Amino Acids (1995) 8: 1–13

Amino
Acids

The regularities of the changes of amino acid physico-chemical properties within the genetic code

Review Article

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Accepted January 25, 1994

Summary. All the codons of the genetic code can be arranged into the closed one-step mutation ring, containing three periods of the same sequence of mutations (2,3,3,3,1,3,3,3,1,3,3,3,1,3,3,2,3,3,3). The codons of Gly play a role of the connecting element between the end of the third, and the beginning of the first period of the genetic code. The reactivity of amino acids, expressed by the reaction rates of aminolysis reaction of N-hydroxysuccinimide esters of protected amino acids with p-anisidine, changes periodically with the respect to the mutation periods of the genetic code. Chou-Fasman P_α as well as P_β conformational parameters of amino acids, and also the compositional frequencies of amino acids in proteins, demonstrate the pseudosymmetry pattern with respect to the center of one-step mutation ring, which is situated between Thr ACY and ACR codons.

Keywords: Amino acids – Genetic code – Amino acid reactivities – Chou-Fasman parameters – Compositional frequencies of amino acids

The question of the possible physico-chemical correspondence between the coded amino acids and their codons remains solved up to the date. There are, however, many arguments discussed in the literature, in favor of such correspondence. Almost 30 years ago, Woese (Woese et al., 1966), and independently Volkenstein (Volkenstein, 1966), pointed out that the hydrophobicity-hydrophilicity spectrum of coded amino acids may be correlated with the second (central) base of their codons. In 1980 Hasegawa and Miyata showed that a strong negative correlation appears between the amino acid molecular weights and the degeneracy of correspondent codons (which is related to the discrimination of the third base in the codons). In 1989 Taylor and Coates demonstrated that the first base of codons may be connected to the biosynthetic pathway, i.e.

that the amino acids whose codons possess the same first base are metabolically related to each other. It has been also shown by Jungck (Jungck, 1978) that the polarity and bulkiness of amino acids together, can be used, with considerable confidence to predict the anticodon structure. The correlation between both: hydrophobicity and hydrophilicity of amino acids and the structure of their anticodons was discussed in 1978 by Weber and Lacey. The problem of the existence of the relationship between the anticodons and physico-chemical characteristics of amino acids was reviewed in 1983 by Lacey and Mullins.

From the papers published in recent years and related to the problems depicted above, the paper of Sjöström and Wold (Sjöström and Wold, 1985) deserves attention. These authors demonstrated that in the multivariate space, composed of 20 variables connected to the different physico-chemical parameters of proteinaceous amino acids (pK_{NH_2}, pK_{COOH}, pI, molecular weight, side chain Van der Waals volume, seven ^1H- and ^{13}C-NMR scales and eight hydrophobicity-hydrophilicity scales) the amino acids belonging to A, U, and C families of the codons (the term "family", or "class" of codons is used here for the groups of codons possessing the same base in the central position) form the clusters, whereas those belonging to the G family are rather randomly distributed within this space. That means that the amino acids of A, U, and C families possess the similar physico-chemical properties, whereas those of G family are of the different character, one in respect to the others. The similar results were also reported in 1989 by Di Giulio.

In our previous papers we have shown that such the important amino acid characteristics, like: free enthalpies of activation $\Delta G^{\#}$ of aminolysis reaction of N-hydroxysuccinimide esters of amino acids (see Siemion and Stefanowicz, 1992a, 1992b), Chou-Fasman conformational parameters P_α and P_β (Siemion, 1994a) compositional frequencies of amino acids in proteins (Siemion, 1994b) change periodically within the genetic code, when it is arranged into a periodical system by the regular set of one-step mutations.

The periodical arrangement of the genetic code

Each of 64 codons, which create the genetic code, can be transformed into the other one by the proper sequence of one-step mutations. Using the regular sequence of one-step mutations the codons can be arranged into the closed ring (one-step mutation ring). During the construction of one-step mutation ring we followed the rules:

1. The changes of the bases in position **3** of the codons preceded those in position **1**; the changes of the bases in position **1** preceded those in position **2**. By such a procedure the physico-chemical character of coded amino acid was maximally preserved during the correspondent mutation.
2. The mutations of transitional character preceded those of tranversional one. It was in agreement with the observation that in the Nature the transitional mutations appear much more frequently than the transversional ones (see Topal and Fresco, 1976).

3. By the tranversional mutations in the third position of the codons the corresponding bases were exchanged by the complementary ones, e.g. A → U, etc.

The observation of these rules enables the realization of three successive periods of mutations with the following sequence of base changes:

2,3,3,3,1,3,3,3,1,3,3,3,1,3,3,3,2,3,3,3

(the numbers denote here the positions of the codons in which the mutation takes place). In each period there appear 16 codons of the class A, U, or C, respectively, and four codons of the class G. Thus, the distribution of codons among the periods corresponds well with the statement of Sjörstöm and Wold (1985), presented above. As we remember, in the multivariate space, composed of 20 variables, the amino acids coded by the codons of A, U, and G family form the clusters, whereas, the amino acids coded by the codons of G family are randomly distributed within the space. The ends of the third (UG) and the beginning of first (AG) period are connected by four codons of simplest amino acid, Gly, belonging to G family. The one-step mutation ring of the genetic code is presented in Fig. 1.

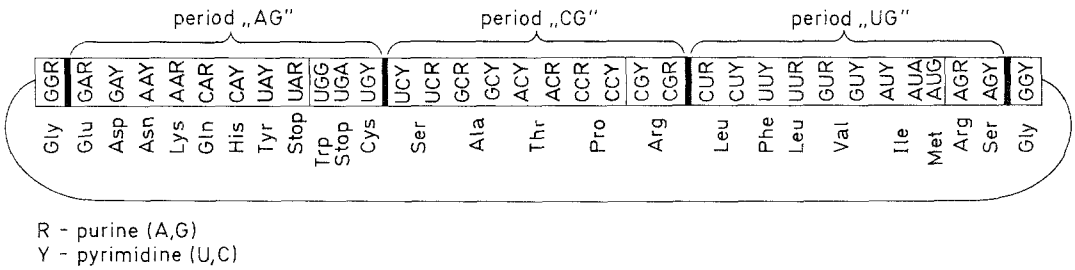


Fig. 1. One-step mutation ring of the genetic code. The vertical bars separate the three periods of the code, the vertical lines within the periods separate the codons of "A", "C", and "U" families, respectively, from the "G" family codons belonging to the respective period

The sequence of amino acids resulted from our one-step mutation procedure is very similar to that obtained by Argyle (1980) in his "amino acid similarity ring". This ring resulted from the statistical analysis of the most frequent replacements of amino acids during the evolution of proteins. The ring presented in Fig. 1 resembles also the amino acid ring constructed by Pieber and Tohà (1983) on the basis of the analysis of codon replacement probability matrix.

The nice regularity of one-step mutations, described by one-step mutation ring, is clearly visible, when the changes in positions 3 of the codons are considered. We have in the ring eight repeated series of mutations, expressed by the sequence: U, A, G, G, A, U, C, C. It is visible that the first four bases in the series are complementary to the next four bases.

Another interesting regularity within the ring is the location of two particular pairs of codons, in which the purine bases in the position 3 of the codons are – as the exception – discriminated by the living systems. There are the pairs: UGG and UGA, coding Trp, and "Stop", respectively, and AUA and AUG, coding Ile and Met. It is shown in Fig. 2 that both these pairs are located very symmetrically

in the ring: flanking from both sides a big fragment of the ring composed of 40 codons.

The ratio of this number to the number of remaining 24 codons is equal of 0.60, whereas its ratio to the number of all the codons of the genetic code is equal 0.625. Thus, the location of the discussed pairs in the ring corresponds well with the golden section of the ring perimeter.

The one-step mutation ring of the genetic code may be presented also in the more compact form, shown in Fig. 3. The codons belonging to the class G are on this picture arranged in a new vertically oriented column, to which the A, U, and C rows are connected. The successive codons of this column are – like the codons in three rows, connected together by the same sequence of mutations:

3, 3, 3, 1, 3, 3, 3, 1, 3, 3, 3, 1, 3, 3, 3.

The ends of A, U, and C rows, as well as the ends of G column, may be additionally closed by a respective mutation in position 1.

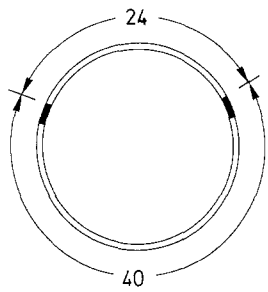


Fig. 2. The location UGG–UGA (Trp-Stop), and AUA and AUG (Ile-Met) codons within one-step mutation ring of the genetic code

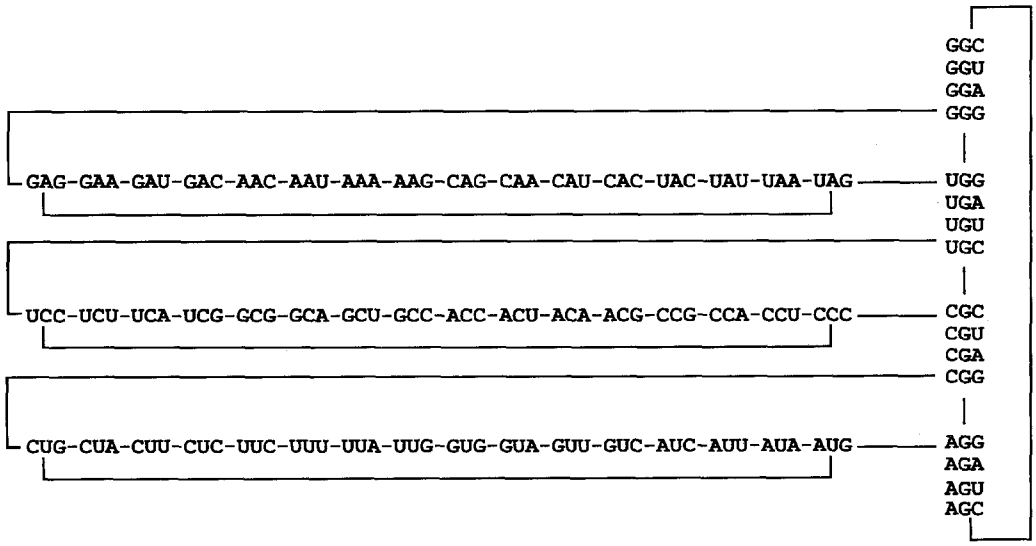


Fig. 3. The compact form of one-step mutation ring of the genetic code

It seems to be of interest that the codons which occupy the same positions in A and U rows, as well as those occupying the same positions in G column and C row (when G codons being read from the bottom to the top of the column) form the pairs, where first two bases are complementary ones, and the third base is exactly the same. It is known, however, that during the process of codon – anticodon complex formation only two first bases are discriminated according to the complementarity principle. The third base, if discriminated, is discriminated as purine (R) or pyrimidine (Y) only, without respect to the number of hydrogen bonds possible. Thus, the pairs of codons mentioned above could be considered as the equivalent ones from the point of view of codon-anticodon recognition process. Therefore we call such the pairs "equivalent" ones.

The compact form of one-step mutation ring of the genetic code enables the visualization of the regularity of base exchanges appearing in the position **1** of the codons. The sequence of the bases in the correspondent families of the codons are the following ones:

G, A, C, U (A family)

U, G, A, C (C family)

C, U, G, A (U family)

A, C, U, G (G family).

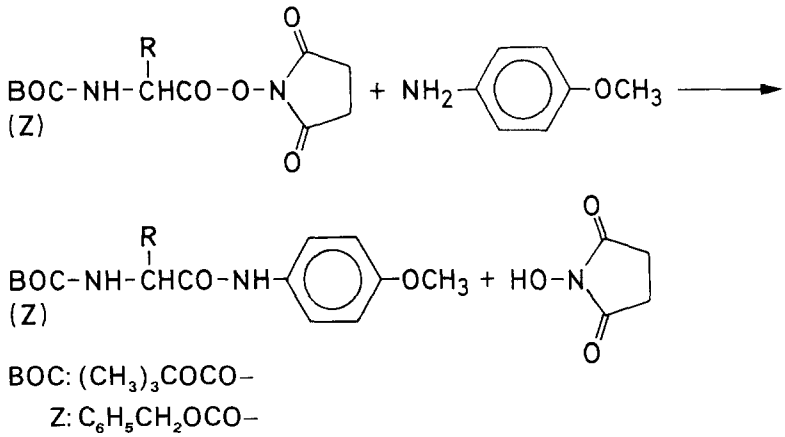
The ordering of the bases is the same in all the families, but the base which ends the sequence in the one family, begins the sequence in the next one.

All these observations testify the very regular organization of the sequence of the codons, anticipated by the one-step mutation ring of the genetic code.

The periodical changes of amino acid reactivity within the genetic code

In the search for the correspondence between the physico-chemical properties of amino acids coded, and their codons, we concentrated our attention on the reactivity of amino acids in aminolysis reaction. The aminolysis of amino acyl derivatives of tRNA's is the crucial step in the biosynthesis of proteins. In this metabolic pathway the codon-anticodon recognition process plays the very important role. Therefore the investigation of the possible dependence of amino acid reactivities on the character of their coding triplets seemed to be very reasonable. The reaction rates of the definite chemical reactions are influenced by the integrity of physico-chemical properties of the correspondent compounds, i.e. by the polar, electronic and sterical effects as well. They can play a role of general parameters, which characterize the sum of physico-chemical properties of the compounds, and therefore seem to be more suitable than any other parameters for the establishing of definite amino acids – codons correspondence.

As the model reaction of aminolysis we used the reaction of N-hydroxysuccinimide esters of protected amino acids with p-anisidine. The reaction follows the Scheme 1:



Scheme 1

p-Anisidine was chosen for the reaction because of the reasonable reaction times and easy monitoring of the reaction progress by the measure of absorption band intensity at 31 000 cm^{-1} (absorption band of free p-anisidine). The reaction was performed in dimethylsulfoxide (DMSO) solution, at the temperature ranging from 20 to 50°C. The concentrations of – p-anisidine equal 0.003–0.006 mol/dcm^3 and those of amino acid esters 0.1–0.5 mol/dcm^3 were used. The obtained for definite temperatures pseudo-first order rate constants k_1 were transformed into the second order rate constants by dividing them by initial concentration of the ester. The measurements enabled the determination of thermodynamic activation parameters: enthalpy of activation ($\Delta H^{\#}$), and entropy of activation ($\Delta S^{\#}$) for every amino acid. Using these values the values of free enthalpy of activation ($\Delta G^{\#}$) were calculated for definite temperatures. The details of our procedure were presented in a separate paper (Stefanowicz and Siemion, 1992).

In the Table 1 the reaction rate constants and the free enthalpy of activation $\Delta G^{\#}$ values for 25°C are presented. From 20 proteinaceous amino acids only the derivatives of Glu and Asp were not examined, because we did not obtained the pure N-hydroxysuccinimide esters of them. When we arranged the obtained $\Delta G^{\#}$ values of 18 proteinaceous amino acids esters in the one-step mutation ring of the genetic code, we can show (see Fig. 4) that these values change periodically, and that this periodicity corresponds quite well with the periodicity of the ring. The $\Delta G^{\#}$ values of amino acids belonging to AG, CG, and UG periods, respectively, increase from both sides of correspondent period, situating Lys, Pro, and Ile, respectively, as the maxima in successive periods.

It seems to be of interest that the amino acids belonging to the families of G and C codons have as a rule (excepting Arg and Pro) the lower values of $\Delta G^{\#}$'s than the amino acids of A and U families. There appears also an interesting regularity regarding the third base of codons. As we noted above, the third base, if discriminated, is discriminated as purine (R) or pyrimidine (Y) only, without respect to the details of chemical structure of it. There are six pairs of such codons, corresponding to six pairs of amino acids: Cys–Trp, Ser–Arg, His–Gln, Glu–Asp, Lys–Asn, and Ile–Met. The case Ile–Met is the special one, because the one of three codons of Ile (AUA) is of the same character (AUR) as Met

Table 1. The values of free enthalpy of activation ($\Delta G^{\#}$) for the aminolysis reaction of N-hydroxysuccinimide esters of N-protected amino acids with p-anisidine (DMSO, 25°C)

Amino acid derivative	$\Delta G^{\#}$ (kJ/mol)
Z–Ser–OSu	89.89
Z–Gly–OSu	91.08
Boc–Cys(Bz)–OSu	92.89
Z–Thr–OSu	93.98
Z–Ala–OSu	94.66
Z–Phe–OSu	94.76
Boc–His(Boc)–OSu	94.59
Z–Asn–OSu	95.51
Z–Tyr–OSu	96.05
Z–Tyr(OBz)–OSu	95.68
Z–Tyr(Z)–OSu	95.09
Z–Trp–OSu	96.24
Boc–Trp–OSu	96.25
Z–Met–OSu	96.65
Z–Gln–OSu	97.30
Z_3–Arg–OSu	97.50
Z–Leu–OSu	97.70
Boc–Lys(Z)–OSu	98.16
Z–Pro–OSu	99.49
Z–Val–OSu	101.70
Z–Ile–OSu	102.60

Z–benzyloxycarbonyl group $C_6H_5CH_2OCO$-; Boc–t-butyloxycarbonyl group $(CH_3)_3C$-OCO-; Bz–benzyl group $C_6H_5CH_2$-; Su–succynimidyl group $(CH_2CO)_2N$-

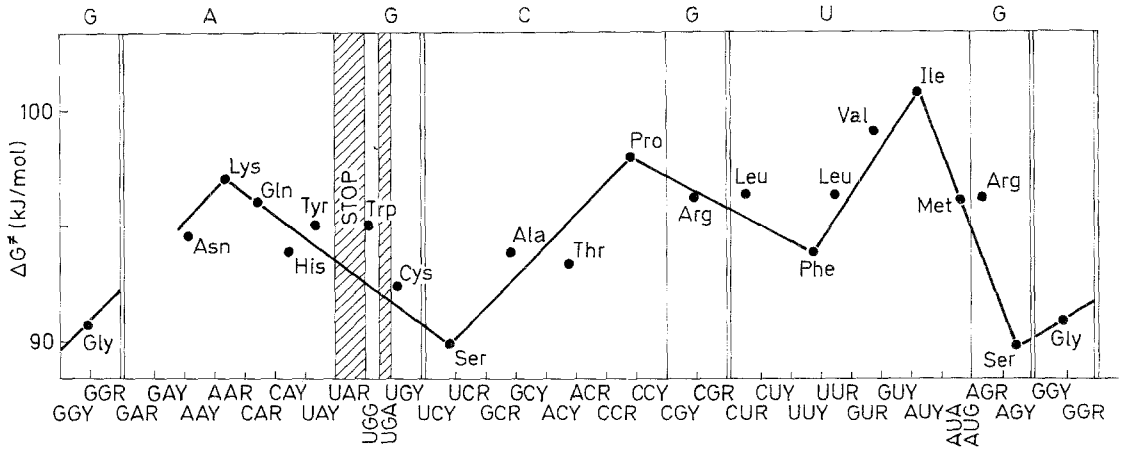


Fig. 4. The periodical dependence of free enthalpy of activation ($\Delta G^{\#}$) values of the aminolysis reaction of N-hydroxysuccinimide esters of protected amino acids with p-anisidine on the codons arranged in one-step mutation ring

codon. We have no data for Glu–Asp pair. However, the differences of $\Delta G^{\#}$'s for the other pairs mentioned above are the following:

Trp(UGR)–Cys(UGY) 3.35 kJ/mol

Arg(AGR)–Ser(AGY) 7.61 kJ/mol

Lys(AAR)–Asn(AAY) 2.65 kJ/mol

Gln(CAR)–His(CAY) 2.71 kJ/mol

Thus, the $\Delta G^{\#}$ values are distinctly larger for amino acids coded by R in the third position of correspondent codons, than for their counterpairs coded by Y in this position.

The principle of equivalency of codons, discussed above, suggests that the equivalent codons should possess the equal $\Delta G^{\#}$ values. Such a situation really takes place for Ser (AGY and UCY codons). The similar values of $\Delta G^{\#}$ (calculated for 30°C) were also noted for the pairs:

Asn (AAY, 96.18 kJ/mol), and Phe (UUY, 95.54 kJ/mol),

Lys (AAR, 98.84 kJ/mol), and Leu (UUR, 98.34 kJ/mol), and

Cys (UGY, 93.74 kJ/mol), and Thr (ACY, 94.66 kJ/mol).

The difference between the correspondent $\Delta G^{\#}$ values increases however, in the pairs:

Trp (UGG, 97.01 kJ/mol), and Thr (ACR, 94.66 kJ/mol),

Ala (GCR and GCY, 95.40 kJ/mol, and Arg (CGR and CGY, 98.27 kJ/mol and it is even larger for the pairs Gln–Val, Tyr–Ile, Gly–Pro, and Ser–Arg. Thus, the assumption presented above has a limited significance only.

The regular changes of Chou-Fasman conformational parameters within one-step mutation ring of the genetic code

In 1974 Chou and Fasman proposed the conformational parameters, which characterize the preponderances of definite amino acids to exist within the peptide chain in a definite conformation. Chou-Fasman P_α, P_β, and P_t parameters (see Chou and Fasman, 1978) determine the probability to adopt by the definite amino acids the α-helical, β-sheet, β-turn conformations, respectively. The parameters were obtained by statistical evaluation of protein structures, determined by X-ray diffraction method. There exists a strong relation between these parameters and important physico-chemical characteristics of amino acids, like the helix propensities obtained from helix-coil transition temperatures of synthetic poly-amino acids (Chou and Fasman, 1974), and experimental thermodynamic β-sheet propensities (Kim and Berg, 1993). Charton and Charton (1983), who studied the dependence of these parameters on different physico-chemical properties of amino acid side chains, showed that whereas the steric influences dominate in determination of $P\alpha$, and P_t values, the inter- and intramolecular forces play a dominant role in determination of P_β parameters.

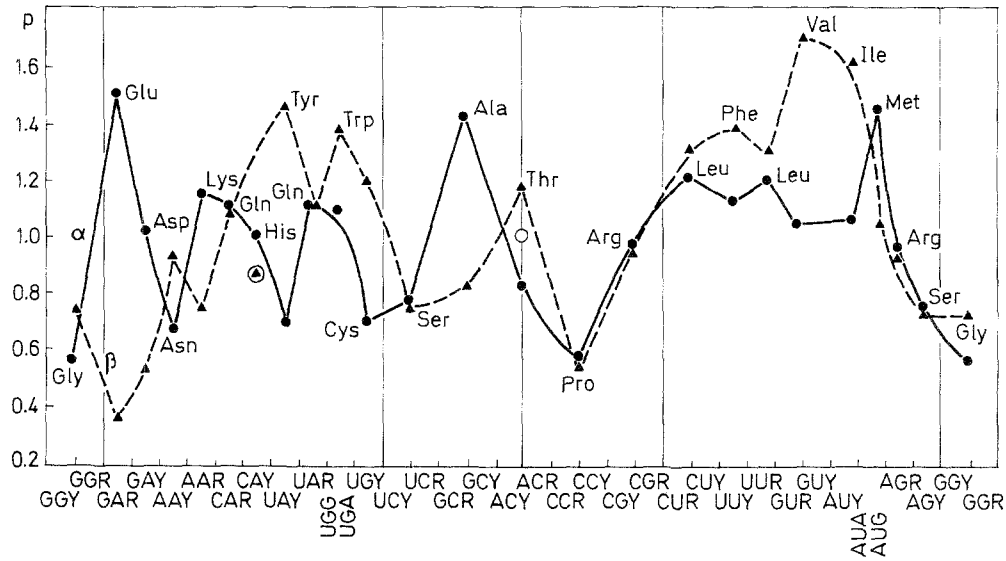


Fig. 5. The changes of P_α (solid line) and P_β (broken line) Chou-Fasman conformational parameters of proteinaceous amino acids within the one-step mutation ring of genetic code. The vertical lines separate the periods of the code. The vertical line in the middle of the diagram corresponds to C_2 pseudosymmetry axis for P_β changes, the circle situated on this line denotes the place of the location of C_2 pseudosymmetry axis for P_α changes

To see if there appears the regularity of the changes of P_α and P_β parameters within one-step mutation ring of the genetic code, we constructed the diagram, where the points reflecting P values were located in the middle of areas occupied by the codons of correspondent amino acids. Some difficulty with the construction of the diagram was connected to "Stop" (UAG, UAA, and UGA) codons. However, in Mycoplasma, as well as in mitochondria, UGA triplet is used for coding Trp (Fox, 1987), and in Tetrahymena UAG and UAA triplets code Gln (Hanyu et al., 1986; Andreasen et al., 1987). Therefore we attributed the "Opal" (UGA) codon to Trp, and both UAR codons to Gln.

The results of this analysis is shown in Fig. 5. It can be seen from this figure that the curves, reflecting the changes of P_α, as well as P_β parameters within the genetic code show the pseudosymmetry pattern with respect to the center of the diagram, situated between ACY and ACR Thr codons. The left and the right part of the diagram, obtained for P_β parameters, may be superimposed, one on the other, by the rotation across C_2 pseudosymmetry axis, depicted by the line in the center of the figure. On the other hand, both parts of the curve reflecting the changes of P_α parameters can be also superimposed by the rotation across the second C_2 pseudosymmetry axis, which is perpendicular to the previous one. Its location is depicted by the circle in the center of diagram. In the last case the rotation leads to superimposing of the minima of the right part of the diagram on the maxima of the left part – and vice versa.

The result of the analysis corresponds well to the conclusions of Charton and Charton, cited above. They have shown that P_α and P_β parameters differ in their physico-chemical basis.

It can be seen from the figure that only the P_β – His parameter violates the regularity presented. We must, however, note that no similar regularity was obtained by us for the changes of P_t parameters, characterizing the tendency of amino acid to be a part of β-turn structure.

The regularity of the changes of compositional frequencies of amino acids in proteins within one-step mutation ring of the genetic code

There are reported in the literature several sets of data concerning the frequencies of appearance of particular amino acids in proteins, like those of Jukes et al. (1975), based on the analysis of 47 heterologous proteins of different origin, Jungck (1978), calculated for 69 heterologous, evolutionary diverse proteins, and Dayhoff et al. (1978), obtained for a pool of 314, each from a different family, of prokaryotic, eucaryotic, and viral proteins.

The curves describing the changes of compositional frequencies of these proteins within the one-step mutation ring of the genetic code are very similar for every set of these data (see Siemion, in press). The diagram which we obtained for the data reported by Jungck is shown in Fig. 6. During the construction of the diagram the same procedure as that used during the analysis of Chou-Fasman parameters changes was applied. The point reflecting the compositional frequencies of definite amino acids were located in the middle of the area occupied by correspondent codons; UAG, and UAA codons were considered to be additional codons for Gln, and UGA codon – the additional codon of Trp.

It can be seen from the figure that the diagram possesses the same pseudo-symmetry pattern, which was observed for the changes of P_α parameters within

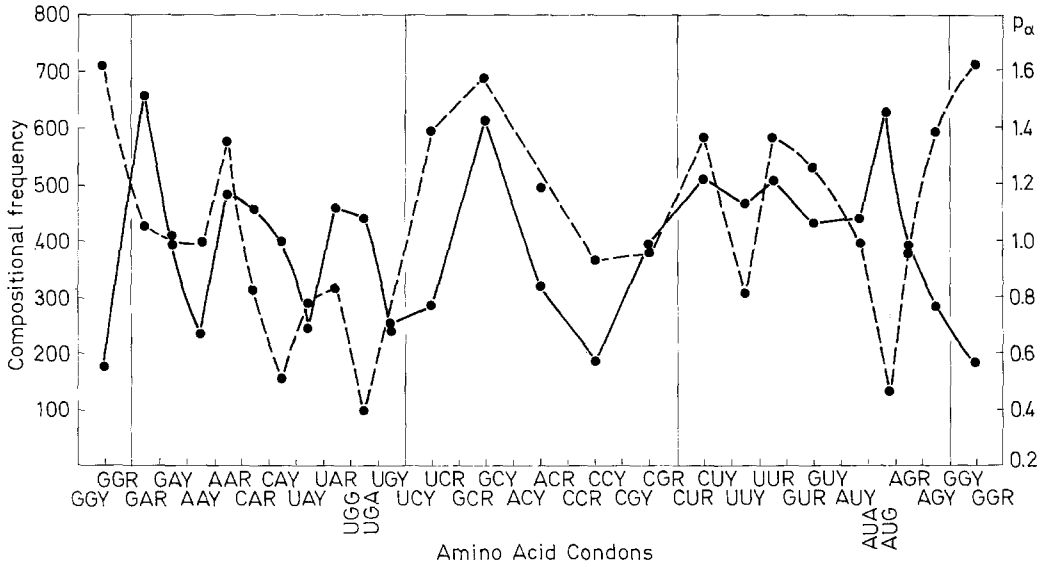


Fig. 6. The comparison of the changes of P_α parameters (solid line), and the changes of the compositional frequencies of amino acids (broken line) within one-step mutation ring of the genetic code

the genetic code. The pseudosymmetry is broken, however, on the beginning of the first (AG) and on the end of the third (UG) periods of the genetic code.

There is also no absolute parallelism in the changes of P_α parameters on one side, and compositional frequencies on the other. The parallelism disappears on the ends of the first and the third periods. Met, which is characterized by the highest P_α value, possesses the lowest compositional frequency. Similarly, Ser and Gly, the amino acids with the lowest P_α's, possess the highest compositional frequencies from all the proteinaceous amino acids.

The one-step mutation ring enables also to visualize the interesting additional regularity as regards the changes of compositional frequencies of amino acids belonging to G, and C families of codons. The correspondent values decrease linearly (see Fig. 7) when the codons of G family are considered. The same – except Ser – is to observe for the amino acids of C family. In the last case, however, the "reading frame" of the successive codons must be shifted in regard to the codons of G family. The comparable values of compositional frequencies can be observed for such pairs of amino acids as Ala (coded by GCA, GCG, GCU, and GCC codons) and Gly (coded by GGA, GGG, GGU, and GGC codons), as well as Thr (ACY) and Ser (AGY), and Pro (CCR, and CCY codons) and Arg (CGY, and CGR codons). The codons of the pairs of amino acids shown above contain complementary bases in their central positions, and the same bases in the first and third positions.

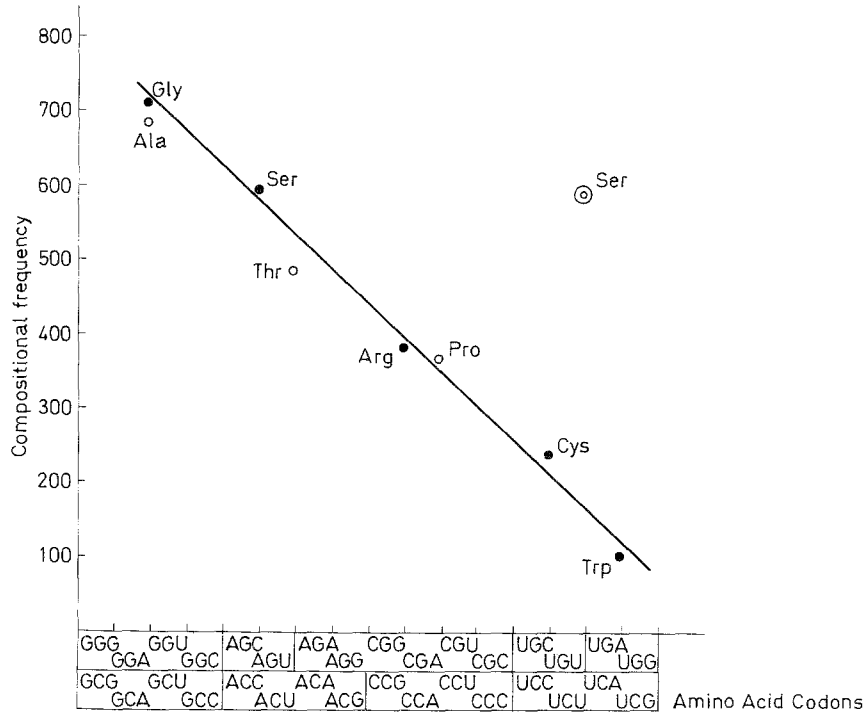


Fig. 7. The linear dependence of compositional frequencies of amino acids belonging to the "G" (solid circles) and "C" (open circles) families of codons on the codon arrangement resulted from the discussed series of one-step mutations. On the abscissa axis the codons of respective amino acids are visualized

It follows from the analyses presented above that the genetic code presents a very well organized periodical system, in which the distinct regularities of the changes of fundamental physico-chemical characteristics of the coded amino acids has been observed.

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Received December 10, 1993