Prediction of solubilities for ginger bioactive compounds in hot water by the COSMO-RS method

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Abstract. The solubilities in water of four main ginger bioactives, 6-gingerol, 6-shogaol, 8-gingerol and 10-gingerol, were predicted using a conductor-like screening model for real solvent (COSMO-RS) calculations. This study was conducted since no experimental data are available for ginger bioactive solubilities in hot water. The σ-profiles of these selected molecules were calculated using Gaussian software and the solubilities were calculated using the COSMO-RS method. The solubilities of these ginger bioactives were calculated at 50 to 200 °C. In order to validate the accuracy of the COSMO-RS method, the solubilities of five hydrocarbon molecules were calculated using the COSMO-RS method and compared with the experimental data in the literature. The selected hydrocarbon molecules were 3-pentanone, 1-hexanol, benzene, 3-methylphenol and 2-hydroxy-5-methylbenzaldehyde. The calculated results of the hydrocarbon molecules are in good agreement with the data in the literature. These results confirm that the solubilities of ginger bioactives can be predicted using the COSMO-RS method. The solubilities of the ginger bioactives are lower than 0.0001 at temperatures lower than 130 °C. At 130 to 200 °C, the solubilities increase dramatically with the highest being 6-shogaol, which is 0.00037 mole fraction, and the lowest is 10-gingerol, which is 0.000039 mole fraction at 200 °C.

1. Introduction
Recently, various alternative and green solvents, such as sub- and supercritical water or fluids have been developed in order to substitute common solvents that have a high level of toxicity. Hot water or subcritical water is an alternative green solvent that has been developed and applied in the extraction process of natural and medicinal plants. This shows that the properties of water have high potential to be discovered, for example, the dielectric constant and viscosity of water. Water is the most abundant,
safe, cheap and environmentally friendly pure solvent. Because of this, water seems to be one of crucial importance for further development of the chemistry of subcritical and supercritical fluids [1].

The current study, which was done by Sarip [2] for ginger using subcritical water extraction, indicates that the extracted bioactives by water depend on the temperature of the process. For example, at 135°C, the bioactive extracted was just 6-gingerol. Whereas, when the extraction was carried out at 165 and 200°C, more bioactives, such as 6-shagaol and 10-gingerol, were extracted. These temperature conditions are a function of the dielectric constant, which reduces as the temperature elevates [3].

The equilibrium and transport properties, such as solubility and diffusion coefficient, are very useful for process design [4]. In order to establish the feasibility of an extraction, the solubility of a substance is a fundamental property [5]. There are four main components of ginger bioactives, which are 6-gingerol, 6-shagaol, 8-gingerol and 10-gingerol. The identification technique of ginger bioactives are well established, so these can be the reference to validate the extraction process using water as the solvent at subcritical conditions or at lower dielectric constant properties. However, physical properties of the bioactives for engineering application such as solubility and diffusivity in solvents are not published.

The activity coefficient is a basic physical-property value needed for the design of separation equipment [6]. The COSMO-RS method [7-8] has the capability of predicting the thermo-physical properties of liquids, such as activity coefficients from a statistical approach by quantum calculations without experimental data, based on a unimolecular quantum chemical calculation, which is an alternative to the structure-interpolating group contribution methods (GCMs). Basically there are two steps for the COSMO-RS calculations standard method: first, to calculate the quantum chemical COSMO for the molecular species involved by extracting the information about the solutes and solvents, and, second, to perform the COSMO-RS statistical calculations with the COSMOtherm program [7-9].

In this work, the COSMO-RS method was applied for the calculation of the activity coefficients for the binary mixtures. NRTL (Non-Random Two-Liquid) was used to fit the activity coefficients calculated by the COSMO-RS method. The interaction parameters in NRTL equation were determined from the calculated activity coefficients by using the COSMO-RS method. The liquid-liquid equilibria (LLE) were calculated by NRTL. Then the solubilities were obtained from LLE. The solubilities of binary mixtures for hydrocarbon + water systems were calculated and compared with the data in the literature. The calculated results are in good agreement with the experimental data. The solubilities of ginger bioactive compounds in water for the binary systems were then predicted.

2. Calculation Method

2.1. Computational Programs:
The predictions of solubilities were carried out using the software package COSMOtherm version 3.2 (COSMOlogic GmbH & Co KG, Leverkusen, Germany) and Gaussian software package version 3.09 (GausView, Gaussian, Inc. USA).

2.2. Calculation Procedures

2.2.1. The calculations were performed on the Density Functional Theory (DFT) level using Gaussian software for each molecule to obtain the COSMO input files for water, hydrocarbon and ginger bioactive molecules. In these calculations, a charge density $\sigma$ of a segment on the molecular surface was calculated in a virtual conductor. The ideally screened molecule energy with screening charge distribution on the surface was used as the database for COSMO files.

2.2.2. The distribution function $P_i(\sigma)$ of the obtained $\sigma$ (figure 1), which is called $\sigma$-profile, for each molecule can give the $\sigma$-profile of the mixture $P(\sigma)$ by using $P_i(\sigma)$ and the mole fraction $x_i$ of component i in the mixture [8, 12]. Detailed equations and the method of calculation have been
described by Shimoyama et al., [12]. The σ-profiles and σ-potential for each molecule were calculated with the COSMOtherm program. The activity coefficients for the binary systems were predicted using the COSMO-RS calculation.

![Figure 1. Schematic illustration of contacting molecular cavities and contact interaction. Source: Klamt & Eckert [8].](image)

2.2.3. The activity coefficients were fitted with the NRTL model and the binary parameters in NRTL were obtained. The equality of activities between the two liquid phases in LLE is written as follows:

\[ x_i^I \gamma_i^I = x_i^II \gamma_i^{II} \]  

(1)

where \( \gamma \) is the activity coefficient, and superscripts I and II mean phases I and II, respectively [10]. The LLE was calculated using the NRTL model. The solubilities were obtained from the LLE. The COSMO-RS calculations standard method [8] was applied in this research and modified to obtain the solubilities of the molecules from the LLE diagram. Figure 2 shows the flowchart for the calculation of solubilities.

![Figure 2. Flowchart of solubility prediction from COSMO-RS](image)
3. Results and Discussion

3.1. Validation of Calculated Results.

Since no experimental data for ginger bioactives are available, the calculations were done part-by-part for the smaller parts of the ginger bioactives. 3-pentanone was selected as it has double O bonding, 1-hexanol has –OH in the formula structure, benzene has ring structure, while 3-methylphenol and 2-hydroxy-5-methylbenzaldehyde have –OH and –CH3 connected to the ring structures. Table 1 shows the properties of the selected hydrocarbon molecules. These five hydrocarbon molecules were selected because they have a similar formula structure of smaller parts of ginger bioactives and the experimental data are available to prove the reliability of the COSMO-RS method. The solubilities of the selected hydrocarbon molecules in five binary systems were then calculated with COSMO-RS and compared with the experimental data, which were 3-pentanone in water, 1-hexanol in water, benzene in water, 3-methylphenol in water, and 2-hydroxy-5-methylbenzaldehyde in water.

Table 1. Hydrocarbon molecules selected properties.

| Product Name | 3-pentanone | 1-hexanol | benzene | 3-methylphenol | 2-hydroxy-5-methylbenzaldehyde |
|--------------|-------------|-----------|---------|----------------|-----------------------------|
| Formula structure | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) | ![Image](image5.png) |
| Molecular Weight | C5H10O | C6H14O | C6H6 | C7H8O | C8H8O2 |
|                | 86.13 | 102.17 | 78.11 | 108.14 | 136.15 |

3.1.1. σ-profiles

Figure 3 shows the σ-profiles and COSMO-cavities of six selected compounds. The σ-profile of water is very broad, almost symmetric, with two peaks from both the negative and positive side, which are around -0.016 e/A^2 and +0.018 e/A^2, resulting from the two polar hydrogen and lone pair of oxygen atoms, respectively. This σ-profile of water was the same as reported by Zhou et al. [11] and almost the same as the results reported by Klant [8].

The interaction energies were determined by the screening charge density σ. The notation of “σ-profile” is used to describe the distribution ps(σ), which describes the amount of surface in the ensemble having a screening charge density between σ and σ+dσ. Regarding the definition of the σ-profile, there are two important σ-moments related to the hydrogen bonds that represent the capability of hydrogen bond (HB) donor (-) and acceptor (+) [8, 11]. A molecule is polar enough if the charge density goes beyond ±0.008 e/A^2. The σ-profile of 1-hexanol is narrowed in the middle region due to non-polar character with the peak being -0.003 e/A^2, which is different to 2-hydroxy-5-methylbenzaldehyde, benzene and 3-methylphenyl, which have quite a symmetric σ-profile and are less broad than water. They also show no intensity in both the hydrogen bonding regions, which is beyond ±0.01 e/A^2.
Figure 3. $\sigma$-profiles of selected hydrocarbons and COSMO-cavities [red:- positive surface screening charges resulting from negative partial charges within molecule, blue:-negative surface charges and green:-neutral charges]

3.1.2. LLE phase diagram for solubilities of hydrocarbons in water

The calculated results from the COSMO-RS method are compared to experimental data for the selected binary systems as shown in figures 4 to 8. Figure 4 shows the comparison of experimental data and calculated results at temperature 20-120 °C, for the solubilities of 3-pentanone in water where the trend of the data almost same and really close to each other with average percentage of difference is 9%. In figure 5, there about 4% difference between experimental data and calculated results for the solubilities of 1-hexanol in water at temperature 20-110 °C. Figure 6 shows the solubilities of benzene in water the percentage of difference is about 19.27% for the temperature 0-80 °C. While the solubilities of 3-methylphenol in water show about 22.85 % difference between experimental data and calculated results. However, in figure 8, the percentage of difference for the solubilities of 2-hydroxy-5-methylbenzaldehyde in water is about 59.11% which is high maybe because less of experimental data are available to compare.

Figure 4. Solubilities of 3-pentanone (1) in water (2).
Figure 5. Solubilities of 1-hexanol (1) in water (2).

Figure 6. Solubilities of benzene (1) in water (2).

Figure 7. Solubilities of 3-methylphenol (1) in water (2).
The results show that the trends of experimental data and calculated results are almost the same for the binary system. The agreement between the experimental and calculated results in this study is not perfect, but it is satisfactory. In addition, a few papers reported that the calculated and experimental results are in good agreement when using COSMO-RS to predict the thermophysical properties of certain compounds [9, 12-14].

3.2. Calculated Results for Solubilities of Ginger Bioactives in Water.
The solubilities of four main components of ginger bioactives were calculated at 50 to 200 °C where the ginger bioactives are in liquid form at this range of the temperature. Additionally, this range of temperature was selected in order to compare with the Subcritical Water Extraction (SWE) of ginger bioactives, which was done by Sarip [2], and in consideration of the operational cost if higher temperatures were applied as well as the stability of the ginger bioactive itself from the degradation. Table 2 shows the formula structures and molecular weights of four main ginger bioactive compounds. The solubilities of these ginger bioactives in water were calculated separately in the binary systems which were 6-gingerol in water, 6-shogaol in water, 8-gingerol in water, and 10-gingerol in water using COSMO-RS method.

Table 2. Ginger Bioactive properties

| Product Name | 6-Gingerol | 6-Shogaol | 8-Gingerol | 10-Gingerol |
|--------------|------------|-----------|------------|-------------|
| Formula structure | ![Structure](image1) | ![Structure](image2) | ![Structure](image3) | ![Structure](image4) |
| Formula Molecular Weight | C_{17}H_{26}O_{4} | 294.39 | C_{17}H_{24}O_{4} | 276.37 |
| | | | C_{19}H_{30}O_{4} | 322.44 |
| | | | C_{21}H_{34}O_{4} | 350.49 |

3.2.1. \( \sigma \)-profiles
The \( \sigma \)-profiles and COSMO-cavities of four ginger bioactive compounds and water are shown in figure 9. The \( \sigma \)-profile of water is used as the reference for comparison with the previous results. The \( \sigma \)-profile for each compound of ginger bioactives is almost the same, which is narrow in the middle
region. 10-Gingerol has the highest peak among the compounds. The σ-profile of 10-gingerol is almost the same as 1-hexanol, as shown in figure 3. This σ-profile shows the molecular polarization or interactions [11]. They show that there is no electrostatic moment or non-polar character in the main parts of the ginger bioactives. However, all the ginger bioactives have a peak beyond +0.01 e/Å², which represents the presence of the hydrogen bond. All the ginger bioactives show a higher screening charge density, which is in the region of HB acceptor region rather than the HB donor region.

![Figure 9. σ-profiles of ginger bioactives and COSMO-cavities](image)

3.2.2. LLE phase diagram for solubilities prediction of ginger bioactives in water.

The solubility for each ginger bioactive compound was calculated separately in the binary systems (6-gingerol in water, 6-shogaol in water, 8-gingerol in water and 10-gingerol in water). The calculated results of the solubilities for ginger bioactives are plotted in the LLE phase diagram for comparison, as shown in figure 10. These solubilities of ginger bioactives were calculated from 50 to 200 °C. The solubilities of 6-gingerol and 6-shogaol are higher than those of 10-gingerol and 8-gingerol. This is because the molecular structures or molecular weights of 10-gingerol and 8-gingerol are bigger than those of 6-gingerol and 6-shogaol. The trends of solubilities for all ginger bioactives are almost the same. The solubilities of these ginger bioactives are very low being less than 0.0001 mole fractions when the temperature is below 130 °C. As the temperature increases from 130 to 200 °C, the solubilities of these ginger bioactives increase dramatically. The highest solubility obtained is from 6-shogaol, followed by 6-gingerol, 8-gingerol and 10-gingerol, which are 0.00037, 0.00029, 0.00007 and 0.00004 mole fraction, respectively, at 200 °C. Ginger bioactives are also sensitive to heat and will degrade as the temperature increases [2].
Figure 10. Solubilities for ginger bioactives (1) (6-shogaol, 6-gingerol, 8-gingerol and 10-gingerol) in water (2).

4. Conclusion
The solubilities of 6-gingerol, 6-shogaol, 8-gingerol and 10-gingerol were calculated with COSMO-RS in order to establish the feasibility of water as the solvent at high temperature with lower dielectric constant. The $\sigma$-profiles of 6-gingerol, 6-shogaol, 8-gingerol and 10-gingerol show that the compounds have the slight possibility of polar characteristic with the existence of hydroxide group in the structure. The molecules interaction and polarization are also shown in $\sigma$-profile. The COSMO-RS method can be used to calculate the LLE phase diagram. The solubilities of these ginger bioactives increase dramatically after the temperature increase from 130 to 200 °C. This shows that at high temperature, the dielectric constant of water decreased and mimic the properties of common non-polar solvent in engineering application especially extraction. The solubilities of ginger bioactives in hot water can be predicted with COSMO-RS method without extensive experimental work.

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