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Physical Chemistry

Quantum-Chemical Modeling of the Mechanisms of Synthesis of Pyrimidine and Purine

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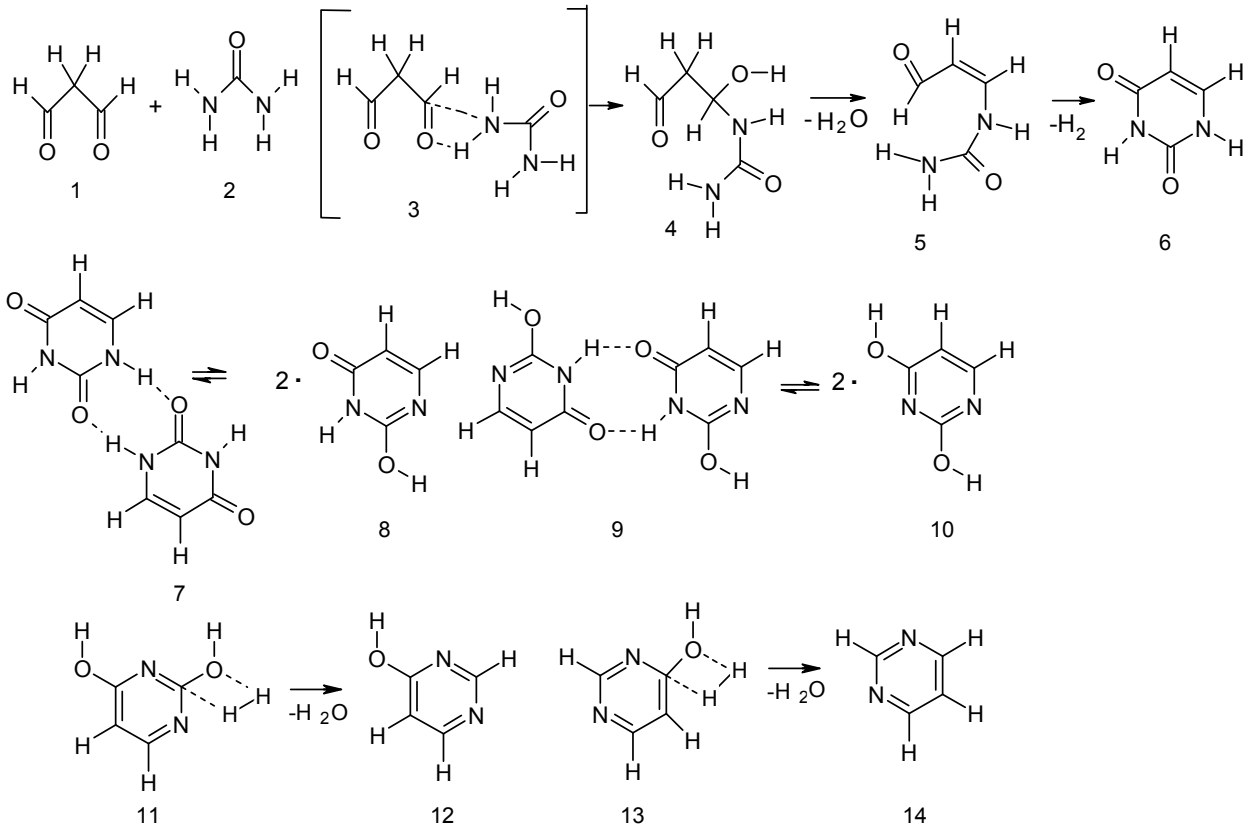
ABSTRACT. The models of the mechanisms of synthesis of unsubstituted pyrimidine and purine by quantum-chemical method of DFT (Density Functional Theory) are constructed. The conclusion is made that the offered models can promote careful and purposeful synthesis of these heterocyclic derivatives, including nucleotide bases.

Key words: *pyrimidine, purine, modeling of mechanisms, DFT calculations.*

Careful and purposeful synthesis of pyrimidine and purine is directly connected with the modeling of mechanisms of these reactions. Modeling of chemical reaction mechanisms can be conceptualized as a detailed description of separate stages by means of structural, energetic and electronic characteristics of reagents, allowing to shed light on the reaction centers and high reactivity bonds. Purposeful excitation and sounding of such bonds is possible by femtosecond laser impulses [1], whose frequency equals the frequency of valent and deformative fluctuations of these bonds. To construct models of the mechanism of careful and purposeful synthesis of pyrimidine and purine with the use of the quantum-chemical nonempirical method – density functional theory (DFT) [2] structural, energetic and electronic characteristics of initial compounds, intermediates of synthesis have been calculated. Calculations were carried out using the program ''Priroda'' [3] in reaction coordinate mode with PBE [4] approximation and its update mPBE [5] and BLYP [6] functional.

To model the mechanism of synthesis of unsubstituted pyrimidine the synthesis scheme of 2,4-dioxy-6-methylpyrimidine, developed by A.Katritsky [7], has been used. The model of the mechanism of pyrimidine synthesis has been constructed on a basis of calculation of separate stages of charge on carbon and nitrogen atoms (q_C, q_N) and of activation ($\Delta E^{\#}$) and reaction energy (ΔE) (scheme 1). According to this scheme, at the first stage as a result of interaction of aldehyde of malone (1) with urea (2) through transition state (3) an enolic product (4) is formed. The energy diagram of this stage, or dependence of the full energy (E) on reaction coordinate (R_{CN}) is presented in Fig.1. From this figure it is clear that the energy of activation of the first stage $\Delta E^{\#} = 119.0$, and the energy of reaction ΔE = -57.9 kJ/mol, which specifies the exothermal character of this stage.

At the second stage a quasicyclic product can be formed (5) from enolic product (4) by separation of water there. The energy of activation of this stage $\Delta E^{\#} = 34.5$, and the energy of reaction ΔE = -74.3 kJ/mol. The low barrier and exothermicity of the process specifies the possibility of real existence of an intermediary. As a result of closing of a cycle and separation of molecular hydrogen the intermediate product – 2,4-dioxypyrimidine is formed. The activation energy of this stage $\Delta E^{\#} = 114.7$, and the



Scheme 1. The mechanism of pyrimidine synthesis

energy of reaction $\Delta E = -74.8$ kJ/mol. Thus, the third stage as well as the former two first constitute the exothermal process.

Synthesis of unsubstituted pyrimidine (14) from 2,4-dioxypyrimidine (6) can proceed as a result of (7) → (8) and (9) → (10) lactam-lactim tautomeric transformation, in the way of the cycle-dimeric mechanism. Mechanisms of proton transfer in pyrimidine derivatives are well studied by quantum-chemical methods [8-10]. The activation Energy of (7) → (8) transformation $\Delta E^{\#} = 113.9$, and energy of reaction $\Delta E = 81.3$ kJ/mole, and for (9) → (10) transformation $\Delta E^{\#} = 80.0$, and $\Delta E = 16.5$ kJ/mol. This endothermic process is characteristic of tautomeric transformations.

As a result of interaction of dienolic product (10) with molecular hydrogen (11) water is separated and the enolic product (12) is formed. Energy of activation of (11) → (12) process $\Delta E^{\#} = 44.6$, and energy of reaction $\Delta E = -117.5$ kJ/mole. For its part, the enolic product (12) also by interaction with molecular hydrogen (13) and then by separation of water, forms a definite product of synthesis – unsubsti-

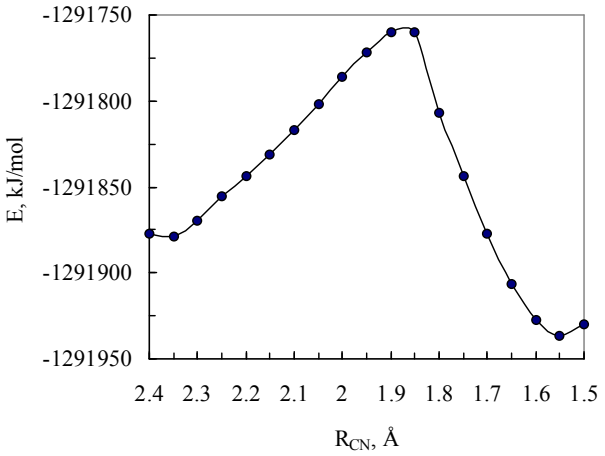


Fig. 1. Dependence of total energy (E) of transformation (1) + (2) → (4) on the coordinate of reaction (R_{CN}).

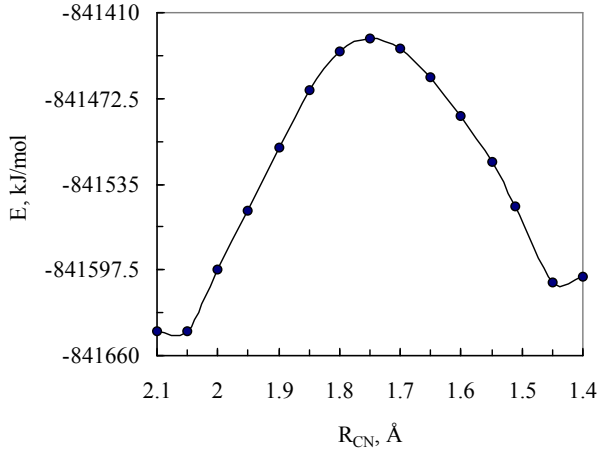
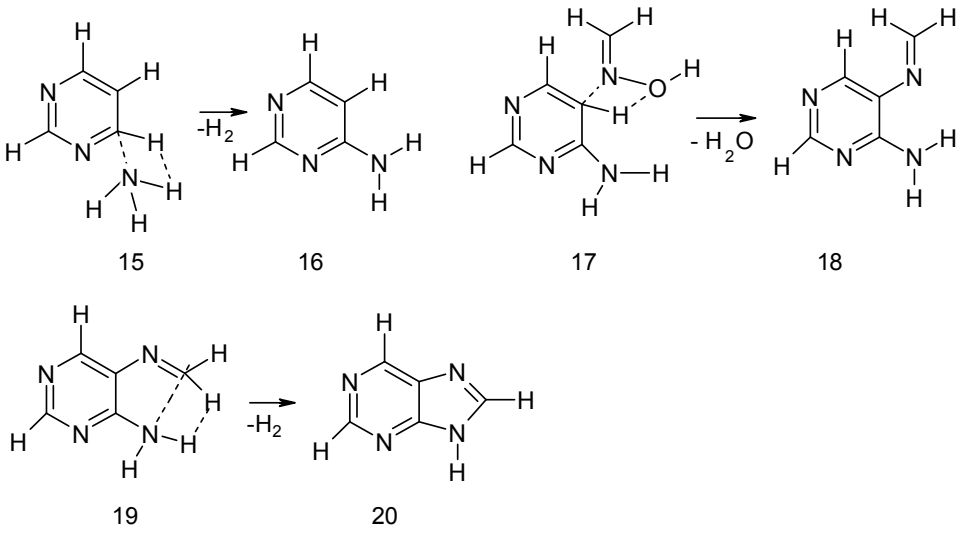


Fig. 2. Dependence of total energy (E) of transformation (15) → (16) on the coordinate of reaction (R_{CN}).



Scheme 2. The mechanism of purine synthesis

tuted pyrimidine (14). Energy of activation of (13) → (14) process $\Delta E^{\#}$ = 142.4, and energy of reaction ΔE = -162.7 kJ/mol. Thus, the process of synthesis of pyrimidine cycle comes to an end with energy separation in a considerable quantity.

Synthesis of unsubstituted purine is carried out on the basis of pyrimidine or imidazole [11]. The first type of processes synthesis was given by Traube [12], way back in 1900; under the impact of formic acid he carried out cyclization of triamino substituted purine which then transformed into guanine [12].

In the proposed model of the mechanism of synthesis of unsubstituted purine the first stage is amination by ammonia of the 6th position pyrimidine (scheme 2). In this position the charge on the atom of carbon q_C = +0.142, and on the atom of nitrogen of ammonia q_N = -0.400, which specifies the nucleophilic substitution, therefore it forms 6-aminopyrimidine (16) and molecular hydrogen is separated. The energy diagram of the first stage of purine synthesis, or dependence of the full energy on reaction coordinate (R_{CN}) is presented in Fig. 2. From this figure it is visible that energy of activation $\Delta E^{\#}$ = 113.1, and energy of reaction ΔE = 35.0 kJ/mol. On the atom of the 5th position the carbon atom of 6-aminopyrimidine we have negative charge q_C = -0.295. Accordingly for amination of this position with a kind of the electrophilic agent it is selected up formaldoxime, with a positive charge on nitrogen atom q_N=+0.020. In the 5th position of 6-aminopyrimidine by transitive state (17), as a result of electrophilic substitution and separation of water 5-formimin-6-aminopyrimidine (18) is formed (scheme 2). Energy of activation of the second (17) → (18) stage $\Delta E^{\#}$ = 118.0, and energy of reaction ΔE = -170.2 kJ/mol. Last third stage is closing of the cycle of imidazole in 5-formimin-6-aminopyrimidine (18) by transitive state (19). As a result molecular hydrogen is separated and unsubstituted purine (20) is formed. Energy of activation of transformation (19) → (20) $\Delta E^{\#}$ = 141.2, and energy of reaction ΔE = 78.2 kJ/mol. Unlike pyrimidine synthesis the last stage of purine synthesis is an endothermic process with energy absorption in a small amount.

Thus, having used the proposed models the participation in the synthesis of purine and pyrimidine bonds has been revealed. It has high reactivity in accordance with frequency of fluctuation, which makes possible their purposeful excitation and sounding with femtosecond laser impulses, or breakage of these bonds and formation of new bonds.

ფიზიკური ქიმია

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