



Solubility predictions of acetanilide derivatives in water: Combining thermochemistry and thermodynamic modeling



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ABSTRACT

Knowledge about solubility in water is required for crystallization processes, for the development of structure-property relationships, for the establishment of solubility scales, assessing environmental contamination, and for validating thermodynamic models. Approaches are desired that allow predicting solubility without the use of any experimental solubility data. Most methods that have been proposed to predict aqueous solubility of organic compounds face low prediction reliability and the lack of model interpretability. This work proposes the use of a thermodynamic approach for the prediction of solubility of acetanilide and its derivatives in water. This approach requires fusion enthalpy and fusion temperature as well as the activity coefficient of the respective acetanilide derivative. The latter was obtained by the equation of state PC-SAFT, which uses thermochemistry data as input for model parametrization. The thermochemical data on acetanilide and its derivatives (vapor and sublimation pressures, sublimation and fusion enthalpies) were collected from the literature and evaluated for internal consistency. In order to validate the final solubility prediction model, aqueous solubility of acetanilide and 17 derivatives were predicted and compared to experimental solubility data from literature at 298.15 K as well as to an ideal solubility model, which assumes ideal mixture behavior. The results showed that mixtures of acetanilides + water are highly non-ideal, and the average deviations between solubility data and ideal solubility model could be reduced by two orders of magnitude by using PC-SAFT for the solubility predictions. More promising, PC-SAFT was found to allow predicting the temperature dependence of the aqueous solubility accurately, while ideal solubility model failed to quantitatively describe temperature-dependent solubility.

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1. Introduction

Knowledge about solubility is required for the design and optimization of crystallization processes, for the development of structure-property relationships [1,2], for the establishment of solubility scales [3,4], for waste-water treatment [5], and for validating thermodynamic models [6–10] and solubility estimation

procedures [11] in which intermolecular interactions are crucial. Aqueous solubility is further used as characteristic scale in diverse classification systems. Classification systems, solubility scales or structure-property relationships are increasingly used in the early stages of research or process design in order to evaluate the economic benefit of processes under investigation. The reason behind that is the fact that measuring solubility is usually time-consuming and often requires a high amount of substance, thus being also cost-intensive. Thus, a method for predicting the aqueous solubility of organic compounds is most desirable in academia and research areas in chemical engineering, biotechnology, pharmaceutical and cosmetic science. This is especially important for compounds with very poor aqueous solubility as in these cases experimental solubility values might be highly uncertain.

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A predictive method of choice should be a compromise between easy usage and physical basis. The computational prediction of solubility of organic compounds in water has been the goal of many researchers in the last two decades. Several diverse methods have been proposed for the computation of solubility, among them are the use of mechanistic models [12], neural networks [13], models based on structure-property relationships [14], and also engineering thermodynamic models such as COSMO-RS [15] or equations of state such as perturbed-chain statistical associating fluid theory (PC-SAFT) [16]. Works published in the literature so far show that solubility models play an increasingly important role in process design. However, as Johnson and Zheng [17] stated, “very few applications of solubility models in the prospective design of new compounds were uncovered”, is speculated to be caused by “low prediction reliability and the lack of model interpretability”. Although this statement is more than 10 years old, it still holds true, although many predictive methods have arisen and applied especially in the last decade. However, the low accuracy of solubility predictions in water is still a major drawback, as the relative deviation between experimental data and modeling results are often unacceptably high. Partially, high model errors are caused by the fact that several aromatic organic compounds are very poorly soluble in water, causing low absolute deviations in high relative errors. Nevertheless, poor prediction reliability forces researchers to use experimental screening methods or solubility correlations instead of direct solubility predictions. Such correlations use the aqueous solubility data for model parametrization (e.g. Refs. [7,18]) or huge solubility databases as learning platforms or training sets (e.g. in neural networks).

This work aims to overcome these shortcomings by presenting accurate solubility predictions of acetanilide and its derivatives in water. Aniline derivatives such as acetanilide and acetanilide derivatives have been widely used as intermediate chemicals, and thus solubility data is readily available; thus, these components are appropriate to demonstrate model validation. Some applications of acetanilide derivatives include the fields of colorants and of herbicides [19,20], which makes them important also for environmental issues.

Recent studies have shown that thermodynamic solubility models might be predictive for the accurate calculation of aqueous solubility if reliable data from thermochemistry is available [6,8,21]. It has been shown in these works that the use of experimental sublimation pressures for the pure-component parameters estimation is a reasonable way if experimental vapor pressures are experimentally not accessible. Further, only reliable sublimation-pressure data were used in these works for the parameter estimation. Despite the fact that this approach assumes the solid to behave as supercooled liquid (which certainly neglects effects in the solid) and despite the fact that only pressure-temperature data were used in these works, modeling phase behavior of mixtures were reasonably accurate. Considering acetanilide and its derivatives, experimental thermochemistry data of the pure components already exist (e.g. Refs. [22–36]), but are still scarce and often very uncertain. Thus, additional experimental studies are required that provide precise thermochemistry data. Based on our experience, most accurate and reliable results can be obtained by using, comparing and cross-evaluating different experimental techniques for a compound under study.

In sum, this work will provide new thermochemistry data for acetanilide and its derivatives, containing sublimation data, fusion properties and formation properties. These data will be used in order to parameterize the thermodynamic solubility model, which then will be finally used to predict aqueous solubility of acetanilide and its derivatives. The focus of the work is to provide model predictions that are obtained completely independent of any

experimental solubility data, to address the non-ideality of acetanilide + water mixtures and to validate the assumptions behind the estimation of the PC-SAFT parameters.

2. Materials and methods

2.1. Materials

Samples of acetanilide, ethoxybenzene and benzene were of the commercial origin (Sigma-Aldrich) with purity of ≥ 99 mass %. Supplier information, purification methods and GC purity of the materials are listed in Table 1.

The sample of acetanilide used in the transpiration experiments was purified by fractional sublimation in vacuum. Sample of ethoxybenzene, used in solution experiments was not additionally purified. Benzene was used as solvent in solution experiments, and it was carefully purified by fractional distillation prior to use. The degree of purity was determined using a GC equipped with an FID. A capillary column HP-5 was used with a column length of 30 m, an inside diameter of 0.32 mm, and a film thickness of 0.25 μm . No impurities (greater than 0.001 mass fraction) could be detected in the samples used for the thermochemical measurements. Provenance and purity of samples studied in this work are given in Table 1.

2.2. Thermochemical data

Sublimation pressures and sublimation enthalpies of acetanilide at different temperatures were measured using the transpiration method (for details see Refs. [37–40] and ESI).

Sublimation enthalpies of acetanilide derivatives at 298.15 K were calculated from their fusion enthalpies. For calculation of the sublimation enthalpy of 4-ethoxyacetanilide the solution enthalpy of ethoxybenzene in benzene was measured. Details on the calorimetric procedure are given in the ESI.

2.3. The solubility model

The acetanilides under study are solids in the considered temperature range. In order to predict solubility of the acetanilides in water, a thermodynamic expression based on a simplified solid-liquid equilibrium condition was applied. The solubility of acetanilide (or its derivative) i , expressed as its mole fraction at saturation in the aqueous phase x_i^{aq} is predicted by:

$$x_i^{aq} = \frac{1}{\gamma_i} \cdot \exp \left\{ \frac{\Delta_{cr}^l H_m^{T=T_{fus}}}{RT} \left(1 - \frac{T_{fus}}{T} \right) \right\} \quad (1)$$

The simplified equilibrium condition neglects heat-capacity effects, which have only a marginal influence for the mixtures and the temperature range considered in this work. Using heat capacity differences caused slightly increased solubility values predicted with PC-SAFT. Application of Eq. (1) requires the melting properties of the acetanilides i , i.e. the fusion temperature T_{fus} and the fusion enthalpy $\Delta_{cr}^l H_m$ at T_{fus} , respectively. The applicable temperature

Table 1

Sample provenance table and purity of the components after purification. SA = Sigma-Aldrich Co. LLC.

Compound	Supplier	Purification method	GC purity (mass fraction)
acetanilide	SA, 98%	fractional sublimation	0.999
ethoxybenzene	SA, 99%	—	0.999
benzene	Ekos-1, 99%	distillation	0.999

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