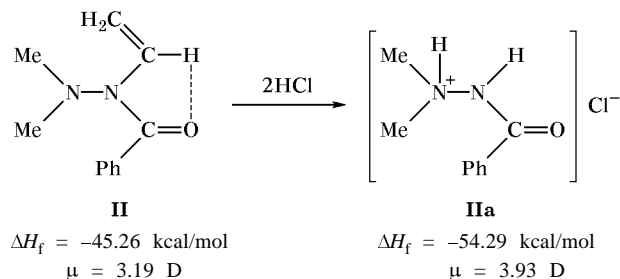
Scheme 1.



that, according to the ^1H NMR data [2], enehydrazines are characterized by *E* configuration of the hydrazine fragment with respect to symmetrically substituted double bond [2].

Variation of the IR spectrum on reaction of enehydrazide **II** with HCl in carbon tetrachloride unambiguously indicates removal of vinyl group from the molecule (the corresponding absorption bands disappear from the spectrum) and formation of secondary acyclic amide group: the observed $\nu(\text{NH})$ and $\nu(\text{C}=\text{O})$ frequencies, 3400 and 1690 cm^{-1} , respectively, are consistent with the spectra of benzohydrazides [12]. Amide II (1510 cm^{-1}) and amide III bands (1315 cm^{-1}) are also present. Taking into account appearance of new bands, $\nu(\overset{+}{\text{N}}\text{CH}_3)$ 2820, $\delta(\overset{+}{\text{N}}\text{CH}_3)$ 1420, and $\nu(\text{N}-\text{N})$ 910 cm^{-1} , the observed IR pattern indicates protonation of 1,1-dimethyl-2-benzoylhydrazine (**IIa**) at the N^β atom (Scheme 2). No other tautomeric forms were detected.

Scheme 2.



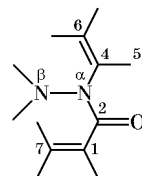
The results obtained are in agreement with our previous data for hydrazides derived from carboxylic and fluorocarboxylic acids, which are protonated at the amino nitrogen atom [12].

According to the AM1 calculations, lactam form **Ia** is more favorable than lactim tautomer by a $\Delta\Delta H$ value of 13.04 kcal/mol. Analogous results ($\Delta\Delta H = 14 \text{ kcal/mol}$) were obtained by Feshin *et al.* [19] who studied protonation of carboxylic acid hydrazides *ab initio*.

The results of our calculations indicate the existence in molecules **I** and **II** of shortened intramolecular contacts $\text{C}=\text{O}\cdots\text{H}-\text{C}=\text{C}$ 2.068 Å, which are considerably shorter than the sum of the corresponding van der Waals radii. These data support the presence of intramolecular hydrogen bond which stabilizes the *Z* configuration. The assumed orientation of the enone fragment in **I** with respect to the N–N bond is additionally stabilized by attractive interaction between the 1-H atom and hydrogen atom of one of the methyl groups at the terminal nitrogen atom (shortened $\text{H}\cdots\text{H}$ contact, 2.02 Å).

Table 1 contains the geometric parameters of compounds **I** and **II**, optimized by the AM1 procedure. It is seen that molecule **II** is characterized by greater acoplanarity of the enehydrazine fragment and carbonyl group. The torsion angle $\text{N}^\alpha\text{N}^\beta\text{C}^2\text{C}^1$ is 9°, while the corresponding angle in molecule **I** is 2° (for atom numbering, see Scheme 3). The enehydrazine moiety in both molecules is fairly planar: the torsion angle $\text{C}^6\text{C}^4\text{N}^\alpha\text{N}^\beta$ does not exceed 3°. The fragment involved in intramolecular hydrogen bond is also flattened (within 1–5°), which undoubtedly creates favorable steric conditions for hydrogen bonding and effective conjugation.

Scheme 3.



The benzene ring in molecule **II** is almost orthogonal to the carbonyl group plane (the corresponding torsion angle is 92°), while the vinyl group in the enone fragment of **I** forms an angle of 38° with respect to the carbonyl group plane. Analysis of the geometric parameters shows that steric conditions in molecule **I** are more favorable for formation of

Table 1. Geometric parameters of molecules **I** and **II**, optimized by the AM1 method^a

Bond	<i>d</i> , Å		Angle	ω, deg		Angle	φ, deg	
	I	II		I	II		I	II
C=O	1.24	1.24	NNC ²	117.9	117.7	N ^α N ^β C ² C ¹	4.3	9.0
N–N	1.38	1.38	N ^α C ² C ¹	119.9	119.8	N ^α C ² C ¹ C ⁷	–155.0	52.3
N ^α –C ²	1.42	1.42	OC ² N ^α	118.5	118.8	OC ² N ^α N ^β	–176.0	–171.5
C ¹ –C ²	1.48	1.49	N ^α C ⁴ C ⁶	127.8	127.9	C ⁶ C ⁴ N ^α N ^β	2.1	2.9
N ^α –C ⁴	1.41	1.41	N ^α C ⁴ C ⁵	112.0	112.1	H ⁵ C ⁴ N ^α N ^β	–177.8	–177.8
C ⁴ –C ⁶	1.34	1.34	C ⁴ N ^α C ²	118.5	117.5	H ⁵ C ⁴ N ^α C ²	5.1	–1.3

^a For atom numbering, see Scheme 3.

a π - p - π -type cross-conjugated system with participation of multiple bonds surrounding the N–N group.

The p , π -conjugation in hydrazine derivatives was studied in most detail using hydrazones as examples [3]. Only scanty data are available for the other derivatives. As a result of conjugation, the whole enehydrazine fragment tends to adopt a planar conformation. However, the N^β atom in the enehydrazides under study has a pyramidal configuration, the sum of the bond angles thereat being 337° and 343° for compounds **I** and **II**, respectively; the height of the nitrogen pyramid is 0.65–0.7 Å. A conclusion can be drawn that hybridization of the terminal nitrogen atom (N^β) is closer to sp^3 . Obviously, these conditions determine the accessibility of unshared electron pair on the terminal nitrogen atom to nucleophilic attack and protonation. The sum of the bond angles at the N^α is almost equal to 360°, and the pyramid height is close to zero; these data indicate the maximal p -character of the nonhybridized atomic orbital.

The results of calculations revealed a composite molecular orbital formed by five individual atomic orbitals with various contributions. For compound **I**, these contributions are as follows: N^α 86.23, C² 6.86, C⁴ 2.88, C¹ 1.74, O 1.16%, and for compound **II**, N^α 86.53, C² 6.77, C⁴ 2.76, C¹ 1.69, O 1.17%. These values are consistent with formation of a cross-conjugated system with maximal localization of electron density on the N^α atom.

The structure of cyclic tautomer **Ia**, formed by reaction of compound **I** with hydrogen chloride, may be represented as a ring with alternating deviations of nodal atoms from the plane within a torsion angle of 2–6°. The N–H bond in the ring-fixed amide fragment declines from the C–N plane by 15°. The carbonyl group deviates insignificantly (by 2°). The N–N bond length increases to 1.51 Å relative to 1.384 Å in initial enehydrazide **I**, while the C²–N^α

bond, in contrast, acquires an “amide character” and shortens from 1.422 to 1.382 Å, the latter value being typical of amides. The geometric parameters are consistent with the spectral data.

Comparative analysis of the π -orders (P^π) of principal bonds in initial enehydrazide **I** and predominant tautomer **Ia** also indicates a pronounced amide p , π -conjugation (specific delocalization of the unshared electron pair on the nitrogen over the π -C=O bond. This follows from increased π -order of the C–N bond (0.288) and reduced π -order of the C=O bond (0.766; see Table 2). The π -order of the C²–C¹ bond in aromatic enehydrazide **II** is considerably lower (0.044) than in its analog **I** (0.059). This is consistent with rupture of π , π -conjugation between the aromatic ring and the carbonyl group, which are turned apart through an angle of 92°. In addition, the π -order of the N–N bond in compound **Ia** is considerably reduced (to 0.019) against the value 0.043 for initial compound **I** and especially relative to the corresponding value for protonated enehydrazide **IIa** (0.06). These data indicate strong differences in the electron density delocalization in the initial enehydrazides and products of their transformations.

Table 2. π -Orders of bonds (P^π) in initial compounds **I** and **II** and their protonated forms **Ia** and **IIa**, according to the results of AM1 calculations^a

Bond	I	Ia	II	IIa
N–N	0.043	0.019	0.043	0.06
N ^α –C ²	0.198	0.288	0.199	0.189
C=O	0.805	0.766	0.823	0.835
C ² –C ¹	0.059		0.046	0.044
N ^α –C ⁴	0.113		0.111	
C ⁴ –C ⁶	0.922		0.927	

^a For atom numbering, see Scheme 3.

Thus enehydrazides react with proton donors, chloroform and phenol, to form intermolecular complexes. The reaction of enehydrazide **I** with a mineral acid, HCl, gives a cyclic product protonated at the N^β atom, which exists as two tautomers **Ia** and **Ib**. Enehydrazide **II** reacts with hydrogen chloride with formation of acyclic product **IIa** protonated at the amino nitrogen atom. The spectral parameters of the initial compounds and products of their transformations agree well with the results of AM1 quantum-chemical calculations.

EXPERIMENTAL

Initial compounds were synthesized by the procedures described in [20]. The IR spectra were measured on a Specord 75IR two-beam spectrophotometer; cells with a layer thickness of 0.01 to 0.5 cm were used. In order to eliminate distortions of the shape of the νOH band of phenol in the presence of bases, a cell of the same thickness containing a solution of the base was placed in the reference channel. The concentration of phenol was 5×10^{-4} M, and that of the base, 3×10^{-2} M. The temperature measurements were performed with the aid of a temperature adapter (Karl Zeiss, Jena) with a calibrated thermocouple.

Solutions of enehydrazides in dry carbon tetrachloride (2 ml) were purged with dry HCl over a period of 2, 10, and 20 min (in succession), each time the IR spectrum was recorded.

AM1 calculations were performed using MOPAC.6 software package [21].

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