Chemical Physics Letters 710 (2018) 16–25

Contents lists available at ScienceDirect

Chemical Physics Letters

journal homepage: www.elsevier.com/locate/cplett

Research paper

Catalytic abiotic synthesis of uracil from cysteine and urea: Theoretical studies

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HIGHLIGHTS

- Urea serve as a catalyst in the suggested uracil formation mechanism.
- The majority of transformations occur with the transfer of protons.
- The highest activation energy barrier is 42.8 kcal/mol.

ARTICLE INFO

Keywords:
DFT
Transition states
Uracil
Cysteine
Catalysis

ABSTRACT

An abiotic synthesis of nucleobases from amino acids is of critical importance as it sheds a light on potential pre-life chemical reactions. However, information about reaction pathway is often not available directly from laboratory experiments. In contrary, computational simulations allow to learn chemical transformations directly. In the present study, we investigated one of promising routes of uracil synthesis from cysteine, using density functional theory at the M06-2X/6-311G(d,p) level. We suggested that the solvent (urea) facilitates the reaction acting as self-catalyst. Proposed reaction pathway involves seven reactions with the highest activation energy barrier equal to 42.8 kcal/mol.

1. Introduction

An investigation of abiotic synthesis of nucleobases from various organic compounds is of keen interest [1–9]. As it was demonstrated in widely known Miller–Urey experiments, the majority of amino acids can be synthesized from inorganic compounds under conditions, similar to conditions on early Earth [9,10]. For the last two decades, all five nucleobases have been synthesized from formamide (and other simple single-carbon compounds) in the absence of oxygen [11–16]. Investigation of synthetic pathways of such reactions could indirectly represent potential pre-life chemical reactions [17]. For instance, Springsteen's group successfully synthesized purine and adenine from formamide [18]. These experimental studies were then well explained by computational simulations that elucidate the mechanisms of the corresponding syntheses [12,13,19–21].

Overall, computational simulations, e.g. quantum chemical computations, represent a suitable tool to reveal details about intermediates and transition states along the reaction pathways [20]. Utilization of simulation tools allows extracting the information about selected vital species (products and reactants), intermediates and transition states, that appear along the reaction pathway [15]. Information about transition states could not be extracted directly from experiments, as prebiotic experiments always involve complex mixtures, making the interpretation of outcomes difficult [15,21]. Thus, quantum chemical studies allow evaluating routes among various possible reaction pathways [21].

As it was recently experimentally demonstrated, amino acids dissolve in urea "melt" solutions, but only cysteine can be further transformed to uracil [14,22]. One of potential pathways for this reaction has been previously proposed [22], but we suggested the existence of alternative pathways. Thereafter, we evaluated a new pathway of cysteine to uracil synthesis using density functional theory (DFT) approach. The newly introduced pathway is compared with the previously proposed mechanism.

2. Materials and methods

We utilized the combination of Minnesota density functional M06-

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https://doi.org/10.1016/j.cplett.2018.08.057
Received 31 July 2018; Accepted 23 August 2018
Available online 24 August 2018
0009-2614/

2X [23–25] with standard valence triple zeta basis set with polarization functions 6-311G (d,p)[26]. The M06-2X benchmark and 6-311G (d,p) basis set were selected because of the successful performance of this bundle in carbohydrate chemistry modeling [16,23–25,27,28]. Moreover, we have previously demonstrated that M06-2X/6-311G (d,p) level of theory is suitable for earlier introduced cysteine-to-uracil transformation pathway [22].

Density functional calculations were carried out with the Gaussian 09 software package [29]. All the relevant stationary points on the potential energy surface were located using full geometry optimizations without any symmetric restriction, local minima or first-order saddle points. For each step, we conducted vibrational frequency calculations. The intrinsic reaction coordinate (IRC) calculations were evaluated to check whether there is a connection between the calculated initial states, the transition states, and product geometries. For the further discussion, the energetic properties are based on the zero-point energy (ZPE) corrected relative energies.

3. Results and discussion

It has been demonstrated, that the urea catalytic mechanism is more favorable than the non-catalytic mechanism (both thermodynamically and kinetically)[22]. Upon this consideration, in this work, we analyzed the catalytic pathway. We suggested that the potential pathway goes through seven main steps: (1) formation of 3-mercapto-2-ureidopropanic acid, (2) formation of 2-(carbamoylamino)-3-(carbamoylsulfanyl)propanoic acid, (3) formation of 2-(carbamoylamino)-3-(carbamoylsulfanyl)propanoyl carbamate, (4) formation of 2-(ureidocarbonyl)-2-(carbamoylamino)ethyl carbamothioate via nucleophilic attack of the urea, (5) formation of [2-(carbamoylamino)prop-2-enoyl]urea through proton-transfer induced release of carbamothioic acid, (6) formation of 1-(hexahydro-2,4-dioxopyrimidin-5-yl)urea; (7) formation of uracil [14]. Scheme 1 represents the transformations that occur through that pathway.

Schematic energy profile along the reaction pathway for the each step is presented in Fig. 1. ΔE_0 is the zero-point energy corrected relative energy (in kcal/mol) for the initial reactants, corresponding transition states, intermediates, and products.

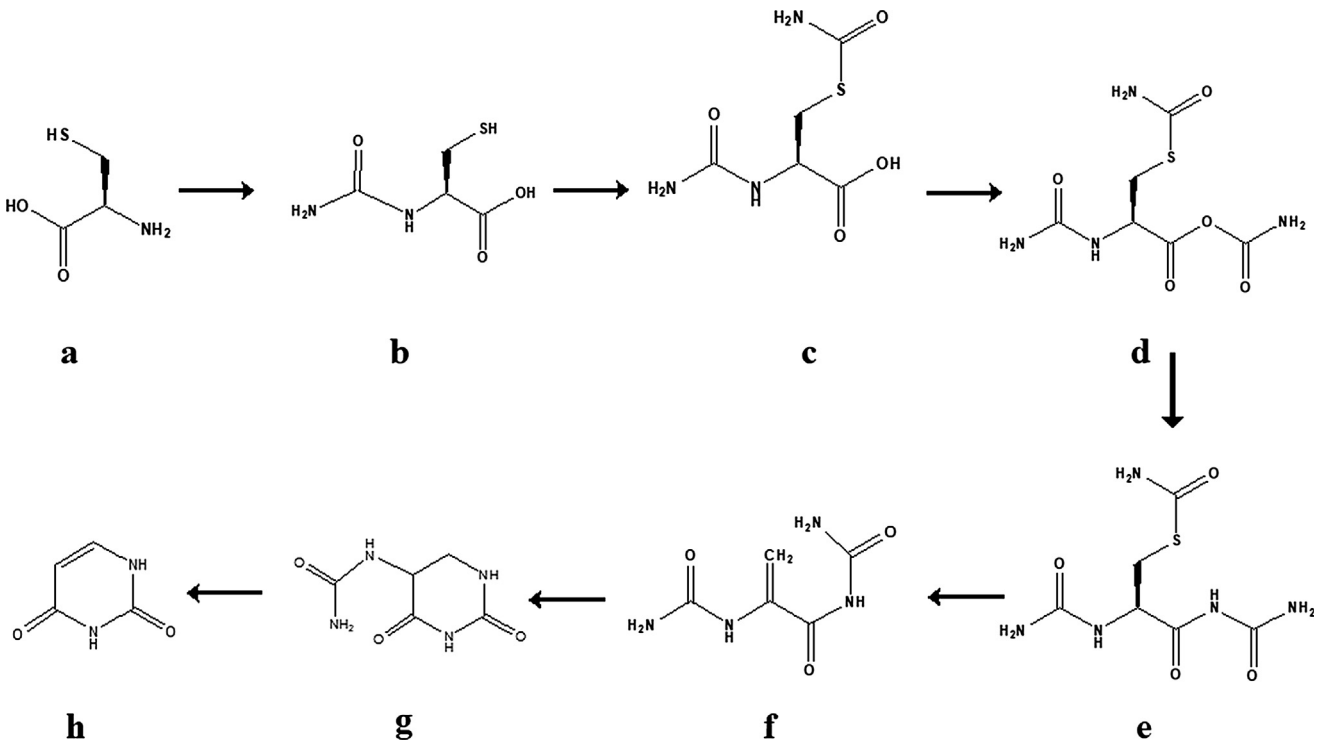
Atomic distances are presented in Å for all figures below; color representations: red for oxygen, blue for nitrogen, grey for carbon, and white for hydrogen. Small arrows represent the vibrational mode corresponding to the single imaginary frequency in the transition states.

3.1. Step 1: The formation of 3-mercapto-2-ureidopropanic acid

With the assistance of one urea molecule acting as the catalyst, this reaction consists of three elementary reaction steps: (a) nucleophilic addition of cysteine to urea, (b) proton-transfer through catalytic urea, and (c) elimination of ammonia [22]. In overall, for the step 1, the highest energy barrier for the formation of 3-mercapto-2-ureidoproanic acid amounts to 28.1 kcal/mol (Fig. 1).

In the initial reaction complex (Figs. 2, 1**a**) a short hydrogen bond (1.367 Å) is formed between the urea and hydroxyl group of cysteine. Nitrogen from the urea's imino group tends to form H-bond with the amino group of cysteine (2.143 Å). H-bonding there affects increasing nucleophilicity of cysteine in the transition state structure (Figs. 2, 1**aTS**).

Cysteine attacks the C of the carbonyl group of urea, forming a new N−C bond between cysteine and urea, resulting in 2-{[diamino(hydroxy)methyl]amino}-3-mercaptopropanic acid intermediate (Figs. 2, 1**b**). Next, we observe the proton transfer (Figs. 2, 1**bTS**). The activation energy amounts to 8.0 kcal/mol (see Fig. 1). In the following process, ammonia is eliminated following intra-molecular proton transfer from the hydroxyl group to the deprotonated mercapto group (black arrow in Figs. 2, 1**cTS**), and the target 3-mercapto-2-ureidopropanic acid is formed (Figs. 2, 1**d**). The activation energy of this reaction is 4.7 kcal/mol.



Scheme 1. Transformations pathway: a – cysteine; b –3-mercapto-2-ureidopropanic acid; c – 2-(carbamoylamino)-3-(carbamoylsulfanyl)propanoic acid; d – 2-(carbamoylamino)-3-(carbamoylsulfanyl)propanoyl carbamate; e – 2-(ureidocarbonyl)-2-(carbamoylamino)ethyl carbamothioate; f – [2-(carbamoylamino)prop-2-enoyl]urea; g – 1-(hexahydro-2,4-dioxopyrimidin-5-yl)urea; h – uracil.