# Solvation of salicylic acid in pure, methanol-modified and water-modified supercritical carbon dioxide: Molecular dynamics simulation

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## ABSTRACT

In the present work, solvation of the salicylic acid in pure, methanol-modified and water-modified (by adding 0.035 methanol or 0.0079 water mole fraction) supercritical carbon dioxide (sc-$CO_2$) at 318 K and 0.7 g/cm$^3$ has been studied by computer simulation techniques. It was shown that solvation of salicylic acid in pure sc-$CO_2$ is governed by electron donor–acceptor interactions and proceeds more slowly than in modified sc-$CO_2$, where salicylic acid forms solvate complex with co-solvent by means of hydrogen bonding through carboxyl group. Salicylic acid hydroxyl group participates only in intramolecular hydrogen bond and does not interact with solvent molecules. The salicylic acid–co-solvent complexes are stable: the duration of their existence is much higher than lifetime of other hydrogen bonds in the fluid. The behavior of two co-solvents is different: methanol exists in the form of monomers and hydrogen-bonded dimers in the supercritical fluid, the water molecules tend to form microclusters with spatially-branched structure.

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## 1. Introduction

Modern supercritical fluid technologies are effective and eco-friendly alternatives to the "traditional" methods of extraction, separation, purification and micronization of some pharmaceutical products. One of such compounds, salicylic acid is widely being used as a key ingredient in the number of anti-inflammatory, antipyretic, analgesic, antiseptic drugs and so on. Traditional methods of treatment of salicylic acid and its derivatives use toxic reagents and solvents, which requires complex purification stage. Thus, application of supercritical fluid technologies is thought to be attractive way for "green" processing of salicylic acid.

During the last decades, numerous experimental works on solubility of salicylic acid in pure and modified with polar co-solvents supercritical carbon dioxide (sc-$CO_2$) have been carried out [1–12]. Only few works were devoted to simulation of more complex fluid mixtures containing salicylic acid [13–15], in which little attention was paid to molecular aggregation phenomena, such as cluster formation, while solvation mechanisms were not investigated at all.

Here, we report study of salicylic acid solvation in pure and modified (with 0.035 methanol mole fraction and 0.0079 water mole fraction) sc-$CO_2$ at 318 K and 0.7 g/cm$^3$. Methanol is one of the most commonly used co-solvents. As for water, it is attractive modifier from the point of view of the Green Chemistry [16–18]. In recent years the possibility of water use as co-solvent has been widely investigated [19–21] despite its little miscibility with the sc-$CO_2$ at relatively low temperatures. Interpolation of the data obtained for 313 and 323 K [22] to the studied region of the phase diagram reveals that the solubility of water in the sc-$CO_2$ at 318 K and 0.7 g/cm$^3$ is not more than 0.008 mol fraction. Obtained results can be useful for adjustment of parameters of supercritical fluid extraction and related technological processes.

The process of dissolution of the solids is accompanied by destruction of its crystal lattice, the weakening of intermolecular interactions, solvation of the solute molecules and the emergence of interactions with the solvent. The study of crystalline structure of salicylic acid [23] has shown that salicylic acid molecules form cyclic dimers (Fig. 1) via hydrogen bonding between carboxyl groups (O3—H2···O2′ and O3′—H2′···O2). Salicylic acid dimers in crystal are not bound to each other with hydrogen bonds (HBs) since hydroxyl groups form intramolecular HBs with carbonyl oxygen atoms (O1—H1···O2 and O1′—H1′···O2′). Thus, molecular dynamics study of the dissociation process of hydrogen-bonded
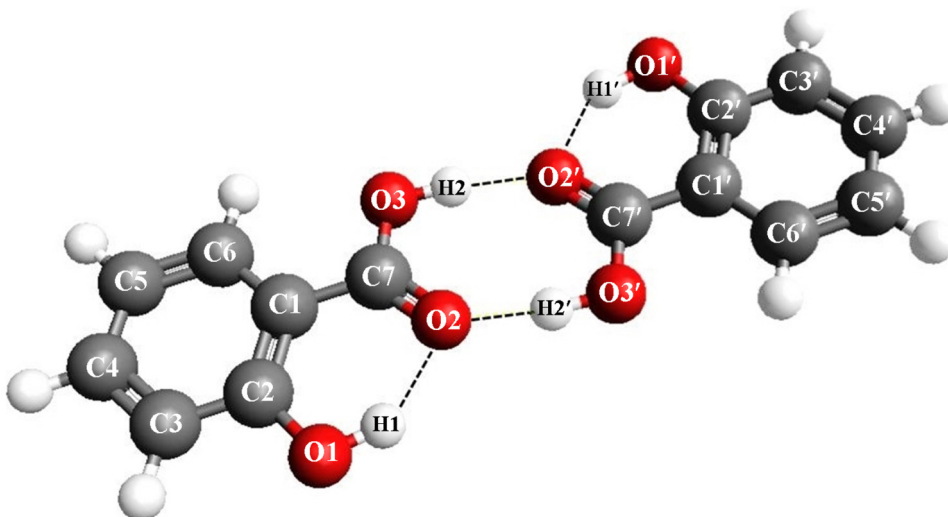
**Fig. 1.** Optimized structure of salicylic acid dimer used asinitial configuration in furthercomputer simulation studies.

salicylic acid dimer and the formation of solvates in supercritical fluid can provide sufficiently realistic information about the mechanism of salicylic acid dissolution and solvation at the model level.

## 2. Computer simulation

### 2.1. Simulation of the salicylic acid dimer

Using density functional theory (DFT) techniques and CPMD-3.13.2 software [24], we obtained optimized structure of salicylic acid monomer and dimer. The BLYP functional [25,26] was used to treat the exchange-correlation interaction between electrons. The interaction between the core and valence electrons was described by ultrasoft pseudopotential in the Vanderbilt form [27] with a plane wave cutoff of 25 Ry. The Brillouin zone was sampled at the $\Gamma$-point only. The length of cubic box was set 40 Å. Calculated structural parameters of salicylic acid molecule in monomeric and dimeric form are given in the Table 1. As can be seen HBs formation between salicylic acid molecules results in increase in C7=O2 and O3—H2 bond lengths by 0.02 Å and reduction in C7—O3 bond length by 0.04 Å. The increase in O2···H1 distance by 0.015 Å and reduction in O2···H1—O1° by 0.7° indicates insignificant deformation of the intramolecular HBs in the dimer compared with the monomeric form of the salicylic acid.

Noting the good agreement of calculated parameters with known literature data [16,28–30] (Table 1), we can conclude that

obtained geometry configuration of salicylic acid dimer is correct and can be used in further simulation of ternary systems.

### 2.2. Simulation of salicylic acid solvation in supercritical fluids

The study of salicylic acid solvation in pure and modified sc-$CO_2$ was performed by classical molecular dynamics simulation method implemented in Gromacs-4.5.4 software [31]. The first step was to simulate the pure and binary solvents: three cubic boxes with periodic boundary conditions were created. They contained:

4627$CO_2$ molecules,

4627$CO_2$ molecules and 168 methanol molecules (0.035 mol fraction of methanol),

4627$CO_2$ molecules and 37 water molecules (0.0079 mol fraction of water).

The box length corresponded to density 0.7 g/cm³, the temperature was taken to be 318 K. Equilibration run was 500 ps. EPM2 [32] potential model was adopted for $CO_2$, SPC/E [33] potential model – for water, while potential for methanol was derived from OPLSAA force field [34]. Here and below, we introduce the notation: I – $CO_2$, II – co-solvent, III – salicylic acid.

The second step was the simulation of the ternary systems. Optimized salicylic acid dimer was placed into the equilibrated boxes containing the pure or the binary supercritical solvent. Production run was 500 ps with time step 1 fs. Data were recorded in the log file over each interval of 0.1 ps. The averaging was carried out by

**Table 1**
Structure parameters of salicylic acid molecule (interatomic distances in Å and angles in degrees) in salicylic acid monomeric, dimeric and crystalline forms.

| Distancesand angles | DFT calculations | | | Experiment | |
| --- | --- | --- | --- | --- | --- |
| | Monomer This work | Dimer This work | Monomer B3PW91/aug-cc-pVDZ [23] | Cristal Neutron diffraction[28,29] | X-ray diffraction [30] |
| C7—O3 | 1.380 | 1.340 | 1.346 | 1.300 | – |
| C7—O2 | 1.250 | 1.270 | 1.231 | 1.231 | – |
| C2—O1 | 1.360 | 1.385 | 1.339 | 1.360 | – |
| O3—H2 | 0.980 | 1.020 | 0.969 | 0.986 | 0.910 |
| O1—H1 | 1.000 | 1.000 | 0.988 | 0.954 | 0.960 |
| O2···H1 | 1.730 | 1.745 | 1.704 | 1.766 | 1.770 |
| O2···O1 | 2.630 | 2.630 | 2.593 | 2.608 | 2.621 |
| O3—C7—O2 | 120.2 | 120.2 | 120.7 | 121.0 | – |
| O2—C7—C1 | 124.7 | 122.2 | 124.3 | 123.0 | – |
| C7—C1—C2 | 118.7 | 121.7 | 118.5 | 119.7 | – |
| C1—C2—O1 | 122.6 | 122.2 | 122.5 | 122.8 | – |
| H2—O3—C7 | 106.3 | 107.5 | 106.3 | 112.4 | – |
| O2···H1—O1 | 146.7 | 146.0 | 147.8 | 145.4 | 146.0 |