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QUANTUM-CHEMICAL INVESTIGATIONS OF PYRIMIDINONES-4. 1. TAUTOMERISM OF 2-OXOPYRIMIDINONES-4

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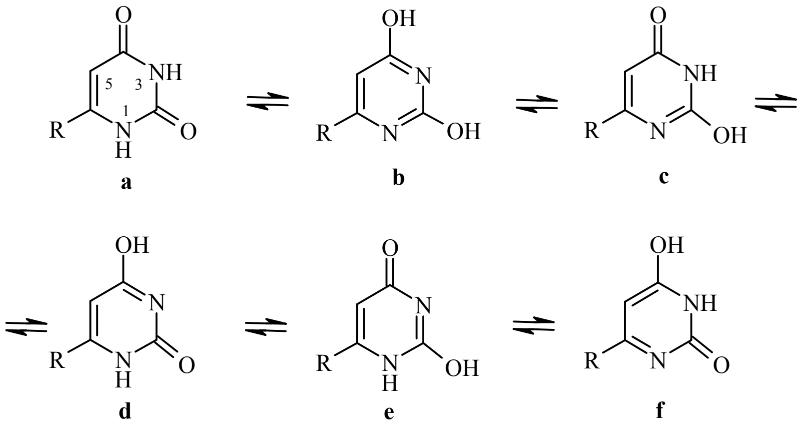
Semiempirical quantum-chemical calculations have been carried out of the molecules of 2-oxopyrimidinones-4. The geometry and electronic structures and the stabilities of the tautomeric forms have been analyzed.

Keywords: 2-oxopyrimidinones-4, gas phase, quantum-chemical calculations, AM1 and PM3 methods, reactivity, tautomerism, point dipoles.

Pyrimidinones-4 are of great theoretical and experimental interest for organic synthesis and biochemistry. The molecules of 2-oxopyrimidinones-4 can exist in six tautomeric forms:



1 R = H; **2** R = CH_3; **3** R = C_6H_5

According to Katritzky [1], tautomeric forms of types **a-f** arise as a result of migration of a mobile H atom. This process is extremely rapid [2] which rules out the effective use of ^1H NMR spectroscopy to determine the predominant tautomeric form. The ambiguous reactivity [3-5] of anions of structures **a-f** arises from the presence of four potential reactive centers, $N_{(1)}$, $N_{(3)}$, $O_{(2)}$, and $O_{(4)}$.

Many studies of a series of compounds of uracil, cytosine, and thymine have been carried out recently using quantum-chemical methods [6-9], but the tautomers of 2-oxopyrimidinones-4 with substituents R = H, CH_3, and C_6H_5 in position 6 have not been investigated theoretically.

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The effectiveness of the AM1 and PM3 approximations for determining the comparative stability of the tautomers of compound **2** in the gas phase has been demonstrated [9, 10].

In this work the influence of polar solvents on the tautomeric equilibrium of forms **a-f** [10, 11] for compounds **1-3** has been studied within the limits of the point dipole (PD) model [12-14] using the PM3 method. This approach permits the description of the electrostatic interactions between the polar solvent and the reacting system. In the calculations the distances between the PD and the reactive centers were taken as constant.

The data in Table 1 show that in the gas phase and in solution the preferred tautomeric form for compounds **1-3** is **a**, followed in terms of stability by form **c** in all cases. Tautomeric form **3d** is more stable than **3c**, but only in solution.

As expected the structures **a-f** are deformed on transferring from the gas phase to the model "liquid", i.e., when the molecules of the tautomers are surrounded by the PD of the solvent. For example, in form **a** with different substituents the lengthening of the N–H and C=O bonds of the four reactive centers is accompanied by small changes in the lengths of the bonds in the ring (Table 2). In structure **1a** the bonds $N_{(1)}$–H, $C_{(2)}$=O, $N_{(3)}$–H, and $C_{(4)}$=O are lengthened by 0.010, 0.012, 0.012, and 0.013 Å respectively as a result of interaction with the PD. In form **2a** the analogous lengthenings are 0.011, 0.011, 0.013, and 0.013 Å respectively, while in form **3a** they are equal to 0.014, 0.011, 0.004, and 0.012 Å. Evidently these changes arise from shifts of the electron density in the N–H and C=O bonds to attacking dipoles of the medium.

Shortening of the bond lengths in the heterocyclic ring in tautomers **a** occurs in all cases on passing into solution and is also explained by partial shift of the electron density of the heteroatoms of the ring. For example, in **1a** the electron density at $N_{(1)}$ is decreased by 0.029 e, at $C_{(2)}$ by 0.26 e, at $N_{(3)}$ by 0.035 e, and at $C_{(4)}$ by 0.036 e.

The fact that the corresponding bonds between these atoms are shortened in solution while the electron density on the atoms is reduced indicates that the electron density is shifted from the atoms to the neighboring bonds which leads to a strengthening bonds and a decrease in their length. Significantly the electron density shift in form **b** is different. For example, in the tautomeric **1b** in solution the negative charge on atoms $N_{(1)}$ and $N_{(3)}$ reaches its greatest value (to 0.115 and 0.128 e respectively), which causes lengthening of the $C_{(6)}$–$N_{(1)}$ and $N_{(1)}$–$C_{(2)}$ bonds by 0.019 and 0.004 Å respectively.There is also a shift of electron density from the bonds

TABLE 1. Relative Enthalpies of Formation* ΔH_f^0 for the Tautomeric Forms **a-f**, Calculated by the PM3 Method (kcal/mol)

Compound	Phase	**b**	**c**	**d**	**e**	**f**
1	Gas	7.4	6.6	8.9	21.9	15.0
	Solution	16.9	9.3	22.7	36.8	39.4
2	Gas	8.1	7.4	8.7	21.9	15.9
	Solution	48.0	13.8	17.4	38.0	36.4
3	Gas	8.3	7.8	8.6	22.1	16.2
	Solution	34.5	12.1	7.8	38.4	176.1

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* The enthalpy of formation of tautomeric form **a** was taken as the starting point for the calculations.

TABLE 2. Bond Lengths and Charges on the Atoms for the Most Stable Tautomeric Forms of Compounds **1-3** in the Gas Phase and in Solution*, Calculated by the PM3 Method

Form	Bond lengths, Å						Charge on the atoms, e			
	$N_{(1)}$–H	$C_{(2)}$–$O_{(2)}$	$N_{(3)}$–H	$C_{(4)}$–$O_{(4)}$	$O_{(2)}$–H	$O_{(4)}$–H	$N_{(1)}$	$O_{(2)}$	$N_{(3)}$	$O_{(4)}$
1a	0.995 (1.005)	1.224 (1.236)	0.999 (1.011)	1.220 (1.223)			0.087 (0.116)	-0.012 (0.023)	-0.385 (-0.500)	-0.351 (-0.482)
1c		1.338 (1.362)	0.998 (1.012)	1.221 (1.233)	0.952 (0.958)		-0.271 (-0.391)	-0.232 (-0.207)	0.077 (0.106)	-0.364 (-0.479)
2a	0.996 (1.007)	1.225 (1.236)	0.999 (1.012)	1.220 (1.223)			0.087 (0.113)	-0.389 (-0.501)	-0.013 (0.017)	-0.355 (-0.484)
2c		1.334 (1.362)	0.998 (1.013)	1.221 (1.232)	0.952 (0.956)		-0.264 (-0.383)	-0.233 (-0.208)	0.074 (0.097)	-0.368 (-0.475)
3a	1.001 (1.015)	1.225 (1.236)	0.999 (1.013)	1.220 (1.232)			-0.083 (0.098)	-0.391 (-0.487)	-0.011 (0.012)	-0.356 (-0.471)
3c		1.342 (1.333)		1.349 (1.338)	0.952 (0.953)	0.952 (0.952)	-0.240 (-0.309)	-0.191 (-0.215)	-0.233 (-0.380)	-0.218 (-0.199)
3d	1.001 (1.017)	1.218 (1.236)		1.347 (1.332)		0.953 (0.957)	+0,070 (0.130)	-0,356 (-0.524)	-0.286 (-0.435)	-0.223 (-0.199)

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* Figures in parentheses are for the tautomers in solution.

$N_{(1)}$–$C_{(2)}$ and $C_{(2)}$–$N_{(3)}$ to the bond $C_{(2)}$–OH, as a consequent of which the $N_{(1)}$–$C_{(2)}$ and $C_{(2)}$–$N_{(3)}$ are lengthened by 0.004 and 0.020 Å, and the $C_{(2)}$–OH is shortened by 0.008 Å. The electron density on atom $C_{(2)}$ is decreased by 0.064 e, but the negative charge on atom $O_{(2)}$ is increased by 0.026 e.

The estimantion of the relative stability of the tautomeric forms **a-f** is of importance in interpreting the mechanism of alkylation of the anions of 2-oxopyrimidinones-4 [15]. It is natural that the most stable tautomeric form should participate to a great extent in these reactions. The energetic advantage of tautomer **a** is determined primarily by the symmetrical position of the carbonyl groups relative to $N_{(3)}$ center. The neighboring positive charges on the atoms $C_{(2)}$ and $C_{(4)}$ stabilize the negative charge on atom $N_{(3)}$ to a considerable extent, which determines the greater suitability of tautomeric structures **a** in comparison with the others. There are many facts in the literature [15, 16] which confirm our conclusion that the oxo form predominates over the hydroxy forms.

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