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QUANTUM-CHEMICAL DESCRIPTION OF THE PROTOTROPIC TAUTOMERISM OF PYRIMIDINE BASES

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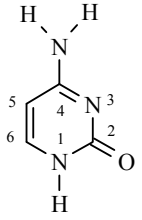
The energy characteristics of the tautomeric transformations of cytosine, thymine, and uracil have been calculated within the framework of the quantum chemistry theory of functional density. It was concluded that the directions of the tautomeric conversions are characterized by energies of activation calculated according to the theory of functional density.

Keywords: thymine, uracil, cytosine, quantum-chemical calculations, prototropic tautomerism, functional density theory, energy of activation.

Prototropic tautomerism in nitrogen-containing heteroaromatic compounds has been well studied by experimental [1-4] and theoretical [5-11] methods, and general conclusions have been drawn that tautomeric keto and amino forms are canonical, the equilibrium constant depends on the structure of the compound and the solvent, and proton transfer is effected according to a cyclic dimer mechanism. Particular attention has been paid to the study of tautomeric conversions of pyrimidine bases with the aim of a qualitative description of the uncommon tautomeric forms and processes [12-16], and also clarification of the possibility of the existence of intermolecular hydrogen bonds [17-19]. Interest in the theoretical investigation of prototropic tautomeric conversions has grown with the appearance of calculating programs putting into effect the methods of the theory of functional density (TFD), which effectively reproduces the energy and electronic characteristics of complex molecular systems [20].



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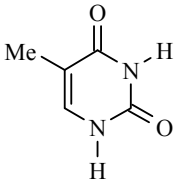

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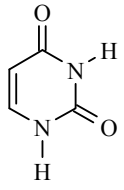

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In recent years work has appeared devoted to the qualitative description of the tautomerism of cytosine [21-24], thymine [25], and uracil [26, 27]. However there is no uniform energy description in the literature of the tautomeric conversions of pyrimidine bases. Consequently we have calculated, within the framework of TFD, the energy characteristics of the processes of proton transfer in every kind of dimer of cytosine **1**, thymine **2**, and uracil **3**. The calculations were carried out with the Priroda program [29] in reaction coordinate mode using the PBE functional [30] and its modification mPBE [31]. Furthermore, for comparison we reverted to the functional BLYP [32, 33] and the local density approach of [34].

On the basis of the calculated data the dependence has been plotted of the relative total energy (E) on reaction coordinates (R_{NH}) for the processes of proton transfer along the intermolecular hydrogen bond in every possible dimer of cytosine (Fig. 1), thymine, and uracil.

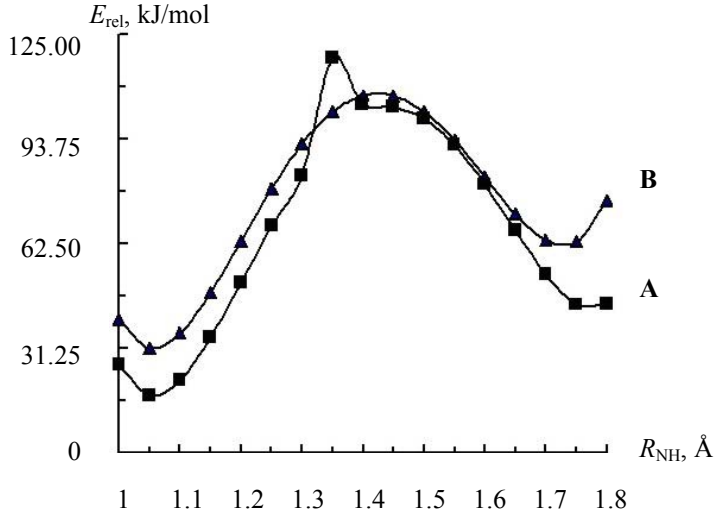
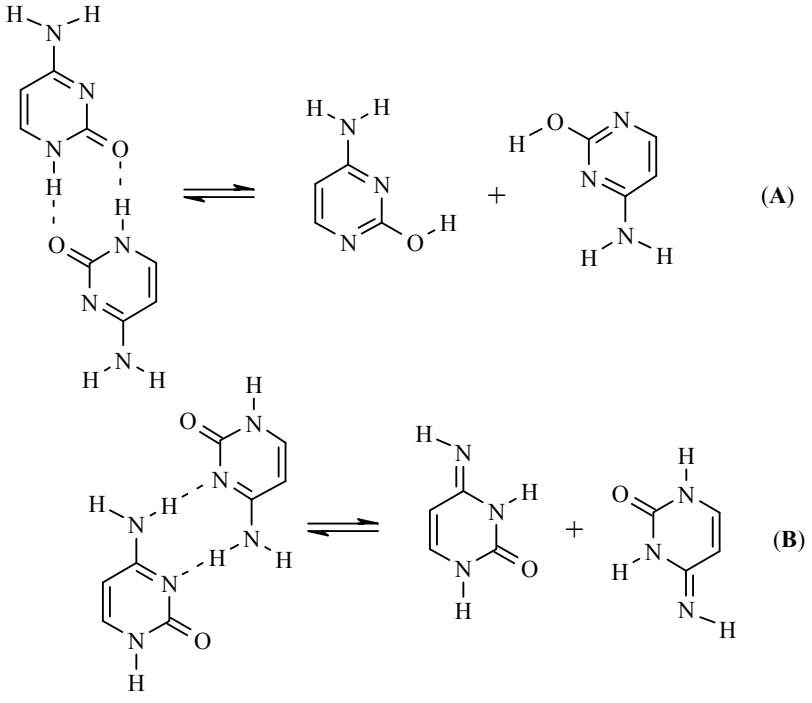


Fig. 1. Dependence of the relative total energy E_{rel} for the transfer of proton on reaction coordinates (R_{NH}) for the tautomeric conversions **A** and **B** of cytosine.



In Fig. 1 it is evident that for tautomeric conversion **A** the energy of activation ΔE_{act} = 100.6 and the energy of the reaction ΔE = 27.1; for tautomeric conversion **B** ΔE_{act} = 75.4 and ΔE = 31.8 kJ/mol. Consequently tautomeric conversion **B**, which from the disposition of nucleotide bases in DNA corresponds to the horizontal interaction, proceeds at a lower energy barrier than the analogous conversion **A**, capable of being put into action for a vertical stacking interaction.

This is in agreement with the known concept that the stacking interaction is not donor–acceptor in nature unlike a hydrogen bond. At the same time the barrier at 100.6 kJ/mol is not so high as to make a transfer of proton in a vertical direction impossible. This circumstance enables the suggestion that the stacking interaction may have a partial donor–acceptor character.

Analogous energy dependencies are given in Fig. 2 for the tautomeric conversions **C**, **D**, and **E** of thymine.

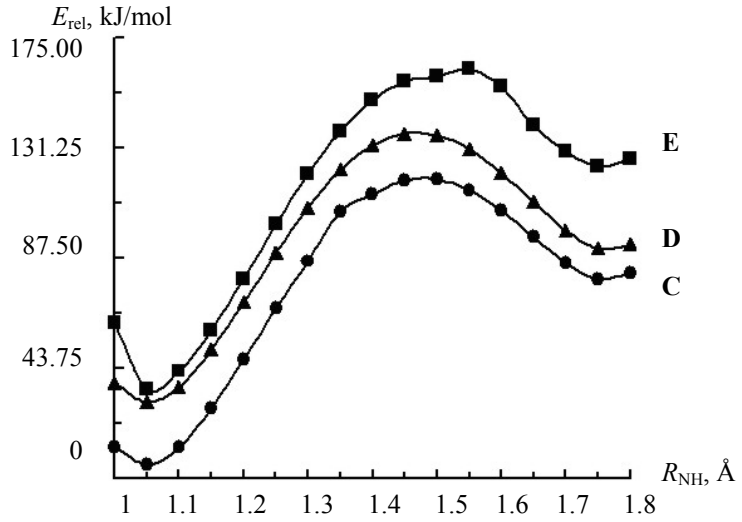
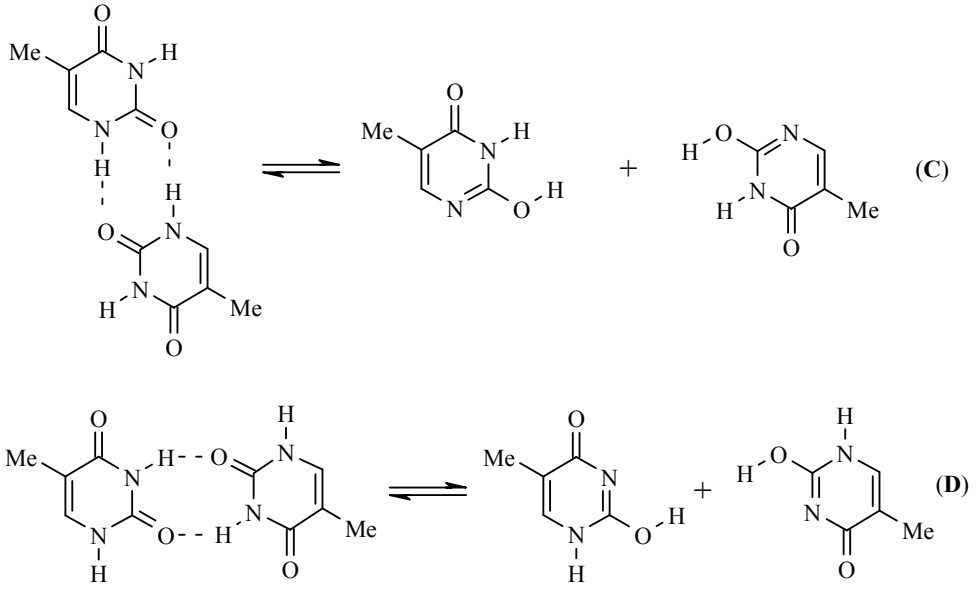
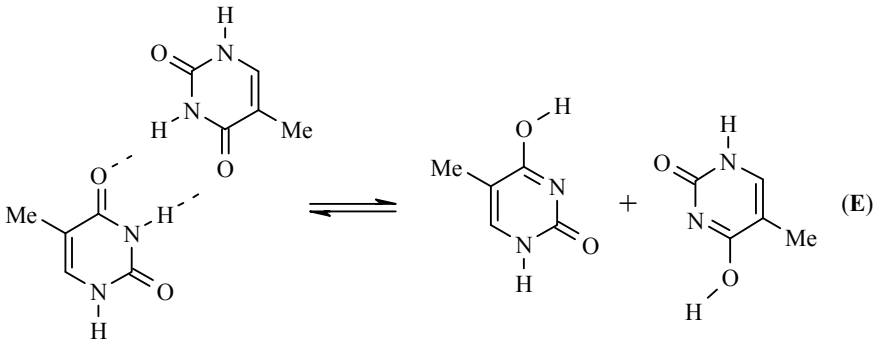


Fig. 2. Dependence of E_{rel} for proton transfer on reaction coordinates R_{NH} for tautomeric conversions **C**, **D**, and **E** of thymine.





(**E**)

It is seen from Fig. 2 that for tautomeric conversion **C** the energy of activation ΔE_{act} = 106.1 and the energy of the reaction ΔE = 68.9 kJ/mol; for **D** ΔE_{act} =124.4 and ΔE = 88.7; for **E** ΔE_{act} = 106.6 and ΔE = 62.6 kJ/mol. This means that for thymine the tautomeric conversion **D** with its horizontal interaction is linked with surmounting the highest energy barrier. Consequently the conclusion drawn above on the relatively prototropic tautomerism of cytosine is not observed for thymine.

For uracil, as for thymine, three types of analogous tautomeric conversions **F**, **G**, and **H** are also possible. It is seen from Fig. 3 that for tautomeric conversion **F** the energy of activation ΔE_{act} = 110.7 and the energy of the reaction ΔE = 74.4; for **H** ΔE_{act} = 170.0 and ΔE = 91.9; for **G** ΔE_{act} = 103.9 and ΔE = 64.1 kJ/mol. The energy of activation shows that tautomeric conversion **H** with its horizontal interactions is effected with more difficulty, but the vertical interactions **F** and **G** are relatively facile. This result agrees qualitatively with that obtained for thymine.

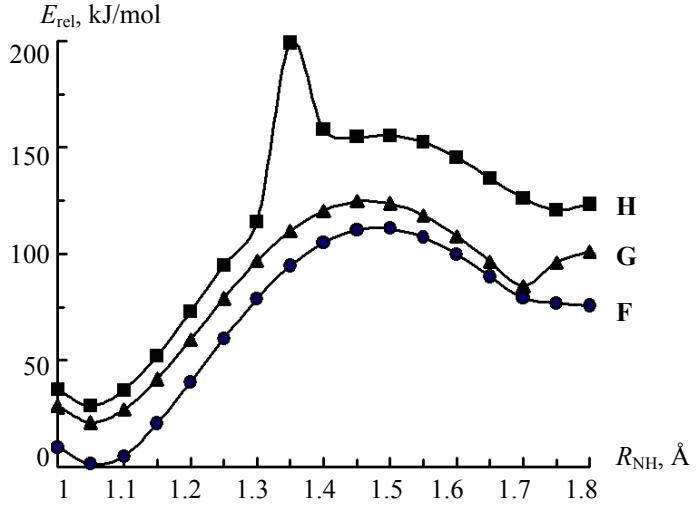


Fig. 3. Dependence of E_{rel} for proton transfer on reaction coordinates R_{NH} for the tautomeric conversions **F**, **G**, and **H** for uracil.

At the same time, as is seen from the data of activation energy, a methyl group in position 5 of the pyrimidine ring makes the process of tautomeric conversion **D** with its horizontal interactions easier in comparison with the analogous conversion **H** of uracil ($\Delta\Delta E_{act}$ = 46.2 kJ/mol). This is explained by the electron-donating effect of the methyl group on the proton-accepting oxygen atom of the carbonyl group located in the *para* position.

As a result of the comparative quantum-chemical description of prototropic tautomerism of pyrimidine bases it is possible to draw the general conclusion that the directions of the tautomeric conversions are characterized by the energies of activation calculated according to TFD.

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