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Thermodynamic models for determination of the solid–liquid equilibrium of oxytocin in (acetonitrile + acetone) binary solvent mixtures

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ABSTRACT

In this paper, we focused on solubility and solution thermodynamics of oxytocin. By gravimetric method, the solubility of oxytocin was measured in (acetonitrile + acetone) binary solvent mixtures from 278.15 K to 328.15 K under atmosphere pressure. The solubility data were fitted using modified Apelblat equation, a variant of the combined nearly ideal binary solvent/Redich–Kister (CNIBS/R–K) model and Jouyban–Acree model. Computational results showed that the modified Apelblat equation was superior to the other two equations. In addition, the thermodynamic properties of the solution process, including the Gibbs energy, enthalpy, and entropy were calculated by the van't Hoff analysis. The experimental results showed that acetonitrile could be used as an effective anti-solvent in the crystallization process.

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1. Introduction

The neurohypophysial hormone oxytocin ($C_{43}H_{66}N_{12}O_{12}S_2$, CASRN: 50-56-6, shown in Fig. 1), or OT for short, is a white crystalline powder, which is a neuropeptide produced in the hypothalamus and released by neurohypophysis into the bloodstream, for its hormonal effects. It is named after the "quick birth" (ωκνξ = quick; τοκοξ = birth) which it causes due to its uterotonic activity [1,2]. Hypothalamic oxytocinergic neurons also project to specific central areas involved in the modulation of pain and in motivation, sense of well-being, and sexual performance. OT is the first peptide hormone to have its structure determined and the first to be chemically synthesized in biologically active form [1,2]. The solubilities of organic compounds in different solvents play an important role for understanding the solid–liquid equilibria (SLE) or phase equilibria in the development of a crystallization process, or liquid–liquid equilibria in extraction and extractive or azeotropic distillation processes [3–5]. More particularly, knowledge of an accurate solubility is needed for the design of separation processes such as extractive crystallization and the safety of operating different processing units such as distillation columns, adsorption units, and extraction plants. The solubility of OT can also supply basic and theoretical data for industrial production. To determine proper solvents and to design an optimized production process, it is necessary to know the solubilities of OT in different solvents [3–5,13]. To our knowledge, we find no report of the solubility of OT in (acetonitrile + acetone) binary solvent mixtures.

In this work, the solubility of OT in (acetonitrile + acetone) binary solvent mixtures was measured from 278.15 K to 328.15 K under atmosphere pressure. The modified Apelblat equation, a variant of the combined nearly ideal binary solvent/Redich–Kister (CNIBS/R–K) model and Jouyban–Acree model were applied to correlate with the experimental data. This is the first attempt at modeling the solubility of OT in (acetonitrile + acetone) binary solvent mixtures using these specific thermodynamic models. The thermodynamic properties of the dissolution process, including enthalpy, entropy and Gibbs energy, were calculated by means of van't Hoff analysis and Gibbs equation.

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2. Experimental

2.1. Materials

Oxytocin (98% wt) was purchased from Aladdin (China). Its purity was measured by high performance liquid chromatography (HPLC type DIONEX P680 DIONEX Technologies). Acetonitrile and acetone for dissolving were supplied by Shanghai Shenbo Chemical Co., Ltd., China. The purities of the solvents were determined in our laboratory by gas chromatography and their mass fraction purities were higher than 0.997. Meanwhile, all chemical reagents were used without further purification. The properties of these solvents are presented in Table 1.

2.2. Apparatus and procedures

The solubility of oxytocin was investigated, in various solvents, by the analytical stirred-flask method, and we used the gravimetric method to measure the compositions of the saturated solutions. Saturated solutions of oxytocin, which were produced by 8 mL solvent mixtures and some excess oxytocin, were prepared in a spherical, 10 mL Pyrex glass flask with a bottle stopper (avoid evaporation of solvent during experimental steps). The flask was maintained in a jacket glass vessel full of water at the desired temperature through circulating water, whose temperature was controlled by a thermostat with an accuracy of ±0.1 K that was supplied from a constant-temperature water bath (type HWC-52, ShangHai Cany Precision Instrument Co., Ltd.). And the actual temperature was measured by a thermometer (uncertainty of ±0.05 K) inside the vessel. For each measurement, some excess oxytocin were added to a known volume of solvent mixtures. Continuous stirring was achieved for fully mixing the suspension using a magnetic stirrer at the required temperature. The stirring continued for about 24 h to ensure the solid–liquid equilibrium and the solution was allowed to settle for 12 h or more before sampling for achieving a static state [6–8]. The supernatant was taken, filtered, and poured into a volumetric flask preweighed by using an analytical balance (Sartorius, BS210s, Germany). The volumetric flask was used to prevent a situation from happening in the next step, that the volume of 1 mL solution supernatant reduced because of filtering undissolved substance inadvertently. At last, 1 mL solution supernatant was transferred into 5 mL breaker with a cover and weighted immediatedly. This breaker had been weighted before. The transfer process is very short. The temperature remained about the same in a short span of time. All breakers without covers were put into a dryer at about 330 K and weighted weekly until reaching constant weight. All determinations were repeated three times to check reproducibility, and then an average value was given. In order to ensure that there is no change of the material OT before and after the experiments, we used unused OT and recrystal OT (collect the crystals from 5 mL breaker) to do a contrast test about their solubilities. The result showed that the solubilities of unused OT and recrystal OT were same in acetonitrile and acetone. This point implied that the material OT was not changed. Other methods, such as X-ray diffraction or other spectra, can be chosen for afterward researcher.

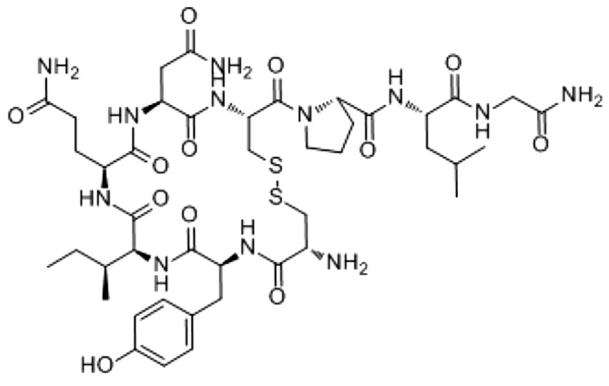

Fig. 1. Chemical structure of oxytocin.

The mole fraction solubility of oxytocin (x) in (acetonitrile + acetone) binary solvent mixtures is calculated by Eq. (1). The mole fraction of acetonitrile (x_A) in the binary solvent mixtures is calculated by Eq. (2).

$$x = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \tag{1}$$

$$x_A = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \tag{2}$$

where m_1, m_2, m_3 represent the mass of oxytocin, acetonitrile, acetone, and M_1, M_2, M_3 represent the molar mass of the oxytocin, acetonitrile, acetone, respectively.

3. Results and discussions

3.1. Solubility data and thermodynamic models

The solubility data of oxytocin (x) in (acetonitrile + acetone) binary solvent mixtures with the temperature ranging from 278.15 K to 328.15 K are presented in Table 2, and graphically showed in Fig. 2. We could find that oxytocin had high solubility in pure acetone. The solubility in acetone showed the strongest positive dependency on temperature. The solubility of oxytocin depends not only on the temperature but also on the structure of the solvent. Polarity follows the order: acetonitrile > acetone. As is seen from the Fig. 2, the solubility of OT increases with decreasing polarity of the solvent.

3.2. Modified Apelblat equation

On the basis of the solid-liquid phase equilibrium theory, the relationship between mole fraction of the solubility and temperature is generally described by modified Apelblat equation. This model is firstly used by Apelblat [9,10], which can give a relatively accurate correlation with three parameters:

$$\ln x = A + \frac{B}{T/K} + C\ln(T/K) \tag{3}$$

where T is the experimental temperature in K, and A, B and C are the regression curve parameters in the equation which are listed in Table 3.

3.3. CNIBS/R–K model

The relationship of the experimental isothermal mole fraction solubility and binary solvent compositions is described by the Combined Nearly Ideal Binary Solvent/Redich–Kister (CNIBS/R–K) model [11–15], which is one of the theoretical models for calculating the solute solubility in binary solvents and represented in Eq. (4):

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