

## Acid–Base Properties and Prototropic Tautomerism of Isomeric 1,2,4-Triazin-3- and -5-ones

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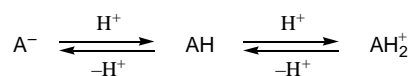
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**Abstract**—The acidity and basicity constants of isomeric phenyl(aryl)-1,2,4-triazin-3- and -5-ones in aqueous solution were determined by spectrophotometry:  $pK_a = 7.3\text{--}6.2$ ;  $pK_{BH^+} = 0.1\text{ to }-2.2$ . 1,2,4-Triazin-3-ones are weaker bases than the corresponding 1,2,4-triazin-5-ones. According to the AM1 calculations, the most thermodynamically favorable tautomer in the gas phase is the oxo form: namely, 2*H*-tautomers of the neutral bases and 2,4-*H*,*H*<sup>+</sup>-tautomers of the conjugate acids.

1,2,4-Triazinones are structurally similar to fragments of some natural macromolecules. Also, 1,2,4-triazine ring constitutes a part of several recently developed medicines, chemical means for plant protection, and other biologically active compounds [1–3]. The biological activity of 1,2,4-triazinone derivatives is largely determined by their ability to take up or lose a proton [4]. 1,2,4-Triazinones behave as both acids and bases [5]. The basic centers in these compounds may be both nitrogen atoms in the heteroring and exocyclic oxygen atom. Protonated 1,2,4-triazinones can also give rise to prototropic tautomerism, and tautomeric equilibria intrinsic to their ionized and neutral forms may be different.

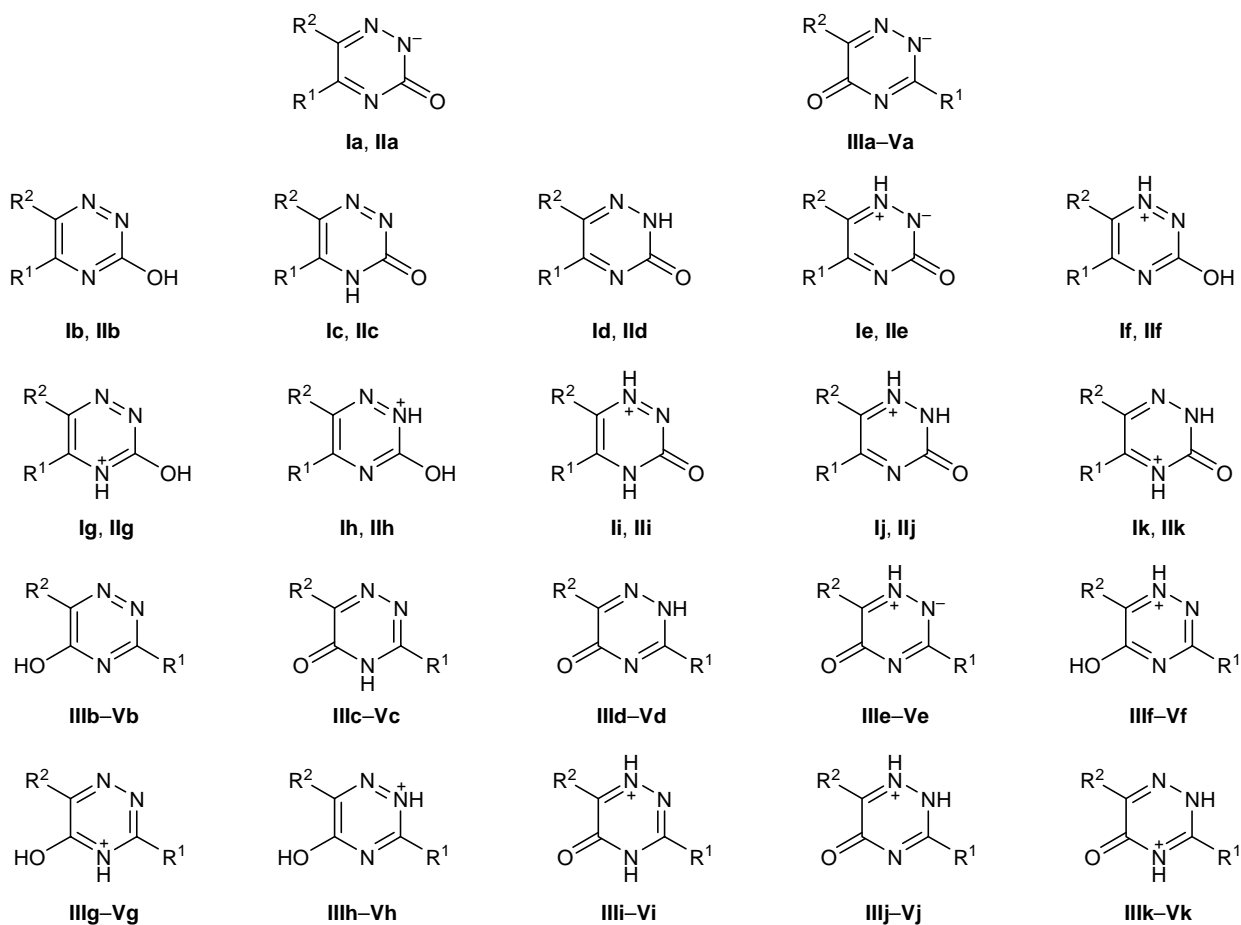


Quantitative data on protolytic equilibria with participation of 1,2,4-triazinones were given in original publications [6–12, 14–20] and were summarized in [5, 13]. According to published data, in most cases substituted 1,2,4-triazin-3- and -5-ones in solution exist preferentially in the oxo form and the 2*H*-tautomer as a rule prevails [5]. The  $pK_a$  and  $pK_{BH^+}$  values of a large number of amino-1,2,4-triazinones were reported in [11, 16, 17]. It was shown that their acid dissociation occurs in the pH range from 7 to 12 and that they undergo protonation at pH 1 to 5. However, despite

a large number of the examined compounds, the basicity and acidity of the 1,2,4-triazinone ring itself cannot be estimated unambiguously, for the amino group is also capable of participating in protolytic equilibria. The acidity and basicity constants of the simplest 1,2,4-triazinones remain so far unknown.

In the present work we determined by spectrophotometry the acid dissociation constants ( $pK_a$ ) and basicity constants ( $pK_{BH^+}$ ) of a series of substituted 1,2,4-triazin-3-ones **I** and **II** and 1,2,4-triazin-5-ones **III–V** in which the substituent (a phenyl or aryl group) occupies different positions in the heteroring. The gas-phase enthalpies of formation of tautomeric forms of the neutral bases and their conjugate acids were calculated by the AM1 semiempirical method. Comparison of experimental data on protolytic equilibria in solution with the results of theoretical calculations for the gas phase was repeatedly showed to be appropriate [21, 22]. Our choice of the AM1 approximation was based on the good applicability of this method for calculation of thermodynamic parameters of aromatic nitrogen-containing heterocycles [23, 24].

Taking into account that prototropic tautomerism is possible for both neutral bases and conjugate acids of 1,2,4-triazin-3- and -5-ones **I–V**, one anionic form (**a**), four neutral tautomers (**b–e**), and six monocationic forms (**f–k**) may be presumed. Obviously, the thermodynamic stabilities of the neutral tautomers and the corresponding conjugate acids should be different.

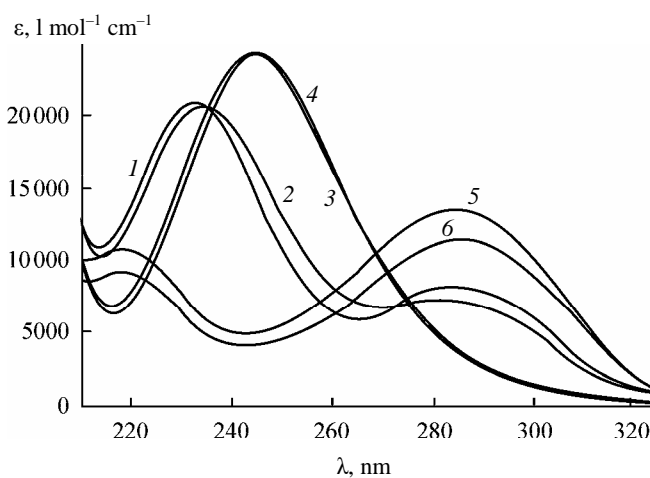


**I, III**, R<sup>1</sup> = Ph, R<sup>2</sup> = H; **II, IV**, R<sup>1</sup> = H, R<sup>2</sup> = Ph; **V**, R<sup>1</sup> = 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = H.

First of all, we recorded the UV spectra of compounds **I–V** in an organic solvent (ethanol) and buffer solutions. Figure 1 shows the UV spectra of triazinone **III** at different pH values. It is seen that the spectra of **III** in ethanol and in a buffer solution with pH 5.39 are very similar; therefore, they can be assigned to the same neutral form. In going to buffer solutions with pH > 7, we observed a considerable blue shift of the absorption maximum, presumably due to formation of anion A<sup>-</sup>. An analogous pattern was also typical of the other examined compounds.

The electron absorption spectra of triazinones **I–V** in solutions with different acidities are characterized by three absorption bands which correspond to anion A<sup>-</sup>, neutral base AH, and cation AH<sub>2</sub><sup>+</sup> (Fig. 1). All these compounds show a red shift of the absorption maxima in going from the anion to neutral base and then to monocation. This pattern is typical of aromatic nitrogen-containing heterocycles [25, 26]. However, the spectral variations observed in going from anion to neutral molecule and from neutral molecule to mono-

cation are different for compounds **I–V** (Table 1). This may be due to specificity of conjugation between the phenyl substituent and the heteroring in each particular



**Fig. 1.** UV absorption spectra of 3-phenyl-1,2,4-triazin-5-one (**III**) in solutions: (1) pH 8.17, (2) pH 7.15, (3) pH 5.39, (4) ethanol, (5) H<sub>0</sub> 8.7, (6) H<sub>0</sub> -9.4.

**Table 1.** UV spectra,  $\lambda_{\max}$ , nm (log  $\epsilon$ ), of 1,2,4-triazin-3- and -5-ones **I–V** in media with different acidities

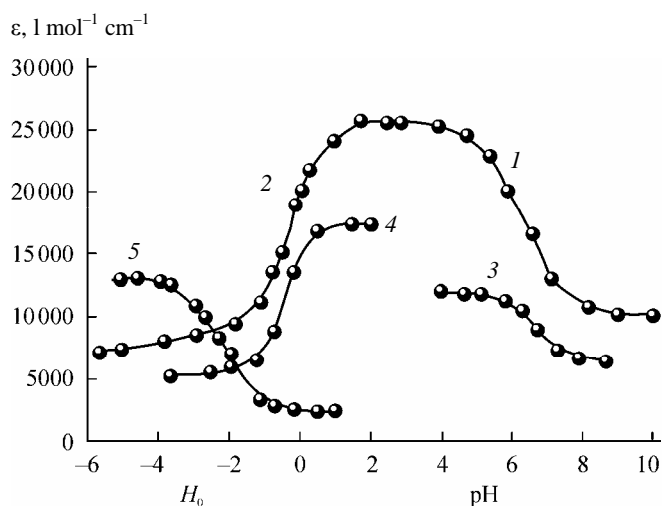
Comp. no.	Anion $A^-$		Neutral base AH		Cation $AH_2^+$	
	$\lambda_{\max}$ , nm (log $\epsilon$ )	pH	$\lambda_{\max}$ , nm (log $\epsilon$ )	pH	$\lambda_{\max}$ , nm (log $\epsilon$ )	$-H_0$
<b>I</b>	300 (3.978), 240 (3.892)	7.85	285 (3.973)	2.96	320 (3.982)	6.32
<b>II</b>	–	–	–	–	260 (4.204)	6.32
<b>III</b>	230 (4.322), 290 (3.778)	8.17	248 (4.415)	3.96	290 (4.114)	8.7
<b>IV</b>	270 (3.903), 330 (3.903)	7.85	300 (4.161)	2.30	370 (4.279)	6.32
<b>V</b>	240 (4.190), 290 (3.845)	7.3	255 (4.255)	2.30	295 (4.079)	1.92

**Table 2.** Acidity and basicity constants of 1,2,4-triazinones **I–V** in aqueous solution, calculated by Eqs. (1) and (2)

Comp. no.	Deprotonation					Protonation				
	$\lambda$ , nm	$pK_a$	$x$	$r$	$n$	$\lambda$ , nm	$pK_{BH^+}$	$m$	$r$	$n$
<b>I</b>	356	$7.78 \pm 0.01$	$0.98 \pm 0.06$	0.995	6	345	$-2.26 \pm 0.02$	$0.98 \pm 0.05$	0.996	6
<b>II</b>	–	–	–	–	–	230	$-1.19 \pm 0.01$	$1.06 \pm 0.06$	0.998	5
<b>III</b>	255	$6.21 \pm 0.08$	$0.91 \pm 0.05$	0.993	6	250	$-0.2 \pm 0.01$	$0.94 \pm 0.07$	0.992	9
<b>IV</b>	265	$6.62 \pm 0.03$	$0.94 \pm 0.07$	0.997	6	305	$0.07 \pm 0.01$	$0.88 \pm 0.05$	0.997	5
<b>V</b>	275	$6.48 \pm 0.03$	$0.96 \pm 0.05$	0.992	5	255	$-0.42 \pm 0.03$	$0.97 \pm 0.03$	0.990	5

case, for the substituent occupies different positions in the triazine ring at different distances to the oxo group.

The acidity and basicity constants of compounds **I–V** were calculated from the dependences of their molar absorption coefficients  $\epsilon$  (measured at analytical wavelengths) upon pH and  $H_0$ . The plots of  $\epsilon$  versus



**Fig. 2.** Plots of the molar absorption coefficient  $\epsilon$  versus acidity of the medium: (1) deprotonation of 3-phenyl-1,2,4-triazin-5-one (**III**) ( $\lambda = 255$  nm), (2) protonation of 3-phenyl-1,2,4-triazin-5-one (**III**) ( $\lambda = 250$  nm), (3) deprotonation of 3-(*p*-tolyl)-1,2,4-triazin-5-one (**V**) ( $\lambda = 255$  nm), (4) protonation of 3-(*p*-tolyl)-1,2,4-triazin-5-one (**V**) ( $\lambda = 270$  nm), (5) protonation of 5-phenyl-1,2,4-triazin-3-one (**I**) ( $\lambda = 345$  nm).

pH and  $H_0$ , corresponding to deprotonation and protonation of heterocycles **I–V**, have an S-like shape typical of equilibrium processes [27]. Let us consider the dependence of  $\epsilon$  for triazinone **III** on the acidity of the medium, which is shown in Fig. 2. Raising the acidity from pH 8 to 4 leads to increase in  $\epsilon$  due to protonation of anion  $A^-$ . Further increase in the acidity of the medium in the range from pH 2.5 to  $H_0 - 2$  is accompanied by reduction in  $\epsilon$ , which is explained by protonation of neutral molecule AH to give cation  $AH_2^+$ . These data were used to determine the molar absorption coefficients  $\epsilon$  for the anion, neutral molecule, and cation according to Stewart–Granger [27]. On the basis of these values, as well as of the experimental points corresponding to jumps on the S-shaped curves (Fig. 2), we calculated ionization ratios  $I$  following the Vierordt procedure [28]. The plots of  $\log I$  versus pH ( $H_0$ ) for compound **III** are linear. It should be noted that the slopes of these relations approach unity (Table 2).

In keeping with Yates–McClelland [Eqs. (1) and (2)] [27, 29], the  $pK_a$  and  $pK_{BH^+}$  values of compound **III** were assumed to be equal to the ratio of the free term in the linear dependence of  $\log I$  on the corresponding acidity function to its slope.

$$\log I = -x \text{pH} + pK'_a, \quad pK_a = pK'_a/x; \quad (1)$$

$$\log I = -m H_0 + pK'_{BH^+}, \quad pK_{BH^+} = pK'_{BH^+}/m. \quad (2)$$

The acidity constants  $pK_a$  differ insignificantly, by less than 1 log unit, indicating that the anions thus formed have similar structures and that substituents weakly affect the character of protolytic equilibria. On the other hand, the basicity constants  $pK_{BH^+}$  of 1,2,4-triazin-3-ones and 1,2,4-triazin-5-ones differ by almost 2.5 log units, which may be due to different effects of the oxo groups in positions 3 and 5 of the heteroring, as well as different characters of conjugation between the phenyl group in positions 3, 5, and 6 and electronic system of the heteroring.

In order to gain a more detailed interpretation of the experimental data, we calculated the enthalpies of formation of all possible tautomers of compounds I–V by the AM1 semiempirical method. In addition, we also took into account the possibility for *cis*–*trans* isomerism originating from rotation of the hydroxy group about the C–O bond. It was found that in some cases, the *s-cis/s-trans* isomerism was crucial: the thermodynamic stabilities of the conformers differed by up to 10 kcal/mol.

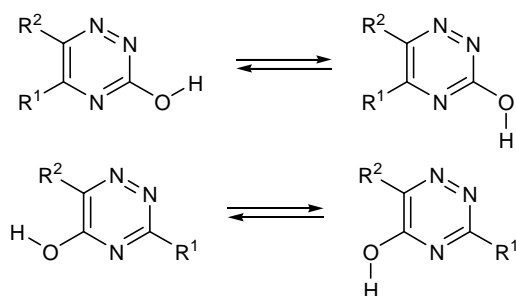


Table 3 contains the results of calculations performed for 1,2,4-triazin-3-ones **I** and **II** and 1,2,4-triazin-5-ones **III**–**V**. In both cases, the most thermodynamically favorable tautomer of the neutral base is *2H* (**Id**–**Vd**), in agreement with the conclusions drawn in [5]. The enthalpies of formation ( $\Delta H_f^0$ ) of *4H*-tautomers **Ic**–**Vc** insignificantly differ from those found for the corresponding *2H*-structures **Id**–**Vd**: on the average, by 3–5 kcal/mol. Among the protonated forms, the most thermodynamically stable is 2,4-*H,H*<sup>+</sup>-tautomer **Ik**–**Vk**; which is also consistent with published data [13]. The low stability of cationic tautomers **Ij**–**Vj** may be explained by destabilizing effect of mutual repulsion between the neighboring NH fragments.

## EXPERIMENTAL

The UV absorption spectra were measured on a Perkin–Elmer Lambda-40 spectrophotometer. The concentration of sulfuric acid in aqueous solutions was

**Table 3.** Gas-phase enthalpies of formation of different tautomeric forms of neutral and 1,2,4-triazin-3- and -5-ones **I**–**V**, calculated by the AM1 method<sup>a</sup>

Comp. no.	$\Delta H_f^0$ , kcal/mol	Comp. no.	$\Delta H_f^0$ , kcal/mol
<b>Ib</b>	66.85 <sup>b</sup>	<b>If</b>	221.23 <sup>b</sup>
<b>Ic</b>	63.33	<b>Ih</b>	217.25 <sup>b</sup>
<b>Id</b>	59.67	<b>Ik</b>	211.95
<b>IIb</b>	66.49 <sup>b</sup>	<b>IIc</b>	224.79 <sup>b</sup>
<b>IIc</b>	64.22	<b>IIh</b>	220.97 <sup>b</sup>
<b>IIe</b>	59.81	<b>IIk</b>	220.95
<b>IIIb</b>	63.81 <sup>b</sup>	<b>IIIh</b>	213.97 <sup>b</sup>
<b>IIIc</b>	60.14	<b>IIIi</b>	217.38
<b>IIId</b>	63.33	<b>IIIk</b>	208.01
<b>IVb</b>	66.05 <sup>b</sup>	<b>IVh</b>	218.96 <sup>b</sup>
<b>IVc</b>	60.41	<b>IVi</b>	212.58
<b>IVd</b>	66.42	<b>IVk</b>	214.77
<b>Vb</b>	55.58 <sup>b</sup>	<b>Vh</b>	204.69 <sup>b</sup>
<b>Vc</b>	52.64	<b>Vi</b>	208.33
<b>Vd</b>	55.39	<b>Vk</b>	198.63

<sup>a</sup> An additional correction for mutual repulsion between lone electron pairs on the neighboring nitrogen atoms (10 kcal/mol) [39] was taken into account for the following tautomers: **Ib** (*s-cis*), **Ib** (*s-trans*), **Ic**, **Ig** (*s-cis*), **Ig** (*s-trans*), **IIb** (*s-cis*), **IIb** (*s-trans*), **IIc**, **IIg** (*s-cis*), **IIg** (*s-trans*), **IIIb** (*s-cis*), **IIIb** (*s-trans*), **IIIc**, **IIIg** (*s-cis*), **IIIg** (*s-trans*), **IVb** (*s-cis*), **IVb** (*s-trans*), **IVc**, **IVg** (*s-cis*), **IVg** (*s-trans*), **Vb** (*s-cis*), **Vb** (*s-trans*), **Vc**, **Vg** (*s-cis*), and **Vg** (*s-trans*).

<sup>b</sup> For the most stable *s-cis/s-trans* conformer.

determined by potentiometric titration with an accuracy of  $\pm 0.2$  wt %. The acidity functions  $H_0$  were taken from [30]. The acid–base properties were studied in aqueous buffers with a ionic strength  $\mu$  of 0.01, which were prepared by the procedure described in [31]. The model heterocyclic compounds were synthesized and purified by known methods [32–37]. Quantum-chemical calculations were performed with the aid of MOPAC 6.0 software [38]. We failed to determine the acid dissociation constant of compound **II** because of poor solubility of its neutral form.

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