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Solubility and preferential solvation of 2-methyl-4-nitroaniline in mixed solvents of ethyl acetate + (methanol, ethanol, *n*-propanol and isopropanol)

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ABSTRACT

The mole fraction solubility of 2-methyl-4-nitroaniline in binary mixed solvents of (ethyl acetate + methanol), (ethyl acetate + ethanol), (ethyl acetate + *n*-propanol) and (ethyl acetate + isopropanol) was determined experimentally by using static method at temperatures from (278.15 to 313.15) K under atmospheric pressure. The solubility increased with increasing temperature and mass fraction of ethyl acetate. At the same temperature and mass fraction of ethyl acetate, the mole fraction solubility in (ethyl acetate + methanol) was greater than those in the other mixed solvents. The solubility values were correlated with Jouyban–Acree model, van't Hoff-Jouyban-Acree model, modified Apelblat-Jouyban-Acree model, Ma model, and Sun model. The maximum values of relative average deviations and root-mean-square deviations were 0.47×10^{-2} and 2.26×10^{-4}, respectively. Preferential solvation parameters of the solute were also derived by means of the inverse Kirkwood-Buff integrals (IKBI) method. The preferential solvation parameters $\delta x_{1,3}$ are negative in alcohol-rich composition, but positive in intermediate and ethyl acetate-rich composition. The ethyl acetate action may be related to the breaking of the ordered structure of alcohol around the polar moieties of 2-methyl-4-nitroaniline. The positive $\delta x_{1,3}$ values could be explained based on the higher acidic behaviour of 2-methyl-4-nitroaniline molecules interacting with the hydrogen acceptor groups present in ethyl acetate. This work expands the physicochemical information about solid in binary solvent mixtures.

1. Introduction

Solid-liquid equilibrium data are one of the important thermodynamic properties. It can provide necessary information for the design, analysis and optimization of the separation and purification processes in various fields *e.g.* pharmaceutical, chemical, food, petrochemical and material [1]. Solubility alteration of the solid is essential in many industrial applications, and the solvent mixing is one of the most frequent and feasible methods employed in the industry. By using different ratios of the solvents, a wide range of solubility for a given compound can be achieved. In addition, the changing temperature of the system makes a significant contribution in crystallization of a compound [2,3].

2-Methyl-4-nitroaniline (CAS Reg. No. 99-52-5) is widely used in dye, pharmaceutical and pesticide [4–7]. In China, the commercial preparation method of 2-methyl-4-nitroaniline is using 2-totuidine as raw material [7–13]. The synthesis route is shown graphically in Fig. S1 of Supporting material. In such a nitration process, the reaction provides as its product an isomeric mixtures of 2-methyl-4-nitroaniline and 2-methyl-6-nitroaniline. As an important intermediate for pharmaceuticals and dyestuffs, pure 2-methyl-4-nitroaniline is required in making high purity drugs and dyes, where impurities in the starting material may affect the properties of synthesized materials. Thus, during the manufacturing of 2-methyl-4-nitroaniline, purification process needs to be conducted, which is a critical step that determines the quality of final 2-methyl-4-nitroaniline product.

It is well known that solvent crystallization is usually used as an important separation and purification step in the production process. The solubility of solid in different solvents is an important physicochemical property in different areas such as crystallization, separation, liquid extraction, drug formulation. It can be recognized at all steps of drug discovery and development processes. The knowledge of thermodynamic parameters, particularly accurate solubility is needed for the design of process such as extractive

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crystallization and the safety of different operating units. Although it has been a long time since the launch of 2-methyl-4-nitroaniline, up to yet, only the solubility of 2-methyl-4-nitroaniline in some neat solvents has been determined [14]. Besides, the melting point, melting enthalpy and melting entropy of fusion of pure 2-methyl-4-nitroaniline have been determined by Tanaka [15], which are 406.6 K, 24.70 $kJ \cdot mol^{-1}$ and 60.75 $J \cdot K^{-1} \cdot mol^{-1}$, respectively. To the best of our present knowledge, no experimental or theoretical study about the thermodynamics in mixed solvents has been made from bibliographic retrieval. Based on the Ref. [14], the solubilities of 2-methyl-4-nitroaniline are much larger in ethyl acetate than in alcohols. So there is a strong need to determine the 2-methyl-4-nitroaniline solubility in mixed solutions and build better models for describing these behaviours. On the basis of the considerations mentioned above, in this work, we carry out the systematic studies on solubility of 2-methyl-4-nitroaniline in mixed solvents formed by ethyl acetate, methanol, ethanol, *n*-propanol and isopropanol at temperatures from (278.15 to 313.15) K. In the following, the solubility data are correlated with different models, and the IKBI approach [16–18] is applied to evaluate the preferential solvation of 2-methyl-4-nitroaniline in the binary mixtures.

2. Experimental

2.1. Materials and apparatus

2-Methyl-4-nitroaniline was provided by Beijing Ouhe Chemical Technology Co., Ltd, China with a mass fraction of 0.979. It was purified three times via crystallization in (ethyl acetate + ethanol) mixtures with a volume ratio of 60:40. The final content of 2-methyl-4-nitroaniline used in solubility measurement was 0.997 in mass fraction, which was confirmed using a high-performance liquid chromatography (HPLC, Shimadzu-6A). The five solvents (methanol, ethanol, *n*-propanol, isopropanol and ethyl acetate) were provided by Sinopharm Chemical Reagent Co., Ltd., China. The purities of these solvents were all no less than 0.993 in mass fraction, which were determined by gas chromatography (GC Smart (GC-2018)). The detailed information of these chemicals used in this work was presented in Table 1.

The schematic diagram of solubility determination apparatus was shown graphically in Fig. S2 of Supporting material. The experimental apparatus consisted of a 100 mL jacketed glass vessel, a magnetic stirrer and a thermostatic water bath (Model: QYHX-1030) with a standard uncertainty of 0.05 K, which was produced by Shanghai Joyn Electronic CO., Ltd., China. A condenser was used and attached to the jacketed glass vessel to prevent the solvent from evaporating. The actual temperature was displayed by using a mercury glass micro thermometer inserted in the inner chamber of the glass vessel. An analytical balance (model: BSA224S) having a standard uncertainty of 0.0001 g was employed to determine the mass of the solvent, solute and saturated solution.

2.2. Preparation of solvent mixtures

The solvent mixtures were prepared by using the analytical balance (model: BSA224S) in the present work. The mixed solvent in the glass vessel was about 60 mL, which standard uncertainty was estimated to be 0.0001 g. The mass fractions of ethyl acetate in the binary mixtures varied from 0.1 to 0.9. The glass vessel was covered with a stopper to prevent the solvent from escaping during the preparation process of solvent mixtures. During the experiment process, the atmospheric pressure was about 101.1 kPa.

2.3. Solubility measurement

In this work, the solid–liquid equilibrium of 2-methyl-4-nitroaniline in binary solvent mixtures of (ethyl acetate + methanol), (ethyl acetate + ethanol), (ethyl acetate + *n*-propanol) and (ethyl acetate + isopropanol) was determined by using the static method [19–23], and the high-performance liquid phase chromatograph (HPLC, Shimadzu-6A) was used to determine the solubility of 2-methyl-4-nitroaniline in different solvent mixtures.

For each experiment, an excessive amount of 2-methyl-4-nitroaniline was added to the jacketed glass vessel filled with about 60 ml solvent mixtures. Continuous stirring was achieved by using a magnetic stirrer at a desired temperature to mix the suspension rigorously. The equilibration time of the solution was determined repeatedly by analyzing the liquid phase, which was taken out using a pore syringe filter (PTFE 0.2 μm) connected with a 0.2 μm pore filter. If the analytical results didn't vary, the mixture was assumed to be in equilibrium. In order to ensure that sampling was performed at equilibrium conditions, two types of experiments were performed, one starting from a supersaturated solution, in which the solid phase precipitated to reach equilibrium and the other starting from a non-saturated solution, in which solid dissolved to reach equilibrium. When the solution arrived at equilibrium, the stirring was turned off for 1 h to allow any undissolved solid to be precipitated from the solution. The upper liquid phase was taken out with a 2 ml of preheated or precooled syringe attached with the filter (PTFE 0.2 μm), and transferred quickly to a 25 ml pre-weighed volumetric flask. The flask was weighed again by using the analytical balance. Subsequently, the sample was diluted to 25 mLwith methanol, and analyzed by using the high-performance liquid chromatography.

2.4. Analysis method

The composition of 2-methyl-4-nitroaniline was analyzed by the Shimadzu-6A high-performance liquid chromatography (HPLC). The chromatographic column was a unimicro Kromasil C18, 5 μm (250 mm × 4.6 mm) column, which temperature was 303 K. The wavelength of the UV detector was set to 390 nm. Pure methanol was used as mobile phase with the flow rate of

Table 1
Detailed information of 2-methyl-4-nitroaniline and the selected solvents.

Chemicals	Molar mass /g·mol^{-1}	Source	Initial mass fraction purity	Purification method	Final mass fraction purity	Analytical method
2-methyl-4-nitroaniline	152.15	Beijing Ouhe Chemical Technology Co., Ltd, China	0.979	Recrystallization	0.997	HPLC[a]
Methanol	32.04	Sinopharm Chemical Reagent Co., Ltd., China	0.993	–	0.993	GC[b]
Ethanol	46.07		0.995	–	0.995	GC
n-Propanol	60.06		0.994	–	0.994	GC
Isopropanol	60.06		0.994	–	0.994	GC
Ethyl acetate	88.11		0.995	–	0.995	GC

[a] High-performance liquid chromatography.
[b] Gas chromatography.