



Drug Discovery–Development Interface

Benzoic Acid and Chlorobenzoic Acids: Thermodynamic Study of the Pure Compounds and Binary Mixtures With Water

Thomas Reschke¹, Kseniya V. Zherikova², Sergey P. Verevkin^{3,4,5}, Christoph Held^{1,*}¹ Laboratory of Thermodynamics, Department BCI, Technische Universität Dortmund, D-44227 Dortmund, Germany² Nikolaev Institute of Inorganic Chemistry of Siberian Branch of Russian Academy of Sciences, 630090 Novosibirsk, Russia³ Department of Physical Chemistry, University of Rostock, D-18059 Rostock, Germany⁴ Department of Science and Technology of Life, Light and Matter, University of Rostock, D-18059 Rostock, Germany⁵ Department of Physical Chemistry, Kazan Federal University, 420008 Kazan, Russia

ARTICLE INFO

Article history:

Received 17 September 2015

Revised 15 December 2015

Accepted 18 December 2015

Available online 6 February 2016

Keywords:

solubility
thermodynamics
statistical thermodynamics
stability
drug interactions
activity coefficient
physicochemical properties
poorly water-soluble drugs

ABSTRACT

Benzoic acid is a model compound for drug substances in pharmaceutical research. Process design requires information about thermodynamic phase behavior of benzoic acid and its mixtures with water and organic solvents. This work addresses phase equilibria that determine stability and solubility. In this work, Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) was used to model the phase behavior of aqueous and organic solutions containing benzoic acid and chlorobenzoic acids. Absolute vapor pressures of benzoic acid and 2-, 3-, and 4-chlorobenzoic acid from literature and from our own measurements were used to determine pure-component PC-SAFT parameters. Two binary interaction parameters between water and/or benzoic acid were used to model vapor-liquid and liquid-liquid equilibria of water and/or benzoic acid between 280 and 413 K. The PC-SAFT parameters and 1 binary interaction parameter were used to model aqueous solubility of the chlorobenzoic acids. Additionally, solubility of benzoic acid in organic solvents was predicted without using binary parameters. All results showed that pure-component parameters for benzoic acid and for the chlorobenzoic acids allowed for satisfying modeling phase equilibria. The modeling approach established in this work is a further step to screen solubility and to predict the whole phase region of mixtures containing pharmaceuticals.

© 2016 American Pharmacists Association®. Published by Elsevier Inc. All rights reserved.

Introduction

Benzoic acid is of relevance in different industrial applications, especially in chemical industry and pharmaceutical industry. It is widely used as a platform chemical for organic substances applied in the fields of pharmaceuticals, fine chemicals, polymers, cosmetics, and foodstuffs.¹ The thermodynamic modeling of phase equilibria containing benzoic acid is crucial for designing and optimizing separation and purification processes. Crystallization can be considered the commonly used unit operation for separation

and purification of solids but also extraction is widely used. Crystallization and extraction processes require information about solubility of the solid as well as of the liquid-liquid equilibria (LLE) depending on the kind of solvent and temperature, respectively.

In the pharmaceutical industry, benzoic acid is used as a model compound for drug development.² The reason is mainly that many drugs contain benzene rings and carboxyl groups and the representative poor solubility in water that is a major concern in pharmaceutical research.^{3–7} In the pharmaceutical industry, solubility in different solvents is a decisive property. On the one hand, solubility data are required for production processes of pharmaceuticals.⁸ On the other hand, solubility determines the bioavailability (and therewith the effectivity) of a pharmaceutical. Solubility data of benzoic acid in different solvents are readily available at 298 K² and also at other temperatures.^{1,9–12} In the pharmaceutical industry and research, the approaches of Hildebrand and Scott¹³ and Hansen and Skaarup^{14,15} are most accepted to describe Gibbs energy-related properties (and thus solid-liquid phase equilibria [SLE]). Cosolvency models for the prediction of solubility have been reviewed by Jouyban.¹⁶ Besides the availability of such theoretical tools from

Abbreviations used: ARD, absolute relative deviations; C, Tian-Calvet microcalorimeter equipped with the Knudsen cell; K, Knudsen effusion method; LLE, liquid-liquid equilibria; PC-SAFT, Perturbed-Chain Statistical Associating Fluid Theory; T, transpiration method; VLE, vapor-liquid equilibria.

This article contains supplementary material available from the authors by request or via the Internet at [10.1016/j.xphs.2015.12.020](http://dx.doi.org/10.1016/j.xphs.2015.12.020).

* Correspondence to: Christoph Held (Telephone: +49-231-755-2086; Fax: +49-231-755-2572).

E-mail address: christoph.held@bci.tu-dortmund.de (C. Held).

pharmaceutical research, solubility has also been described using thermodynamic models, such as g^E models or equations of state. Promising thermodynamic models are Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT),^{17–19} Nonrandom Two-Liquid Segment Activity Coefficient (NRTL)-SAC,²⁰ or Conductor-like Screening Model Segment Activity Coefficient-SAC.²¹ The solubility of benzoic acid in water and in aqueous mixtures has further been described using models such as cubic-plus-association equation of state,¹¹ NRTL,¹² universal quasichemical (UNIQUAC),¹ and the Wilson model.¹

In the chemical industry, benzoic acid is present in many industrial processes. Benzoic acid is an intermediate in the toluene oxidation process (The Dow Chemical Company, 1955), in which it usually also undergoes further purification.²² Moreover, benzoic acid participates in hydrolysis of organic nitriles in presence of enzymes.²³ However, most of the published works focused on extraction unit operations, in which benzoic acid is extracted from aqueous solutions,^{24–27} or where benzoic acid was applied as an entrainer.²⁸ In the pharmaceutical research and industry, unstable phase regions have to be known for formulations.^{29–31} For all such applications, thermodynamic modeling of phase equilibria of water and/or benzoic acid mixtures is very important. The liquid-liquid and the vapor-liquid phase equilibria (VLE) of aqueous mixtures containing carboxylic acids have been often modeled with UNIQUAC functional-group activity coefficients,^{32,33} but a thermodynamic model presenting VLE or LLE for water and/or benzoic acid mixtures is not published to our knowledge.

In addition, the benzoic acid derivatives are of a practical and theoretical interest. In this work, we focus on the chloro-substituted benzoic acids. These compounds are used for the manufacture of sweeteners, anti-inflammatory pharmaceuticals, and fungicides or herbicides.³⁴ Compared to benzoic acid, information on experimental data and phase behavior modeling of chlorobenzoic acids is very restricted in the literature. Moreover, the experimental data sets on vapor pressures of chlorobenzoic acids need to be proved for internal consistency.³⁵

The main objective of this work is to develop a modeling strategy within the PC-SAFT framework to model phase equilibria of water and/or benzoic acid and water and/or chlorobenzoic acid mixtures. A special attention is given to the simultaneous modeling of VLE, LLE, and SLE using the same set of model parameters. This modeling strategy is expected to be transferable to other aqueous mixtures containing aromatic carboxylic acids.

Materials and Methods

Materials

Commercial sample of 4-chlorobenzoic acid (Sigma-Aldrich, 99%) was further purified by the fractional sublimation in vacuum. Differential scanning calorimetry and gas chromatography equipped with flame ionization detector were used to determine the degree of purity. No impurities greater than 0.002 (in mass fraction) could be detected in 4-chlorobenzoic acid used for the vapor pressure measurements.

Vapor Pressure Measurements

Vapor pressures of 4-chlorobenzoic acid at different temperatures were measured using the transpiration method.³⁶ About 0.5 g of solid 4-chlorobenzoic acid was dissolved in acetonitrile and mixed with small glass beads in a glass beaker. Acetonitrile was evaporated from the beaker under vigorous stirring with a spatula and a gentle heating, producing glass beads coated uniformly with 4-chlorobenzoic acid. These coated glass beads were placed in a thermostatted

U-shaped saturator. A well-defined stream of nitrogen gas was passed through the saturator at a constant temperature (controlled to within 0.1 K), and the transported material was collected in a cold trap. The amount of condensed sample was determined by weighing with microbalances with a 0.0001 g resolution. The absolute vapor pressure p_i at each temperature T was calculated from the amount of the product collected within a definite time period. Applying Dalton's law to the nitrogen stream saturated with the substance i , values of p_i were calculated with Equation 1 as follows:

$$p_i = m_i \times R \times T_a / V \times M_i; \quad V = V_{N_2} + V_i; \quad (V_{N_2} \gg V_i), \quad (1)$$

where $R = 8.314462 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$; m_i is the mass of the transported compound; M_i is the molar mass of the compound; V_i is the volume contribution to the gaseous phase; V_{N_2} is the volume of the carrier gas; and T_a is the temperature of the soap bubble meter used for measurement of the gas flow. The volume of the carrier gas V_{N_2} was determined from the flow rate and the time measurement. Experimental results are given in Table 1. The standard uncertainties (u) of the measured vapor pressures have been calculated to be as follows:

$$u(p/p_a) = 0.005 + 0.025(p/p_a) \text{ for } p < 5 \text{ Pa} \quad (2a)$$

$$u(p/p_a) = 0.025 + 0.025(p/p_a) \text{ for } 5 \text{ Pa} < p < 1000 \text{ Pa} \quad (2b)$$

To validate system operation, the vapor pressures of naphthalene and benzoic acid^{37,38} were determined at $p = 1 \text{ Pa}$ to 500 Pa . Experimental vapor pressures of naphthalene and benzoic acid obtained using transpiration agreed with the results reported in the literature^{37,38} to within 0.5% to 2.5%.

PC-SAFT

The Model

To model the phase behavior of benzoic acid and 2-, 3-, and 4-chlorobenzoic acid, PC-SAFT was applied. It was proposed by Gross and Sadowski³⁹ in 2001 and allows modeling the residual Helmholtz energy a^{res} as function of particle number N , volume V , and temperature T , and therewith both volumetric properties and thermodynamic equilibria of pure fluid and mixtures.

$$a^{\text{res}} = a^{\text{hc}} + a^{\text{disp}} + a^{\text{assoc}} \quad (3)$$

According to Equation 3, a^{res} is composed of the repulsive hard chain contribution a^{hc} of the reference fluid and the attractive dispersive and associative contributions, a^{disp} and a^{assoc} , respectively. The exact derivation of these contributions can be found in the original theories from Barker and Henderson⁴⁰ and Wertheim.^{41,42} The modeling of a nonassociating pure component in PC-SAFT requires 3 pure-component parameters, namely the number of segments in the hard chain m^{seg} , the diameter of each segment σ_i , and the dispersion-energy parameter u_i . For components that are capable of hydrogen bonding, 2 additional pure-component parameters are required, the association-energy parameter $\epsilon^{A_i B_i}$ and the association-volume parameter $\kappa^{A_i B_i}$.

To allow modeling multicomponent systems, segment diameter and dispersion-energy parameter between 2 unlike molecules i and j are derived from the arithmetic and geometric-mean rules according to Berthelot and Lorentz:

$$\sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j) \quad (4)$$

$$u_{ij} = \sqrt{u_i u_j}(1 - k_{ij}) \quad (5)$$

Download English Version:

<https://daneshyari.com/en/article/2484545>

Download Persian Version:

<https://daneshyari.com/article/2484545>

[Daneshyari.com](https://daneshyari.com)