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Ternary phase diagrams of ethyl paraben and propyl paraben in ethanol aqueous solvents

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ABSTRACT

Three ternary phase diagrams of ethyl paraben, ethanol, water and propyl paraben, ethanol, water have been determined. The liquid–liquid phase separation has been reported in these three ternary diagrams. In pure water the ethyl paraben and propyl paraben solubility is both below 1 mg/g, while in pure ethanol the solubility is more than three orders of magnitude higher. While the solution saturated with propyl paraben is homogeneous at 30.0 °C, and the solution saturated with ethyl paraben is homogenous at 40.0 °C, however, the higher temperatures induce liquid–liquid phase separation in the ethanol–water mixtures, and the ternary phase diagrams contain five different regions. The size of the liquid–liquid phase separation region increases with increasing temperature. The systematic changes of thermodynamic properties between butyl paraben, propyl paraben and ethyl paraben have been investigated.

1. Introduction

Crystallization from solution is a method central to the production of a wide range of organic fine chemicals and pharmaceuticals. To understand and control the crystallization process, it is essential to establish the equilibrium between homogenous liquid and solid phase, and sometimes more complex phase equilibriums are investigated like solvent mixtures, racemic mixtures and co-crystals. While binary solvent mixtures are commonly used in industrial crystallizations, the corresponding ternary phase diagrams are not well explored and neither are the crystallization behaviors in systems exhibiting liquid–liquid phase separation. On example thought, spherical crystallization is carried out in solvent mixtures and often near the liquid–liquid phase separation (LLPS) boundary [1,2]. The morphology of polymer blends is largely determined by the interplay between liquid–liquid phase separation and crystallization [3–7]. The accurate interpretations of phase equilibriums and thermodynamic behaviors for the different ternary mixtures are fundamental and important keys to improving solvent extraction techniques [8–11]. LLPS is known in colloid physics and in the protein area as a gas–fluid [12,13] and a fluid–fluid [14–16] transitions, respectively. LLPS has a great impact on the metastable zone during the crystallization process [17], as well as on the nucleation in supersaturated protein solutions [18,19]. The liquid–liquid phase separation makes crystallization difficult in system including protein [20,21], oiling out (LLPS) impedes crystallization of some drugs [22,23] and the liquid–liquid phase separation hinders both primary and secondary nucleation in crystallization of droplets [24].

Parabens are alkyl esters of *p*-hydroxybenzoic acid. Fig. 1 shows the molecular structures of the ethyl paraben, propyl paraben and butyl paraben. They have a relatively low toxicity [25], and the compounds or their salts are the most common preservatives in use today, found in thousands of cosmetic, toiletries, food and pharmaceutical products [26]. Combinations of parabens appear to have synergistic effects on bacteria [27,28], and hence as preservative, ethyl-, propyl- and butyl paraben are often used in combination with one or more [29]. Perlovich [30], Giordano [31], Feng [32,33], Yang [34,35], Manzo [36] and Kapalavavi [37] have investigated the thermodynamics of parabens, the relationships between crystal structures and physical properties of parabens, the nucleation and crystallization of parabens and solubility in subcritical water, respectively.

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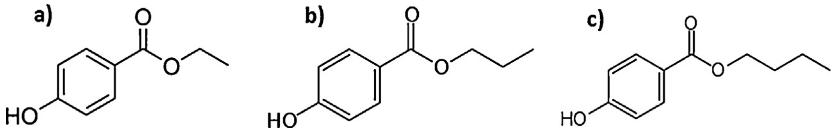

Fig. 1. Molecular structures of the (a) ethyl paraben, (b) propyl paraben and (c) butyl paraben.

In the previous study, we have reported the system of butyl paraben (BP)–ethanol (E)–water (W) [38], which turns out that in a certain temperature range, paraben enforces a liquid–liquid phase separation in the ethanol–water mixtures. The aim of this work is to investigate the phase behaviors of the ternary systems propyl paraben + water + ethanol and ethyl paraben + water + ethanol in the temperature range from 40.0 °C to 50.0 °C. We report direct observation of the liquid–liquid phase separation, and determinations of solid–liquid solubility of parabens in ethanol–water mixture.

2. Materials and methods

2.1. Materials

Ethyl paraben (EP) and propyl paraben (PP) of purity >99.0% by mass were purchased from Aldrich and were used without further purification. Table 1 shows the specifications of these chemical materials. Ethanol (99.7% by mass) was purchased from Solveco chemicals from VWR, and distilled water was used.

2.2. Procedures

2.2.1. Solubility of paraben

Solubility of ethyl paraben at 50.0 °C and propyl paraben at 40.0 °C and 50.0 °C was determined by the gravimetric method [39] in pure water and pure ethanol, and in 10%, 30%, 50%, 70% and 90% by weight ethanol (on solute free basis) in ethanol–water mixtures, at which temperature the liquid–liquid phase separation was observed. The temperature was controlled by a thermostat bath with uncertainty of ±0.01 °C. The temperature measurements had been calibrated against a mercury precision thermometer (Precision, Arno amavell, 6983 kreuzwerthelm with uncertainty of ±0.01 °C).

Solutions were prepared in 200 ml glass bottles. To about 50 ml of solvent in each bottle at 50.0 °C solid paraben was added in excess of the solubility. Saturation was reached by dissolution, assuring there was solid phase in the solution at equilibrium. The solutions were kept under agitation 400 rpm for more than 12 h to assure that equilibrium had been established. Then the agitation was turned off and the solid material was allowed to settle for half an hour. A 10 ml syringe in its unbroken plastic bag was put into the water bath for several minutes in order to reach the same temperature as the solution. Then the syringe with needle was used to sample (2 to 4 ml) the solution in the glass bottle. A filter (PTFE 0.2 μm) was attached to the syringe through which the solution was distributed into two small pre-weighed plastic bottles (1–2 ml each). Each bottle was quickly covered to prevent evaporation and weighed with its content. Then the cover was removed and the samples were dried in ventilated laboratory hoods at room temperature (about 25.0 °C). The solid residue mass was recorded repeatedly throughout the drying process to complete dryness. Sometimes more than a month was required since the solid phase tended to form a cake at the liquid surface thus slowing down the evaporation. Every day the cake in each plastic bottle was mechanically broken by each pre-weighed small stick, which was kept in each plastic bottle, respectively, to sustain the evaporation. The weight of the final dry sample was used for calculation of the solubility of course with appropriate correction for the weight of the cover and the stick. The balance (Mettler AE 240) used during the experimental work had a resolution of ±0.00001 g. The same steps were repeated at 40.0 °C for ethyl paraben.

Table 1
Specifications of chemical materials.

Chemical name	Source	Initial mass fraction purity	Purification method
Ethyl paraben	Aldrich	>0.990	None
Propyl paraben	Aldrich	>0.990	None
Ethanol	Solveco chemicals	0.997	None

2.2.2. Liquid–liquid phase separation

The ternary phase diagrams of ethyl paraben, water and ethanol and propyl paraben, water and ethanol were investigated at 40.0 °C or 50.0 °C. A 300 ml glass bottle with plastic cover was put in a thermostat bath whose temperature was controlled with uncertainty of ±0.01 °C. The balance (Tamro HF-300G, A&D Company) used during the experiment work had a resolution of ±0.001 g.

The different regions were explored by adding of ethyl paraben, water or ethanol step by step. First, at 50.0 °C a starting point in the ternary phase diagram was selected, and a 100 ml mixture of ethyl paraben, water and ethanol with desired proportions was prepared in a 300 ml glass bottle. The solution was stirred by a magnetic stirrer at 200 rpm. Then, one of the components, ethyl paraben, water or ethanol, was added into this solution step by step, allowing 30 min of equilibration at each step, until a different phase appeared (for example the clear solution changed to cloudy or the solution started to contain undissolved solid ethyl paraben). Then, the other two components were added in smaller steps to revert back to the previous phase region. The phase boundary was defined as being between two steps back and forth where the phase changing was established to occur. The processes of adding different materials from different starting points were repeated to clarify the location of the phase boundary more precisely and establish the properties of the full phase diagram of ethyl paraben, water and ethanol at 50.0 °C. By repeating this procedure, ternary diagrams of propyl paraben, water and ethanol at 40.0 °C and 50.0 °C were determined.

2.2.3. Melting point and melting enthalpy

Melting points and enthalpy of fusion at the fusion temperature of the solid parabens were determined by differential scanning calorimetry (DSC), TA Instruments, DSC 2920. The calorimeter was calibrated against the melting properties of indium. Samples (2 to 3 mg) of paraben were heated by 5.0 °C/min from about 7.0 °C to approximately 50.0 °C above the melting temperatures of parabens, respectively, then cooled down to 7.0 °C, and repeated two times for each sample (totally five samples). All the determinations of solubility, ternary phase diagram, melting point and melting enthalpy, were at pressure 0.10 MPa.