Journal of Molecular Liquids xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Thermodynamic studies on solubility and protonation constant of acetaminophen at different ionic strengths and various temperatures

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ARTICLE INFO

Article history:
Received 1 June 2014
Received in revised form 23 July 2014
Accepted 21 August 2014
Available online xxxx

Keywords:
Acetaminophen
Solubility
Protonation constant
Ionic strength and temperature

ABSTRACT

The total solubility and protonation constant of acetaminophen were determined in aqueous solution in different experimental conditions of ionic strength (0.1–2.0 mol dm^{-3} NaCl) and temperature (20–35 °C) using a combination of potentiometric-spectrophotometric method. Using the pC_H of dissolution and the protonation constant determined in the same condition allowed us to calculate the solubility of neutral species of the drug at different ionic strengths and various temperatures. The enthalpy and the entropy changes of dissolution and the protonation constant were determined at different ionic strengths using temperature variation method. The values of solubility and the thermodynamic parameters for dissolution and protonation equilibria of acetaminophen were also determined at zero ionic strength using a Debye–Hückel type equation and discussed on ionic strength and temperature.

1. Introduction

Acetaminophen (*N*-acetyl-*p*-aminophenol), also known as paracetamol, is a nonsteroidal drug with potent antipyretic and analgesic actions but with very weak anti-inflammatory activity [1,2]. When administered to humans, it reduces levels of prostaglandin metabolites in urine but does not reduce synthesis of prostaglandins by blood platelets or by the stomach mucosa [3]. This compound is extensively used as an alternative to aspirin without the secondary effects of the salicylates on the gastric mucosa [4]. Some clinical studies [5,6] have shown that there is not any advantage of analgesic or anti-inflammatory doses of ibuprofen over acetaminophen as symptomatic treatment for patients with osteoarthritis. This compound reduces fever by blocking the formation and release of prostaglandins in the central nervous system and inhibiting the action of endogenous pyrogens at the hypothalamic thermoregulatory centers [7–9]. Acetaminophen-induced liver damage is normally seen only with daily doses greater than 4 g [10,11]. Using acetaminophen more than this amount is associated to hepatic toxicity and renal failure despite of its apparent innocuous character [12,13]. A recent report has indicated that acetaminophen should not be used more than 325 mg in one dosage. Because of its potent analgesic and antipyretic actions, acetaminophen is generally regarded as an NSAID. However, it lacks the other typical actions of NSAIDs, such as antiplatelet activity and gastrotoxicity. Acetaminophen is rapidly and almost completely absorbed following ingestion [14]. Studies have shown that the maximum absorption of the drug occurs in the small intestine with negligible absorption in the stomach [15,16]. In spite of its wide use, the mechanism of action of acetaminophen has not been fully elucidated. It is only a weak inhibitor of prostaglandin synthesis in vitro and appears to have very weak anti-inflammatory activity, although some reduction of tissue swelling after dental surgery has been reported [17,18].

The first step to determine the physicochemical properties of a drug is to make it soluble in a solvent. So, it is necessary to measure the solubility behavior of a drug in a solvent especially at various temperatures and different ionic strengths which can yield a thermodynamic description of the system including enthalpy and entropy changes of dissolution process.

Most drugs have acidic or basic functionalities. Depending on both pH and the protonation constant of the drug, different chemical species may exist in the solution, including cationic, anionic, or neutral species, which often have different properties with respect to solubility, UV absorption, etc. The ionized species is usually more soluble in water, while the neutral form is more lipophilic [14,19].

In the present work, the thermodynamic properties (protonation constant, solubility, enthalpy and entropy changes of protonation and dissolution) of acetaminophen are determined in different temperatures (20–35 °C) and various ionic strengths (in the range of 0.1 to 2.0 mol dm^{-3} NaCl) in aqueous solution using a combination of spectrophotometric and potentiometric methods. The parameters which define the dependency on ionic strength were analyzed with the aim of obtaining further information with regard to their variation as a function of the charges involved in the protonation reaction. Moreover, a

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http://dx.doi.org/10.1016/j.molliq.2014.08.033
0167-7322/

Debye–Hückel type equation was established for the dependence of protonation constant and the thermodynamic parameters on ionic strength.

2. Experimental

2.1. Materials

Acetaminophen, Scheme 1, was obtained as a gift from Temad Pharmaceutical Company (Iran). The purity of the drug, checked by alkalimetric titration, was higher than 99%. Hydrochloric acid and sodium hydroxide solutions (Merck), prepared from concentrated ampoules, were standardized against sodium carbonate and potassium hydrogen phthalate, respectively. Sodium chloride solutions were prepared by weighing the pure salt previously dried in an oven at 110 °C. All dilute solutions were prepared from double-distilled water with a conductance equal to 1.2 ± 0.1 μS.

2.2. Apparatus

The electromotive force was measured using a Metrohm model 781 pH ion-meter (resolution ±0.1 mV), using a combined glass-pH electrode (model 6.0258.000). All titrations were carried out in a 80 mL thermostated double-walled glass vessel.

Spectrophotometric measurements were performed on a UV–vis Shimadzu 2100 spectrophotometer with a Pentium 4 computer and using thermostated matched 10 mm quartz cells. The measurement cell was of the flow type. A peristaltic pump allowed circulation of the solution under study from the potentiometric cell to the spectrophotometric cell, so the absorbance and the emf of the solution could be measured simultaneously. To exclude carbon dioxide from the system, a stream of purified nitrogen was passed through a sodium hydroxide solution and then bubbled slowly through the reaction solution.

2.3. Procedure

All measurements were performed over the temperature range from 20 to 35 °C at atmospheric pressure. To obtain the solubility of acetaminophen, a saturated solution was prepared by addition of an excess of the drug to solutions containing NaCl (0.1 to 2.0 mol dm^{-3}) as supporting electrolytes using double distilled water. The solid–liquid mixtures were then stirred in a mechanical shaker for 2 h. Samples were then allowed to stand in water baths kept at the appropriate temperature (±0.1 °C) for 24 h to reach the equilibrium. The saturated solutions were centrifuged and then filtered through a cellulose membrane filter. The emf and the absorbance of the diluted solutions were recorded in the range of 200 to 300 nm. The concentration of the drug in each solution was determined using a calibration curve which previously prepared. In order to permit conversion between molarity and mole fraction concentration scales, the density of the saturated solutions was determined with a digital density meter (Anton Paar, model DMA 4500 M, precision ±0.00001 g cm^{-3}).

The protonation constant was evaluated from the measurement of absorbance versus emf by titration of acetaminophen solution (5.0×10^{-5} to 8.0×10^{-5} mol dm^{-3}) with 0.1 mol dm^{-3} sodium hydroxide solution both with the same ionic strength at the desired temperature. In the first step, the electrode system calibration was performed by the Gran's method [20]. For this purpose a measured amount of an acidic solution (0.01 mol · dm^{-3} HCl), at the same condition of temperature and ionic strength to be used in later experiments, was placed in the double-wall thermostated vessel. The acidic solution was then titrated with a strong base (0.1 mol · dm^{-3} NaOH, each addition 50 μL). The potential was allowed to stabilize after each addition of the titrant and the recorded emf values were then used to obtain the cell parameter (E°), and electrode calibration slope, Nernstian parameter (k). The procedure was continued to pH ≅ 3. Usually, 10 to 12 additions are enough for this purpose. It is necessary to add that the slope, k, of the Nernst equation was very close to its theoretical value and always in the range of 59.1–59.2. In the second step, 25 mL of an acidic solution (0.01 mol dm^{-3} HCl) of acetaminophen (5.0×10^{-5} to 8.0×10^{-5} mol dm^{-3}) was added to above solution with appropriate amounts of NaCl solution to achieve a total desired ionic strength. The solution was again titrated with a sodium hydroxide solution (0.1 mol dm^{-3} with sufficient NaCl solution to achieve a desired constant ionic strength). The emf and the absorbance values (in the range of 200 to 300 nm and interval of 0.5 nm) were then determined. The procedure was repeated in different ionic strengths and various temperatures. The recorded emf values were then converted to pC_H ($-\log [H^+]$) using the method described in the literature [21]. In solution, the measured potential of the cell can be written as:

$$E_{cell} = E^{\circ}_{cell} + k \cdot \log \left[H^+\right] + k \cdot \log \gamma_{H^+} + E_{LJ} \quad (1)$$

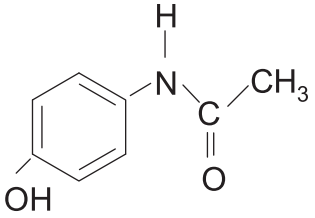
where E°_{cell} is the standard potential of the cell, E_{LJ} is the liquid junction potential, $k = 2.303RT/F$ in which R, T and F have the usual meaning, and γ_{H^+} is the activity coefficient of hydrogen ion. Difficulties in computing the activity coefficients of hydrogen ion in aqueous solutions with different ionic strengths and various temperatures lead to measurement of emf (electromotive force) versus H^+ concentration in solution. Because the ionic strength of the solution is kept constant, in each run, so the activity coefficient of hydrogen ion is constant too. The non-ideality of solutions is then included in E'_a (the specific constant of the potentiometric cell in the acidic region), so

$$E_{cell} = E'_a + k \cdot \log\left[H^+\right] \quad (2)$$

where E'_a is $E^\circ_{cell} + k \cdot \log \gamma_{H^+} + E_{LJ}$. The hydrogen ion concentration can be expressed as:

$$\left[H^+\right] = (M_{HCl}V_0 - M_{NaOH}V_1)/(V_0 + V_1) \quad (3)$$

where M_{HCl} and M_{NaOH} are the molarities of hydrochloric acid and sodium hydroxide, V_0 and V_1 are the initial volume of hydrochloric acid and the added volume of sodium hydroxide solution, respectively.



Scheme 1. The chemical structure of acetaminophen.

3. Results and discussion

3.1. Solubility

The total solubility, S_t, of the drug depends on concentration of the different species of acetaminophen (anionic and neutral) present in a solution, according to the following protonation equilibria:

$$L^- + H^+ \rightleftarrows HL \qquad K = \frac{[HL]}{[H^+][L^-]} \quad (4)$$

$$S_t = [HL] + [L^-] \quad (5)$$

where K is the protonation constant of acetaminophen (see hereafter) and HL and L^- are the different species of the drug involved in the protonation equilibria studied. If we designate the solubility of the neutral

Please cite this article as: H. Chahiyan, et al., Thermodynamic studies on solubility and protonation constant of acetaminophen at different ionic strengths and various temperatures, J. Mol. Liq. (2014), http://dx.doi.org/10.1016/j.molliq.2014.08.033