Solvation of *para*-hydroxybenzoic acid and its esters (methylparaben, propylparaben) in supercritical carbon dioxide. Computer simulation

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ABSTRACT

The study of solvation structures formed by *para*-hydroxybenzoic acid (*p*-HBA) and its methyl (methylparaben, MP) and propyl (propylparaben, PP) esters in methanol-modified (0.03 mol fraction of methanol) supercritical carbon dioxide at the density of 0.772 g/cm^3 and the temperature of 328 K has been made using classical molecular dynamics. It is shown that the solvation occurs through the formation of stable hydrogen bonds between the solutes and the cosolvent. Changes in solvation mechanism depending on the alkyl substituent in the sequence of *p*-HBA – MP – PP are considered. For *p*-HBA a hydrogen bond via the carboxyl hydrogen is typical, and the probability of the formation of hydrogen bonds by the hydroxyl hydrogen is much smaller. In the case of MP and PP when carboxyl hydrogen is substituted by alkyl group, the hydrogen bonds via the hydroxyl hydrogen have a much greater probability of formation and existence duration. Besides, MP and PP, unlike *p*-HBA, have a high probability of forming hydrogen bonds with methanol as proton acceptor via carbonyl oxygen. This feature can provide an advantage of protic compounds such as low molecular weight alcohols, by selection of cosolvent to improve parabens solubility in supercritical CO$_2$.

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1. Introduction

Field of application of supercritical (SC) fluid technologies is continually expanding in the last decades. One of lots of directions is the use of SC fluid extraction for the quantitative determination of antioxidants and preservatives in cosmetic products for the purpose of safety control [1].

Parabens, including methylparaben (MP) and propylparaben (PP), are popular preservatives applied actually to all types of cosmetics, and to a lot of food and pharmaceuticals for inhibiting the growth of microorganisms. The advantages of parabens are the following: a broad range of activity, inertness and low cost. Their toxicity is considered to be low due to the rapid hydrolysis in vivo to the parent acid (*para*-hydroxybenzoic acid, *p*-HBA), which is rapidly conjugated and excreted.

Nevertheless, the question of the safety of using parabens remains unsolved. It was proved that they have a raised estrogenic activity, leading to the development of cancer [2]. Acceptable standards for the use of parabens are regularly reassessed and reduced. Nowadays, the maximum (total or individual) permissible

parabens concentration by European standards of 2014 is 0.0014 mass fraction, expressed as *p*-HBA. In order to protect consumer health quantification methods for simultaneous analytical monitoring are been developed for the proper use of antioxidants and preservatives in cosmetics. SC fluid extraction is applied as one of the most effective methods for the isolation of solutes from solid samples [1].

Parabens and *p*-HBA solubilities in SC CO$_2$ in various parts of phase diagram are studied in a series of publications [3–7]. Literature data for solubility at T = 328 K (the temperature at which three compounds were investigated: *p*-HBA, MP and PP) are compared illustratively in Fig. 1a. It is found that the parabens solubilities are 2 orders of magnitude higher than the *p*-HBA solubility, and PP solubility at P ~20 MPa is approximately twice as high as of MP solubility. Unfortunately, there is almost no information in the literature about the effect of polar cosolvents capable of forming hydrogen bonds (HBs) with a solute. The only found data are obtained for PP at T = 308 K, with acetone at concentration of 0.035 mol fraction as the co-solvent. They are compared with PP solubility in pure SC CO$_2$ at the same temperature in Fig. 1b. PP solubility in the presence of acetone is several times as high as in pure solvent.

As it is shown by studies of substances similar to *p*-HBA and parabens, the use of low molecular weight alcohols for increasing
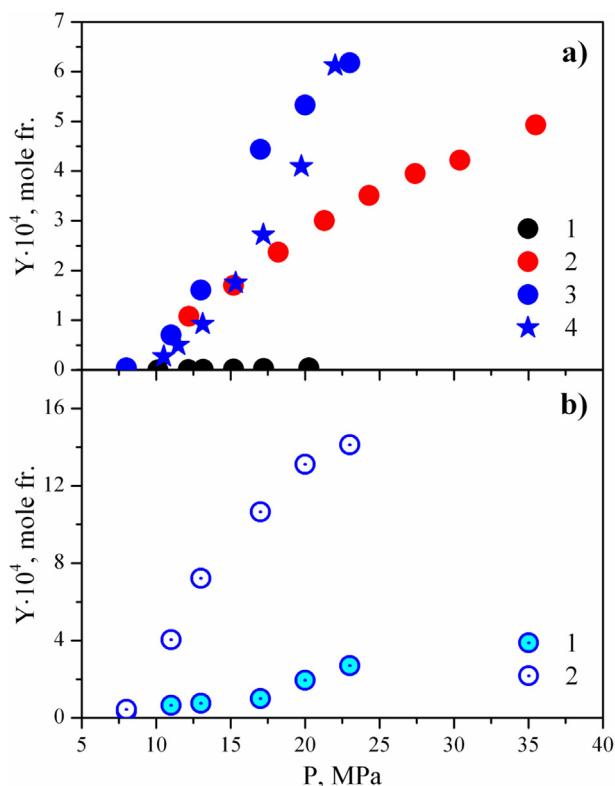
Fig. 1. Solubility Y in SC CO₂ according to literature data. a) 328 K, in pure SC CO₂: 1 – *p*-HBA [7], 2 – MP [3], 3 – PP [5], 4 – PP [6]; b) 308 K: 1 – PP in pure SC CO₂ [6], 2 – PP in acetone-modified (0.035 mol fraction) SC CO₂ [6].

Table 1
Average numbers of HBs formed by solute molecules with a cosolvent, n_{HB}(III–II) and the average numbers of the HBs, formed by individual atoms of solutes $n_{H(III)O(II)}$, $n_{O(III)H(II)}$. Average coordination number of CO₂ $n_{C(III)O(I)}$ and a cosolvent $n_{C(III)O(II)}$ oxygens around of the alkyl carbons C_{alcyl} of solutes.

Solute		*p*-HBA	MP	PP
n_{HB}(III–II)		1.30	1.15	1.29
$n_{H(III)O(II)}$	H1(III)O(II)	0.27	0.85	0.83
	H2(III)O(II)	0.90	–	–
$n_{O(III)H(II)}$	O1(III)H(II)	0.08	0.06	0.07
	O2(III)H(II)	0.05	0.33	0.44
	O3(III)H(II)	0.00	0.01	0.00
$n_{C(III)O(I)}$		–	5.05	3.85
$n_{C(III)O(II)}$		–	0.21	0.10

results the conformers of the lowest energy (Fig. 2) were selected for each substance. Configurations of these conformers were used as initial data in the further simulation by classical MD.

Simulated systems contained 10328 CO₂ (I) molecules, 320 methanol (II) molecules (0.030 mol fraction) and 3 molecules of a solute (*p*-HBA, MP or PP – III).

In the first stage a cubic cell with periodic boundary conditions, was created containing a binary solvent. The volume of the cell corresponded to the system density ρ = 0.772 g/cm³. After energy minimization the equilibration was carried out during 0.5–1 ns. Then, the cell containing three solute molecules was "embedded" by binary solvent. The length of the cell edge was again corrected to maintain the density equal to 0.772 g/cm³. Equilibration of ternary systems was then carried out during 2 ns. The product simulation time was 2 ns with a time step of 1 fs. The data were collected every 0.1 ps for further analysis. The analysis of the obtained trajectories using a graphic program VMD was performed at each step [27].

3. Results and discussion

The molecular mechanism of selective solvation can be determined by analyzing the localization of functional groups around cosolvent solute. We have introduced the symbols of the individual atoms of *p*-HBA, MP and PP for convenience (Fig. 2).

Radial distribution functions (RDFs) O(III)H(II) and H(III)O(II) (Fig. 3) allow to estimate in the first approximation the probability of hydrogen bonding with a co-solvent via the individual atoms of the solute. To determine the existence of HB, we use geometric criterion $R_{O\cdots O} \leq 3.5$ Å, $R_{O\cdots H} \leq 2.6$ Å, ∠(H—O···O) ≤ 30°. Since the HB length is defined as the sum of the van der Waals radii of its constituent atoms, it is permissible to use a universal geometric criterion for all bonds O—H···O, including those formed by various substances [28,29]. The possibility of hydrogen bonding can be estimated accordingly from the behavior of RDFs at distances less than 2.6 Å. As we can see, parabens are characterized by a high degree of cosolvent localization near hydroxyl hydrogen H1, whereas for *p*-HBA, it is several times as low and the localization of methanol at the carboxyl hydrogen H2 is more typical. Methanol localization near *p*-HBA oxygen atoms, as well as around the hydroxyl O1 and carboxyl O3 parabens oxygens is not significant. The peaks at parabens RDFs O1(III)H(II) and *p*-HBA RDF O3(III)H(II) are located at distances ~3.4–3.5 Å, which corresponds to the methanol molecules, localized not directly near the oxygen atoms but near the bonded hydrogens. The methanol localization near parabens carbonyl oxygens O2 is high, unlike *p*-HBA, and it is higher for PP than for MP, that is enhanced by lengthening of the alkyl group. This is due to enhancing in the charge density on the carbonyl oxygen (by ab initio CPMD data, the value of its point charge is −0.440 |e| for *p*-HBA, −0.578 |e| for MP и −0.675 |e| for PP) affected by the electron donating ability of the alkyl chain.

2. Simulation details

P-HBA, MP and PP in methanol-modified SC CO₂ were simulated by classical molecular dynamics (MD) in software package Gromacs-5.0.7 [14]. This package supports the force field OPLSAA [15], which was used for *p*-HBA, MP, PP and methanol. Potential model which reproduces CO₂ critical parameters in the best way was used for CO₂ molecule [16]. Verlet algorithm [17] was adopted to integrate the equations of motion for the whole system. The Nosé-Hoover thermostat was employed to maintain constant temperature T = 328 K in the NVT ensemble [18,19]. Modified Ewald summation method [20,21] was used to account for corrections of the long-range electrostatic interactions. LINCS algorithm [22] was used for bond length limiting.

Geometric optimization and calculation of the charge characteristics of possible conformers were carried out in the software package CPMD-3.13.2 [23]. Exchange-correlation functional BLYP [24,25], Vanderbilt pseudopotential [26] with the cutoff-energy of the plane waves of 25 Ry were chosen. According to the ab initio

solubility in SC CO₂ is more effective than using acetone [8–10]. The cause of solubility increasing is a selective solvation of solute molecules by cosolvent due to the formation of stable HBs [11–13].

In this paper, the molecular mechanism of *p*-HBA, MP and PP solvation in methanol-modified SC CO₂ (0.03 mol fraction of methanol) at T = 328 K and ρ = 0.772 g/cm³, corresponding to the experimental pressure of 21.3 MPa, is studied using computer simulation. We have considered the probability of hydrogen bonding between solute and cosolvent, the distribution of the HBs by the solute functional groups, the duration of the HBs existence. On the base of these characteristics the selective solvation of *p*-HBA and parabens by methanol molecules and its features, depending on the length of the alkyl group have been studied.