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СРАВНЕНИЕ ВЗАИМОДЕЙСТВИЙ L-АСПАРАГИНА С ПРОИЗВОДНЫМИ ПИРИДИНА, ПИРИДОКСАЛЬ-5′-ФОСФАТОМ И ПИРИДОКСИНОМ, В ВОДНЫХ РАСТВОРАХ: ТЕРМОДИНАМИЧЕСКИЕ АСПЕКТЫ

Е.Ю. Тюнина, О.Н. Крутова, А.И. Лыткин

Елена Юрьевна Тюнина *

Лаборатория “Термодинамика растворов неэлектролитов и биологически активных веществ”, Институт химии растворов им. Г.А. Крестова, РАН, ул. Академическая, 1, Иваново, Российская Федерация, 153045
E-mail: tey@isc-ras.ru *

Ольга Николаевна Крутова, Александр Иванович Лыткин

Кафедра аналитической химии, Ивановский государственный химико-технологический университет, Шереметевский пр., 7, Иваново, Российская Федерация, 153000
E-mail: kdvkonkpd@yandex.ru, alytk@mail.ru

Взаимодействия белков с различными биологически активными веществами (гормонами, лекарственными препаратами, энзимами и т.п.) лежат в основе многих биохимических процессов, протекающих в организме. В рамках долгосрочной задачи по исследованию различных аспектов процессов взаимодействия между модельными соединениями белков и гетероциклическими соединениями, входящими в структуру многих энзимов и лекарственных средств, проведено термохимическое исследование водных растворов, содержащих амид аспарагиновой кислоты (L-аспарагин) и перидоксаль-5′-фосфат. Калориметрические измерения энтальпии растворения аспарагина в водном растворе с добавками перидоксаль-5′-фосфата выполнены на изопериболическом калориметре растворения ампульного типа при 298,15 K. Погрешность измерения единичного теплового эффекта не превышала 0,2%. Относительная суммарная погрешность измерения энтальпий растворения не превышала 0,7%. На основании полученных экспериментальных данных и использования компьютерной программы HEAT были рассчитаны константы связывания и термодинамические параметры (lgK, Δ_cG, Δ_cH, Δ_cS) комплексообразования между исследуемыми реагентами. Проведено сравнение аффинности аминокислоты к взаимодействию с перидоксаль-5′-фосфатом и пиридоксином. Выявлены особенности их поведения в водном растворе. Показано, что взаимодействие L-аспарагина с пиридоксином приводит к образованию более стабильного комплекса, чем с перидоксаль-5′-фосфатом. Этот факт можно объяснить наличием более объемной фосфатной группы, которая, по-видимому, затрудняет взаимодействие перидоксаль-5′-фосфата с амидом аспарагиновой кислоты. Кроме того, в молекуле перидоксаль-5′-фосфата присутствуют внутримолекулярные водородные связи между альдегидными CHO и фенольными OH группами, которые должны разрушаться при взаимодействии перидоксаль-5′-фосфата с аминокислотой, что требует дополнительных энергетических затрат. Таким образом, селективность взаимодействия и стабильность образуемых комплексов регулируются, в основном, факторами структурной и энергетической комплементарности.

Ключевые слова: термодинамика, растворы, калориметр, L-аспарагин, пиридоксаль-5′-фосфат, пиридоксин

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COMPARISON OF L-ASPARAGINE INTERACTIONS WITH PYRIDINE DERIVATIVES, PYRIDOXAL- 5′-PHOSPHATE AND PYRIDOXINE, IN AQUEOUS SOLUTIONS: THERMODYNAMIC ASPECTS

E.Yu. Tyunina, O.N. Krutova, A.I. Lytkin

Elena Yu. Tyunina *

Laboratory of Thermodynamics of Solutions of Non-electrolytes and Biologically Active Substances, G.A. Krestov Institute of Solution Chemistry, RAS, Akademicheskaya st., 1, Ivanovo 153045, Russia
E-mail: tey@isc-ras.ru *

Olga N. Krutova, Alexandr I. Lytkin

Department of Analytical Chemistry, Ivanovo State University of Chemistry and Technology, Sheremetevskiy ave., 7, Ivanovo 153000, Russia
E-mail: kdvkonkpd@yandex.ru, alytk@mail.ru

Interactions of proteins with various biologically active substances (hormones, drugs, enzymes, etc.) underlie many biochemical processes in the body. As part of the long-term task to studying various aspects of the interaction between model protein compounds and heterocyclic compounds that are into the structure of many enzymes and drugs, the thermochemical study of aqueous solutions containing aspartic acid amide (L-asparagine) and peridoxal-5′-phosphate was carried out. Calorimetric measurements of the enthalpy of L-asparagine dissolution in an aqueous solution with pyridoxal-5′-phosphate additives were performed on an ampoule-type isoperibolic dissolution calorimeter at 298.15 K. The error of measuring single heat effects was below 0.2%. The relative combined uncertainty in the measurements of the enthalpies of dissolution was not more than 0.7%. Based on the obtained experimental data and the using the HEAT computer program, the binding constants and thermodynamic parameters (lgK, $\Delta_c G$, $\Delta_c H$, $\Delta_c S$) of the complex formation between the reagents under study were calculated. A comparison of the affinity of amino acids to interaction with pyridoxal-5′-phosphate and pyridoxine was carried out. The features of their behavior in an aqueous solution are revealed. It is shown that the interaction of L-asparagine with pyridoxine leads to the formation of a more stable complex than with peridoxal-5′-phosphate. This fact may be explained in terms of a bulky phosphate group that hinders apparently the interaction of POP with aspartic acid amide. In addition, the peridoxal-5′-phosphate molecule contains intramolecular hydrogen bonds between aldehyde CHO and phenolic OH groups, which must be destroyed by the interaction of peridoxal-5′ - phosphate with an amino acid, which requires additional energy expenses. Thus, the selectivity of the interaction and the stability of the formed complexes are mainly regulated by the factors of structural and energy complementarity.

Key words: thermodynamics, solutions, calorimetry, L-asparagine, pyridoxal-5′-phosphate, pyridoxine

INTRODUCTION

Proteins, the structural elements of with are amino acids, function in composition of certain supramolecular assemblies, which are the basis of the molecular organization of biological systems [1-4]. Supramolecular structures play an important role in many biochemical processes (protein folding, transport of drugs, biosynthesis, regulation of activity, enzyme stability, etc.). Investigation on the nature and driving forces of the interaction between drugs and proteins, determination of their selectivity and preferred types of binding are still relevant. Nitrogen-containing heterocyclic organic compounds have been the subject matter for pharmacologists, medicinal chemists and physicists for the past decades to find the relationship between chemical structure and biological activity [5,6]. Investigation of the interactions between pyridine derivatives and model compounds of protein (amino acids, peptides) is of special interest. Studies on physicochemical properties of their aqueous solutions play crucial role in understanding the nature of molecular interactions in more complex liquid mixtures.

L-Asparagine (Asn), as one of the common amino acids in most plants, is not only a building block of proteins but also plays an important role in the transportation and storage of nitrogen and nitrogenous metabolism of plants [1, 7]. It has carboxamide as the side chain's functional group. Asparagine has a high propensity to hydrogen bond, since the amide group can

accept two and donate two hydrogen bonds. In addition, Asn can also be used in pharmaceutical synthesis [6, 7].

Pyridoxine (PN), or 2-methyl-3-hydroxy-4,5-bis(hydroxymethyl) pyridine, (vitamin B6) and pyridoxal-5´-phosphate, or 3-hydroxy-2-methyl-5-[(phosphonoxy)methyl]-4-pyridinecarboxaldehyde, pyrdoxal-5´-phosphate (PLP) are pyridine derivatives. Pyridoxine (PN) is precursor of various coenzymes and deficiency of these may lead to malfunctioning in living world at epidemic levels. Owing to many such vital roles of vitamin B6 in different biological processes, its deficiency or over doses create various disorder in living systems [8]. PLP is one of the most important coenzymes in living organisms. PLP derivatives catalyze a variety of metabolic processes including amino acids, lipids and carbohydrates metabolism, and play the key role in the hormones, neurotransmitters and heme biosynthesis [9]. The most common type of enzymatic reaction requiring pyridoxal phosphate as coenzyme is transamination, the transfer of the α-amino group of an amino acid to the α-carbon of an α-keto acid [10].

It is well known that drugs, vitamins and enzymes most often act through the formation of molecular complexes as intermediates. Such complexes are mainly results of weak molecular interactions which are important in physicochemical aspects [2-4, 9]. It should be noted that the pyridoxal phosphate functions as a coenzyme by virtue of the ability of its aldehyde group to react with the α-amino group of the amino acid substrate to yield a Schiff's base between the enzyme-bound pyridoxal phosphate and the amino acid. It had been shown [11, 12] that the formation of sufficiently stable Schiff bases of PLP and amino acids occurs at pH 7.4 when the aldehyde group of PLP interacts with the NH_2 group of amino acids. In the pH (3-6) range, the ability of amino group to involve in the covalent bonding with PLP is significantly reduced.

In this paper, we report the interaction of L-asparagine with PLP in aqueous solution using calorimetric method. From a comparison of the thermodynamic results of this study with our earlier data [13], the conclusions on the stability of complexes between Asn and ligands (PN, PLP) will be drawn.

EXPERIMENTAL PART

L-Asparagine (CAS No. 305-84-0, Sigma-Aldrich, ~ 0.99 purity) and pyridoxal-5´-phosphate (CAS No. 853645-22-4, Sigma-Aldrich, ≥ 0.98 purity) were used as received from the suppliers. The solutes were used without further purification after drying for 24 h at 356.15 K in a vacuum until constant weight. They were kept in desiccators at least for 48 h before use. Sample solutions were prepared in double-distilled and degassed water (with specific conductivity 3.1 $\mu S \cdot cm^{-1}$, pH 5.4). All solutions were prepared by weight using a Sartorius-ME215S balance (with an accuracy of 1×10^{-5} g). In our case, the concentration of PLP was fixed while the molalities of the amino acid varied. The uncertainty in the molality of the solutions was estimated within $\pm2\times10^{-4}$ $mol \cdot kg^{-1}$.

Measurements of the thermal effects of dissolution of crystalline samples of Asn in the aqueous solutions were performed at 298.15 K, using a precise hermetic isoperibol ampoule-type calorimeter fitted with a 110 mL reaction vessel. The description of the construction of calorimeter and the measuring procedure has been described in depth previously [13,14]. The calorimetric measurements for sample were performed at least twice and average values are reported. The error of measuring single heat effects was below 0.2%. The relative combined uncertainty in the measurements of the enthalpies of dissolution was not more than 0.7%.

RESULTS AND DISCUSSION

The enthalpies of solution of crystalline Asn in aqueous solution containing pyridoxal-5´phosphate, $\Delta_{sol}H_m$, obtained are presented in Table 1.

Table 1

Enthalpies of dissolution of crystalline L-asparagine in pure water and in aqueous solution with pyridoxal-5'-phosphate as a function of amino acid molality at T=298.15 K

Таблица 1. **Энтальпии растворения кристаллического L-аспарагина в чистой воде и в водном растворе пиридоксаль-5'-фосфата в зависимости от концентрации аминокислоты при T=298,15 K**

m/mol·kg^{-1}	Water	Water+PLP
	$\Delta_{sol}H_m$(w)/kJ·mol^{-1}	$\Delta_{sol}H_m$(w+L)/kJ·mol^{-1}
0.0018	22.77	24.84
0.0020	22.79	24.96
0.0034	22.88	25.28
0.0038	22.91	25.39
0.0048	22.96	25.52
0.0048	22.97	25.55
0.0059	23.02	25.66
0.0086	23.13	25.96
0.0111	23.22	26.09
0.0130	23.29	26.17
0.0145	23.35	26.20
0.0167	23.45	26.24
0.0182	23.54	26.29
0.0204	23.70	26.39

*Concentration of PLP is $1.3\cdot10^{-3}$ $mol \cdot kg^{-1}$

* концентрация ПЛФ 1,3 10^{-3} моль/кг

The molecules can be in three possible forms: acidic, neutral and basic depending on the pH. Distribution of particular chemical forms of the substances was determined by the RRSU computer program [15]. The diagrams of the fraction of the ionic forms of the amino acid and the pyridine derivatives depending on the pH of the medium were earlier presented in our works [13, 16]. The amino acid, Asn, ([HL]) exists as zwitterions $[HL]^{\pm}$ in water (pH 5.4), the amino group is protonated ($-NH_3^+$), while the carboxyl group is ionized ($-COO^-$) [13]. The side amide group of Asn does not carry a formal charge under any biologically relevant pH conditions. The neutral PN ligand exists as the zwitterionic form where N in the pyridine ring is protonated and the phenolic group is deprotonated [13]. At pH 5.4, pyridoxine (PN) is predominantly zwitterions and partially monodeprotonated form (H_2L^+), whereas pyridoxal-5′-phosphate (PLP) exists as a mixture of predominantly monoanions $[H_2L]^-$ and partially dianions $[HL]^{2-}$ [16]. Thus, the solute-co-solute interactions can be interpreted by considering the dominant forms of the amino acid and vitamins B-group species present in the pure water.

The important issue is the thermochemistry of the interaction between various ligands and amino acids. Calorimetry is a direct method to obtain the thermodynamic parameters of complex formation ($\lg K_c$, $\Delta_c G$, $\Delta_c H$, $\Delta_c S$) and to designate the driving forces of binding. The enthalpies of transfer, $\Delta_{tr}H_m$, of Asn from solvent (water) to the ligands (L) solutions were calculated from the experimental enthalpies for Asn dissolution in a pure solvent (w), $\Delta_{sol}H_m(w)$, and in an aqueous solution containing ligand (L), $\Delta_{sol}H_m(w+L)$:

$$\Delta_{tr}H_m = \Delta_{sol}H_m(w+L) - \Delta_{sol}H_m(w) \qquad (1)$$

The $\Delta_{sol}H_m(w+L)$ and $\Delta_{tr}H_m$ values formed a basis for calculation of the thermodynamic functions of complex formation. Enthalpy of solution of Asn in pure water was found to be (22.04±0.17) kJ·mol^{-1}, which agrees with the available literature values being (22.57±0.11) kJ·mol^{-1} [17] and (21.64±0.05) kJ·mol^{-1} [18]. Figs. a and b show the influence of increasing Asn concentration on the $\Delta_{tr}H_m$ values. For the systems under investigation the $\Delta_{tr}H_m$ values increase as the concentration of amino acid increases until nearly constant values are reached. The binding isotherms of these systems displayed a non-linear dependence of the $\Delta_{tr}H_m$ on the concentration of Asn. Such behavior suggests complex formation in the test systems.

The thermodynamic functions of complex formation were calculated using the initial concentrations of reagents and experimental values of the enthalpies of transfer by means of the computer program HEAT [15, 19], in which the search for the unknown parameters ($\lg K_c$, $\Delta_c H$) are reduced to the numerical minimization of the F functional given by

$$F=\sum_{i=1}^{N} w_i(\Delta_{tr}H_{i,exp} - \Delta_{tr}H_{i,calc})^2 \qquad (2)$$

where $\Delta_{tr}H_i$ is the enthalpy effect from the i-th reaction, N is the number of experiments and w_i is a weighted factor. Thus, the mathematical treatment of the $\Delta_{tr}H_m = f(m)$ dependences allows to simultaneously estimate the stability constant and the enthalpy of complex formation. The binding stoichiometry was also given as parameters when fitting the binding isotherm. To remove the contributions of protolytic equilibriums from thermodynamic parameters of complex formation, the values of the equilibrium constants and thermal effects of the possible secondary reactions of Asn and PLP dissociation were introduced into the calculation program [13, 16, 17]. It was found out that the best matching of our experimental points and calculated data occurs when complex with 1:1 stoichiometry is assumed to form for the Asn – L – water system. In order to highlight the nature of the interactions between above ligands and amino acid thermodynamic parameters were calculated. The thermodynamic parameters presented in Table 2 are associated with 1:1 complexation models for aqueous solution.

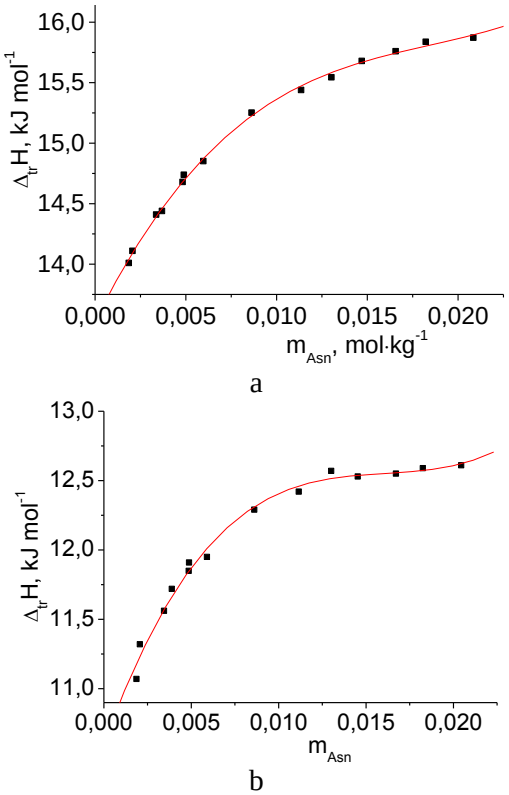

Fig. Isotherms of L-asparagine binding with pyridoxine [13] (a) and pyridoxal-5`-phosphate (b) in aqueous solutions (T=298.15 K)
Рис. Изотермы связывания L-аспарагина с пиридоксином и пиридоксаль-5`-фосфатом в водных растворах (T=298,15 K)

Table 2

Apparent thermodynamic parameters of the complex formation of L-asparagine with pyridine derivatives in water with pH 5.4 at T=298.15 K

***Таблица 2*. Кажущиеся термодинамические параметры комплексообразования L-аспарагина с производными пиридина в воде (pH 5,4) при T=298,15K**

Complex	Asn:PLP	Asn:PN [13]
$\lg K_c$	3.953±0.001	4.234±0.003
$\Delta_c G$ (kJ mol^{-1})	-22.54±0.10	-24.14±0.20
$\Delta_c H$ (kJ mol^{-1})	12.51±0.06	15.51±0.13
$T\Delta_c S$ (kJ mol^{-1}K^{-1})	35.05±0.4	39.64±0.52

Free energy and entropy of complex formation were calculated in term of the well-known thermodynamic equations:

$$\Delta_c G = - RT \ln K_c \quad (3)$$

$$\Delta_c G = \Delta_c H - T\Delta_c S \quad (4)$$

As it is known [13, 19, 20], the acting forces contributing to the binding of Asn with pyridine derivatives include hydrophobic effect, van der Waals force, hydrogen bond, and electrostatic attraction. Beside, the thermodynamic parameters of complex formation reflect also the contributions from other processes: destruction of solvation shells of the solutes (dehydration) and hydration of the complex obtained. For the Gibbs free energy, a negative value indicates that it is a spontaneous process.

In case of Asn – PLP – water and Asn – PN – water systems, the positive entropies and positive enthalpies indicated that the interaction forces of Asn and the ligands are mainly hydrophobic character. The positive values of $\Delta_c S$ obtained are normally regarded as an evidence of hydrophobic interaction [13, 19, 20]. In addition, the water molecules that are arranged in an orderly way around the ligands and amino acid acquire a more random configuration during interactions between solutes. Thus, the interactions of Asn with PLP and PN are accompanied by endothermal effects caused by the partial dehydration of solutes.

Interaction between the amino acid with above pyridine derivatives depends on the type of their substituents. These compounds differ in the number and position of hydroxyl, methyl, carboxylic, and methoxyl substituents. The ligand PN is comprised of aliphatic and aromatic alkoxide groups as well as pyridine nitrogen atom. Pyridoxal-5´-phosphate has a phosphate group at the side chain -CH_2-O-P(O)-$(OH)_2$, and also OH group in the *para*-position of side chain -CH_2-OH has been replaced with the carbonyl group compared to pyridoxine. The O and N atoms in the considered molecules are the best sites for forming the hydrogen bonds with both water molecules and amino acid zwitterions. In addition, the pyridine aromatic ring in the compounds is a source of electron which can interact with the hydrogen atoms of water molecule and co-solute.

Pyridoxine and pyridoxal-5´-phosphate, which have polar substituents in the pyridine ring and are zwitterions and negatively charged ions respectively at pH 5.4, form complexes with the amino acid Asn. The thermodynamic parameters (Table 2) of complex formation for pyridoxine are higher than that for pyridoxal-5´-phosphate. Apparently, the presence of phosphate group decreases the stability of amino acid complexes of pyridoxal-5´-phosphate compared to pyridoxine. This behavior may be explained in terms of a bulky phosphate group that hinders apparently the interaction of PLP with aspartic acid amide. On the other hand, in pyridoxal-5´-phosphate the intramolecular hydrogen bonds between aldehyde CHO and phenol OH groups are present [21]. These have to be disrupted during interaction PLP with Asn in aqueous solution, and this, in turn, requires additional energy expenses.

CONCLUSION

Thus, the present study shows that Asn forms complexes of 1:1 stoichiometry with PLP and PN in aqueous medium. The stability of Asn complexes obtained is higher for pyridoxine than that for pyridoxal-5`-phosphate. The enthalpy and entropy of complexation are, in magnitude, like those of typical molecular complexes of moderate strength. Selectivity of interaction and stability of the complexes are mainly governed by the principles of geometric and energetic complementarity.

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