ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 4, pp. 676–681. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © L.D. Popov, S.I. Levchenkov, I.N. Shcherbakov, A.A. Tsaturyan, O.I. Askalepova, O.V. Maevskii, A.A. Zubenko, V.A. Kogan, 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 4, pp. 596–601.

Synthesis, Physicochemical Study, and Quantum-Chemical Simulation of Hydrazones Based on 2-Hydrazinoimidazoline

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Received April 4, 2013

Abstract—2-Imidazolinylhydrazones of salicylic aldehyde, 2-*N*-tosylaminobenzaldehyde, and 1-phenyl-3-methyl-4-formylpyrazolone-5 are synthesized and studied by the IR, NMR, and electronic spectroscopy. Quantum chemical calculations of geometry and total energy of possible tautomers in a vacuum and ethanol solution are carried out. It is shown that in all cases diazine tautomers are the most stable.

Keywords: hydrazones, modeling, tautomerizm, DFT calculations

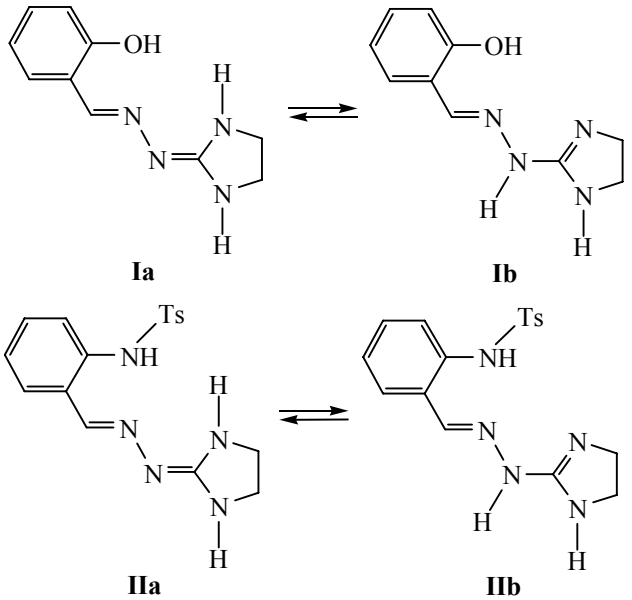
DOI: 10.1134/S1070363214040124

Interest of researchers to hydrazinoimidazoline and hydrazones on its basis is caused most of all by their high biological activity. Series of hydrazine-imidazoline hydrazones and their antimicrobial, fungicidal, cytotoxic, and anticancer activity is studied in [1–4]. Imidazolinylhydrazones as well as other representatives of this class of compounds exhibit a high complex formation ability. Complexes on their basis are also biologically active. Pt(II) and Pd(II) complexes with hydrazinoimidazoline are described [5–7]. Former is considered to be a possible analog of cysplatine [7]. The preparation of copper(II) dimeric complexes on the basis of pyridin-2-carbaldehyde imidazolylhydrazone containing two mononuclear [Cu(L)Br] fragments bound with the sulfate bridge was reported [8]. Nevertheless, systematic studies of complex formation ability of imidazolinylhydrazones are absent up to now.

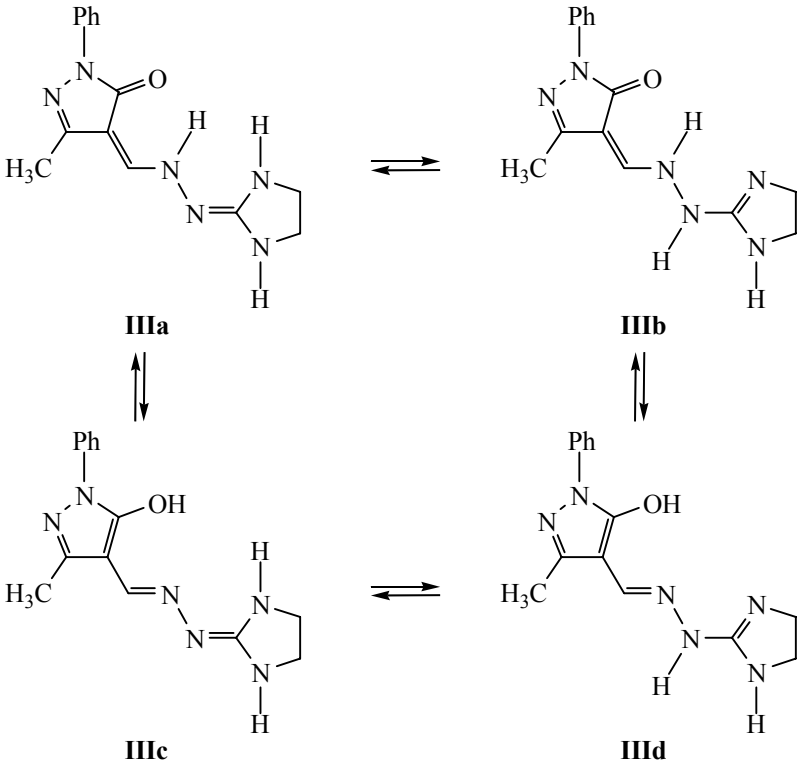
We report here on results of synthesis, physico-chemical study, and quantum-chemical simulation of 2-imidazolinylhydrazones of salicylic aldehyde, 2-*N*-tosylaminobenzaldehyde, and 1-phenyl-3-methyl-4-formylpyrazolone-5. The composition and structure of isolated compounds are established from elemental analysis, mass, IR, electronic, and ^{1}H NMR spectra (see Experimental).

For compounds **I**–**III** a series of tautomeric forms is possible. All of them may be divided in two groups, the diazine (**a**) and hydrazone (**b**) tautomers (Scheme 1).

Scheme 1.



Scheme 2.



For imidazolinylhydrazone of 1-phenyl-3-methyl-4-formylpyrazolone the tautomerism of aldehyde fragment with the formation of pyrazolone (**a, b**) or hydroxypyrazole tautomers (**c, d**) must also be considered [9–12] (Scheme 2).

In the mass spectra of compounds **I–III** peaks related to molecular ions are found (*m*/*z* 204, 357, and 284 respectively). The presence in the IR spectrum of compound **III** of an absorption band at 1699 cm^{-1} corresponding to the stretching vibrations of C=O bond permits a conclusion that this substance exists in the pyrazolone form. In the ^1H NMR spectra of compounds **I–III** a singlet of four protons of methylene groups and broadened singlet of two NH-groups are observed. It suggests that all the compounds exist in diazine form due to the transfer of hydrazone proton to the imidazoline nitrogen atom. Upon addition of D_2O the signals of OH protons (for compound **I**) and NH groups are completely suppressed indicating their involvement in the exchange. Note also than in the ^1H NMR spectra of the other imidazolinylhydrazones the singlet signal of protons of CH_2 groups of imidazoline fragment is also registered [2, 3]. For imidazolinylhydrazones of 2-aminobenzophenone and 3-hydroxy-5-pregnan-20-one the X-ray diffraction analysis showed that these compounds existed also in diazine form in the crystalline state [3, 13].

For more detailed evaluation of the relative stability of tautomeric forms of hydrazones **I–III** a quantum chemical calculation of total energy, electronic and spatial structure of possible tautomers within the frame of density functional theory (DFT) in a vacuum and in ethanol solution was carried out. Hybride exchange-correlational B3LYP functional was used [14–16]. Geometric structure of molecules under consideration was preliminary optimized by all natural variables without the limitations by symmetry. Minimum points on the potential energy surface were identified for each structure by calculation of matrix of force constants and normal vibration frequencies. Expanded 6-311+G(*d,p*) basis was set used. The consideration of the effect of solvent was performed within the approximation of polarizable continuum model, PCM [17].

The most stable form of hydrazone **I** is diazine tautomer **Ia** (Fig. 1). Hydrazone tautomer **Ib** is destabilized with respect to form **Ia** in a vacuum by 8.0 kcal/mol, in ethanol solution the difference in energy of tautomers decreases to 7.3 kcal/mol (Table 1).

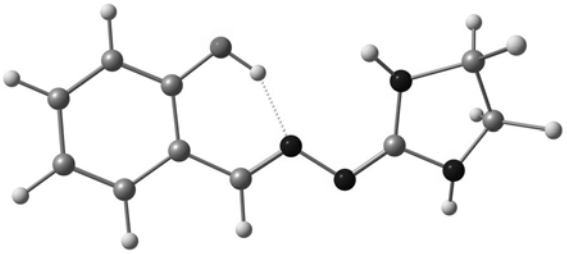


Fig. 1. Structure of the most stable form of compound **I** in a vacuum according to the calculated data.

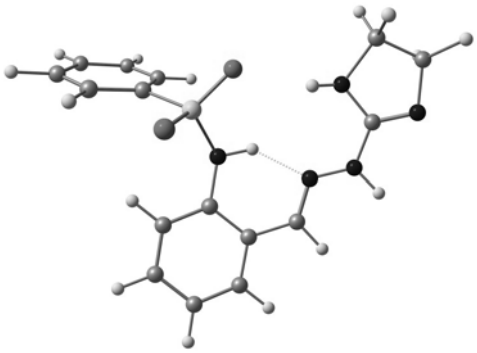


Fig. 2. Structure of the most stable form of compound **II** in a vacuum according to the calculated data.

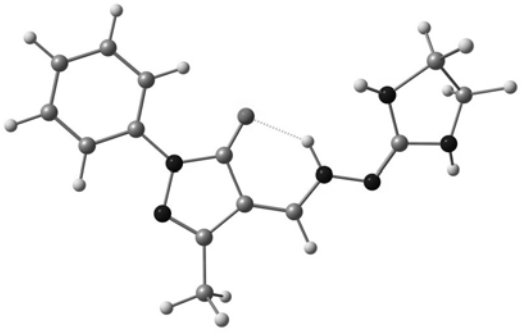


Fig. 3. Structure of the most stable form of compound **III** in a vacuum according to the calculated data.

Note that realization of quinone tautomeric forms for compound **I** is practically impossible because the energy of the most stable among them in a vacuum is by more than 30 kcal/mol higher than that of tautomer **Ia**.

In the case of 2-*N*-tosylaminobenzaldehyde imidazolinylhydrazone the difference in total energy of tautomers **IIa** and **IIb** in a vacuum is 8.8 kcal/mol. In going to ethanol solution it also decreases insignificantly to 7.5 kcal/mol (Table 1, Fig. 2).

The structure of compound **III** offers more possibilities for prototropic tautomerism than in the case of hydrazones **I** and **II**. Due to that calculation of total energy was carried out for tautomers **IIIa–IIId** as well as for the forms potentially possible in the case of acylpyrazolone derivatives corresponding to proton transfer to the nitrogen atom of pyrazole ring [9, 11, 18–21]. Nevertheless, the form most stable among them in a vacuum occurred to be by 12.5 kcal/mol less stable than pyrazolonodiazine tautomer **IIIa** (Fig. 3). Pyrazolonodiazine tautomer **IIIb** is destabilized against the latter by 9.4 kcal/mol while total energy of hydroxypyrazole tautomers **IIIc** and **IIId** in a vacuum is only by 2.5 and 3.9 kcal/mol higher than that of compound **IIIa** (Table 1). But in ethanol solution DE values of hydroxypyrazole tautomers significantly increase, and it is possible to suggest that in solution the presence of only pyrazolonodiazine tautomer **IIIa** may be expected. Results of calculations agree well with the ^{1}H NMR and IR spectroscopy data for compound **III**.

The presence of labile protons as well as of nitrogen atoms capable of addition of protons in hydrazones **I–III** implies the possibility of various protolytic equilibria in the solutions of substances under study. Protolitic properties of the compounds **I–III** were studied by potentiometry and electronic spectroscopy.

The potentiometric titration of water-ethanol solutions of hydrazones **I–III** showed that in all cases in the pH range 2–12 only two equilibria including evidently the protonated, molecular, and monodeprotonated forms of hydrazones are observed.

$$H_2L^+ \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} HL \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} L^-.$$

Table 1. Total energy (a. u.) and relative stability (ΔE, kcal/mol) of tautomer forms of compounds **I–III**

Comp. no.	Total energy, a .u.		ΔE, kcal/mol	
	vacuum	ethanol	vacuum	ethanol
Ia	–682.69020	–682.71408	0	0
Ib	–682.67749	–682.70244	8.0	7.3
IIa	–1442.55825	–1442.58821	0	0
IIb	–1442.54415	–1442.57626	8.8	7.5
IIIa	–947.08497	–947.11583	0	0
IIIb	–947.06996	–947.10216	9.4	8.6
IIIc	–947.06603	–947.09315	2.5	14.2
IIId	–947.07881	–947.10466	3.9	7.0

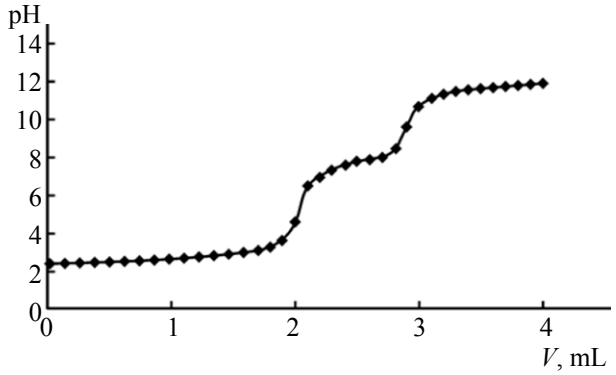


Fig. 4. Curve of potentiometric titration of 2×10^{-3} M solution of compound **II** containing equimolar amount of HCl with 0.1 M NaOH solution.

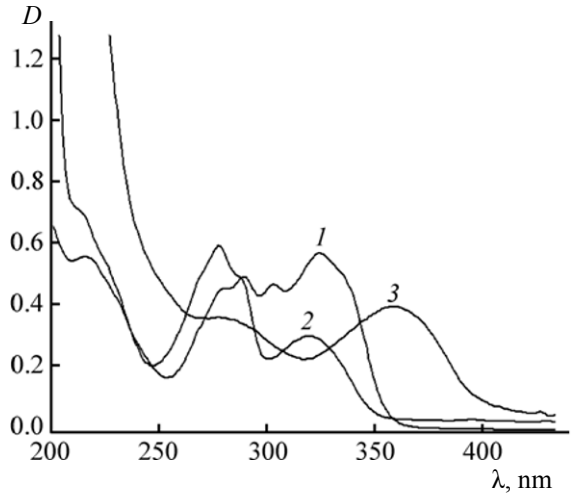


Fig. 5. Electron absorption spectra of 2×10^{-5} M solution of hydrazone **I** in water–ethanol mixture in (*1*) neutral, (*2*) acidic (c_{HCl} 0.5 M), and (*3*) alkaline (c_{NaOH} 0.05 M) medium.

Potentiometric titration curves for all compounds under study resemble one another. Therefore we present only the titration curve for compound **II** (Fig. 4).

The calculation of ionization constants was carried out according to formula (1) obtained by the combined solution of the equations of material balance and electroneutrality.

$$pK_{ai} = pH + \log \frac{(1-a)c_R - [H^+] + [OH^-]}{ac_R + [H^+] + [OH^-]}. \quad (1)$$

Here K_{ai} is the *i*th ionization constant, a is the neutralization degree, C_R is the total concentration of hydrazone [18]. Values of constants characterizing the equilibria of protonation (pK_{a1}) and deprotonation (pK_{a2}) for compounds **I–III** and calculated from the potentiometric data are listed in Table 2.

The investigation of electron absorption spectra of hydrazones **I–III** in water-ethanol solutions at different pH showed that the long-wave absorption band corresponding to n–π* transfer in acidic medium undergoess a slight blue shift (5 nm for compounds **I**, **II** and 10 nm for hydrazone **III)**. In the alkaline medium long-wave absorption band undergoes a red shift by 35, 25, and 10 nm respectively which is caused by the formation of deprotonated form of hydrazones (Fig. 5).

EXPERIMENTAL

Elemental analysis was carried out on a Perkin-Elmer 240 C instrument in the laboratory of micro-analysis of Southern Federal University. IR spectra were registered on a Varian Scimitar 1000 FT-IR spectrometer in the range 400-4000 cm^{-1} from suspensions in mineral oil. ^1H NMR spectra were taken on a Varian Unity 300 (300 MHz) spectrometer in DMSO-d_6 using a pulse Fourier regime, internal reference HMDS. Mass spectra were obtained on a Bruker Autoflex II spectrometer with the electrospray ionization. Electron absorption spectra were recorded on a Varian Cary 50 Scan spectrophotometer in the range 200–800 nm. Measurements of pH and potentiometric evaluation of ionization constants were carried out on Ecotest-120 pH-meter-ionometer.

Quantum-chemical calculations were carried out employing Gaussian'03 [22] program. For the preparation of data and visualization of the results ChemCraft program [23] was used.

For the synthesis of hydrazones commercially available hydrazinoimidazoline dihydrobromide was used.

Hydrazones **I–III** were prepared as follows. Hot solution of 2 mmol of hydrazinoimidazoline dihydro-

Table 2. Values of ionization constants of hydrazones **I–III** found by potentiometric method

Comp. no.	pK_{a1}	pK_{a2}
I	5.6 ± 0.1	7.6 ± 0.1
II	3.0 ± 0.2	8.0 ± 0.1
III	4.4 ± 0.1	8.8 ± 0.1

bromide in 10 mL of ethanol was treated with equimolar amount of sodium acetate, and the resulting mixture was refluxed for 10 min. After that a hot solution of 2 mmol of salicyl aldehyde, 2-*N*-tosylaminobenzaldehyde, or 1-phenyl-3-methyl-4-formylpyrazolone-5 in 10 mL of ethanol was added. The reaction mixture was refluxed for 2 h and left overnight. The obtained precipitate was filtered off, washed with water and ethanol, and crystallized from ethanol.

2-[(4,5-Dihydro-1*H*-imidazol-2-yl)hydrazonomethyl]phenol (I). Yield 0.25 g (60%). Mp > 250°C. IR spectrum, ν, cm^{-1}: 3250 ν(OH), 3172 ν(NH), 1670, 1601 ν(C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 11.158 s (1H, OH), 8.234 s (1H, CH-azomethine), 7.42 d (1H, *J* 7.8 Hz, CH-arom.), 7.20 br.s (2H, NH), 7.13-7.18 m (1H, CH-arom.), 6.80–6.85 m (2H, CH-arom.), 3.456 s (4H, CH_2). Electron absorption spectrum (ethanol), λ, nm (ε, L cm^{-1} mol^{-1}): 289 (27550), 324 (28150). Mass spectrum: *m*/*z* 204, 187, 177. Found, %: C 59.14, H 6.03, N 24.54. $C_{10}H_{12}N_4O$. Calculated, %: C 58.81, H 5.92, N 24.43.

***N*-{2-[(4,5-Dihydro-1*H*-imidazol-2-yl)hydrazonomethyl]phenyl}-4-methylbenzolsulfonamide (II).** Yield 0.32 g (45%), mp 225°C. IR spectrum, ν, cm^{-1}: 3314, 3140 ν(NH), 1657 ν(C=N), 1332 $\nu_{as}(SO_2)$, 1154 $\nu_s(SO_2)$. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 11.55 s (1H, NH), 8.23 s (1H, CH-azomethine), 7.58–7.65 m (3H, CH-arom.), 7.4 br.s (2H, NH), 7.32 d (2H, CH-arom., *J* 9.0 Hz,), 7.02–7.18 m (3H, CH-arom.), 3.56 s (4H, CH_2), 2.49 s (3H, CH_3). Electron absorption spectrum (ethanol), λ, nm (ε, L cm^{-1} mol^{-1}): 285 (9200), 305 (8500). Mass spectrum: *m*/*z* 357, 329. Found, %: C 57.25, H 5.26, N 19.31. $C_{17}H_{19}N_5O_2S$. Calculated, %: C 57.13, H 5.36, N 19.59.

4-[(4,5-Dihydro-1*H*-imidazol-2-yl)hydrazonomethyl]-5-methyl-2-phenyl-2*H*-pyrazol-3-ol (III). Yield 0.29 g (50%). mp > 250°C. IR spectrum, ν, cm^{-1}: 3120,3064 ν(NH), 1699 ν(C=O), 1624, 1595 ν(C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 16.190 s (1H, NH), 8.196 br.s (2H, NH), 7.97 d (2H, CH-arom., *J* 7.8 Hz,), 7.27–7.32 m (2H, CH-arom.), 7.03 t (1H, CH-arom., *J* 7.8 Hz,), 7.622 s (2H, CN-arom.), 6.864 s (2H, CH-azomethine), 3.568 s (4H, CH_2), 2.084 s (3H, CH_3). Electron absorption spectrum (ethanol), λ, nm (ε, L cm^{-1} mol^{-1}): 269 (27550), 305 (6050). Mass spectrum: *m*/*z* 284, 185, 177, 152. Found, %: C 58.91, H 5.77, N 29.34. $C_{14}H_{16}N_4O$. Calculated, %: C 59.14, H 5.67, N 29.56.

ACKNOWLEDGMENTS

The work was carried out with the financial support of Russian Fundation for Basic Research (grant no. 12-03-3691-mol_a)

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