Salicylic acid, acetylsalicylic acid, methyl salicylate, salicylamide, and sodium salicylate in supercritical carbon dioxide: Solute – cosolvent hydrogen bonds formation

Valentina E. Petrenko *, Marina L. Antipova, Darya L. Gurina

G.A. Krestov Institute of Solution Chemistry of the Russian Academy of Sciences, Akademicheskaya str., 1, Ivanovo 153045, Russia,

ARTICLE INFO

ABSTRACT

Solvate structures of salicylic acid and its derivatives (acetylsalicylic acid, methyl salicylate, salicylamide, and sodium salicylate) in supercritical carbon dioxide modified by polar cosolvent (methanol, 0.03 mol fraction) at density of 0.7 g/cm^3 and temperature of 318 K were studied by means of molecular dynamics simulations. It was found that salicylic and acetylsalicylic acids form stable hydrogen-bonded complexes with methanol through hydrogen atom of the carboxyl group. In methyl salicylate molecule the carboxyl hydrogen is substituted by methyl radical, that is why strong hydrogen bonds with methanol are not typical for it. Salicylamide is able to form hydrogen bonds with methanol through several functional groups (preferably as proton donor), but their probability and lifetimes are lower than those for salicylic acid – methanol and acetylsalicylic acid – methanol hydrogen bonds. The continuous rearrangement of salicylamide solvation shell due to forming and breaking solute – cosolvent hydrogen bonds was observed. Sodium salicylate is in the form of undissociated ion pair in supercritical carbon dioxide, despite the presence of a polar co-solvent, but it is characterized by very high selective solvation. It is able to form hydrogen bonds with several (up to 6) methanol molecules simultaneously. Unlike other compounds considered, it forms highly stable hydrogen bonds as a proton acceptor.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

The phenomena of solvation of salicylic acid (SA) and its derivatives in supercritical media are of considerable interest caused by development of perspective supercritical technologies for pharmaceutical industry as well as ongoing fundamental research on the effect of the type and location of functional groups on the solubility of chemical analogs and role of specific solute – cosolvent interactions in the solvation process.

Solubility of SA and its derivatives in supercritical carbon dioxide (sc-CO$_2$) was the subject of numerous experimental studies [1–17]. It was found that the solubility of SA and acetylsalicylic acid (ASA) in the presence of polar cosolvents (acetone, low molecular weight alcohols) is increased by several times [1,2,4,9,12–14]. This was assumed to be due to formation of solute – cosolvent hydrogen bonds (HBs). In [15–17] the data on solubility of methyl salicylate (MS) and salicylamide (SAm) in pure sc-CO$_2$ in a wide range of thermodynamic states were reported, whereas information about the

cosolvent effect is absent. It can be assumed, that the temperature and pressure are the only effective factors to regulate the MS and SAm solubility, and cosolvent addition is not considered expedient. We will try to reveal the causes of this phenomenon based on a comparative analysis of solvated structures and intermolecular interactions. As for sodium salicylate (SodS), we did not find in the literature data on its solubility, although there are studies of chemical processes with its participation in sc-CO$_2$ environment. [18].

In the present study, we investigate solute (SA, ASA, MS, SAm, SodS) – cosolvent (methanol, 0.03 mol fraction) interactions in sc-CO$_2$ at T = 318 K and ρ=0.7 g/cm^3 by means of computer simulations. The data for the SA, ASA and MS were obtained earlier [19], the results of simulation of SAm and SodS are published for the first time.

The distribution of cosolvent molecules around the solute, probability and mechanisms of hydrogen-bonded complexes and solvated shells formation as well as HBs lifetimes are discussed. Features of the selective solvation related to the nature of the functional groups of the solutes are analyzed on the basis of the results obtained.

* Corresponding author.
  E-mail address: vep@isc-ras.ru (V.E. Petrenko).

2. Simulation details

Molecular dynamics simulations were performed with Gromacs-4.5.4 software package [20] in the NVT ensemble. A cubic simulation box with periodic boundary conditions contained 4627 CO_2, 143 methanol and 1 solute (SA, ASA, MS, SAm, SodS) molecule. The Nosé-Hoover thermostat was employed to maintain constant temperature [21,22]. Verlet algorithm [23] was adopted to integrate the equations of motion for the whole system. Modified Ewald summation method [24,25] was used to account for corrections of the long-range electrostatic interactions. LINCS algorithm [26] was used for bond length constraints.

The initial geometry of solute molecules was obtained by optimization using density functional theory with the pseudopotential theory and plane-wave basis set, realized in the software package CPMD-3.13.2 [27]. Exchange-correlation functional BLYP [28,29], Vanderbilt and Goedeker pseudopotentials [30] with the cutoff-energy of the plane waves of 80 Ry were chosen. To avoid the influence of periodic images the cubic cell edge length of 25 Å was chosen.

It was found that SodS in an optimal configuration is an ion pair (Figs. 1 and 2). There was a question whether it is dissociated into ions in the methanol-modified sc-CO_2. To test this, two simulations were carried out. In the first one SodS was placed in a cell as an ion pair. Dissociation and the diffusion of the ions in the volume of fluid were not observed. In the second simulation salicylate ion and sodium ion were placed in the cell being separated by a large amount of solvent. From the first step of equilibration ions began to move closer to each other, and eventually formed the ion pair. The simulation results of both systems after reaching the equilibrium were identical. Thus, it was found that SodS in sc-CO_2 medium is in form of undissociated ion pair, despite the presence of a polar cosolvent. Potential model which reproduces CO_2 critical parameters in the best way was used for CO_2 molecule [31]. Potentials based on the parameters of the OPLSAA force field [32] were used for methanol, SA and its derivatives.

Equilibration time of binary CO_2 – methanol mixture was 500 ps. The length of the cubic box edge corresponded to density of 0.7 g/cm^3, and temperature was 318 K. After equilibration, one solute molecule was inserted into simulation box. The length of the box edge was again corrected to maintain density equal to 0.7 g/cm^3. Equilibration of ternary systems then was carried out for 500 ps. The product simulation time was from 500 to 1000 ps with a time step of 1 fs. The data were collected each 0.1 ps for further analysis.

3. Results and discussion

Localization of solvent (I) and cosolvent (II) molecules around functional groups of the solute (III) can be determined on the basis of atom–atom radial distribution functions (RDFs) g(r). Furthermore, the behavior of oxygen – hydrogen RDF at r ≤ 2.6 Å (r = 2.6 Å is threshold value for intermolecular OH distance adopted in the HB criterion used in this work) allows to qualitatively estimate the probability of solute – cosolvent HB formation.

The RDFs H(III)O(II) and O(III)H(II), which are shown in Fig. 1 and 2, demonstrate that high localization of methanol at distances r ≤ 2.6 Å is observed only in the vicinity of the hydrogen atom H2 of SA and ASA carboxyl groups, hydrogen atoms H3 and H4 of SAm amide group, hydrogen atom H1 of SodS hydroxyl group and oxygen atoms O2 and O3 of SodS carboxyl group. The probability of hydrogen bonding with methanol is significantly higher for SA and ASA than for SAm. At the same time, it is much higher for the ionic compound SodS, than for other solutes. Also the localization of cosolvent hydrogens at the ion Na$^+$ is characteristic for SodS. Aver-

Table 1
Average numbers n_{HB} of HBs formed by O and H atoms (see Fig. 1, 2) of solute (III) with cosolvent (II), and total (average for solute molecule) HBs number n_{HB}(III–II) in the sc-CO_2.

Solute n_{HB}		SA [19]	ASA [19]	MS [19]	SAm	SodS
H(III)O(II)	H1(III)O(II)	0.00	–	0.00	0.00	0.72
	H2(III)O(II)	0.91	0.97	–	–	–
	H3(III)O(II)	–	–	–	0.33	–
	H4(III)O(II)	–	–	–	0.40	–
O(III)H(II)	O1(III)H(II)	0.06	0.00	0.07	0.11	0.25
	O2(III)H(II)	0.03	0.06	0.02	0.17	1.49
	O3(III)H(II)	0.01	0.00	0.00	–	1.77
	O4(III)H(II)	–	0.07	–	–	–
n_{HB}(III–II)		1.01	1.10	0.09	1.01	4.23

age coordination number calculated by integrating RDF Na(III)O(II) to a 1st minimum [33] is 3.96.

The first peak in RDFs O3(III)H(II) and N(III)H(II) for SA, ASA and SAm is observed at r > 3 Å which indicates that methanol molecules are located around corresponding hydrogen atoms and not directly around carboxyl oxygen O3 or nitrogen N. Hydroxyl hydrogens H1 of SA, MS and SAm molecules are engaged in intramolecular HB O1–H1...O2 therefore they do not participate in hydrogen bonding with cosolvent. The fact that the hydroxyl hydrogen H1 of SodS, unlike molecular compounds, forms HB with methanol, demonstrates that there is no intramolecular HB in salicylate-ion.

SodS is characterized by a clear localization of a cosolvent around oxygen atoms, indicating the existence of strong HBs, whereas the picture is different for other solutes. The RDFs O2(III)H(II) of ASA and SAm have small yet clearly defined peaks at r ≤ 2.6 Å, indicating formation of HB, in which methanol acts as proton donor and carbonyl oxygen O2 as proton acceptor. In the case of SAm the probability of existence of such HB is quite high, despite the fact that the atom O2 is engaged in intramolecular HB. It is due to the proximity of the amide hydrogens forming unstable HBs with methanol. For SA and MS, which also have intramolecular HBs, these peaks are considerably lower, as in case of SA methanol molecules are distinctly localized near the carboxyl hydrogen H2, while for MS such localization of methanol molecules is not typical at all. ASA have not intramolecular HB, and the peak in the RDF O2(III)H(II) is comparable in height with the peak in the RDF O4(III)H(II). This indicates that the probabilities of formation of HB with cosolvent via both carbonyl oxygens O2 and O4 are similar. As it is evident from the behavior of the RDF O1(III)H(II), ASA is not capable of forming HB with the cosolvent through the hydroxyl oxygen O1. In contrast, for SA, MS and SAm such HB is more probable than HBs through O2 and O3, because hydroxyl oxygens O1 of these compounds, unlike ASA, are more available for contact with cosolvent molecules.

The geometric criterion ($R_{O\cdots O} \leq 3.5$ Å, $R_{O\ldots H} \leq 2.6$ Å, $\angle HOO \leq 30°$) of HB was used for accurate estimation of HBs existence between the molecules. The results are listed in Table 1, in which n_{HB}(III–II) is the average number of HBs between solute and cosolvent in the modified sc-CO_2. The contributions of the individual atoms of the solute (Figs. 1 and 2) in the n_{HB}(III – II) were also determined. The results confirm that in the case of SA and ASA the stable HBs with methanol are formed only with the participation of the carboxyl hydrogen H2. Contribution of other functional groups of the solute in interaction with the cosolvent is much smaller. This preference indicates the existence of stable solvated complexes. HBs formation between MS and methanol is random and short-time. The average number of HBs formed by SAm molecule is comparable to that for SA and ASA, but the distribution of the HBs by functional groups is different: more than 70% are HBs formed by two hydrogen atoms of the amide group, and their contributions are unequal. The fraction of HBs formed by H4 atom which is distant from other functional groups (Fig. 1 and 2) is higher, while the neighborhood with the car-