Article

Synthon Chemistry. Theoretical Study on the Formation of Glutamic Acid, Glutamine, Lysine and Arginine

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Simple Summary: Based on the synthonic theory on the formation of the first proteinogenic amino acids on Earth, starting from three synthons: methylene, nitrene and carbon monoxide, four amino acids were built: glutamic acid, glutamine, lysine and arginine. This paper represents a theoretical study based on density functional theory quantum calculations. It has been considered that all formation reactions of proteinogenic amino acid precursors should take place at low temperatures in the presence of nitrogen as reaction medium. The aim of this paper is to find the most likely reaction pathways of the four precursors of amino acids mentioned above.

Abstract: This paper represents a thermodynamic and chemical reactivity study regarding the possible formation of four proteinogenic amino acids: glutamic acid, glutamine, lysine and arginine, starting from three synthons: methylene, nitrene and carbon monoxide. All intermediates are specified: neutral molecules and radicals involved in the formation of these four proteinogenic amino acids. The study is based on the synthonic theory of the formation of the first proteinogenic amino acids and their corresponding polypeptides. The thermodynamic quantitative data are obtained from mechanical-quantum calculations mainly by the DFT-B88-LYP methods, DZVP basis set.

Keywords: aziridinonic radicals; proteinogenic amino acids; synthons.

1. Introduction

The appearance of life is undoubtedly related to the formation of proteinogenic amino acids and proteins. Researches related to biology, chemistry and biochemistry offers a plethora of information regarding the synthesis of proteinogenic racemic amino acids, starting with simple structure chemical compounds which are constituents of the so called primordial atmosphere and interstellar compounds [1-5].

In previous work [6], we reported that the first precursors of proteinogenic amino acids and their corresponding polypeptides would have been obtained somewhere outside the Earth from three synthons: methylene, nitrene and carbon monoxide. These precursors, carried by a celestial body (comet) in the form of diazomethane, hydrazoic acid and diazocarbonyl, at low temperatures in contact with the components of the primary atmosphere, formed on Earth the first proteinogenic amino acids and the first polypeptides [1, 7-14]. It should be noted that the first polypeptides formed from their precursors and not from amino acids [6]. In previous works [15-18] we studied the

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pathways of formation of 14 proteinogenic amino acids: glycine, alanine, serine, cysteine, aspartic acid, asparagine, threonine, valine, leucine, isoleucine, methionine, proline, phenylanaline and tyrosine. In this paper we extend our studies on the construction of four new proteinogenic amino acids: glutamic acid, glutamine, lysine and arginine. From the beginning we have pursued two important aspects in the conception of our chemical reactivity studies:

a) In the formation of each amino acid precursor, more reaction pathways were researched. From these ones were chosen only the reaction pathways where in the chemical reactions involved, we have to deal only with continuous decreases of the energies of the reaction systems in the passing from the initial states towards the final states;

b) Nitrogen-stabilized synthons and precursors as diazo derivatives, on contact with the components of the primary atmosphere, form a complex mixture of compounds, including proteinogenic amino acids.

2. Computational details

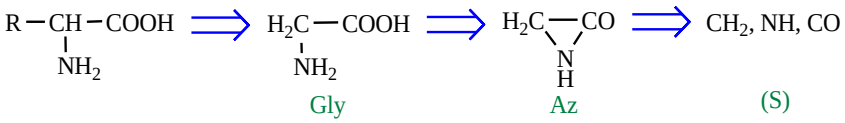
The structures of chemical sample were refined by performing an optimized geometry calculation in mechanic using successively: augmented MM3 parameters, MOPAC AM1 parameters and DGauss with B88-LYP, GGA functional with the DZVP basis sets [19-24].

The structure corresponding to the reaction path, with all kinetic energy removed at every step, are calculated also in DGauss using B88-LYP, GGA, functional with DZVP sets.

Specifically, the structures of the reactants and reaction products were established. We explored the whole conformational space between the reactants in all the interradical reactions studied in this paper. From the multiple reaction pathways, for each case, we chose the favored transformations in terms of energy. "Only" for these, we refer to entropies and enthalpies of reaction. The reaction pathways were searched, in which a continuous decrease of energies exists in the passing from reactants to final products. When Gibbs free energies were calculated, we started from intermediate states between reactants and reaction products and the reactions were reconstituted in both directions. Regarding the evaluation of entropies, we mention that we took into account the parameters included in the CacheWork System Library, version 7.5.0.85 [25].

3. Results and Discussion

According to a general retrosynthetic scheme (Scheme 1), three synthons: methylene, nitrene and carbon monoxide first form a key compound, aziridinone. This one, with the same three synthons, would form glycine and amino acid precursors. In contact with the components of the primary atmosphere (H_2O, CO_2, NH_3, H_2S) proteinogenic amino acids would result. This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.



Scheme 1. Retrosynthese. Formation of proteinogenic amino acids.

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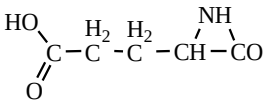
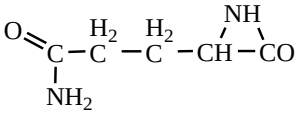
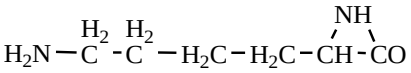
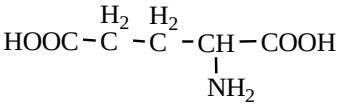
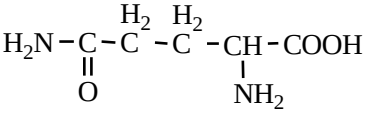
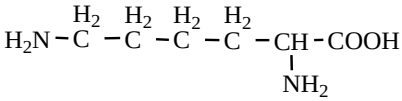
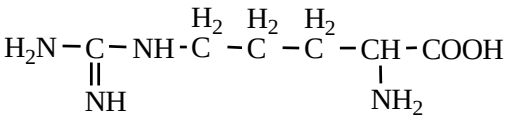
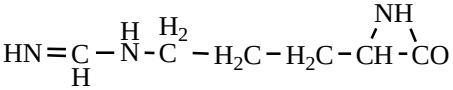
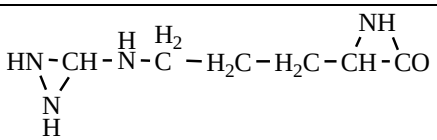
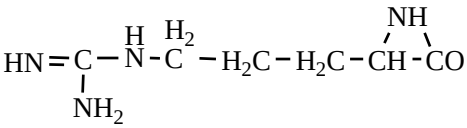
3.1. Thermodynamics

In order to construct the four proteinogenic amino acids: glutamic acid, glutamine, lysine and arginine, the formation enthalpies of all reactants and final products involved in the reactions were first calculated (Table 1).

Table 1. Enthalpies of formation. Radicals and neutral molecules.

No	Compound	M*	Enthalpies of formation, ΔH (a.u.**)
1	HOH	1	-76.42235
2	NH_3	1	-56.54148
3	CO_2	1	-188.60664
4	HOCN	1	-168.59948
5	HNCO	1	-168.68799
6		1	-475.10555
7		1	-455.21869
8		1	-420.44289
9		1	- 551.59855
10		1	-531.70836
11		1	-496.93417
12		1	- 606.44072
13		1	-474.5927
14		1	-529.8759
15		1	- 529.9517

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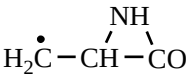
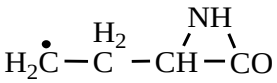
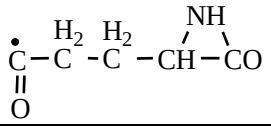
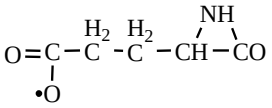
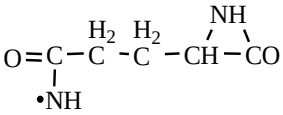
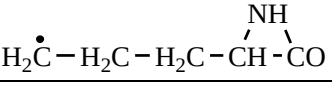
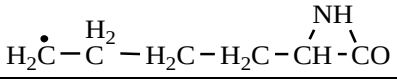
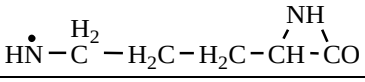
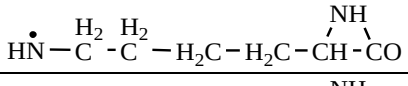
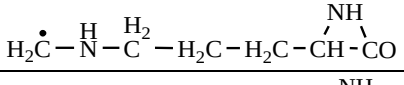
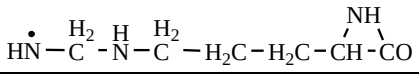
16	CH_2	3	-39.13453
17	NH	3	-55.21622
18	CO	3	-113.11143
19	$\dot{C}H_3$	2	-39.81778
20		2	-246.56109
21		2	-285.84935
22		2	-339.19404
23		2	-474.44754
24		2	-454.54709
25		2	-325.14956
26		2	-364.43809
27		2	-380.49105
28		2	-419.78497
29		2	-419.78828
30		2	-475.12378
31	$\dot{C}N$	2	-92.71590
32	$\dot{N}CO$	2	-168.01587

M* - spin multiplicity

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

Further, in Table 2 are shown the chemical transformations, considered by us as being the most likely to form proteinogenic amino acids. We mention that the formation of these four proteinogenic amino acids started from the C-methyl-aziridinonyl radical. The conditions under which this radical would form from aziridinone and methylene, have been presented in previous work [6].

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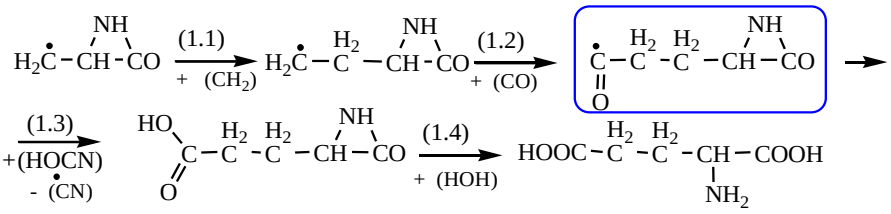
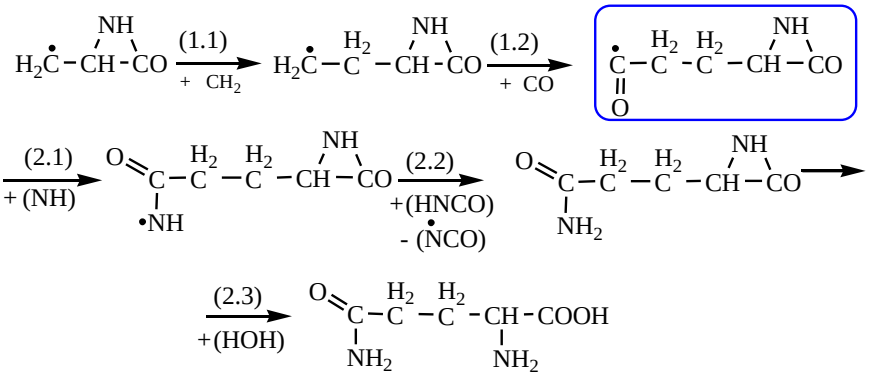
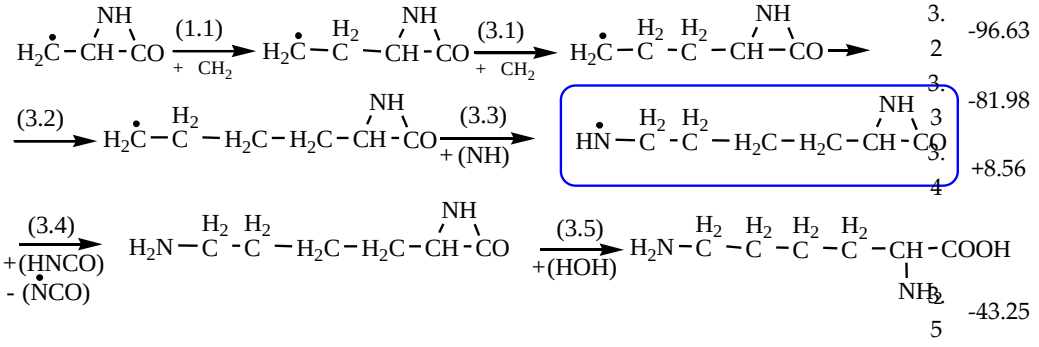
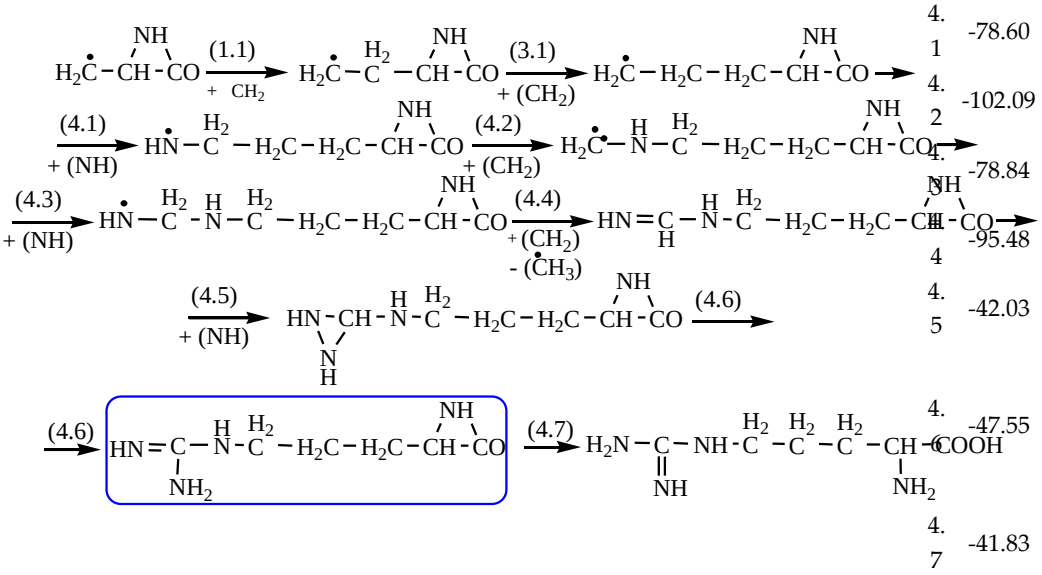
Table 2. Reaction enthalpies (ΔHr). Formation of glutamic acid, glutamine, lysine and arginine.

No	Amino acid	Reactions	Id	ΔH_r (kcal/mol)
1	Glutamic acid		1.1 1.2 1.3 1.4	-96.47 -146.37 +10.27 -44.33
2	Gluta-mine		2.1 2.2 2.3	-85.86 -55.42 -42.24
3	Lysine		3.1 3.2 3.3 3.4 3.5	-103.96 -96.63 -81.98 +8.56 -43.25
4	Arginine		4.1 4.2 4.3 4.4 4.5 4.6 4.7	-78.60 -102.09 -78.84 -95.48 -42.03 -47.55 -41.83

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The reactions enthalpies are given in the last column of Table 2. It can be easily observed that we deal only with exothermic reactions. The only endothermic reaction (reaction 1.4, Table 2) was chosen in the idea of having such a transformation that could occur at the contact between the radical precursors and the carbon dioxide, a component of the primary atmosphere. In Table 2, we have highlighted the precursors of proteinogenic acids: glutamic acid, glutamine, lysine and arginine. In the case of proteinogenic acids: glutamic acid, glutamine and lysine, it is possible for the precursors to form these amino acids by reactions with other reaction partners, cyanic acid or isocyanic acid, compounds that can be obtained by reactions between two synthons: CO and NH. We did not consider this type of reactions (noninterradical) that can be endothermic. The main thing for us was that the precursors obtained only by interradical reactions, to be able to form proteinogenic amino acids on contact with the components of the primary atmosphere. We talk about reaction conditions at approximately normal temperatures, where activations are possible.

Concerning the glutamic acid formation, two successive chain reactions with methylene and carbon monoxide (reactions 1.1 and 1.2, Table 2) are sufficient to form the glutamic acid precursor. Neither reaction 1.4 (Table 2) is excluded.

Next, glutamine formation is easy to explain. The glutamic acid precursor in reaction with nitrene (reaction 2.1, Table 2) leads to glutamine precursor. Upon contact with water, the last one forms glutamine. In this case we can assume that glutamic acid precursor in reaction with ammonia, a component of the primary atmosphere, could lead to glutamine too. Lysine would be formed only by chain reactions starting from aziridinone and methylene to C-butyl-aziridinonyl radical. This one, with nitrene, forms the N-radical precursor of lysine (reaction 3.3, Table 2). In the case of lysine, we can admit that the C-butyl-aziridinonyl precursor in reaction with ammonia also form lysine.

Things are much more complicated in the case of arginine formation. We have studied many possibilities regarding the formation of this proteinogenic amino acid. From all of these, we suppose the variant that seems to us the most probable.

Specifically, by chain reactions, with methylene three times and with nitrene twice times (reactions 1.1, 3.1, 4.1, 4.2 and 4.3, Table 2) an N-radical would be formed which, by dehydrogenation, would lead to an iminic compound, neutral molecule (reaction 4.4, Table 2). This one, by cyclization with nitrene (reaction 4.5, Table 2) followed by isomerization (reaction 4.6, Table 2), leads to arginine precursor which of course contains the guanidyl residue.

3.2. Pathways of reaction

In Table 3, the initial and final enthalpies of the reactants and the final states of all intermediates regarding the formation of glutamic acid, glutamine, lysine and arginine are successive presented.

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Table 3. Enthalpies (ΔHi and ΔHf) and free energies Gibbs (ΔG). Formation of glutamic acid, glutamine, lysine and arginine.

No	Amino acid	Id	ΔH_i (a.u.)	ΔH_f (a.u.)	ΔG (200/300 K) (a.u.)
1	Glutamic acid	1.1	-285.69562	-285.84935	-285.777418 -285.788200
		1.2	-474.45599	-474.44754	-474.359952 -474.371476
		1.4	-398.96078	-398.19404	-399.112234 -399.123452
2	Glutamine	2.1	-454.41026	-454.54709	-454.44971 -454.461347
3	Lysine	3.1	-324.98388	-325.14956	-325.050811 -325.061845
		3.2	-364.28409	-364.43809	-364.312185 -364.323576
		3.3	-419.65431	-419.78497	-419.641710 -419.653361
4	Arginine	4.1	-380.36578	-380.49105	-380.376115 -380.387412
		4.2	-419.62558	-419.78828	-419.644448 -419.656134
		4.3	-475.00450	-475.12378	-474.964783 -474.976590

Free energy Gibbs (ΔG) calculations, at two low temperatures, confirm the meaning of the chemical transformations chosen by us.

At the end of this paper we return to the imposed conditions, respecting the decreasing of energies of the reaction systems in the passing from the initial states to final ones (Figure 1.a).

The reactions studied and presented in Table 3 are analogous to reaction 2.1 from Table 2. We chose a single example of a reaction that would occur differently (reaction 1.4, Table 2), the illustration being shown in Figure 1.

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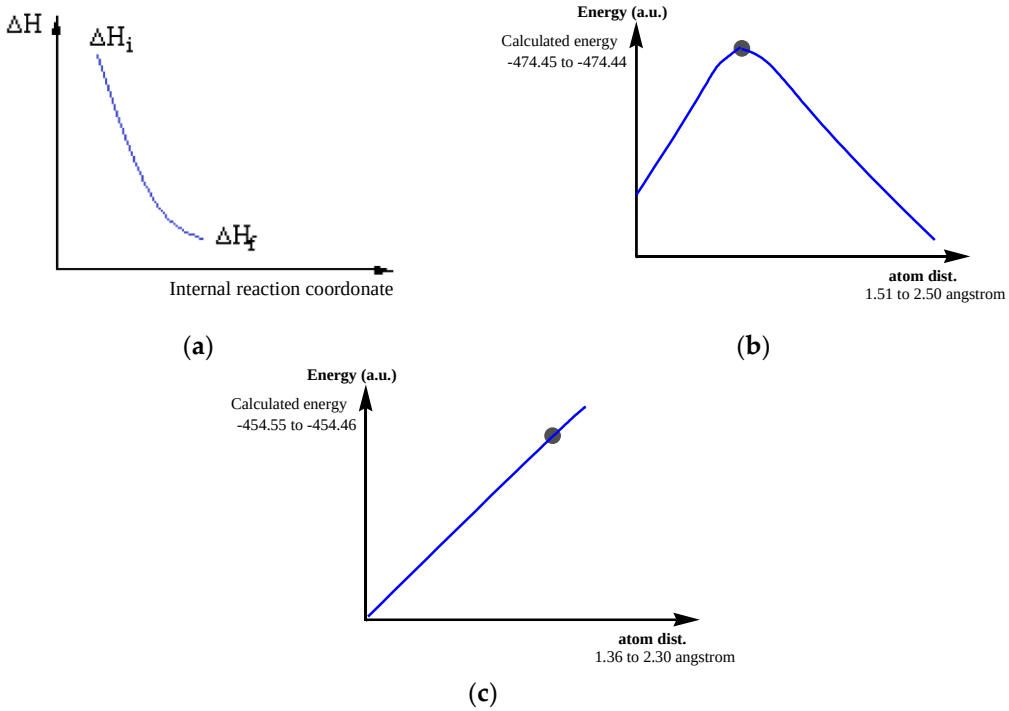

Figure 1. Reaction maps. (a) General allure of all reaction pathways; (b) reaction 1.4 (Table 2); (c) reaction 2.1 (Table 2).

All map reactions of 1.4 type, were not taken into account in the formation of the precursors of the four proteinogenic amino acids studied. We considered that at low temperatures, only interradical reactions can occur. It is natural to consider that in contact with the components of the primary atmosphere, many reactions can occur, which also include the neutral molecular systems which would lead to the formation of proteinogenic amino acids.

4. Conclusions

Starting from the C-methyl-aziridinonyl radical by chain reactions with methylene, nitrene and carbon monoxide, the precursors of glutamic acid, glutamine, lysine and arginine were obtained. All the formation reactions of the proteinogenic amino acid precursors mentioned above are exothermic. Chemical reactivity studies, free energy Gibbs calculations, ΔG, confirm the possibility of these reactions to be occurred.

We find interesting the cycle of reactions by which the guanidyl residue of arginine would have formed, until the precursors met with the components of the primary atmosphere (so at very low temperatures). Guanidine is easily obtained in the laboratory [26-29].

Author Contributions: Conceptualization, G.S.; methodology, G.S.; software, G.S. and N.C.L.; validation, G.S., I.-D.N. and N.C.L.; formal analysis, G.S. and N.C.L.; investigation, G.S. and N.C.L.; resources, G.S.; data curation, G.S. and N.C.L.; writing—original draft preparation, G.S. and A.-M.G.; writing—review and editing, G.S. and A.-M.G.; visualization, G.S., I.-D.N. and A.-M.G; supervision, G.S. and I.-D.N. All authors have read and agreed to the published version of the manuscript.

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