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SYNTHON CHEMISTRY: THEORETICAL STUDY ON THE FORMATION OF PROLINE, PHENYLANALINE AND TYROSINE

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Abstract

According to the "synthon theory" on the formation of the first proteinogenic amino acids from three synthons: methylene, nitrene and carbon monoxide, at low temperatures, aziridinone would have formed. This, in contact with the same three synthons, forms the precursors of the 20 proteinogenic amino acids. These precursors, on contact with the components of the primary atmosphere, formed the first proteinogenic amino acids. The aim of this paper is to find the interradical reactions, which would have formed the precursors of proline, phenylalanine and tyrosine. The paper is a continuation of other studies on obtaining these amino acids in order to correlate them with their essential and non-essential character. As procedure, the quantitative results: enthalpies of formation, enthalpies of reaction, free energies, profile of reaction pathways were obtained by DFT calculations (B88-LYP).

Keywords: aziridinone, aziridinone radicals, phenylalanine, proline, tyrosine

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1. Introduction

In the previous work (Surpateanu, 2018), the synthonic theory of the formation of the proteinogenic amino acids and of the corresponding polypeptides was presented in detail. Specifically, three synthons: methylene, nitrene and carbon monoxide would form aziridinone at low temperatures (below 0 ^{o}C), in nitrogen. Aziridinone, is considered a key compound in the formation of proteinogenic amino acid precursors and polypeptides. Some of the amino acid precursors would form polypeptide precursors by copolymerization. The complex mixture of precursors with other radical compounds, possibly carried by a comet, on contact with the components of the primary atmosphere, would have formed the first proteinogenic amino acids and their first corresponding polypeptides, on Earth. Interestingly, the first polypeptides would not have formed from the first proteinogenic amino acids, but from their precursors.

In previous works (Surpateanu et al., 2019; Surpateanu et al., 2020a, 2020b) we have shown in detail the reaction pathways in the formation of these molecular systems. Intermediates are involved: neutral molecules and radical that should be formed as a result of interradical and photochemical reactions, without so-called high energy activation states. In other words, in the path from reactants to the final reaction products, the energies of the molecular systems involved must decrease in a continuous way (without activation).

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The aim of this paper is to find the most likely reaction pathways of the three precursors of proline, phenylalanine and tyrosine. The study completes the obtaining precursors of all 20 proteinogenic amino acids. Finally, the aim is to establish a correlation between the essential and non-essential character of proteinogenic amino acids and the probabilities of formation of their precursors.

2. Computational details

The structures of the compounds (molecular systems) involved in the formation reactions of the precursors of: proline, phenylalanine and tyrosine, were constructed by the successive application of mechano-quantum procedures: MM3, AM1 (MOPAC) and B88 LYP (DZVP) (Dewar et al., 1984; Stewart, 1989). Reaction pathways and transition states were constructed by DGauss calculations using B88 LYP and B88 PW91 (CGA) with the DZVP basis sets (Atkins and Paula, 2006; Parr and Yang, 1989; Salahub, 1987; Solomons and Fryhle, 2004). We took into account an advanced degree of accuracy in all calculations. For each pair of reactants, all reaction possibilities were searched and only energy-favored transformations were considered.

The most stable structures of the studied molecular systems, including the corresponding structures of the reaction pathways with all kinetic energies optimized at each step, are calculated in DGauss, using the functional B88-LYP GGA, with the basis sets DZVP. These calculations require the introduction of a data set corresponding to the geometries of the proposed transition states. From the so-called transition states, the reaction pathways were constructed forward and reverse towards the final and initial products of the reactions. The Cache, Fujitsu calculus library was used (CWL, 2006).

3. Results and discussion

According to Eqs. (1), aziridinone is first formed from synthons. This one, next, with the same three synthons (CH_2, NH and CO) form the radical precursors of proteinogenic amino acids. Some of them, by copolymerization, form polypeptidic precursors (AzR), also with radical structures (PPR). Finally, upon contact with the components of the primary atmosphere (CA = HOH, NH_3, CO_2, H_2S), it would lead to proteinogenic amino acids (PAA) and to their corresponding polypeptides (PP).

3.1. Thermodynamics

In this paper we present our results regarding the formation of proline, phenylalanine and tyrosine starting from the n-propyl-aziridinonyl intermediate radical - 16 (Table 1). Its construction was detailed in a previous work (Surpateanu et al., 2020a).

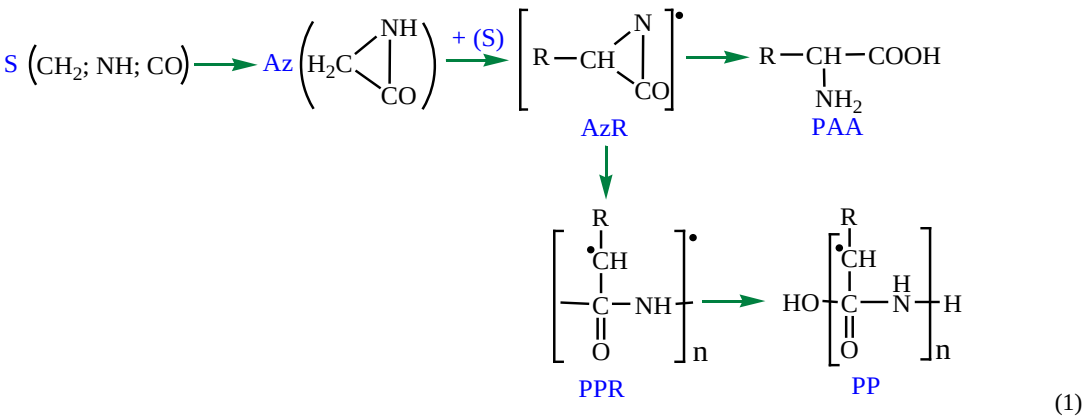
Regarding the construction of these three amino acids, we specify that there are many common structural elements. In Table 1 we present together all the intermediates and all the reactants involved in the formation of these three amino acids. The formation enthalpies were used to calculate the reaction enthalpies ΔH_r (Table 2). The reactions noted with N_r index in Table 2 are shown in detail in Eqs. (2-4). The notation for these reactions starts with reaction 1.1 (Table 2).

The calculations of the reaction enthalpies ΔH_r clearly show that there are only exothermic reactions to the formation of the precursor radical intermediates of these three amino acids. Compared to the reactions regarding the formation of the proteinogenic amino acids studied in previous works (Ghiorghita and Surpateanu, 2019; Surpateanu et al., 2019; Surpateanu and Ghiorghita, 2019; Surpateanu et al., 2020a, 2020b) in the case of proline, phenylalanine and tyrosine formation, new cyclization and elimination reactions occur. The cyclization reaction concerns the formation of the tetrahydropyrolic and cyclohexane cycles. The elimination reaction refers to the aromatization of cyclohexane and cetocyclohexane fragments.

We recall that more many variants of formation of radical precursors have been studied. Among them were chosen those that correspond to the energy criterion announced at the beginning of this paper. The negative reaction enthalpies ΔH_r, were at the basis of the selection of the precursor formation reactions. Some general remarks can be made if we consider the absolute values of the reaction enthalpies in Table 2.

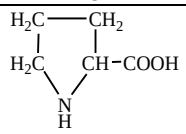
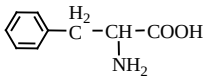
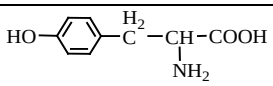
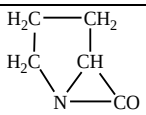
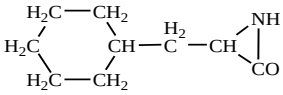
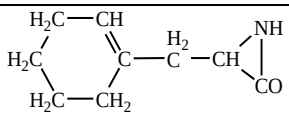
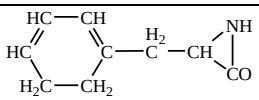
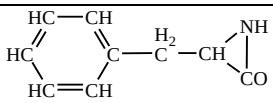
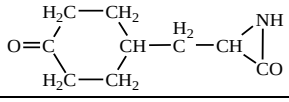
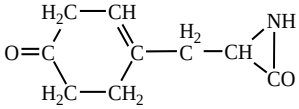
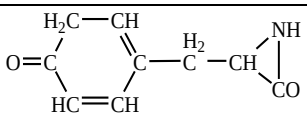
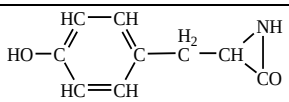
The chain reactions are provided thermodynamically favoured in respect to the cyclization and elimination reactions. The last place would be in the case of elimination reactions, the extraction of hydrogen by methylene in the sense of formation of the C = C double bond generating radical.

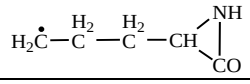
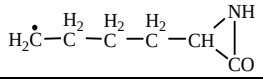
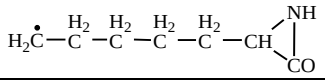
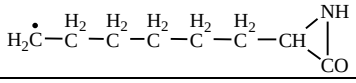
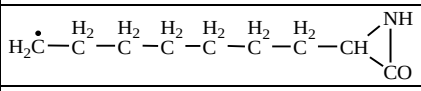
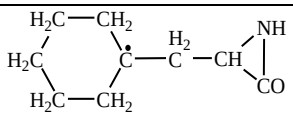
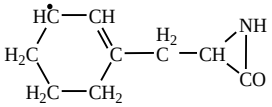
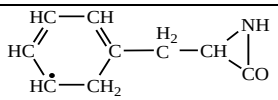
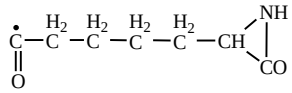
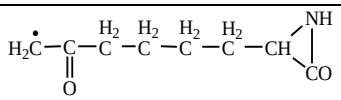
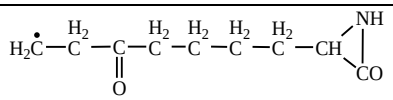
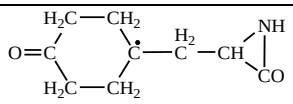
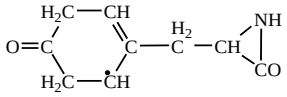
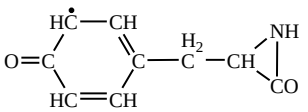
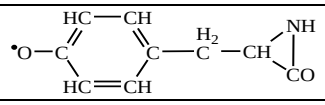
We found interestingly the formation of the proline precursor intermediate containing two condensed cycles following a strongly exothermic reaction. The most interesting in this work is the formation of the hydroxyl group of tyrosine. After a normal chain ($-\dot{C}H_2....CO$ and $-\dot{C}H_2....CH_2$) the ketone group is preserved until the cyclohexanone fragment is formed. The formation of C = C double bond precursor radical, at the α-ketone carbon level is interesting too. This would be that upon contact with water (a component of the primary atmosphere) (Dalgado, 2006; Shu, 1982), they would stabilize by fixing hydrogen to oxygen. Moreover, if we consider a difference of very low resonance energy of 0.07 kcal/mol between these two resonance structures (29 and 30, Table 2), this behaviour appears to be normal. It should be mentioned that all the reaction pathways chosen for the formation of proline, phenylalanine and tyrosine, met the criterion of decreasing energies along the reaction pathways. In Table 3 there are presented the free energies values ΔG, for four representative reactions, regarding the cyclization and elimination reactions (see formation of the aromatic benzene cycle). As examples, we present the structures of the reaction systems, found and used in establishing the reaction pathways.



(1)

Table 1. Enthalpies of formation *ΔH*. Neutral molecules and radicals involved in the formation of proline, phenylalanine and tyrosine

No	*Compound*	*M**	*Enthalpies of formation, ΔH (a.u.**)*
1	HOH	1	- 76.42235
2		1	-401.09536
3		1	-554.69407
4		1	-629.92600
5		1	-324.60778
6		1	-481.78974
7		1	-480.56432
8		1	-479.36228
9		1	-478.20400
10		1	-555.82932
11		1	-554.60976
12		1	-553.41196
13		1	-553.43589
14	CH_2	3	-39.13453
15	CO	3	-113.11143

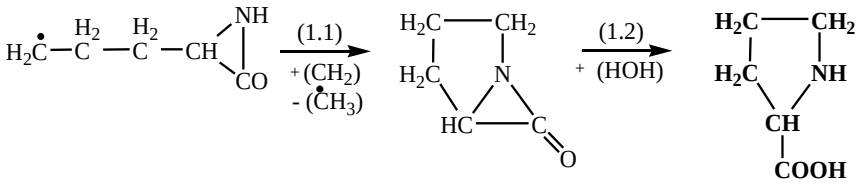
16		2	-325.14956
17		2	-364.43730
18		2	-403.73165
19		2	-443.02583
20		2	-482.32049
21		2	-481.13328
22		2	-479.93629
23		2	-478.74505
24		2	-477.78285
25		2	-517.06202
26		2	-556.36014
27		2	-555.17355
28		2	-553.98031
29		2	-552.80523
30		2	-552.80511
31		2	-39.81779

M - spin multiplicity;**a.u. = atomic units (hartrees); atomic unit = 2625 kJ/mol*

Table 2. Enthalpies, reaction enthalpies and free energies. Formation of proline, phenylalanine and tyrosine

No	***N_r***	***ΔH_i (a.u.)***	***ΔH_f (a.u.)***	***ΔH_r (kcal/mol)***
1	1.1	-364.28409	-364.42557	-88.42
2	2.1	-364.28409	-364.43730	-96.13
3	2.2	-403.57183	-403.73165	-100.28
4	2.3	-442.86618	-443.02583	-100.18
5	2.4	-482.16036	-482.32049	-100.48
6	2.5	521.45562	-521.60753	-95.70
7	2.6	-520.92517	-520.95107	-16.25
8	2.7	-520.26781	-520.38211	-71.72
9	2.8	-519.69885	-519.75408	-34.65
10	2.9	-519.07082	-519.18007	-68.55

11	2.10	-518.49681	-518.56284	-41.43
12	2.11	-517.87958	-518.02179	-89.23
13	3.1	-477.54873	-477.78285	-146.91
14	3.2	-516.91738	-517.06202	-90.76
15	3.3	-556.19655	-556.36014	-102.65
16	3.4	-595.49467	-595.64711	-95.65
17	3.5	-594.96385	-594.99134	-17.24
18	3.6	-594.30808	-594.42755	-74.96
19	3.7	-593.74429	-593.79810	-33.76
20	3.8	-593.11484	-593.22975	-72.10
21	3.9	-592.54649	-592.62302	-48.02



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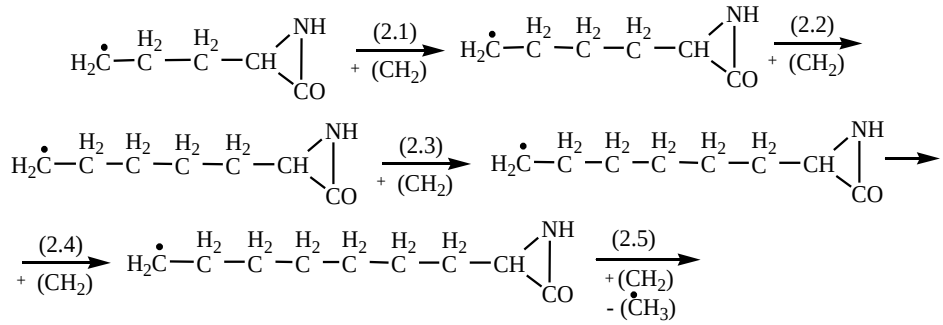

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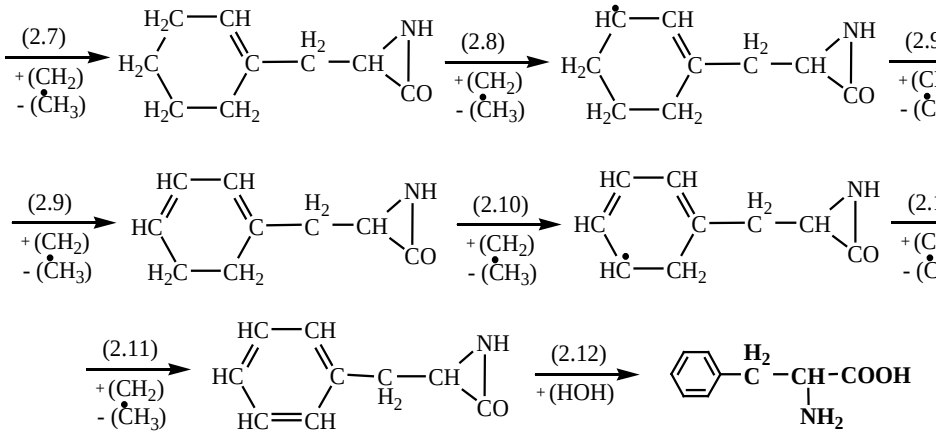


In Fig. 1 it is presented the cyclohexanic fragment formation for reaction R 2.5 (Fig. 1a) and the graphical representation of this reaction (Fig. 1b), by using Cache library.

In Fig. 2a it is presented the chemical way of reaction R 3.6 of a C = C double bond formation, the graphical representation of this reaction being presented in Fig. 2b.

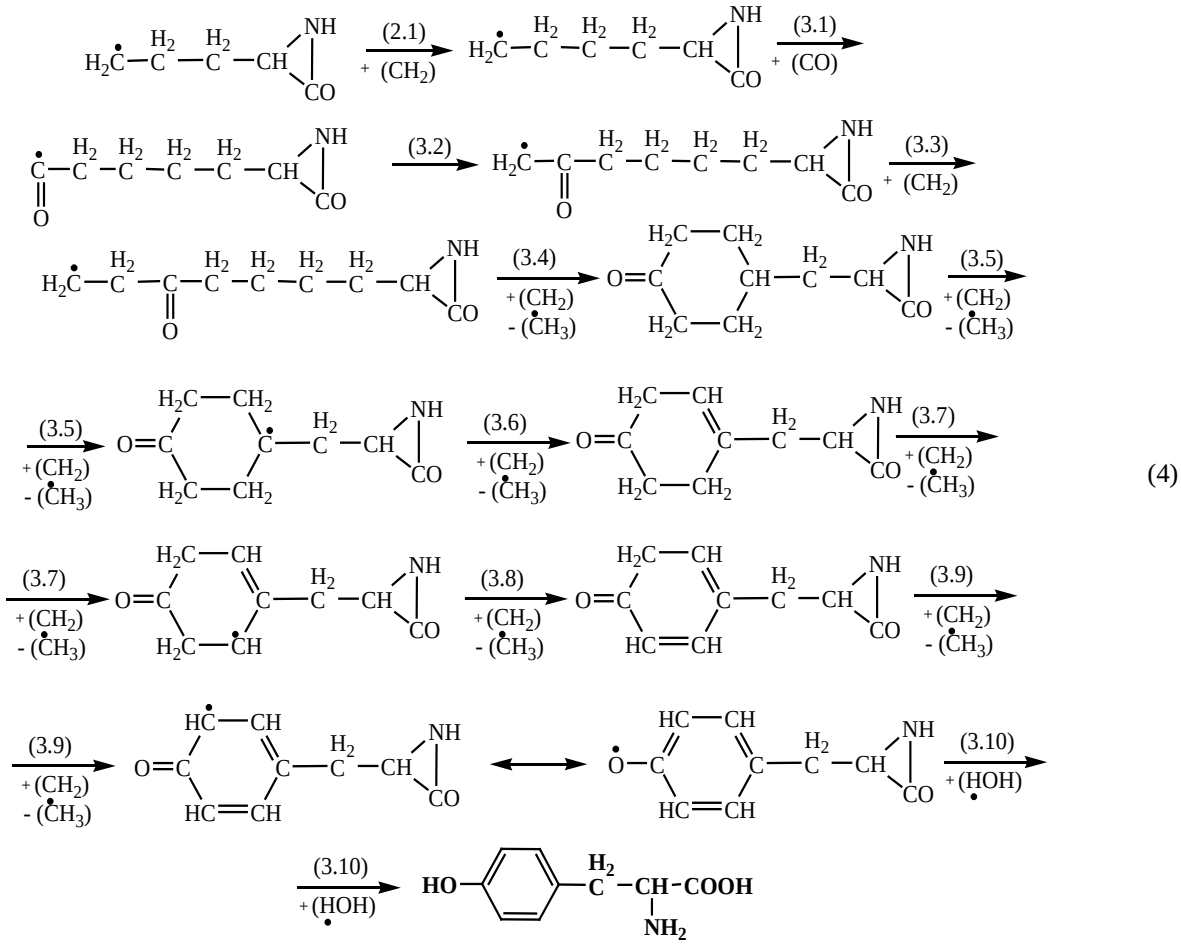
4. Conclusions

Some general conclusions:

1. The paper is a continuation of our studies on the formation of proteinogenic amino acid precursors according to the synthon theory.

2. The three precursors of proline, phenylalanine and tyrosine complete the series of proteinogenic amino acid precursors in the idea of correlating their essential and non-essential character with their probabilities of formation.

3. The tetrahydropyrolic cycle is formed involving an N-H bond. Proline is the only proteinogenic amino acid, which involves for its formation an attack of methylene on an H-N bond from aziridinone.



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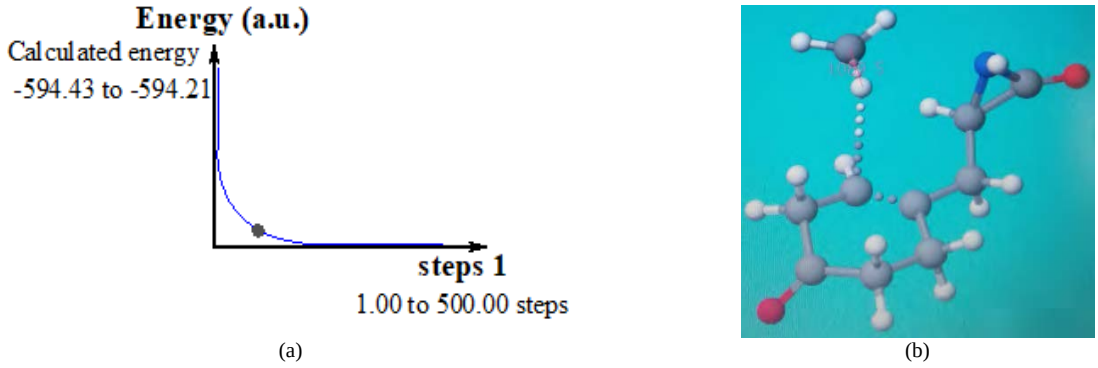
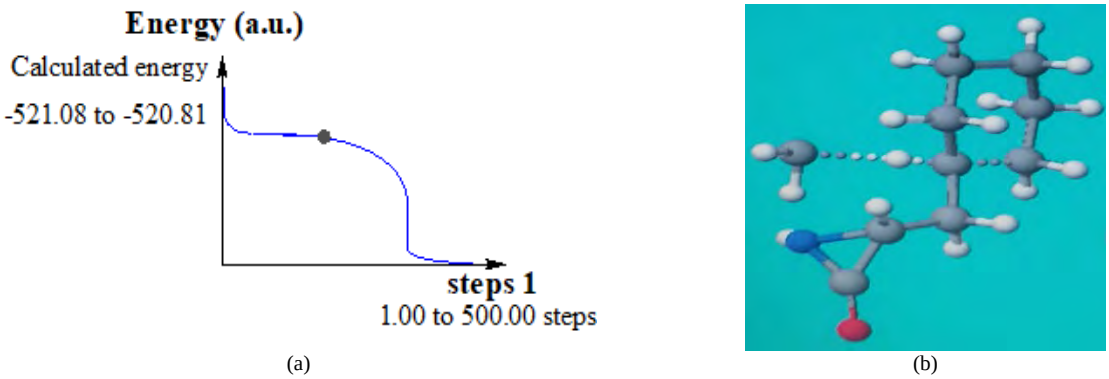


(a) (b)

Fig. 1. Chemical way of reaction 2.5 (cyclohexane fragment formation) (a) Graphical representation of reaction 2.5 (b)



(a) (b)

Fig. 2. Energy variation of reaction 3.6 (C = C double bond formation) (a) Graphical representation of reaction 3.6 (b)

Table 3. Free energies. Cyclization and elimination reactions

No	I_d	*ΔG (200/300 K) (a.u.)*
1	1.1	-364.302431 -364.43001
2	2.5	-521.580210 -521.598121
3	3.4	-595.521310 -595.650211
4	3.6	-594.35811 -594.42971

4. The appearance of the hydroxy group in tyrosine is a consequence of a natural chain reaction ($-\dot{C}H_2 ....CO$) in the synthonic context suggested in this paper.

5. Finding and imposing of so-called "intermediate states" in establishing of reaction pathways is random and very often difficult to realize in terms of achieving the convergence criteria, of high accuracy imposed in this study.

6. The functional B88-LYP DGauss has provided a guarantee regarding the choice of formation reactions of these three proteinogenic amino acids: proline, phenylalanine and tyrosine.

References

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