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Theoretical Study of the Formation of Benzofurotriazines by Reaction of 3-Substituted 1,2,4-Triazines and Fused Azolo[1,2,4]triazines with Resorcinol

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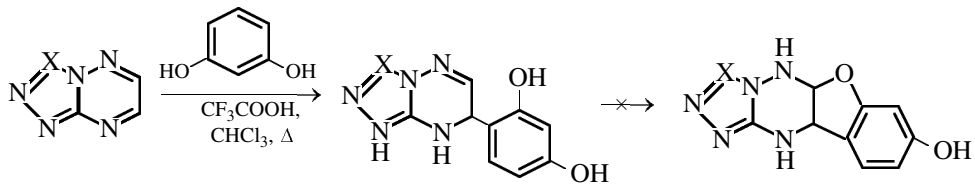
Abstract — 3-Methylthio- and 3-amino-1,2,4-triazines react with resorcinol to give benzofurotetrahydrotriazine derivatives, while reactions of [1,2,4]triazolo[4,3-*b*]- and tetrazolo[1,5-*b*][1,2,4]triazines with resorcinol stop at the stage of resorcinol addition. According to the results of quantum-chemical calculations, the possibility for further cyclization of the resorcinol addition products is determined by the following factors: tautomeric and conformational states of the compounds, which ensure spatial proximity of the hydroxy group to the cyclization center (C^6); charges on the C^6 atom of the triazine ring and oxygen atom of the resorcinol fragment in the conformation most favorable for cyclization; and energies of the highest occupied and lowest unoccupied molecular orbitals of the resorcinol addition products.

Nucleophilic substitution to C=N bonds provides a direct and convenient method for functionalization of 1,2,4-triazines, which makes it possible to introduce various substituents in a single reaction [1, 2]. σ^H-Adducts formed by reactions of nitrogen-containing aromatic heterocycles with nucleophiles may be stable compounds, or they can undergo further transformations, such as aromatization following oxidative mechanism or autoaromatization (S_N^H processes [1]), ring opening, or recyclization. Insofar as azines are polyfunctional compounds, it is quite probable that their reactions with difunctional nucleophiles would result in polycyclic compounds via attack by the second nucleophilic center at another carbon atom of the heteroring [3].

We previously showed that some 3-substituted 1,2,4-triazines and their azole-fused analogs react with a difunctional aromatic nucleophile, resorcinol, to afford polycyclic compounds whose structure depends on the triazine substrate nature [4]. For example, fused 1,2,4-triazine derivatives, [1,2,4]triazolo[4,3-*b*][1,2,4]-triazine (**Ia**) and tetrazolo[1,5-*b*][1,2,4]triazine (**Ib**), react with resorcinol in a protonating solvent (trifluoroacetic acid) to give stable dihydroazolotriazines **IIa** and **IIb** (Scheme 1).

Scheme 1.



Ia, Ib **IIa, IIb** **IIIa, IIIb**

X = CH (**a**), N (**b**).

The presence in the triazine ring of an electron-deficient carbon atom (C^6) allows us to expect subsequent nucleophilic attack which could lead to polycyclic product **III**. However, neither prolonged heating of the reaction mixture under reflux nor heating of compounds **II** in methanol in the presence of bases (triethylamine or potassium *tert*-butoxide) resulted in cyclization. It is known that in some cases

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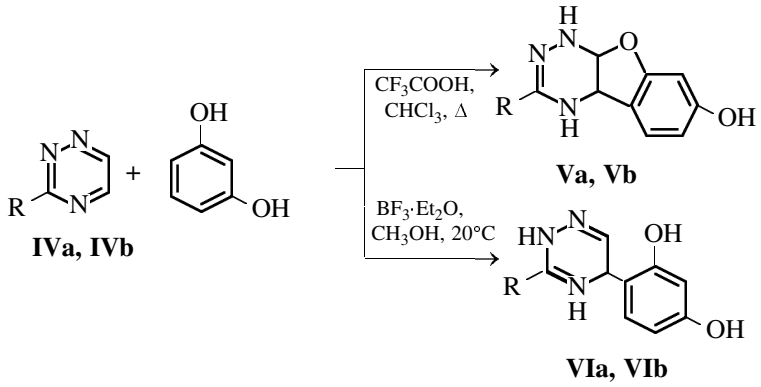
nucleophile addition at the C^6 atom of the triazine ring is favored by elevated pressure (5 to 6 kbar) [5]. In our case, tarring occurred when a high pressure was applied to the reaction mixture.

A different pattern is observed in the reaction of resorcinol with 3-substituted triazines **IV**. Here, the process does not stop at the stage of nucleophile addition to C^5 of the triazine ring. Analogous treatment of 3-methylthio- and 3-amino-1,2,4-triazines **IVa** and **IVb** under the same conditions or at lower temperature resulted in stepwise formation of tricyclic product **V** (Scheme 2). We succeeded in isolating intermediate dihydrotriazine **VI** when a milder activating agent, boron trifluoride–ether complex, was used.

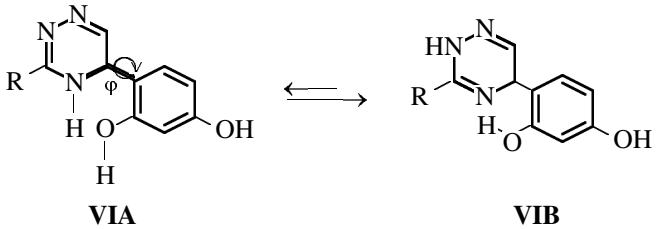
Scheme 2.



R = SMe (**a**), NH_2 (**b**).

In order to elucidate factors determining formation of cyclic or acyclic products and effect of azole ring fusion on the possibility for cyclization to occur, we performed quantum-chemical calculations of adducts **IIa**, **IIb**, **VIa**, and **VIb**. The prototropic tautomeric equilibrium **VIA** $\rightleftarrows$ **VIB** was analyzed in terms of the PM3 semiempirical approximation. It was found that, despite the presence of an O···H–N hydrogen bond in tautomeric form **A**, tautomer **B** having an N···H–O hydrogen bond is energetically more favorable (Scheme 3).

Scheme 3.



VIA **VIB**

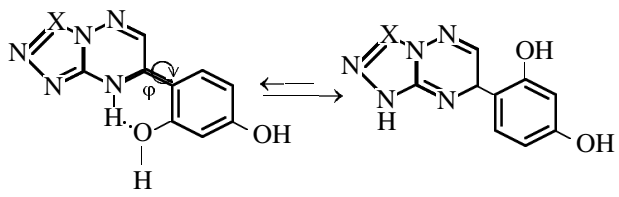
The calculated enthalpies of formation of tautomeric forms **A** and **B** are given in Table 1. It is seen that the energy gap between these forms is not large; therefore, both tautomeric forms should be present in a real solution, tautomer **B** prevailing.

Table 1. Enthalpies of formation of tautomeric forms **A** (ΔH_A) and **B** (ΔH_B)

Comp. no.	ΔH_A, kJ/mol	ΔH_B, kJ/mol
IIa	161.868	189.672
IIb	313.866	346.962
VIa	–15.078	–21.672
VIb	–38.346	–42.84

Unlike compounds **VIa** and **VIb**, the energy gap between tautomers **A** and **B** of compounds **IIa** and **IIb** is much larger, and tautomer **A** with proton localized on N^4 is considerably more favorable (Scheme 4).

Scheme 4.



IIA **IIB**

The calculation results are consistent with the data

Table 2. ^{1}H NMR spectra, δ, ppm (*J*, Hz), of compounds **IIa**, **IIb**, **Va**, **VIa**, and **VIb**

Comp. no.	C^5H	C^6H	5-R	Other protons
IIa	6.32 d (*J* 3.2)	7.20 d (*J* 3.2)	6.20 d.d (1H, *J* 8.1, 2.0), 6.32 d (1H, *J* 2.0), 6.86 d (1H, *J* 8.1), 9.15 br.s (1H), 9.63 br.s (1H)	8.15 s, (1H, $CN_{triazole}$), 7.54 br.s (1H, NH)
IIb	5.39 m	7.22 m	6.20 d.d (1H, *J* 8.2, 2.3), 6.30 d (1H, *J* 2.3), 6.86 d (1H, *J* 8.2), 9.25 br.s (1H), 9.70 br.s (1H)	8.32 br.m (1H, NH)
Va	4.68 d (*J* 1.8)	6.56 d (J 1.8)	6.17 d.d (1H, *J* 8.3, 2.1), 6.42 d (1H, *J* 2.1), 6.88 d (1H, *J* 8.3)	2.37 s (3H, SCH_3), 8.88 br.s (1H), 9.33 br.s (1H), 10.38 br.s (1H, NH, OH)
VIa	4.60–4.88 br.m	3.85–4.30 br.m	6.05–6.38 br.m, 6.61–6.91 br.m (4H, NH+CH_{arom})	2.28 s (3H, SCH_3), 9.73 br.s (3H, NH+2OH)
VIb	4.73–4.88 br.m	4.58–4.62 br.m	6.18–6.36 m, 3H (CHarom)	

of NMR spectroscopy (Table 2). The 5-H resonance in the spectrum of **VIa** is located at δ 4.68 ppm (*J* = 1.8 Hz). The signal shape does not change on addition of deuteroacetic acid or on irradiation at a frequency corresponding to the NH resonance (δ 8.88 ppm). Unlike **VIa**, the 5-H signal in the spectrum of **IIb** appears as a doublet of doublets due to coupling with both C^6H and N^4H. The latter gives rise to a poorly resolved multiplet at δ 8.32 ppm. The same follows from the double-resonance spectrum. Suppression of the N^4H resonance leads to transformation of the C^6 signal into a doublet. Thus the ^{1}H NMR data suggest the existence of compounds **II** as tautomer **A**, while compounds **VI** prefer tautomer **2**.

Hydrogen bonding between the resorcinol oxygen atom and hydrogen on N^4 (Scheme 4) stabilizes such a conformation of **IIa** and **IIb**, in which the hydroxy group of the resorcinol moiety appears maximally distant from the potential reaction center (C^5). Cyclization of compounds **VIa** and **VIb** is possible due to their existence in a more favorable tautomeric form which does not hamper conformational transitions. By contrast, intramolecular hydrogen bond in **IIa** and **IIb** fixes a conformation which is unfavorable for further cyclization.

To verify this assumption, we performed *ab initio* calculations with the STO-3G basis set of the energies of different conformers with respect to the torsional angle φ. Figure 1 shows the calculated dependence of the total energy upon the angle φ. It is seen that the barrier to rotation about the C^5-C_{res} bond for compounds **VI** is twofold: the most favorable conformations are those with φ = 60 and –80°. Intramolecular cyclization of such conformers seems to be feasible. The conformation with φ = 0° is unfavorable owing to steric strain arising from interaction with hydrogen on C^6. The minimum at φ = –80° is somewhat deeper. These data led us to conclude that intramolecular attack by the resorcinol oxygen atom on C^6 occurs outside the triazine ring plane. A different pattern is observed with compounds **II**. The corresponding potential curve for internal rotation contains an additional minimum at φ = 150°, which exactly matches the direction toward the hydrogen atom on N^4 (hydrogen bonding O···H). The formation of intramolecular hydrogen bond is responsible for displacement of one energy minimum of **II** relative to that typical of **VIa** and **VIb**, so that the minimum is observed at φ = –120° rather than –80°. Then, the rotation barrier with respect to φ for compounds **IIa** and **IIb** is threefold with its minima corresponding to φ = 60, 150, and –120°. The latter minimum is the deepest. Obviously, in the respective conformation, the resorcinol oxygen atom is sufficiently distant from the reaction center, and no cyclization occurs. The extra minimum at φ = 150° also hampers cyclization, for it also corresponds to a conformation in which the resorcinol oxygen atom and C^6 are remote from each other. Thus, the possibility for intramolecular cyclization is determined by tautomeric and conformational states of compounds **IIa**, **IIb**, **VIa**, and **VIb**.

Analysis of the charge distribution in molecules **IIa**, **IIb**, **VIa**, and **VIb** displayed a significant difference in the charges on the reaction center (C^6) and oxygen atom of the resorcinol fragment, i.e., just on those atoms which are involved in intramolecular cyclization. Figures 2 and 3 show the calculated dependences of the charges on C^6 and the oxygen

atom upon torsional angle φ. The calculations were performed *ab initio* using the STO-3G basis set.

In the conformations of **VIa** and **VIb**, which are favorable for intramolecular cyclization (φ = 60, –80°), the charge on C^6 is maximal, and the charge on the resorcinol oxygen atom is minimal. A different pattern is observed for compounds **IIa** and **IIb**: Their conformations favorable for intramolecular cyclization are characterized by a minimal charge on C^6; the maximal value was obtained for the conformation with φ = 0°. The cyclization for that conformation is hampered for the above reasons (steric strain due to interaction with the hydrogen atom). The charge on the resorcinol oxygen atom in conformations of **IIa** favorable for intramolecular cyclization (φ = 60°, –80°) has local minima, while compound **IIb** lacks one of these. The global minimum corresponds to the conformation with φ = 150°, which gives rise to intramolecular hydrogen bond. These data indicate once more that the H-bonded system is stable; therefore, intramolecular cyclization is unlikely to occur.

Ab initio calculations (STO-3G) of the conformations favorable for intramolecular cyclization showed that the energies of both highest occupied (HOMO) and lowest unoccupied molecular orbitals (LUMO) of compounds **IIa** and **IIb** are lower than the corresponding energies of compounds **VIa** and **VIb** (Table 3). The lower energies of the frontier orbitals of **IIa** and **IIb** are responsible for the greater stability of their noncyclic forms which are isolated as final products.

Thus the formation of cyclic and acyclic products in the reactions of resorcinol with compounds **Ia**, **Ib** and **IVa**, **IVb** is determined by the following factors. The tautomeric and conformational states of the primary addition products are characterized by spatial proximity of the hydroxy group to the cyclization center (C^6) in **VIa** and **VIb** and their remoteness from each other in **IIa** and **IIb** (steric factor). The charge on C^6 in **VIa** and **VIb** is maximal, and that on the resorcinol oxygen atom is minimal for the most favorable conformation, which facilitates intramolecular cyclization. In the most favorable conformation of **IIa** and **IIb**, the charge on C^6 is minimal, while the charge on the resorcinol oxygen atom is not minimal (charge factor). The HOMO and LUMO energies of **IIa** and **IIb** are lower than the corresponding energies of **VIa** and **VIb**; therefore, the electronic state of of molecules **IIa** and **IIb** does not favor further cyclization (energy factor).

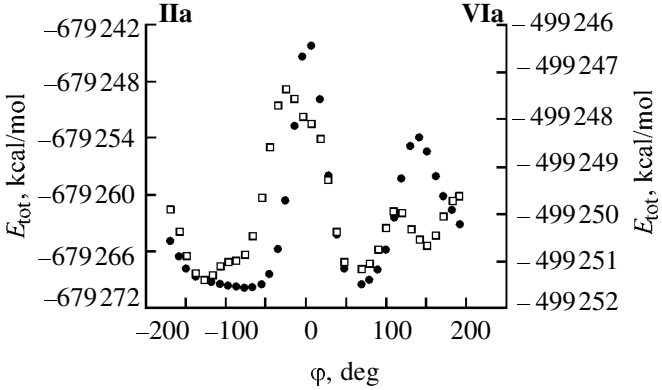


Fig. 1. Total energies (E_{tot}) of different conformers of tautomeric form **B** of compounds **VIa** (dark circles) and **IIa** (light squares) versus torsional angle φ; φ = 0° in a conformer in which the resorcinol oxygen atom points exactly to the reaction center (*eclipsed* conformation).

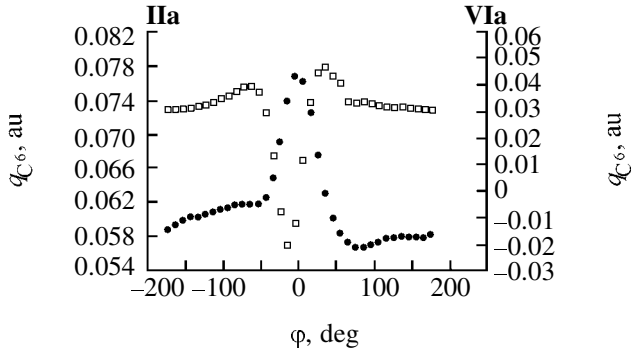


Fig. 2. Charges on the C^6 atom (q_{C^6}) in molecules **VIa** (dark circles) and **IIa** (light squares) versus torsional angle φ; φ = 0° in a conformer in which the resorcinol oxygen atom points exactly to the reaction center (*eclipsed* conformation).

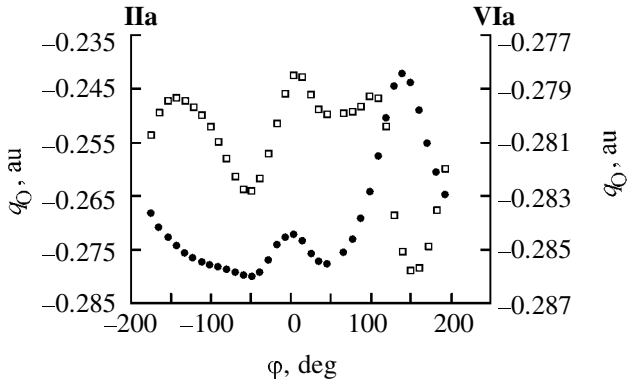


Fig. 3. Charges on the resorcinol oxygen atom (q_O) in molecules **VIa** (dark circles) and **IIa** (light squares) versus torsional angle φ; φ = 0° in a conformer in which the resorcinol oxygen atom points exactly to the reaction center (*eclipsed* conformation).

Table 3. Energies of the frontier molecular orbitals of compounds **IIa**, **IIb**, **VIa**, and **VIb** (*ab initio*, STO-3G basis set)

Comp. no.	φ, deg	E_{HOMO}, eV	E_{LUMO}, eV
IIa	60	–7.015	5.913
	–80	–7.116	5.796
IIb	60	–7.329	5.413
	–80	–7.312	5.241
VIa	60	–6.510	7.185
	–80	–6.489	7.285
VIb	60	–6.556	7.157
	–80	–6.541	7.224

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 MHz using DMSO-d_6 as solvent and TMS as internal reference. Compounds **IIa**, **IIb**, **VIa**, and **IVb** were synthesized by analogy with the procedure reported in [4] with the difference that the reaction mixtures were heated for 1 h in a 2 : 1 mixture of chloroform and trifluoroacetic acid under reflux. Compound **Va** was synthesized as described in [4].

ACKNOWLEDGMENTS

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