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Synthesis and tautomerism study of 6-benzoylmethyl-1,3,5-triazin-2,4-diamine

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ABSTRACT

From the reaction of biguanide with ethyl benzoylacetate, *N*-(6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl)guanidine (**1**) and 6-benzoylmethyl-1,3,5-triazin-2,4-diamine (**2**) were isolated. The structural evaluation of **2** was performed theoretically (DFT calculations) and experimentally (NMR spectroscopy and X-ray crystallography). The effects of solvents and temperature on keto-enol-enaminone tautomeric equilibrium were explored.

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1. Introduction

For a long time, tautomerism has remained an intriguing phenomenon in physical organic chemistry. Hydrogen bonding appears to be one of the most important factors governing tautomeric equilibrium [1]. Resonance-assisted hydrogen bonding (RAHB) is a type of strong hydrogen bond commonly observed in systems where two oxygen atoms are connected by a conjugated spacer containing single and double bonds, such as carboxylic acid dimers or β -enolones, with O...O distances of 2.39–2.55 Å [2]. Over the last few decades, much interest has been focused on the nitrogen and sulfur analogues of such systems, particularly those with strong intramolecular RAHB related to the $\cdots\text{O}=\text{R}_3\text{-NH}\cdots \leftrightarrow \cdots\text{HO}-\text{R}_3=\text{N}\cdots$ tautomeric equilibrium, where R_3 is a resonant spacer of three atoms [3]. In RAHB, the delocalization of electrons increases the strength of the hydrogen bond by increasing both the acidity of the hydrogen bond donor and the basicity of the hydrogen bond acceptor [4]. Similar to other aromatic azaheterocycles with an acylmethyl substituent

[5], tautomerism in acylmethyl-1,3,5-triazines **A** (Fig. 1) can potentially result in the formation of two tautomers stabilized by intramolecular RAHB i.e. enol **B** and enaminone **C**. The six-membered hydrogen bond chelate may involve the triazine nitrogen atom acting as a proton acceptor and oxygen atom as proton donor (in form **B**) or vice versa (in form **C**). The tautomeric equilibrium depends on structural specificity and various external conditions. However, these factors have not been systematically studied for acylmethyl-1,3,5-triazines and some questionable arbitrarily chosen assignments have been appearing [6,7]. In some reported cases, the potential existence of enaminone form **C** was ignored [8,9] even though this form appeared to be predominant in other studies [10,11] and was the only one found in the solid state by X-ray crystallography [12].

Acylmethyl-1,3,5-triazines can be prepared using two general approaches: (1) derivatisation of 1,3,5-triazines using methylene active carbonyl compounds via nucleophilic substitution of chlorotriazines [6,13] or by addition to triazines followed by oxidative aromatisation [6], and (2) the 1,3,5-triazine ring formation via heterocyclization of biguanides or their analogues using β -keto esters [14].

However, using unsubstituted biguanide in the second approach may result in the formation of alternative

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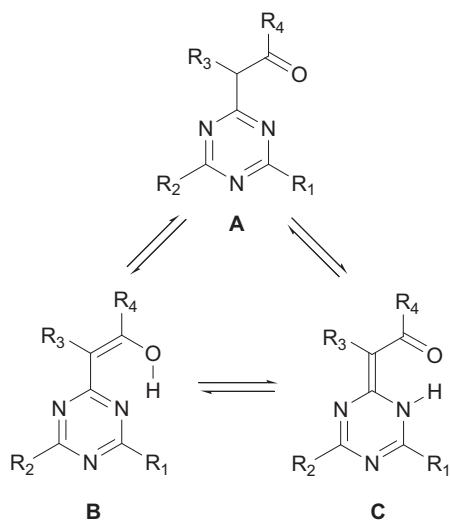


Fig. 1. Tautomerism in acylmethyl-1,3,5-triazines.

products – guanidinopyrimidines [15] or their mixtures with acylmethyl-1,3,5-triazin-2,4-diamines [14,16].

In our continuous investigations [17] on azaheterylguanidines as valuable synthons for the preparation of bioactive compounds, we became interested in the synthesis of *N*-(6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl)guanidine (**1**). However, previously described [15c] reaction of biguanide with ethyl benzoylacetate resulted in the formation of additional product of interesting structure, namely 6-benzoylmethyl-1,3,5-triazin-2,4-diamine (**2**) together with the reported **1**. Derivatives of the 2,4-diamino-1,3,5-triazine scaffold have been reported to exhibit antibacterial [18] and anticancer properties [19]. This prompted us to carry out a thorough structural characterization and biological investigation on **2**. The present paper is devoted to the detailed structural investigations of **2**, particularly tautomerism

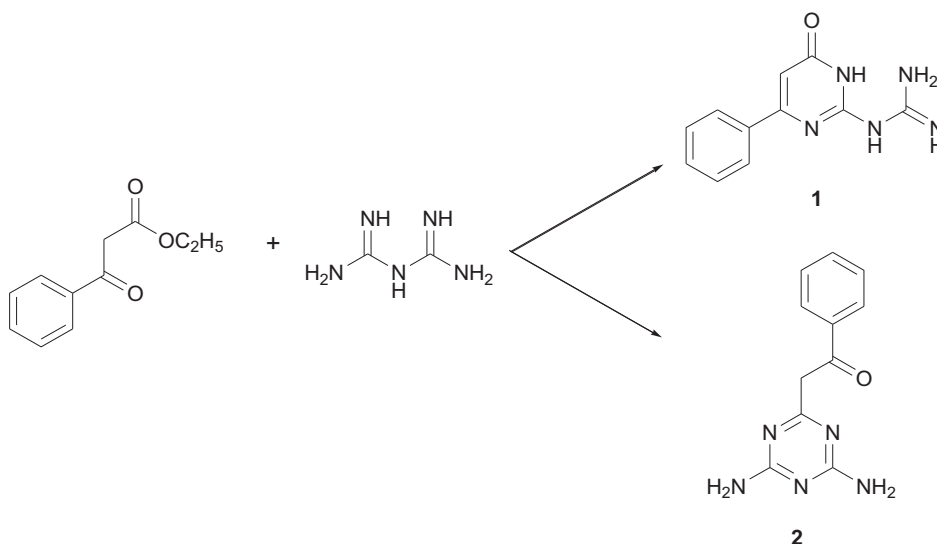
study using NMR spectroscopy, X-ray crystallography and theoretical calculations.

2. Result and discussion

2.1. Synthesis and structural assignments

In the reaction of biguanide with ethyl benzoylacetate in the presence of sodium methoxide, biguanide played the roles of triatomic and pentatomic synthons, affording *N*-(6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl)guanidine (**1**, 37%) and 6-benzoylmethyl-1,3,5-triazin-2,4-diamine (**2**, 26%), respectively (Scheme 1). The two compounds were effectively isolated from the reaction mixture using differential solubility in methanol. The structure of the products was established using NMR spectroscopy and X-ray crystallography.

Two distinct, unequally populated sets of signals were observed in the NMR spectrum of **2** at room temperature in DMSO-*d*₆ solution indicating the existence of two tautomers in the proportion of 7:93. The singlet of methylene protons observed at 4.07 ppm in the ¹H NMR spectrum along with the signals of methylene and carbonyl carbon atoms appearing at 48.8 ppm and 195.5 ppm in the ¹³C NMR spectrum corresponded to the structure of keto form **A**, which was found to be minor (7%) under these conditions (Fig. 2). The characteristic signals of the predominant tautomeric form (signals of methine proton and carbon at 5.67 and 89.2 ppm of ¹H NMR and ¹³C NMR spectra, respectively as well as sharp proton peak at 15.22 ppm and carbon atom at 174.2 ppm) did not allow unambiguous differentiation between enol **B** and enamionone **C**. Moreover, the rapid NMR time scale in interconversion by intramolecular proton transfer between electronegative atoms via RAHB could not be excluded. Significant broadening of signal of quasiequivalent carbon atoms at 162.8 ppm in ¹³C NMR spectrum also suggested this situation.



Scheme 1. Reaction of ethyl benzoylacetate with biguanide.

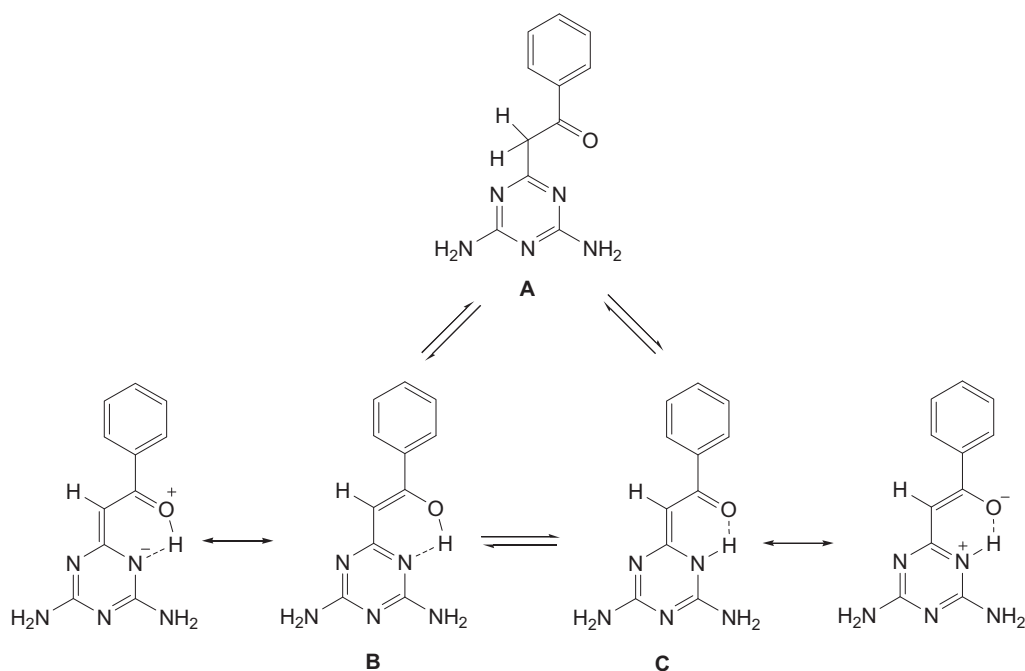


Fig. 2. Tautomerism in 6-benzoylmethyl-1,3,5-triazin-2,4-diamine and intramolecular RAHB.

Table 1

Relative energies for the tautomeric forms of **2** according to *ab initio* calculations.

Method	Relative energies for tautomers, kcal/mol		
	Keto form (A)	Enol form (B)	Enaminone form (C)
B3LYP/6-311G2d,2p	4.50	0.00	3.65
MP2/6-311G2d,2p	3.52	0.00	9.13

2.2. *Ab initio* calculations

In order to clarify the structural assignments, the *ab initio* calculations of the relative energies of the tautomers **A–C** were performed and the ^{13}C chemical shifts were predicted using the gauge independent atomic orbital (GIAO) perturbation method [20].

Table 2

Experimental and calculated [B3LYP/6-311G(2d,2p)] chemical shifts (δ) in ^{13}C NMR spectrum of **2** and deviation between experimental and predicted values ($\Delta\delta$).

Carbon atom	Experimental data, δ ppm		GIAO calculation data, $\delta(\Delta\delta)$ ppm		
	Minor form	Major form	Keto form A	Enol form B	Enaminone form C
C-2	166.9	167.8 (br)	168.99 (–2.09)	167.23 (0.57)	164.92 (2.88)
C-4	166.9	162.8 (br)	168.98 (–2.08)	166.00 (–3.2)	156.29 (6.51)
C-6	172.8	167.5	177.59 (–4.79)	175.59 (–8.09)	163.57 (3.93)
CH ₂ /CH	48.9	89.2	49.31 (–0.41)	94.12 (–4.92)	82.32 (6.88)
C=O/C–OH	195.52	174.2	196.83 (–1.31)	172.88 (1.32)	187.53 (–13.33)
C-1'	136.4	137.3	137.88 (–1.48)	137.57 (–0.27)	141.00 (–3.7)
C-2'	128.6	128.3	130.40 (–1.8)	128.27 (0.03)	128.30 (0.00)
C-3'	n.i	125.7	129.70	129.26 (–3.56)	129.70 (–4.0)
C-4'	133.2	130	134.13 (–0.93)	131.21 (–1.21)	132.85 (–2.85)
C-5'	n.i	125.7	128.76	128.76 (–3.06)	129.36 (–3.66)
C-6'	128.6	128.3	129.64 (–1.04)	126.92 (1.38)	127.97 (0.33)

n.i = not identified

The structures of the tautomeric forms were optimized at the B3LYP/6-31G(d,p) level of theory. Since there was no imaginary frequency in the vibrational spectra, all the tautomers were confirmed to exist at stationary points corresponding to the local minima on the potential energy surface. The relative energies at different level of theories were computed and compared for all the tautomeric forms (Table 1). Based on these results, tautomer **A** was found to be preferred in the gas phase and the order of stability of the tautomeric forms was calculated to be **B** > **A** \approx **C**. However, the energy difference between the forms was found to be <10 kcal/mol.

The absolute shielding (σ) value of carbon in TMS was calculated at the B3LYP/6-311G2d,2p level of theory and was found to be 178.74 ppm. Using this value and absolute shielding values of ring carbon atoms for various tautomers obtained at same level of theory, the chemical shift values

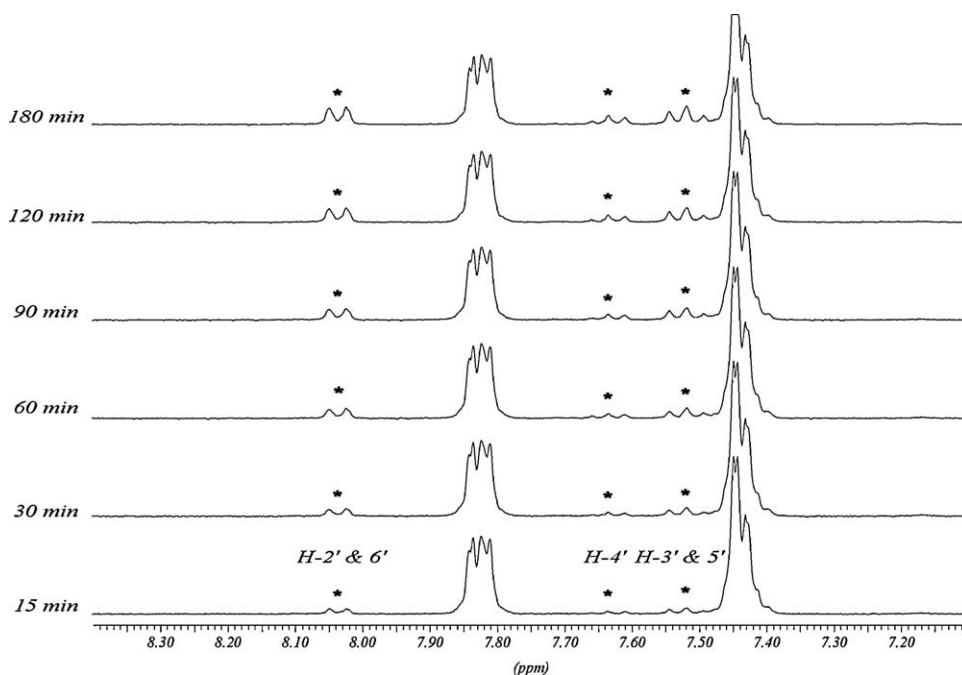


Fig. 3. Tautomerization of **2** in the DMSO- d_6 solution with time after addition of D_2O (20%) at 27 °C. 1H NMR spectra (the phenyl groups signals) depict shift of the equilibrium towards keto form **A** (indicated with asterisk).

Table 3
Kinetic and thermodynamic parameters of D_2O induced tautomerization.

Solvent	Temperature (°C)	$K_T = [A]/[B + C]$	ΔG (Kcal/mol)	$k_1 + k_{-1}$ (10^{-2} min^{-1})	k_1 (10^{-3} min^{-1})	ΔH (kcal)	ΔS (cal/deg)
DMSO d_6 : D_2O 4:1	27	0.201	0.957	1.1	1.2	-	-
DMSO d_6 : D_2O 4:1	32	0.222	0.896	2.5	4.7	2.389	5.691
DMSO d_6 : D_2O 4:1	37	0.243	0.844	6.7	13	-	-

(δ) along with the deviation between experimental and predicted values ($\Delta\delta$) have been calculated (Table 2). An excellent correlation ($r^2 = 0.9994$) was found between the experimental and theoretical values for the keto tautomer **A** (Fig. 2) validating the calculation method. The experimentally obtained values of the ^{13}C chemical shift δ for atoms connecting the triazine and phenyl ring of the major tautomeric form more closely resembled the calculated values for the enol form **B** (Table 2). It is in agreement with generally applicable distinction between enol and enaminone tautomers provided ~ 20 ppm difference of the ^{13}C chemical shift δ values for the carbonyl/enolic carbon atom [5b]. The experimental data were found to correlate better with theoretical values calculated for enolic form **B** rather than with those of enaminone tautomer **C** (cf. Fig. 3b and c). However, detailed comparison of the experimental and

Table 4
Solvent effect on tautomerism of **2**.

Solvent	Temperature (°C)	$K_T = [A]/[B + C]$	ΔG (kcal/mol)
DMSO- d_6	25	0.147	1.144
Acetone- d_6	25	0.135	1.193
Methanol- d_4	25	0.058	1.695

calculated values suggested that the experimental results appeared to be described more accurately as a weighted average of the two forms **B** and **C**. Therefore, the contribution of tautomer **C** cannot be excluded.

2.3. Effects of solvent and temperature on the tautomerism of 6-benzoylmethyl-1,3,5-triazin-2,4-diamine

It has been well recognized that the relative stability of the keto, enol and enaminone tautomers in the solution are dependent on the properties of the solvents [21]. We

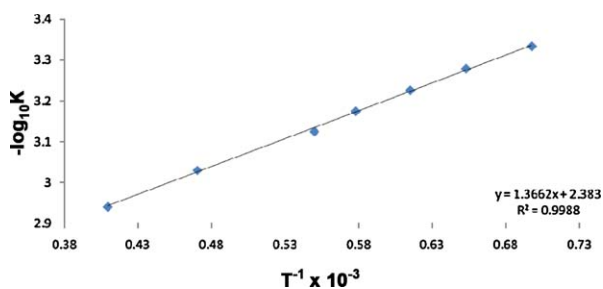


Fig. 4. Plot of equilibrium constant vs temperature.

studied the effect of the solvent on the tautomerism of **2** using ^1H NMR spectroscopy. DMSO- d_6 , acetone- d_6 and methanol- d_4 were used as solvents in the experiments. In all cases, keto form **A** was the minor tautomer (Table 3). The equilibrium was established instantly after dissolving

the sample and remained unchanged after 48 h. The tautomeric equilibrium could be shifted by changing solvent composition. The addition of D_2O to the solution of **2** in DMSO- d_6 (1:4 - D_2O :DMSO- d_6) showed along with the instant suppression of signals of two amino groups and

Table 5

Calculated and experimentally obtained bond lengths and angles for 2-(4,6-diamino-1,3,5-triazin-2(1H)-ylidene)-1-phenylethanone.

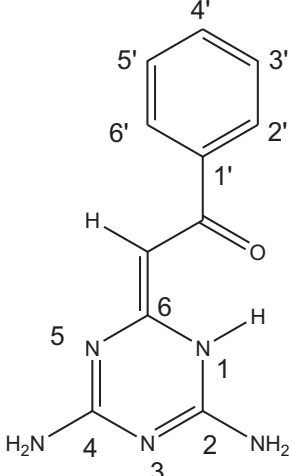
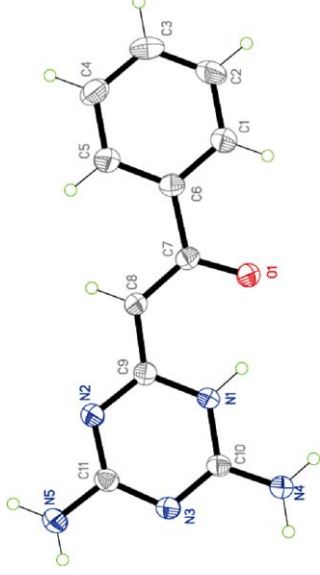
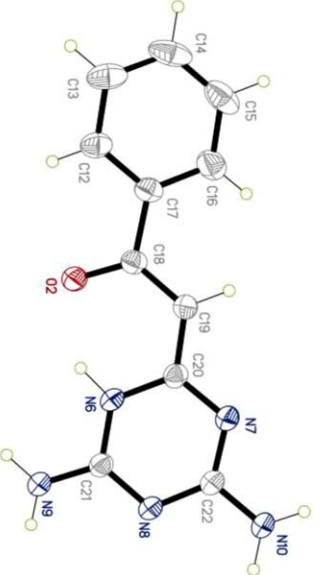
Form B (Theoretical)		Molecule 1 (X-ray)		Molecule 2 (X-ray)	
					
Bond lengths Å		Bond lengths Å		Bond lengths Å	
O–C(8)	1.2668	O(1)–C(7)	1.2815(17)	O(2)–C(18)	1.2762(19)
N(1)–C(2)	1.3515	N(1)–C(10)	1.3617(18)	N(6)–C(21)	1.3577(19)
N(1)–C(6)	1.3947	N(1)–C(9)	1.3671(18)	N(6)–C(20)	1.3680(19)
N(1)–H(1N)	1.0475	N(1)–H(1N)	0.90(2)	N(6)–H(6N)	0.91(2)
N(5)–C(6)	1.3513	N(2)–C(9)	1.3413(18)	N(7)–C(20)	1.3423(19)
N(5)–C(4)	1.3321	N(2)–C(11)	1.3437(18)	N(7)–C(22)	1.346(2)
N(3)–C(2)	1.3216	N(3)–C(10)	1.3293(18)	N(8)–C(21)	1.3283(19)
N(3)–C(4)	1.3658	N(3)–C(11)	1.3556(19)	N(8)–C(22)	1.3554(19)
C(2)–NH ₂	1.3523	C(10)–N(4)	1.3241(19)	C(21)–N(9)	1.322(2)
C(4)–NH ₂	1.3522	C(11)–N(5)	1.3335(19)	C(22)–N(10)	1.332(2)
C(9)–C(8)	1.5034	C(6)–C(7)	1.5038(19)	C(17)–C(18)	1.501(2)
C(7)–C(8)	1.4259	C(8)–C(7)	1.396(2)	C(19)–C(18)	1.397(2)
C(7)–C(6)	1.3925	C(8)–C(9)	1.4024(19)	C(19)–C(20)	1.401(2)
Bond angles, °		Bond angles, °		Bond angles, °	
C(2)–N(1)–C(6)	120.27	C(10)–N(1)–C(9)	120.39(12)	C(21)–N(6)–C(20)	120.80(13)
C(6)–N(5)–C(4)	116.29	C(9)–N(2)–C(11)	116.44(12)	C(20)–N(7)–C(22)	116.54(13)
C(2)–N(3)–C(4)	114.08	C(10)–N(3)–C(11)	115.20(12)	C(21)–N(8)–C(22)	115.48(13)
C(11)–C(9)–C(8)	117.86	C(1)–C(6)–C(7)	118.86(13)	C(12)–C(17)–C(18)	117.97(15)
C(10)–C(9)–C(8)	123.52	C(5)–C(6)–C(7)	122.95(13)	C(16)–C(17)–C(18)	123.58(15)
O–C(8)–C(7)	123.34	O(1)–C(7)–C(8)	123.06(13)	O(2)–C(18)–C(17)	123.72(14)
O–C(8)–C(9)	117.18	O(1)–C(7)–C(6)	117.73(12)	O(2)–C(18)–C(19)	117.06(13)
C(7)–C(8)–C(9)	119.48	C(8)–C(7)–C(6)	119.21(13)	C(19)–C(18)–C(17)	119.22(14)
C(8)–C(7)–C(6)	122.74	C(7)–C(8)–C(9)	123.82(13)	C(18)–C(19)–C(20)	122.88(14)
N(5)–C(6)–N(1)	118.76	N(2)–C(9)–N(1)	119.74(12)	N(7)–C(20)–N(6)	119.46(13)
N(5)–C(6)–C(7)	123.31	N(2)–C(9)–C(8)	120.88(13)	N(7)–C(20)–C(19)	121.48(14)
N(1)–C(6)–C(7)	117.92	N(1)–C(9)–C(8)	119.38(13)	N(6)–C(20)–C(19)	119.05(13)
N(15)–C(2)–N(3)	119.17	N(4)–C(10)–N(3)	120.79(13)	N(9)–C(21)–N(8)	121.13(14)
N(15)–C(2)–N(1)	118.07	N(4)–C(10)–N(1)	117.73(13)	N(9)–C(21)–N(6)	117.55(13)
N(3)–C(2)–N(1)	122.76	N(3)–C(10)–N(1)	121.46(13)	N(8)–C(21)–N(6)	121.32(14)
N(16)–C(4)–N(5)	117.18	N(5)–C(11)–N(2)	116.67(14)	N(10)–C(22)–N(7)	117.26(14)
N(16)–C(4)–N(3)	114.98	N(5)–C(11)–N(3)	116.95(13)	N(10)–C(22)–N(8)	116.50(14)
N(5)–C(4)–N(3)	127.83	N(2)–C(11)–N(3)	126.37(13)	N(7)–C(22)–N(8)	126.23(13)

Table 6
Intramolecular hydrogen bonds for **2**, Å and°.

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(1)–H(1N)...O(1) ^a	0.90(2)	1.89(2)	2.6147(16)	136.3(17)
N(6)–H(6N)...O(2) ^a	0.91(2)	1.84(2)	2.5934(16)	139.6(18)

OH/NH singlet, the time dependent suppression of the methine proton peak at 5.67 ppm and methylene signal at 4.07 ppm in the ¹H NMR spectrum. At the same time, a gradual shift of the tautomeric equilibrium towards keto form **A** was observed (Fig. 3). This time-dependent process was monitored at different temperatures by ¹H NMR spectroscopy and the sample compositions were estimated by integration of the phenyl group signals of the tautomers with 5 min intervals until the equilibration was achieved (Fig. 3, Table 3). Heating was found to shift equilibrium towards keto form **A** (Fig. 4).

The kinetic and thermodynamic parameters of the D₂O induced tautomerization of **2** were calculated [22] (Table 3). A reversible first-order reaction was postulated and the data were fitted [23] to the rate equation to obtain the fittable parameters: (1) enol-enaminone (**B** + **C**) concentration at equilibrium – **A_e**, (2) difference in initial enol-enaminone (**B** + **C**) concentration and the concentration at the equilibrium – (**A₀** – **A_e**), and (3) effective rate constant – (**k₁** + **k₋₁**). The activation energies for the forward and the backward reaction, **E_a** and **E_a'**, respectively, were estimated using the Arrhenius plot. The **E_a** and **E_a'** were obtained as 38.2 and 35.8 kcal mol⁻¹ respectively (Table 4).

2.4. Crystal structure (solid state)

The tautomeric preference of **2** in solid state was determined by an X-ray crystallographic study (Table 5). The single crystal suitable for the analysis was grown by slow evaporation of a methanolic solution of **2**. The asymmetric unit was found to contain two molecules of the compound, two water molecules and one molecule of methanol. Both triazine molecules existed in the crystal as enaminone tautomeric form **C**. The molecular structures of enaminone tautomer were stabilized by the resonance between phenyl and triazine rings connected with the methylene carbonyl bridge as well as by strong intramolecular hydrogen bonding (NH...O=C) (Table 6). In one molecule, the triazine ring was essentially planar (r.m.s. deviation was 0.0244 Å) and almost coplanar with the phenyl ring (dihedral angle was 3.45 (5)°). The triazine ring of the second molecule was also planar with r.m.s. deviation of 0.0145 Å. However, the dihedral angle between the triazine and phenyl rings in this molecule was larger (12.59 (9)°). The comparison of the bond lengths of the six-membered O=C–CH=C–NH chelate of the molecules with the values for the corresponding tautomer obtained by the DFT calculations (Table 5) revealed a potential for intramolecular hydrogen transfer within the crystal. This process is likely to be observed at higher temperatures, but decomposition of the crystal lattice did not allow the experimental confirmation of the tautomerization to enolic tautomer **B**.

3. Conclusion

A new product, namely 6-benzoylmethyl-1,3,5-triazin-2,4-diamine (**2**) was isolated from the reaction of biguanide with ethyl benzoylacetate together with the anticipated formation of *N*-(6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl)guanidine (**1**). The structure of **2** was studied in detail using NMR spectroscopy and X-ray crystallography. The effects of solvents and temperature on keto-enol-enaminone tautomeric equilibrium in **2** were explored. In DMSO, acetone and methanol, keto tautomeric form **A** was minor and its content was found to increase upon addition of D₂O and on heating. The intramolecular RAHB played an important role in stabilization of enol **B** and enaminone **C**. The DFT calculations at the B3LYP/6-311G(2d,2p)//B3LYP/6-31G(d,p) level were also performed to get a clearer understanding of the phenomenon. In the crystal, the enaminone form **C** was identified exclusively.

4. Experimental

¹H NMR spectra in solution were recorded on a Bruker 300 spectrometer. The samples were dissolved either in DMSO-*d*₆, DMSO-*d*₆:D₂O 4:1, CD₃OD and acetone *d*₆. Kinetic parameters were calculated from the ¹H NMR data obtained at 27 °C, 32 °C and 37 °C. Crystal data for **2** were collected on a Bruker APEX diffractometer attached to a CCD detector and graphite-monochromated MoK_α radiation (λ, 0.71073 Å) using a sealed tube at 223(2) K. Absorption corrections were made with the program SADABS [24] and the crystallographic package SHELXTL [25] was used for all calculations.

4.1. General procedure

To biguanidinium sulfate (4.4 g, 20 mmol), sodium methoxide (prepared *in situ* from 1 g of sodium and 100 ml of methanol) was added, followed by slow addition of ethyl benzoylacetate (4.2 ml, 24 mmol). The reaction mixture was heated under reflux for 3.5 h. The precipitated solid **1** was filtered, washed with methanol and water and dried to obtain **1** as white flakes. The solvent was evaporated from the filtrate and solid thus obtained was recrystallized with methanol to obtain **2**.

1-(6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl)guanidine(3,4-Dihydro-4-oxo-6-phenyl-2-pyrimidinyl)guanidine (1**) [15c]:** Yield: 37%; mp 273 °C (decomposed); LC-MS (APCI) *m/z* = 229.1 (MH⁺); ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.24 (1H, s, CH), 7.87 (2H, d, *J* = 7.9 Hz, H-2' and H-6'), 7.38–7.49 (3H, m, H-3', H-4' and H-5'), 8.27 (4H, br. s, NHC(=NH)NH₂), 11.53 (1H, s, NH); IR (KBr): ν NH 3335, CH 3052, 2940, 2665, C=O 1666, 1630, 1508, 1492, 1340, 1239, 1239.

2-(4,6-diamino-1,3,5-triazin-2-yl)-1-phenylethanolone (2**):** Yield: 26%; mp 203 °C (EA); LC-MS (APCI) *m/z* = 229.1 (MH⁺); ¹H NMR (300 MHz, DMSO-*d*₆): δ 4.07*¹ (2H, s, CH₂), 5.67 (1H, s, CH), 6.73* (4H, br. s, two NH₂), 7.09 (4H, br. s, two NH₂), 7.39–7.47 (3H, m, H-3', H-4', and H-5'),

*: peaks corresponding to minor keto form **A**.

7.55* (2H, t, $J = 7.6$ Hz H-3' and H-5'), 7.62* (1H, t, $J = 7.5$ Hz, H-4'), 7.78–7.88 (2H, m, H-2' and H-6'), 7.98* (2H, d, $J = 7.5$ Hz, H-2' and H-6'), 15.22 (1H, s, OH); ^{13}C NMR (75 MHz, $\text{Me}_2\text{SO}-d_6$): 48.8* (CH_2), 89.2 (CH), 125.7 (C-3' and C-5'), 128.3 (C-2' and C-6'), 128.6* (C-2'), 130.0 (C-4'), 133.2* (C-4'), 136.4* (C-1'), 137.3 (C-1'), 162.8 (C-4 and C-6), 166.9* (C-4 and C-6), 167.5 (C-2), 172.8* (C-2), 174.2 (C-OH), 195.5* (C=O); IR (KBr): ν NH_2 3480, CH 3017, C=O 1693, 1580–1602 br., 1534, 1443, 1415, 1223, 1114. Anal. calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_5\text{O}$: C (57.63), H (4.84), N (30.55); found: C (57.58), H (4.70), N (30.34).

^1H NMR (300 MHz, $\text{DMSO}-d_6$:20% D_2O): δ 5.68 (1H, s, CH), 7.37–7.50 (3H, m, H-3', H-4', H-5'), *7.51–7.69 (3H, m, H-3', H-4', H-5'), 7.78–7.90 (2H, m, H-2' and H-6'), 7.98* (2H, d, $J = 7.9$ Hz, H-2' and H-6'); ^{13}C NMR (75 MHz, $\text{Me}_2\text{SO}-d_6$:20% D_2O): 89.2 (CH), 125.8 (C-3' and C-5'), 128.3* (C-6'), 128.5 (C-2' and C-6'), 128.8* (C-2'), 130.5 (C-4'), 133.7* (C-4'), 136.1* (C-1'), 136.8 (C-1'), 162.5 (C-4 and C-6), 166.4* (C-4 and C-6), 167.2 (C-2), 172.9* (C-2), 174.6 (C-OH), 195.5* (C=O).

^1H NMR (300 MHz, CD_3OD): δ 4.57* (2H, s, CH_2), 5.76 (1H, s, CH), 7.35–7.46 (3H, m, H-3', H-4' and H-5'), 7.50* (2H, t, $J = 7.7$ Hz, H-3' and H-5'), 7.62* (1H, t, $J = 7.5$ Hz, H-4'), 7.74–7.87 (2H, m, H-2' and H-6'), 8.02* (2H, d, $J = 7.5$ Hz, H-2' and H-6'); ^{13}C NMR (75 MHz, CD_3OD): 127.1 (C-3' and C-5'), 129.4 (C-2' and C-6'), 129.6, 129.8, 131.5 (C-4'), 134.7, 138.4 (C-1'), 165.0 (C-4 and C-6 br.), 168.3, 170.2 (C-2), 176.6 (C-OH).

^1H NMR (300 MHz, $(\text{CD}_3)_2\text{CO}$): δ 4.06 (1H, s, CH_2), 5.81 (1H, s, CH), 6.13* (4H, br. s, NH_2), 6.41 (4H, br. s, NH_2), 7.42–7.45 (3H, m, H-3', H-4' and H-5'), 7.46–7.68* (3H, m, H-3', H-4' and H-5'), 7.82–7.87 (2H, m, H-2' and H-6'), 8.02 (2H, d, $J = 7.1$ Hz, H-2' and H-6'), 15.12 (1H, s, OH); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): 94.1 (CH), 126.6 (C-3' and C-5'), 129.2 (C-2' and C-6'), 130.9 (C-4'), 137.0 (C-1'), 170.2 (C-2), 172.7 (C-OH).

Crystal Data for 2-(4,6-diamino-1,3,5-triazin-2-yl)-1-phenylethanone (2): $\text{C}_{11.50}\text{H}_{15}\text{N}_5\text{O}_{2.50}$, $M_r = 263.29$, triclinic space group $P-1$, $a = 7.1343(4)$ Å, $b = 11.6996(6)$ Å, $c = 15.4502(8)$ Å, $\alpha = 81.8910(10)^\circ$, $\beta = 77.3160(10)^\circ$, $\gamma = 87.0080(10)^\circ$, $V = 1245.25(11)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.404$ mg/m³, $\mu = 0.103$ mm⁻¹, $T = 223(2)$ K, $R_1 = 0.0517$, $wR_2 = 0.1357$, $\text{GOF} = 1.038$ for 16303 reflections with $I > 2\sigma(I)$.

4.1.1. Computational details

It is generally recognized that the H-bond geometry of RAHB molecules cannot be reproduced at the Hartree-Fock level [26] and that electron correlation can be satisfactorily accounted for both by *ab initio* MP2 (or higher) methods [27] and by DFT calculations [28] with hybrid functional, in particular B3LYP [29,30]. Single point calculations at different levels of theory namely, B3LYP/6-311G(2d,2p), MP2/6-311G(2d,2p) were performed using the B3LYP/6-31G(d,p) optimized geometries and the relative energies (kcal/mol) of tautomers were calculated. The chemical shifts of ^{13}C NMR were also calculated at the B3LYP/6-311G(2d,2p) level using GIAO perturbation method [20]. For valid comparison, the chemical shift of the reference compound (TMS) was carried out at the same level of theory as that for the tautomers. All the calculations have

been performed using Gaussian computational package [31].

4.2. Supporting Information

Crystallographic data for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 771460) as supplementary publication. Copies of the data can be obtained free of charge on application to CCDC 12 Union Road, Cambridge CB21 EZ, UK (Fax: (+44)1223 336-033; email: data_request@ccdc.cam.ac.uk).

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