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Influence of aqueous dimethyl sulfoxide on pyridoxine protonation and tautomerization

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ABSTRACT

The constants of pyridoxine (vitamin B_6) protolytic and tautomeric equilibria were determined by means of potentiometry and spectrophotometry respectively in wide range of binary solvent (aqueous dimethyl sulfoxide) compositions. The free Gibbs energies of pyridoxine molecular and zwitterionic species transfer from water to aqueous DMSO were obtained using method of partition between immiscible phases. These results were employed for discussing the transmembrane transport capability of B_6 vitamin. The influence of mixed solvent composition on pyridoxine protonation was analyzed taking into account the reagents solvation data.

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1. Introduction

Pyridoxine (PN) together with pyridoxal (PL) and pyridoxamine (PM) is known as B_6 vitamin. Their main roles in the human tissues are to be the precursors for synthesis of pyridoxal 5′-phosphate (PLP), an important coenzyme in a variety of enzymes (transaminases, decarboxylases *etc.*) [1]. PLP-dependent enzymes make ~4% of all classified activities [2], influence the amino acids, lipids and carbohydrates metabolism as well as hormones, neurotransmitters and heme biosynthesis [3,4].

It is undoubtedly that protonation of pyridoxine heteronitrogen could change significantly its biological activity. For example, the influence of pyridine nitrogen protonation of more complex compound, PLP, on PLP or its derivatives reactions (*e.g.* transamination) is noticeable [5–8]. However, the effect of pyridoxine heteronitrogen protonation on PN activity in biochemical reactions is still unknown.

In aqueous or aqueous-organic solution, PN exists in two forms, molecular and zwitterionic [9–11] (Scheme 1, K_z):

The influence of tautomeric equilibrium shift on PN reactivity had also never been investigated.

The varying of the solvent composition leading to the change of the reagents solvation states is the key way to control the chemical reaction passing. Changing the ratio of mixed solvent components, one could increase the yield of desired reaction product (*e.g.* possessing required biological activity).

The main aim of present paper is to study the influence of aqueous dimethyl sulfoxide solvent on protolytic and tautomeric equilibria of pyridoxine. In order to achieve the goal we studied the effect of binary solvent composition on protonation constant and tautomeric equilibrium of pyridoxine, and solvation of PN in molecular and zwitterionic form.

The study of PN protonation and tautomerization in mixtures of water with other important organic solvent, ethanol, had been carried out recently [12].

2. Experimental

2.1. Chemicals

Pyridoxine hydrochloride (PN·HCl) of Fisher BioReagents production (New Jersey, USA) was used without purification. The PN content in the reactive was determined by potentiometric titration by NaOH of 0.01000 mol dm^{-3} to be 99.8% (weight).

NaOH of Reakhim production (Slavgorodnee, Russia) was used without purification. The concentrations of NaOH and Na_2CO_3 in its solutions were determined *via* consecutive titration by $HClO_4$ of 0.1000 mol dm^{-3} with phenolphthalein and methyl orange.

$NaClO_4$ of Ural's Factory of Chemicals production (Verkhnyaya Pyshma, Russia) was twice recrystallized and dried at 120 °C until its weight became constant. The purity was controlled by IR-spectroscopy.

Hexane of Reakhim production (Slavgorodnee, Russia) was used without purification. Its purity was controlled refractometrically.

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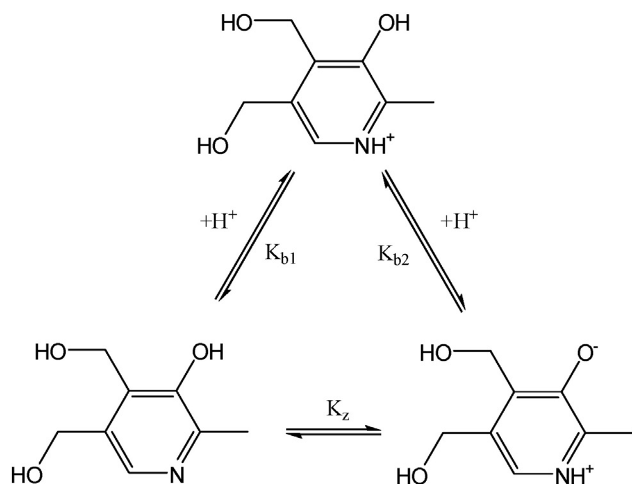


Scheme 1. Protolytic and tautomeric equilibria of pyridoxine.

Dimethyl sulfoxide of Reakhim production (Slavgorodnee, Russia) was used without purification. The residual water content was determined by K. Fischer titration to be 0.19% (weight). The absence of other impurities was proved by NMR- and IR-spectroscopy.

All the binary solvents were prepared *via* mixing the deaerated bidistilled water ($\kappa = 3.6$ μSm cm^{-1}, pH = 6.6) and DMSO (taking into consideration the residual water) weighted in necessary ratio with inaccuracy no >0.01 g.

2.2. Methods

2.2.1. Potentiometry

We chose potentiometry for determining the protonation constants of PN. Like in previous study [12], the indicator glass electrode and silver chloride reference electrode were employed:

$$\mathrm{Ag, AgCl|H_2O\text{-}S, LiCl} \times \mathrm{||H_2O\text{-}S, NaClO_4, PN \cdot HCl, NaOH||glass|0.1\ \ M\,HCl|AgCl, Ag},$$

where S is for organic component of binary solvent (DMSO).

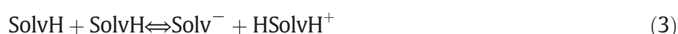
The potential difference between electrodes was measured with error ± 0.1 mV.

The operability of potentiometrical setup was tested using $HClO_4$ solutions with known concentrations (from 0.0001 to 0.1000 mol dm^{-3}) in water and aqueous DMSO [13,14]. The Nernst slope value was 59.3 ± 0.5 mV. In order to eliminate diffusion potential at the boundary between reference electrode and studied solution silver chloride electrode was filled with saturated solution of KCl in water or saturated solution of LiCl in aqueous DMSO.

The following equilibrium processes were considered during the experiment:

$$\mathrm{PN + H^+ \Leftrightarrow PNH^+} \quad (1)$$

$$\mathrm{PN\text{–}H^+ \Leftrightarrow PN^- + H^+} \quad (2)$$



$$\mathrm{SolvH + SolvH \Leftrightarrow Solv^- + HSolvH^+} \quad (3)$$

where process (1) is PN protonation, process (2) is pyridoxine acid dissociation, process (3) is autoprotolysis of mixed solvent.

The protonation constants of pyridoxine were determined *via* titration of aqueous or aqueous-organic solution of PN·HCl of 0.009918–0.01019 mol dm^{-3} and $NaClO_4$. Aqueous or aqueous-organic solution of NaOH of 0.04958–0.1357 mol dm^{-3} and $NaClO_4$ was used as a titrant. The ionic strength was 0.25 ($NaClO_4$). The temperature within the cell was maintained at 25.0 ± 0.1 °C by external control. In addition to the potentiometric titration, the direct pH measurements of the PN·HCl solutions set (concentration range from 0.01043 to 0.02435 mol dm^{-3}) was employed for determining the pyridoxine protonation constants at some dimethyl sulfoxide content. Both methods gave results differing within experimental error.

Potentiometric titration and direct pH measurements data were processed using PHMETR software [15], which approximates the experimental dependence ($\Delta E(\mathrm{mV}) - V_{titr}(\mathrm{ml})$) by the calculated curve.

During the titration the pH value of solution changed in range of 3.0–4.5 units. Such acidity of medium was not enough for process (2) to pass with significant yield. Its exclusion from calculation scheme did not change the results.

The determined macroscopic (without separation on molecular and zwitterionic species yet) constants of pyridoxine protonation are given (Table 1).

The reliability of obtained data is justified by several factors: the precise equipment was employed, the accurate methods of equilibrium constants calculations were used, the statistical reproducibility of results was achieved, the different concentration conditions of the experiment gave the close values of protonation constants, and two different methods, potentiometric titration and direct pH measurements, led to the similar results.

The pyridoxine macroscopic protonation constant determined in present report in water is in a satisfactory agreement with literature data (log K = 4.84 [10], log K = 4.94 [16] and log K = 5.00 [17]).

2.2.2. Immiscible phases partition method

We chose the method of partition between immiscible phases to determine the Gibbs energy change of pyridoxine transfer from water to aqueous DMSO. Experiment was carried out analogically with prescribed one [12].

Two equal volumes (19.97 ml) of hexane and pyridoxine solution in water or aqueous DMSO were placed into hermetically closed flask. The concentration of pyridoxine solution prepared *via* accurate PN·HCl solution neutralization by NaOH was in range from $1.5319 \cdot 10^{-4}$ to $1.5365 \cdot 10^{-4}$ mol dm^{-3}. The flask was put on magnetic stirrer placed into air thermostat. Temperature was maintained at 25.0 ± 0.1 °C. The contents of the flask were stirred during 8 h, and then they were left to stay without stirring for 10 h. The bottom layer (aqueous of aqueous-DMSO solution) was sampled to determine the equilibrium concentration of pyridoxine using calibration graph method of spectrophotometry. Spectral measurements are described in details in Section 2.2.3. The equilibrium pyridoxine concentration in hexane phase was calculated by subtraction of the equilibrium pyridoxine concentration in bottom layer from the total concentration of PN.

Table 1
Pyridoxine protonation constants in aqueous dimethyl sulfoxide at atmospheric pressure[a] and T = 298.2 ± 0.1 K.

X_{DMSO}	l g K_b[b]
0	4.969 ± 0.016 [12]
0.05	4.602 ± 0.015
0.10	4.152 ± 0.016
0.20	3.910 ± 0.012
0.30	3.656 ± 0.016
0.50	3.461 ± 0.020
0.70	3.305 ± 0.014
0.90	4.094 ± 0.021
0.99	4.328 ± 0.022

[a] All experiments were carried out under atmospheric pressure which changed in the range of (0.097 to 0.104) MPa.

[b] There are given the expanded uncertainties for every value with the confidence level of 0.95 and sample size 3–6 experiments.

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