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Current Research in Biopolymers

Alexandrovich DV. Curr Res Biopolymers: CRBP-101.

Review Article

DOI: 10.29011/CRBP-101.000001

Interaction of Radicals in Polypeptides

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Citation: Dementiev VA (2018) Interaction of Radicals in Polypeptides. Curr Res Biopolymers: CRBP-101. DOI: 10.29011/CRBP-101.000001

Received Date: 4 February, 2018; **Accepted Date:** 28 February, 2018; **Published Date:** 08 March, 2018

Abstract

Physical conditions are found for two amino acid residues within a peptide chain when they form a strong "syllable" of polypeptide text. Such a syllable is a durable section of the peptide chain with regard to destructive thermal motion. On the other hand, randomly formed peptide chain in a prebiotic chemical world would consists rather strong syllables because their bonding energy is grater then energy of weak ones' coupling. So, self- recognition of strong and weak syllables through residues radical-radical interaction allows of interpreting the fact that a prebiotic genetic code might work out such complicated biopolymers as polypeptides and their functional abilities.

Introduction

The purpose of this study is to find the most durable parts of the polypeptides, the least exposed to the destructive influence of thermal motion in the environment. On the basis of these findings may be made some self-modification in the Galimov's scenario of primitive genetic code [1,2], which allows to explain the preferential survival of polypeptide complicated texts. Without this modification, it is impossible to answer in the affirmative the important question:

if pre-biological genetic code generates a sequence of random polypeptide texts from individual aminoacids, how could it to perform intricate texts, exhibiting valuable biochemical functions?

There is offered a hypothesis that allows answering this question:

Randomly formed peptide chain with some probability necessarily destroyed by thermal motion of the medium surrounding and of internal motions in the chain itself. The destruction mechanism was investigated earlier [3] when molecular modelling had on a qualitative level shown that this mechanism takes the form of simple rules:

- Destruction occurs rather in regular sections of the molecular chains than in the side branches.
- With the accumulation of vibrational energy in the chain a destruction occurs rather in a single valence bond than in a double bond.
- Cycles (even without conjugated bonds) are the least susceptible to heat damage. This, in particular, is due to the strength of supramolecular systems and their ability to heal some damage by itself.

These rules lead to a suggestion that the proximity of two complex radicals in two adjacent amino acid residues can lead to hardening of the chain section. To do this via internal rotations in the neighboring radicals their atoms must get close enough to have some non-chemical bonds between them - hydrogen or van der Waals type. These additional bonds create a cycle or cycles, which not allow thermal motion to destroy the valence bonds linking the two adjacent residues in such a syllable of the peptide chain.

Thus, in the text of some peptide may be some "Strong syllable", which is not destroyed, once accidentally formed.

"Weak syllables" not containing certain pairs of amino acid residues, may more or less freely collapse udder thermal motion. Peptide recycled material obtained by destruction of relatively long peptide texts may accidentally contain any combination of "syllables" of different quality. However, the new text that contain a large number of weak syllables, will be destroyed more likely than texts containing a large number of strong syllables. And in the Galimov's scenario of evolution will be recognized the mechanism of Darwin's evolution which condemns weak ones to extinction. There will survive the occasional strong texts. These peptide texts can generate useful biochemical functions through their fundamental complexity. And it is the very beginning of biological evolution.

For the transformation of this hypothesis to a workable theory we had run computer experiment on molecular models. It went through all pairs of biology-important amino acid residues and has found out which pairs can be the basis for formation of strong syllables within polypeptide texts. It was done on models generated by ChemOffce systems program Chem3D Pro via text tool by inserting in the text box formula: HGlyR1R2GlyOH, where R1R2 - researched pair of amino acid residues. Two Gly form a hydrogen bond which stabilizes the short α-helix. Between Gly radicals and R1 - R2 radicals can be no additional interactions. This is well illustrated by the peptide HGlyAlaAlaGlyOH, which model is shown in (Figure 1)**.**

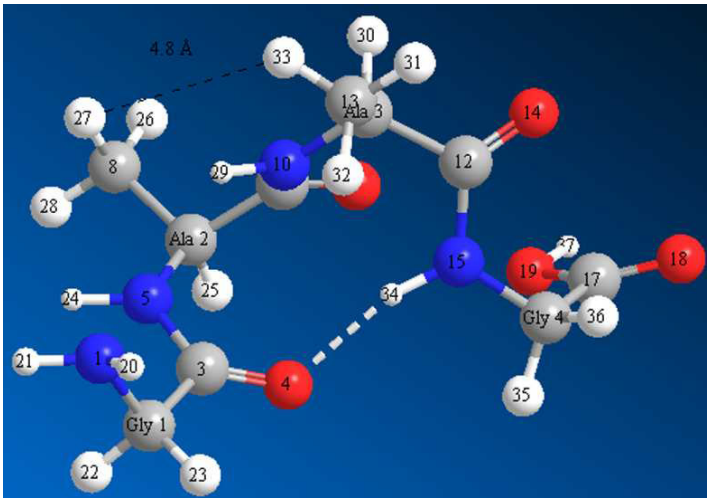

Figure 1: The beginning of the peptide chain is atom 1 of Gly1 residue. End of the chain residue is atom 17 of Gly4 residue. The radicals CH3 of neighboring residues Ala2 and Ala3 are so far apart that the distance of 4.8 Å between their closest protons 27 and 33 exceeds the limit beyond which disappear van der Waals forces. And any internal rotation of the CH3 radicals cannot reduce this distance. The greater distance characterizes mutual arrangement of CH3 radicals with radical's H of Gly1 residue (proton 23) and of Gly4 (proton 36).

This example shows that different sections of a short peptide have different strength with respect to the destructive effect of thermal motion. The most vulnerable peptide skeletons are Gly1 and Gly4 residues. The terminal Gly1 residue may be torn out due to accumulation of heat energy in the vibrational excitation of the single bond Gly1-C3. And as a result of a chance encounter with another, more complicated amino acid residue there may take place the substitution by this other residue. This may result in a different, more complex peptide text of the same length. The terminal Gly4 may be torn out due to accumulation of heat energy in the single bond Gly4-N15. The section Ala2-Ala3 is protected from heat damage somewhat better. Their skeletal bond Ala3-C12 and similar bond within Ala2 come in quite an extended cycle with a hydrogen bond shown by white dotted line. It is not a very robust cycle, but it will increase its durability, as soon as the chain joins the fifth amino acid residue. Then, in addition, hydrogen bond occurs between the fifth and Ala2 residue. As a result, the thermal strength of the skeletons of all residues reinforces itself, except the terminal ones.

Consequently, the weakest syllables in peptide text are the initial and final amino acid residues of the chain, if these residues do not contain radicals, capable of entering into non-chemical bond with the nearest neighbors in the chain. A sequence of internal "Letters" within a peptide text may be considered as less weak syllables if this sequence contains at least four letters, and if any of the two neighboring letters do not interact with each other by their complex radicals. In other cases, the inner part of the text (without terminal letters) should be considered as a strong syllable, not susceptible to thermal destruction at normal temperatures. And if we introduce these rules of polypeptide destruction in Galimov's scenario then our simulation algorithms should automatically lead to the selection of such a primary genetic code, which along the historical development of early chemical world accumulates polypeptides with complicated amino acid residues and inhibits polypeptides of simple texts, as it was confirmed in our paper [4].

These simulation algorithms and programs, of course, will not be able to predict what will be useful biochemical functions in amino acid polypeptide complex texts. But the very preferential accumulation of such complex polypeptides in the primary genetic codes is not an accidental key to the emergence of complex biochemical functionality at randomly encoded protein molecules.

In the next phase of our study we should take advantage of our previously outlined idea [5] that a functionality of a protein of a certain primary structure is itself the key to his longevity in the natural processes of multiple assembly and disassembly, since a protein having a particular function, for some time necessarily is hiding in a particular delay line and, at this time, generally avoids destruction. At the same time, the protein without any function does not receive such a refuge. Therefore, it is more likely to be wiped off the face of the early pre-biological world.

Results of Computer Modelling

The possible interactions between adjacent radicals of amino acid residues are investigated. The study was performed using Chem Offce system [6] for the short peptides in α-helical conformation. In each model should be 4 amino acid residues to form one turn of α-helix stabilized by hydrogen bonding. It is important that there is no room for internal rotations in the peptide backbone. Then, we achieve convergence of atoms of two adjacent radicals by using the internal radicals' rotations and explore a potential well, where may occur relative rotational movements of these two radicals. The depth of the potential well will characterize the degree of additional strength in this section of the polypeptide,

i.e. an extra degree of a supramolecular durability, along with the strength provided by the hydrogen bonds in the skeleton of α-helix.

A table of pairs of amino acid residues which are capable of interacting in the vicinity of their radicals is presented. From the above considerations it is clear that glycine cannot enter in this list. The last column shows the numerical value of the force attribute of syllable in a protein text. Weak syllables are not marked. Strong syllables marked as 1. Ultra-strong syllables marked as 2 (Table 1).

Pair of amino acid residues number	Pair composition from residues numbered list	The energy of radicals bonding, kcal/mole	The distance between the closest radicals atoms, Å	syllable strength indication in a protein text
1	AlaVal 2 - 3	4	3.4	
2	AlaLeu 4	4.06	3.25	
3	AlaIle 5	4.34	3.05	
4	AlaPhe 6	0.23	3.21	
5	AlaPro[1)] 7	0.17	2.08	
6	AlaTrp 8	5.5	2.45; 2.64	
7	AlaSer[2)] 9		>3	
8	AlaThr[3)] 10		>3	1
9	AlaMet 11	0.4	2.36	
10	AlaAsn 12	0	2.99	
11	AlaGln[3)] 13		>3	
12	AlaCys[4)] 14	0	3.7	
13	AlaAsp 15	2	2.98	
14	AlaGlu[3)] 16	0	2.92	
15	AlaTyr 17		>3	
16	AlaHis[3)] 18	0	>3	
17	AlaLys 19	0	2.08	
18	AlaArg[2)] 20	0	2.3	
20	ValVal 3 - 3	0	2.5	
21	ValLeu	4	2.34	
22	ValIle	0	2.39	
23	ValPhe	0	3.21	
24	ValPro	0	2.23	
25	ValTrp	0	2.1	
26	ValSer	0	2.1	
27	ValThr	0	2.1	
28	ValMet	0	2.69	
29	ValAsn[3)] 12	0	2.43	1
30	ValGln[3)] 13	0	>3	1
31	ValCys	0	2.08	
32	ValAsp[3)] 15	0	3.2	1
33	ValGlu[3)] 16	1.1	2.72	1
34	ValTyr	0	3.3	
35	ValHis	0	2.9	
36	ValLys	0	2.9	
37	ValArg	3	2.9	
38	LeuLeu 4 -4	5	2.28	
39	LeuIle	4	2.56	
40	LeuPhe	0	2.44	
41	LeuPro	1.1	2.26	
42	LeuTrp	2	2.76	
43	LeuSer	5	2.71	

44	LeuThr	4	2.1	
45	LeuMet	3.5	2.6	
46	LeuAsn	4.4	2.32	
47	LeuGln	1	2.2	
48	LeuCys	0.5	2.02	
49	LeuAsp	1	2.07	
50	LeuGlu 16	11	2.3	1
51	LeuTyr	2	2.6	
52	LeuHis		>3	
53	LeuLys[2)] 19	1	2.52	1
54	LeuArg[2-5)] 20	23	2.3	1
55	IleIle 5 - 5	0	2.51	
56	IlePhe		>3	
57	IlePro	1.6	2.4	
58	IleTrp	3.3	2.8	
59	IleSer		>3	
60	IleThr	1	2.2	
61	IleMet	1	2.9	
62	IleAsn 12	15.4	2.4	1
63	IleGln	1.2	2.1	
64	IleCys	1.1	2.06	
65	IleAsp 15	13.2	1.98	1
66	IleGlu	4	2.1	
67	IleTyr 17	11	2.9	1
68	IleHis		>3	
69	IleLys	2	2.3	
70	IleArg	2.3	2.25	
71	PhePhe[6)] 6 - 6	7	2.9	
72	PhePro		>3	
73	PheTrp[6)] 8	> 30	2.6	1
74	PheSer	0	2.9	
75	PheThr	0	2.2	
76	PheMet	3.4	2.2	
77	PheAsn 12	14.2	2.4	1
78	PheGln	5	2.6	
79	PheCys	4	2.08	
80	PheAsp	3.1	2.9	
81	PheGlu	4.2	2.11	
82	PheTyr	5	3	
83	PheHis	5.5	1.9	
84	PheLys	1	2.6	
85	PheArg	9.4	1.95	
86	ProPro 7 - 7	Two pairs of protons are bonded with van der Vaals' forces	1.19, 1.81	1
87	ProTrp	3.9	2.19	
88	ProSer[2)]		>3	
89	ProThr[3)]		>3	
90	ProMet	3.1	2.1	
91	ProAsn 12	12.1	2.6	1
92	ProGln[2)]		**>3**	
93	ProCys	1.4	2.4	

94	ProAsp	4	2.5	
95	ProGlu[3)] 16	4	1.8	1
96	ProTyr 17	15.8	2.6	1
97	ProHis	0	2.3	
98	ProLys[6)]	0	1.95	
99	ProArg[2)] 20	30	2.3	1
100	TrpTrp[6)] 8 - 8	22	1.9	1
101	TrpSer	8	2	
102	TrpThr	1	2.25	
103	TrpMet	2	2.3	
104	TrpAsn	7	2.8	
105	TrpGln 13	Two H-bonds are possible	2.4; 1.8	2
106	TrpCys	1	2.3	
107	TrpAsp	0	2.3	
108	TrpGlu	3	2.7	
109	TrpTyr 17	9.0; H-bond	2.3	2
110	TrpHis 18	10	2.8	1
111	TrpLys	1	2.7	
112	TrpArg 20	27.5	2.1	
113	SerSer[2)] 9 -9	H-bond	2.09	2
114	Ser[2)]Thr 10	H-bond	2.07	2
115	SerMet	0	2.2	
116	SerAsn 12	Two H-bonds are possible	1.83; 2.3	2
117	SerGln		>3	
118	SerCys	0	2.3	
119	SerAsp 15	7 Two H-bonds are possible	1.8; 1.9	2
120	SerGlu 16	Two H-bonds	2.3; 2.1; 1.9	2
121	SerTyr		>3	
122	SerHis 18	Two different H-bonds are possible	2.4; 2.4	2
123	SerLys 19	H-bond	1.9	2
124	SerArg 20	Two H-bonds	2.3; 2.1	2
125	ThrThr 10 - 10	7.0; H-bond	2.1	2
126	ThrMet	7	2.5	
127	ThrAsn 12	15.0; Two different H-bonds are possible	2.3; 1.8	2
128	ThrGln 13	Two H-bonds	2.1; 1.9	2
129	ThrCys		>3	
130	ThrAsp 15	7.0; Two different H-bonds are possible	1.8; 1.9	2
131	ThrGlu 16	6.0; Two H-bonds	2.1; 1.8	2
132	ThrTyr	0	2.7	
133	ThrHis 18	6.0; H-bond	2.5	2
134	ThrLys 19	H-bond	2.8	2
135	ThrArg 20	12.0; Two H-bonds	2.3; 2.2	2
136	MetMet 11 -11	2.4	2.5	
137	MetAsn		>3	
138	MetGln		>3	
139	MetCys	0	2.89	
140	MetAsp		>3	
141	MetGlu		>3	

142	MetTyr		>3	
143	MetHis		>3	
144	MetLys		>3	
145	MetArg		>3	
146	AsnAsn[3] 12 - 12		>3	
147	AsnGln 13	7.0; H-bond	2.09	2
148	AsnCys		>3	
149	AsnAsp 15	8.0; Two H-bonds	2.1; 2.2	2
150	AsnGlu	18.0; H-bond	2.14	2
151	AsnTyr	6.0; H-bond	2.25	2
152	AsnHis	6.0; H-bond	1.9	2
153	AsnLys	8.0; H-bond	1.9	2
154	AsnArg	8.0; Three different H-bonds are possible	2	2
155	GlnGln 13 - 13		>3	
156	GlnCys	4	2.2	
157	GlnAsp 15	5.0; Two different H-bonds are possible	2.09; 2.24	2
158	GlnGlu	14.0; Two different H-bonds are possible	2.2; 2.2	2
159	GlnTyr	9.0; H-bond	2.3	2
160	GlnHis	5.0; H-bond	2.1	2
161	GlnLys	4.0; H-bond	2	2
162	GlnArg	10.0; Two H-bonds	2.2	2
163	CysCys 14 - 14	1	2.9	
164	CysAsp	5	2.5	
165	CysGlu		>3	
166	CysTyr		>3	
167	CysHis		>3	
168	CysLys	0	2.91	
169	CysArg		>3	
170	AspAsp 15 - 15	2.0; H-bond	2.6	2
171	AspGlu 16	7.2; Two H-bonds	2.07; 2.2	2
172	AspTyr		>3	
173	AspHis		>3	
174	AspLys 19	4.0; H-bond	1.9	2
175	AspArg 20	13.0; Two H-bonds	2.2	2
176	GluGlu 16 - 16	9.0; H-bond	2.2	2
177	GluTyr	12.0; H-bond	2.2	2
178	GluHis	4.0; H-bond	2.4	2
179	GluLys	3.0; H-bond	2.2	2
180	GluArg	8.0; Two H-bonds	2.2	2
181	TyrTyr 17 - 17	4.0; H-bond	2.1	2
182	TyrHis	11.0; H-bond	2.2	2
183	TyrLys	5.0; H-bond	2.1	2
184	TyrArg	15.0; Two H-bonds	2.1; 2.1	2
185	HisHis18 - 18		>3	
186	HisLys 19	4.0; H-bond	2.3	2
187	HisArg	6.0; H-bond	2.3	2
188	LysLys		>3	

189	LysArg		>3	
190	ArgArg		>3	

Table 1: complexity would get a random protein text.

- Pro is a particular residue with a radical to form a five-membered cycle. Peptide backbone atoms are in this cycle, and it has two consequences. The rigidity of the cycle does not allow radical to get in conjunction with the adjacent radical, which explains the small depth of the potential well. On the other hand, the cycle increases the strength of the peptide skeleton against destructive impact of heat.
- They are capable of hydrogen bonding to the backbone peptide chain into various conformations, thereby reinforcing its own section of the skeleton.
- They are capable of hydrogen bonding to the backbone peptide chain into various conformations, thereby reinforcing its own portion of the skeleton. But in one of the conformations, they may form a hydrogen bond even with a terminal section of glycine, thus protecting both of the terminal glycine from destruction by thermal motion.
- Cys - capable of forming sulfur bridges with remote Cys, providing resistance elements of tertiary protein structure.
- When the long-chain radical such as Arg falls into a deep well formed by the interaction with an adjacent radical complexity of Leu and above, there takes place a rather large cavity in the annular supramolecular structure. Such a cavity may be a candidate for the active part of an enzyme in the future.
- Approaching of these radicals creates a very convenient cavity which can fit for a small molecule. At the same time there will be strengthening of the connection between the radicals.

Conclusion

From the table above, one can see what a complexity would get a random protein text, if an invariable set of amino acids is involved in the cycles of autocatalytic self-assembly and thermal destruction of occurring polypeptides.

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