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DIMER MECHANISM FOR THE TAUTOMERIC CONVERSION OF 4-AMINO-2-OXOPYRIMIDINE

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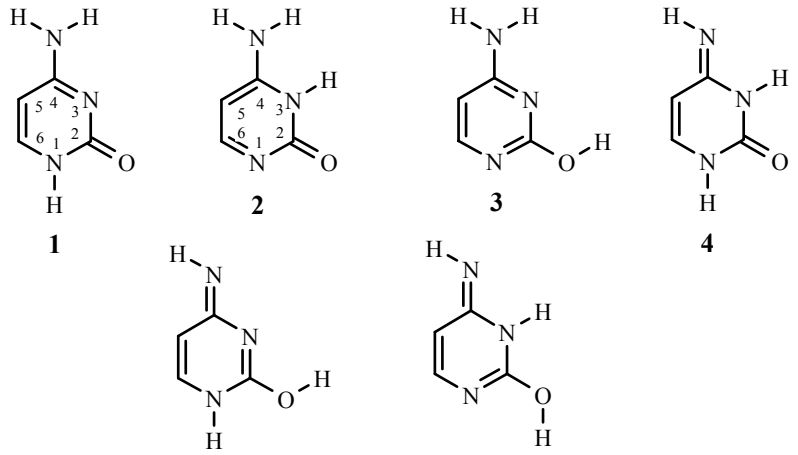
Values of the enthalpy (ΔH), atomic charges (q_i), and bond orders (P_{ij}) for six tautomeric forms of 4-amino-2-oxopyrimidine have been calculated by the semiempirical AM1 quantum-chemical method. It was found that the most stable of these is 4-amino-2-oxo-1H-pyrimidine (cytosine). By analogy with complementary pairs of nucleotide bases, the tautomeric conversion of cytosine and other oxo forms can come about via a dimeric intermolecular mechanism. A novel interpretation is proposed for the conversion of cytosine to 4-amino-2-oxo-3H-pyrimidine as a result of a 1H-3H two stage proton transfer.

Keywords: cytosine, pyrimidine, molecular rearrangement, quantum-chemical calculations, tautomeric conversions.

Both semiempirical [1-3] and non-empirical [4-6] quantum-chemical methods have been widely used for the theoretical investigation of the tautomeric conversions of pyrimidine derivatives including cytosine (4-amino-2-oxo-1H-pyrimidine) [1]. Six possible tautomers of 4-amino-2-oxopyrimidine have been discussed in the studies [2, 7].



1 **2** **3** **4** **5** **6**

The authors note that the stability of the tautomers **1-6** decreases in the series: **1**>**2**>**4**>**3**>**5**>**6** but quantum-chemical calculations [1, 8] have shown the most stable in this series is 4-amino-2-hydroxypyrimidine (**3**). Such a conclusion is supported by experimental data [9]. The overall result in the indicated studies points to

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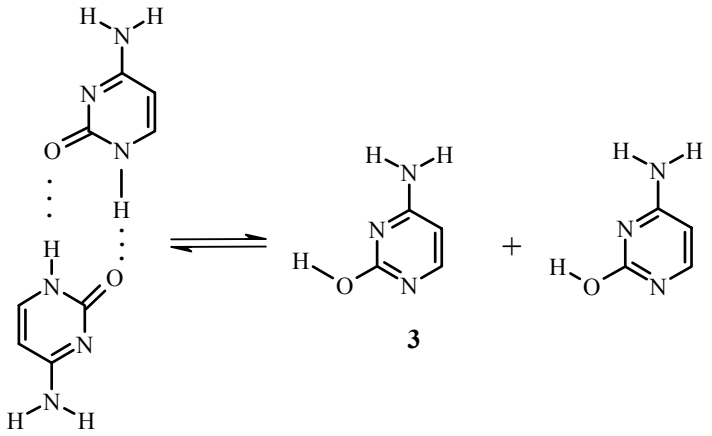
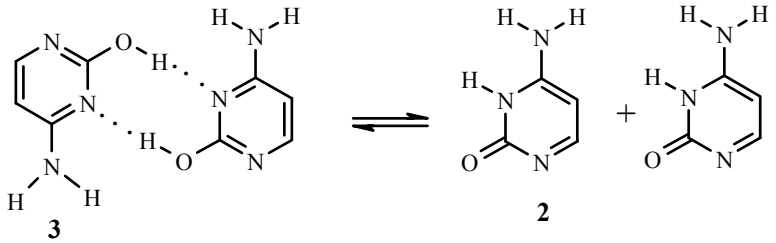
a low stability for imine forms. Based on calculation of total energy by a non-empirical method in [6] on the existence of the tautomeric forms of pyrimidine derivatives it was concluded that tautomeric conversions came about *via* intermolecular hydrogen bonds involving hydroxyl, amine, and carbonyl groups.

With the aim of a systematic study of some physicochemical properties of the tautomeric forms of **1-6** using the AM1 semiempirical quantum-chemical method [10] we have calculated their structural, energetic, and electronic indices. As is evident from Table 1, the amino forms are more stable and, amongst these, the most stable is the 4-amino-2-oxo-1H-pyrimidine (**1**), i.e. one of the most important nucleotide bases cytosine and this is found to be in full agreement with reported literature data [2, 7]. From Table 1 it is also seen that the distribution of the charge on the pyrimidine ring atoms in the investigated tautomers follows a well defined pattern. In particular, the high negative charge (especially for tautomer **2**) on the $C_{(5)}$ atom and positive charge on atom $C_{(6)}$ points to a regioselectivity of electrophilic and nucleophilic addition respectively and this is found to be in full agreement with literature data [10]. The charge on atoms $N_{(1)}$ and $N_{(3)}$ is significantly higher when it is found to be in the sp^3-hybridized form **1** and **2**. This brings about an increase in the "electron stripping" of hydrogen atoms bonded to them. Bearing in mind also that the N–H bond order has quite a low value (P_{NH} = 0.872-0.882) it is possible to account for high mobility of such hydrogen atoms. The situation can be due to the realization of a lactam-lactim tautomeric conversion *via* an intermolecular dimer mechanism:



1 **3**

In the lactim form **3** the $N_{(3)}$ atom appears as an active proton acceptor center (q_3^N = -0.309) in which the hydroxyl proton can be transferred again *via* an intermolecular dimmer mechanism:



3 **2**

Hence the 1H-3H proton transfer can be considered as a two stage process (the energy diagram is given in Fig. 1). The enthalpy of activation $\Delta\Delta H^{\#}$ is 164.9 for the first stage and 110.5 kJ/mole for the second. The whole process is exothermic with a release of some energy $\Delta\Delta H$ = -4.9 kJ/mole).

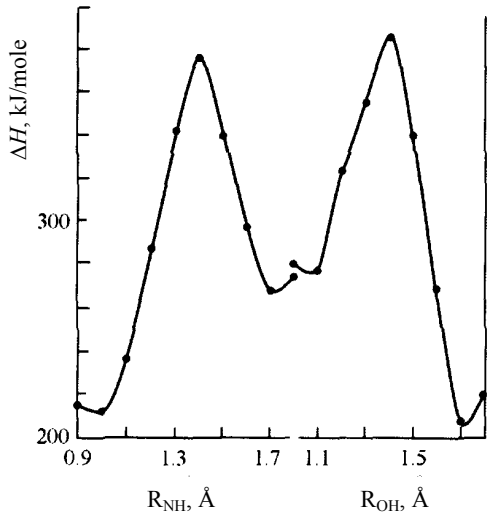


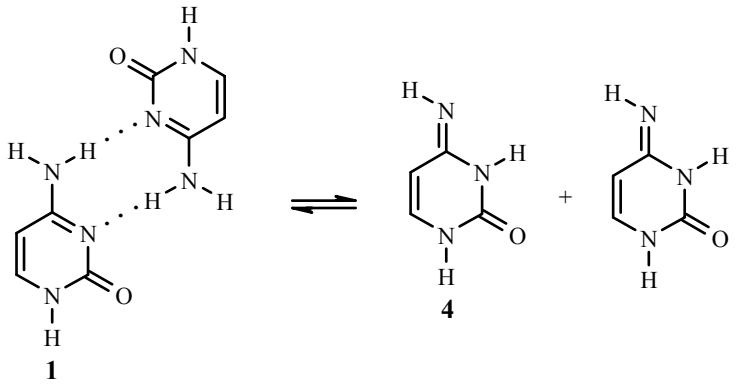
Fig. 1. Energy diagram for the two-stage 1H-3H proton transfer in cytosine. Dependence of the enthalpy ΔH of tautomers **1** and **3** on the reaction coordinates R_{NH} and R_{OH} respectively.

TABLE 1. Values of the Enthalpy (ΔH), Dipole Moments (μ), Atomic Charges (q_i), and Bond Orders (P_{ij}) for the Tautomers **1-6**

Compound	ΔH, kJ/mol	μ, D	q_1	q_2	q_3
1	2	3	4	5	6
1	77.7	6.26	-0.324	+0.348	-0.293
2	80.2	7.00	-0.222	+0.339	-0.349
3	85.7	4.20	-0.195	+0.187	-0.309
4	92.4	4.56	-0.320	+0.398	-0.318
5	168.4	5.11	-0.291	+0.237	-0.238
6	135.4	1.46	-0.285	+0.259	-0.271

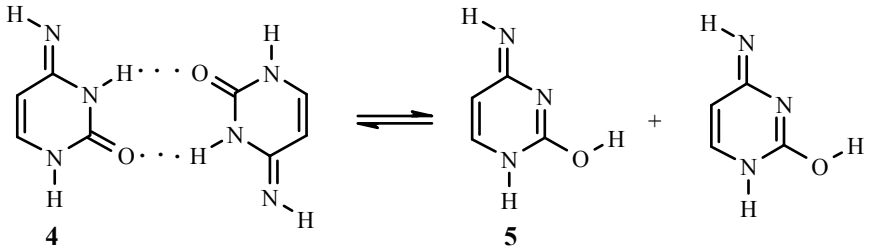
Compound	q_4	q_5	q_6	$P(N_3H)$	$P(N_1H)$
7	8	9	10	11	12
1	+0.228	-0.345	+0.063	—	0.882
2	+0.254	-0.405	+0.065	0.881	—
3	+0.193	-0.339	+0.013	—	—
4	+0.161	-0.296	+0.035	0.872	0.878
5	+0.091	-0.285	+0.007	—	0.800
6		-0.303	+0.002	0.873	—

Formation of the imine tautomers **4**, **5**, and **6** is also possible by an intermolecular mechanism of the conversion of the dimers of cytosine **1**:



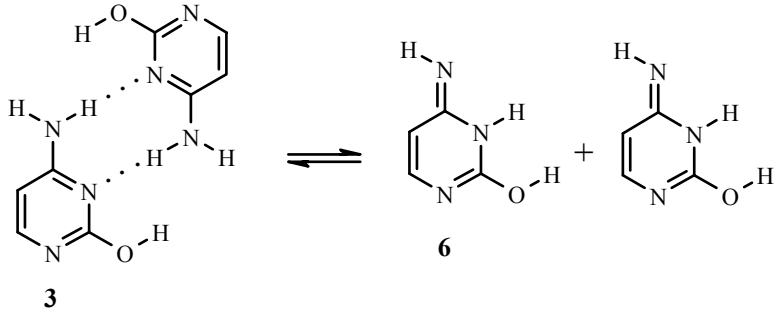
1 **4**

Its imine form **4**



4 **5**

and enol form **3**



3 **6**

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