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КИНЕТИКА РЕАКЦИИ КОФЕРМЕНТА ПИРИДОКСАЛЬ-5′-ФОСФАТА С НЕКОТОРЫМИ АМИНОКИСЛОТАМИ И ПЕПТИДАМИ ПРИ PH=7,35

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Из спектральных данных были определены константы скорости, предэкспоненциальные факторы и энергии активации для реакции кофермента пиридоксаль-5′-фосфата с некоторыми аминокислотами и пептидами в водном буферном растворе при pH=7,35 и температурах 288, 298, 308 K. Изученный ряд аминокислот и пептидов включает: глицин, L-аспарагиновую кислоту, L-глутаминовую кислоту, L-лизин, L-аргинин, диглицин, триглицин, глутамил-L-глутаминовую кислоту, трилизин. В структуре исследуемых аминокислот и пептидов присутствовали различные ионогенные группы (COO^-, NH_3^+) в боковой цепи, а их молекулы отличались друг от друга своим ионным состоянием при pH=7,35. Кинетические параметры оказались зависимыми от структурных особенностей и ионного состояния аминокислот и пептидов. Предэкспоненциальные множители принимают самые высокие значения от 16,9 до 18,6 для реакции с катионной формой аминокислот (L-лизин, L-аргинин и три-L-лизин), что указывает на более высокую вероятность столкновения аниона пиридоксаль-5′-фосфата с положительно заряженными частицами реагента. Более низкие значения от 8,5 до 14,4 характерны для предэкспоненциального фактора в реакции с анионной формой аминокислот (L-аспарагиновой, L-глутаминовой и глутамил-L-глутаминовой кислотами) как результат снижения вероятности их столкновения с анионом кофермента из-за дальнодействующего электростатического отталкивания. Присутствие дополнительных карбоксилатных групп в боковой цепи аминокислоты усиливает индуктивный эффект на реакционную аминогруппу аминокислоты, обеспечивая значительное снижение энергии активации реакции с коферментом. Значения предэкспоненциального фактора уменьшаются при переходе от аминокислот к их пептидам, что связано с уменьшением вероятности столкновения кофермента с более крупными частицами.

Ключевые слова: кинетика, аминокислоты, пептиды, пиридоксаль-5′-фосфат

KINETICS OF REACTION OF PYRIDOXAL-5′-PHPSPHATE CO-FERMENT WITH SOME AMINO ACIDS AND PEPTIDES AT PH=7.35

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The rate constants, pre-exponential factors and activation energies have been determined from spectral data for the reaction of the pyridoxal-5′-phosphate co-ferment with several amino acids and peptides in an aqueous buffered solution at pH=7.35 and temperatures of 288, 298, 308 K. The studied series of amino acids and peptides includes: glycine, L-aspartic acid, L-glutamic acid, L-lysine, L-arginine, diglicine, triglycine, glutamyl-L-glutamic acid, trilysine. The structures of the studied amino acids and peptides contained various ionogenic groups (COO^-, NH_3^+) in the side chain, and their molecules differed from one another in their ionic state at pH=7.35. Kinetic parameters exhibit dependence on structural features and ionic state of amino acids and peptides. The values of the pre-exponential factor take the highest values from 16.9 to 18.6 for the reaction with cationic form of amino acids (L-lysine, L-arginine, and tri-L-lysine) that indicate a higher probability of collision of the pyridoxal-5′-phosphate anion with positively charged particles of reagent. Lower values from 8.5 and 14.4 are inherent in the pre-exponential factor for the reaction with anionic form amino acids (L-aspartic, L-glutamic and glutamyl-L-glutamic acids) as a result of the decrease in the probability of their collision with the co-ferment anion due to long-range electrostatic repulsion. The presence of additional carboxylate groups in the side chain of the amino acid enhances the inductive effect on the reactive amino group of the amino acid, thus providing a significant decrease in the activation energy of the reaction with the co-ferment. The pre-exponential factor values decrease with the transition from amino acids to their peptides, which is associated with a decrease in the probability of collision of the co-enzyme with larger particles.

Key words: kinetics, amino acids, peptides, pyridoxal-5′-phosphate

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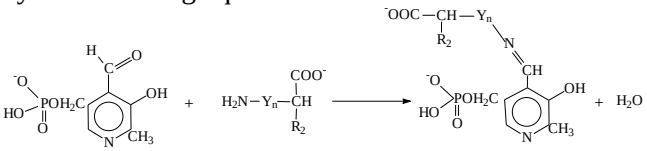
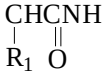
INTRODUCTION

Many metabolic processes of amino acids and peptides are controlled by the pyridoxal-5′-phosphate co-enzyme [1-4]. As it is known, the products of its interaction with amino acids or peptides are Schiff bases [4, 5]. The condensation reaction of an amino acid or peptide to pyridoxal-5′-phosphate can be represented by the following equation:



Here Y stands for a fragment



Side radicals are designated as follows: $R_1=R_2=H$ for glycine and its oligopeptides; $R_1=R_2=(CH_2)_2COOH$ for glutamic acid and its oligopeptides; $R_1=R_2=CH_2COOH$ for aspartic acid; $R_1=R_2=(CH_2)_4CNH_2$ for lysine and its oligopeptides; and $R_1=R_2=(CH_2)_3NHC(NH)NH_2$ in the case of arginine; and the indices n are set to n = 0 for amino acids, n = 1 for dipeptides and n = 2 for tripeptides.

The progress of the reaction of the co-enzyme with amino acids was detected by NMR [6] and UV spectra [7-13], and calorimetrically [7, 14]. According to the data of works [11-13], Schiff bases formed by amino acids exhibit high stability in an aqueous-alcoholic medium at pH = 7. The electronic structure of the resulting Schiff bases was simulated by the quantum chemical method [15].

Previously, the thermodynamics of the reaction of pyridoxal-5′-phosphate with various amino acids [7-9] and peptides [10] was investigated. It was shown that the structure of amino acids and the charges of their ionogenic groups strongly affect the efficiency of binding by pyridoxal phosphate co-ferment. In this work, we carried out a comparative study of the kinetics of the reaction of the pyridoxal-5′-phosphate co-ferment with amino acids and peptides, the ionic forms of which have different charges in an aqueous buffer solution at pH = 7.35. Analysis of the data on the constants of acid dissociation of amino acids [16] and peptides [17-19] shows that in a neutral aqueous solution, the zwitterionic form dominates for glycine (Gly), alanine (Ala), glycyl-glycine (Gly-Gly), and glycyl-glycyl-glycine (Gly-Gly-Gly). The anionic form is dominant in the case of aspartic acid (Asp), glutamic

acid (Glu), and glutamyl-glutamic acid (Glu-Glu). The cations are the main form of lysine (Lys), arginine (Arg), and lysyl-lysyl-lysine (Lys-Lys-Lys) in aqueous solution. The aim of this work is to study the influence of the charge and size of amino acids and peptides on the kinetic parameters of the reaction with the co-enzyme.

EXPEREMENTAL PART

Pyridoxal-5′-phosphate with a purity of 0.98 from Aldrich was used in the experiments. Amino acids and peptides from Merck had a purity of 0.99. Before use, the reagents were dried in a vacuum at 50 °C to constant weight. The progress of the reaction was monitored at temperatures of 288, 298 and 308 K in the wavelength range 250-520 nm using an Agilent 8453 UV-Vis spectrophotometer equipped with kinetics control system Pro-K.2000 for fast reactions. The measurements were conducted in the cells with a thickness of 1 cm placed in a special thermostated chamber of the spectrophotometer. The uncertainty in the solution temperature was 0.1 K. Changes in optical density for a series of solutions at a constant concentration of co-ferment ($0.4 \cdot 10^{-3}$ mol dm^{-3}) with the addition of an excess of amino acid or peptide ($2.0 \cdot 10^{-3}$ mol dm^{-3}) were recorded immediately after mixing the reagents. The reactions were carried out in an aqueous buffer solution containing monobasic sodium phosphate (0.18793 mol dm^{-3}) and dibasic sodium phosphate (0.25488 mol dm^{-3}), at pH = 7.35. The spectra of the reaction mixture were monitored in subtraction mode using the spectrum of the pyridoxal-5′-phosphate of the same concentration as in the stock solution as a zero line. The time resolution was 0.1 s, and the uncertainty in the absorbance measurement was 0.001 in size.

RESULTS AND DISCUTION

The spectral characteristics of Schiff bases formed in the reaction of pyridoxal-5'-phosphate with amino acids and peptides have been studied and described by us earlier [3, 5]. A typical view of changes in optical density with time at the maxima of absorption bands is shown in Figure for the reaction of the co-ferment with L-lysine. With the accumulation of the reaction product, a decrease in the absorption intensity at 375 nm and the appearance of absorption bands of the Schiff base at 275-280 nm and 430-440 nm are observed in the spectra. The appearance of new bands is caused by a change in the state of the aromatic pyridine ring during the formation of Schiff bases. The conjugation of an aromatic electronic system with a double bond between carbon and nitrogen atoms leads to a noticeable shift of the initial absorption band of the co-ferment. In the case of the fastest of the studied reactions with the participation of L-lysine, changes in the spectrum of the solution were observed not earlier than 1.5 s after mixing the reagents. Achievement of constant optical density values indicates the completion of the reaction of the co-ferment with amino acids and peptides within 600 s.

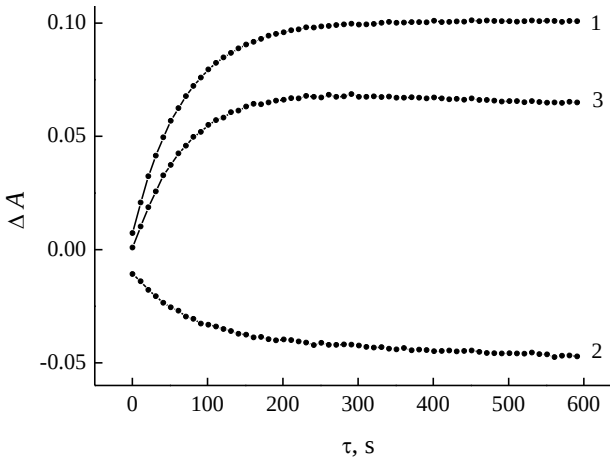


Fig. Changes in absorbance over time during the reaction of pyridoxal-5'-phosphate (0.04 mM) with L-lysine (2 mM) measured at 308 K in the maxima of absorption bands: (1) 278 nm; (2) 375nm; and (3) 438 nm

Рис. Изменение поглощения со временем в ходе реакции пиридоксаль-5'-фосфата (0,04 mM) с L-лизином (2 mM), измеренные при 308 К в максимумах полос поглощения: (1) 278 нм; (2) 375 нм; (3) 438 нм

Application of the kinetic equation for the formal first order gives the most accurate description of the experimental data for this reaction

$$k_{ef} = \frac{1}{\tau} \ln \frac{A_0 - A_\infty}{A_\tau - A_\infty} \quad (1)$$

Here, A_0, A_τ, A_∞ are the optical densities of the reaction mixture at the beginning of the process, at time τ and at the end of the reaction for the selected operating wavelength. The use of data for two different bands at 278 or 430-440 nm leads to the same calculated values of the rate constant, but in the first case, the values are determined with a smaller error. For example, for the reaction with lysine, the values of k_{ef} are determined to be (0.0071±0.0001) s^{-1} at 278 nm and (0.0075±0.0003) s^{-1} at 430 nm; for trilysine, the k_{ef} values are (0.0189±0.0001) s^{-1} at 278 nm and (0.0184±0.0004) s^{-1} at 433 nm. Therefore, the rate constants were calculated from the data for the operating wavelength of 278 nm for all the reactions studied. The obtained values of the rate constant are shown in Table 1. The given values indicate a moderately fast course of the reaction, which is typical for many biochemical processes. Rate constants exhibit dependence on temperature and structural features of amino acids and peptides.

Table 1

Effective rate constants of the reaction of pyridoxal-5'-phosphate with amino acids and peptides in an aqueous buffer solution at pH=7.35 and various temperature

***Таблица 1.* Эффективные константы скорости реакции пиридоксаль-5'-фосфата с аминокислотами и пептидами в водном буферном растворе при pH=7,35 и различной температуре**

Amino acid / peptide	$k_{ef}\times10^3$, s^{-1}		
	288 K	298 K	308 K
Gly	6.8±0.3	9.1±0.3	17.0±0.5
Gly-Gly	8.3±0.3	12.9±0.3	
Gly-Gly-Gly	10.7±0.4	14.9±0.4	24.6±0.4
L-Ala	2.3±0.3	5.0±0.3	10.0±0.3
L-Asp	3.6±0.4	7.0±0.5	13.2±1.2
L-Glu	6.2±1.5	10.6±1.8	
L-Glu-L-Glu	7.1±0.4	11.5±0.4	17.0±0.4
L-Lys	3.3±0.1	7.1±0.1	14.6±0.2
L-Lys-L-Lys-L-Lys	9.1±0.2	18.9±0.2	36.0±0.2
L-Arg	3.3±0.3	7.8±0.3	16.0±0.3

The temperature dependence of the effective rate constants allows to calculate the values of the pre-exponential factor, $\ln k_0$, and the activation energy of the reaction, E*, according to equation (2)

$$\ln k_{ef} = \ln k_0 - \frac{E^*}{RT}, \qquad (2)$$

where R is the universal gas constant, and T is a the temperature. The obtained values of k and E for the studied reactions are given in Table 2.

Table 2

Values of pre-exponential factor, ln k_0, and activation energy, E^*, for the reaction of pyridoxal-5'-phosphate with amino acids and peptides in an aqueous buffer solution at pH=7.35

***Таблица 2.* Значения предэкспоненциального коэффициента, ln k_0, и энергии активации, E^*, для реакции пиридоксаль-5'-фосфата с аминокислотами и пептидами в водном буферном растворе при pH=7,35**

Amino acid / peptide	ln k_0	E^*, kJ mol^{-1}
Gly	9.0±3.1	33.2±5
Gly-Gly	8.4*	31.5*
Gly-Gly-Gly	7.6±1.3	29.1±3.3
L-Ala	16.6±0.3	54.0±0.7
L-Asp	14.4±0.1	47.8±0.2
L-Glu	10.7*	37.7*
L-Glu-L-Glu	8.5±0.5	32.2±1.3
L-Lys	17.2±0.05	54.8±0.1
L-Lys-L-Lys- L-Lys	16.9±0.1	51.6±1.1
L-Arg	18.6±0.7	58.1 ±1.7

Note: *approximate estimation
Примечание: * приблизительная оценка

Analysis of the data makes it possible to clarify the effect of the charge and size of amino acids and peptides on the kinetic parameters of their interaction with the co-ferment. As it can be seen, in the series of the studied systems the values of the pre-exponential factor $\ln k_0$ take the highest values from 16.9 to 18.6 for the reaction with L-lysine, L-arginine, and tri-L-lysine, which exist in solution at pH = 7.35 in a cationic form due to the presence of one or more side protonated amino groups. It is known that pyridoxal-5'-phosphate in neutral aqueous solution exists in anionic form [20]. An increase in $\ln k_0$ values indicate a higher probability of collision of the pyridoxal-5'-phosphate anion with cations of amino acids and peptides. However, high values of activation energy, which change from 51.6 to 58.1 kJ mol^{-1}, lead to a decrease in the rate constants for the reaction of the co-ferment with these amino acids.

The presence on amino acid molecules of an excess negative charge, which is induced by the side ionized carboxylate group, reduces the chance of their collisions with the co-ferment anion as a result of long-range electrostatic repulsion. Thus, lower values from 8.5 and 14.4 are inherent in the pre-exponential factor $\ln k_0$ for the reaction with L-aspartic, L-glutamic and di-L-glutamic acids. The presence of additional carboxylate groups in the side chain of the amino acid enhances the inductive effect on the reactive amino group of the amino acid, thus providing a significant decrease in the activation energy of the reaction with the co-ferment up to 32.2 kJ mol^{-1}. As a result of this effect, the reaction rate constants increase significantly, especially noticeable for di-L-glutamic acid.

Comparison of the data for amino acids (glycine, L-glutamic acid, L-lysine) with the same data for their peptides (diglycine, triglycine, di-L-glutamic acid, tri-L-lysine) shows a decrease in $\ln k_0$ values when going from amino acids to their peptides. This is associated with a decrease in the probability of collision of the co-ferment with larger peptide particles, and this effect rises as the length of the peptide chain increases. On the other hand, the replacement of the carboxyl group, which is bound to the C_α atom in the amino acid molecule, by the amide fragment, which is located near the reactive amino group in the peptide molecule, causes a decrease in the activation energy of the reaction. As a result of these two effects, the rate constant of the reaction of the co-ferment with a peptide depends in a complex way on the length of its molecule.

CONCLUSIONS

We have studied the kinetics of the reaction of pyridoxal-5′-phosphate co-enzyme with a series of

amino acids and peptides in an aqueous solution at pH = 7.35 and temperature of 288, 298, 308 K. The structures of the studied amino acids and peptides contained various ionogenic groups (COO^-, NH^{3+}) in the side chain, and their molecules differed from one another in their ionic state at pH = 7.35. The rate constants, pre-exponential factors and activation energies of the reaction have been determined from spectral data.

The reaction rate constants vary within a limited range of values in the series of amino acids and peptides studied at a constant temperature (from 0.010 to 0.036 s^{-1} at 308 K), indicating that the reaction mechanism remains the same for the entire series. It has been established that the rate constants vary significantly with temperature.

The data obtained show that the ionic state of amino acid molecules strongly affects the probability of their collision with a negatively charged co-ferment. This is confirmed by an underestimation of the pre-exponential factor for the reaction with anionic forms of amino acids (aspartic and glutamic acids), and an increase in its values in the case of cationic forms (lysine, arginine). The introduction of an additional carboxyl group into the side chain of an amino acid is accompanied by a decrease in the activation energy of the reaction due to the enhancement of the inductive effect on the reaction amino group. Comparison of the data for amino acids and their peptides shows a decrease in the pre-exponential factor for the latter, indicating a reduction in the probability of collisions with larger particles.

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