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

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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.


## 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 K[2] and also at other temperatures.[1,9-12] In the pharmaceutical industry and research, the approaches of Hildebrand and Scott[13] 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.

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