



Features of solvation of phenolic acids in supercritical carbon dioxide modified by methanol and acetone



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ABSTRACT

The study of solvation of three phenolic acids, 3,4,5-trihydroxybenzoic acid (gallic acid), 3,4-dihydroxybenzoic acid (protocatechuic acid), and 4-hydroxy-3,5-dimethoxybenzoic acid (syringic acid), in pure, methanol-modified and acetone-modified (0.03 and 0.06 mol fraction) supercritical (SC) carbon dioxide has been carried out by computational methods. Structural features of hydrogen-bonded complexes formation in modified SC media have been researched by using classical molecular dynamics at different densities corresponding to the experimental pressures 20 and 30 MPa and temperatures from 313 to 333 K. The results obtained have revealed that an increase of fluid density and cosolvent concentration provide increasing the average number of hydrogen bonds formed by the solute with cosolvent. Ab initio calculations of formation energy of hydrogen-bonded complexes solute – cosolvent have been performed. Solvation free energy of the phenolic acids in SC CO₂ with and without cosolvents was evaluated by means of the Bennett's acceptance ratio method. The solvation free energy has been found to be strongly dependent on the number of hydrogen bonds solute – cosolvent. Cosolvent-induced solubility enhancement values were also calculated. The results indicate that the increase in solubility of the phenolic acids is observed by passing from the pure SC CO₂ through acetone-modified to methanol-modified solvent. Moreover the order of cosolvent-induced solubility enhancement magnitude depends on the number of hydrogen bonds solute – cosolvent and greatly on the concentration of the latter.

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1. Introduction

During the last two decades, the supercritical fluids are of great interest for both experimenters as well as theorists. Against the background of traditional solvents, supercritical fluids are distinguished by a number of advantages: low viscosity, high diffusion, high dissolving power, the possibility of varying the fluid properties by changing the temperature and/or pressure. The most popular among supercritical fluids is carbon dioxide, which is nontoxic, nonflammable, unexplosive, largely inert, environmentally safe, cheap and has low critical parameters ($T = 304.1$ K, $P = 7.38$ MPa). Of particular interest is the phenomenon of increasing the solubility of organic compounds in supercritical carbon dioxide modified by adding both polar (simple aliphatic alcohols, water, acetone [1–5]) and non-polar (ethane, pentane, cyclohexane, hexane, n-octane and others [6–8]) cosolvents. Increase of the solubility in SC CO₂ modified by a non-polar cosolvent is caused by weak attractive forces between the solute and the cosolvent [9], whereas increase

of the solubility in SC CO₂ modified by a proton-donor and proton-acceptor cosolvents is associated with the occurrence of strong intermolecular interactions between the solute and the cosolvent, namely of hydrogen bonds (HBs) [9–12]. The ability of the compounds to form HBs with cosolvent in modified SC CO₂ and consequently the solvation features of the solute in the fluid media are determined by two groups of factors. The first group includes state parameters (T , P), the nature and concentration of the cosolvent, and the second one includes the type, arrangement and number of functional groups present in the solute molecule. Our previous studies have shown that the mechanism of HBs formation in SC CO₂ modified by various cosolvents is considerably different for heterofunctional compounds of similar chemical nature (salicylic acid derivatives [13,14] and p-hydroxybenzoic acid derivatives [15]), and for the isomers of the individual compound (o-, m- and p-hydroxybenzoic acid [15–17]). Continuing our research, the aim of the present study is to determine the effect of the number of functional groups on the features of the HBs formation solute – polar cosolvent in the SC CO₂ at different modifier concentrations and state parameters.

We are going to focus our attention on three phenolic acids varying in the number of hydroxyl (–OH) ring sub-

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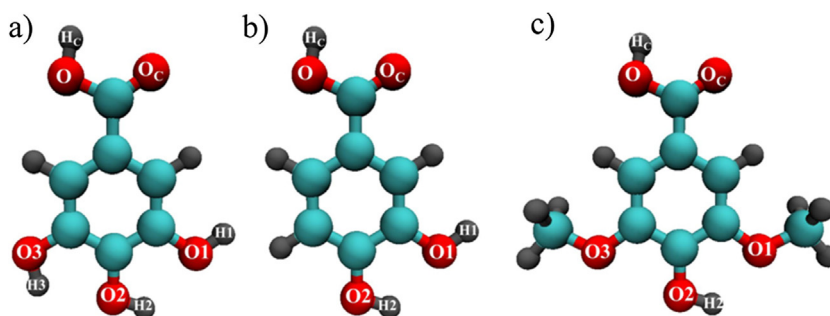


Fig. 1. Solute molecules with individual atoms designations: a) GA, b) PCA, c) SA.

stituents (Fig. 1): 3,4,5-trihydroxybenzoic acid (gallic acid, GA), 3,4-dihydroxybenzoic acid (protocatechuic acid, PCA), and 4-hydroxy-3,5-dimethoxybenzoic acid (syringic acid, SA). To achieve our purpose solvation process of the phenolic acids should be considered on the molecular level. Structural and energetic features of solvation complexes should be studied, and thermodynamic analysis (i.e. estimation of solvation free energy of solutes) should be performed. The computer simulation methods are advantageous to obtain such type of the information. Moreover these methods were successfully used by us for studying solvation processes of different bioactive compounds in SC CO₂ [13–19]. Despite numerous works devoted to computer simulation of supercritical solutions of small organic solutes [20] the molecular simulation of the gallic, protocatechuic and syringic acids in SC CO₂ is still not carried out. As far as we know, data about the features of the solvation of GA, PCA and SA are also not represented by now in the literature although in addition to the fundamental interest, these compounds are also of practical importance. Having a wide range of pharmacological properties (antioxidant activity, antimicrobial, anti-inflammatory properties and etc.) these compounds are used in the pharmaceutical and food industries [21–23]. Supercritical fluid extraction has been shown to be a suitable technique for extracting the phenolic acids from natural sources in very careful way [24,25]. Recent experimental studies have shown that the solubility of GA, PCA and SA in SC CO₂ is very low in a wide range of state parameters [24,26,27], that is why the additives of polar cosolvents are successfully used to increase this solubility as well as the selective extraction of the phenolic acids [28–30].

In order to achieve our aim we studied the behavior of GA, PCA and SA in pure and modified SC CO₂ in temperature interval 313 K–333 K at five densities (which corresponded to the experimental pressure 20 MPa and 30 MPa for SC CO₂) by computer simulation. The influence of thermodynamic state parameters, concentration of methanol and acetone (0.03 and 0.06 mol fraction) on the number of HBs between the solute and cosolvent molecules, the energy of hydrogen-bonded complexes formation, solvation free energy of the solutes have been considered. Features of the phenolic acids solvation connected with the different number of ring substituents have been analyzed.

2. Simulation details

Classical molecular dynamics (MD) simulations were performed using Gromacs-5.0.7 [31] software package. The OPLSAA force field [32] with the potential energy described by a sum of bond, angle, and dihedral deformation energies, and pairwise additive 12–6–1 (van-der-Waals + electrostatic) interactions between non-bonded atoms was used for solute and cosolvent molecules. For carbon dioxide we utilized potential model which is modification of rigid model of Zhang and Duan [33] and reproduces CO₂ critical parameters in the best way [34]. The combined Lennard-Jones parameters

Table 1
Thermodynamic state parameters of simulated systems: Temperature T, Density ρ (CO₂), experimental Pressure P_{EXP}.

State	T, K	ρ , g/cm ³	P _{EXP} , MPa
A	323	0.785	20
B	313	0.911	30
C	323	0.872	30
D	333	0.831	30

between atoms of different molecules were calculated as geometric means of the corresponding parameters. NVT ensemble was used to study the structural properties of ternary mixtures. Verlet algorithm [35] was adopted to integrate the equations of motion. The temperature was controlled by Nosé-Hoover thermostat [36,37]. Modified Ewald summation method [38,39] was used to account for corrections of the long-range electrostatic interactions. Constraints were implemented using the LINCS algorithm [40].

Simulated systems contained one molecule of solute (due to the low solubility of the acids), 10328 CO₂ and 320 cosolvent molecules or 10008 CO₂ and 640 cosolvent molecules (corresponded to 0.03 or 0.06 mol fraction of cosolvent, respectively).

In the first step cubic boxes with periodic boundary conditions for each of four thermodynamic states (Table 1) were created containing a pure SC CO₂. After energy minimization the equilibration was carried out during 0.5 ns. Then, the boxes containing 320 or 640 cosolvent molecules were combined with pure SC CO₂. After energy minimization of boxes containing binary solvent the equilibration was carried out during 0.5 ns. In the next step the boxes containing one solute molecule (GA, PCA or SA) were “embedded” by pure or binary solvent. Resulting binary or ternary systems were optimized by the energy minimization, then by a 1 ns equilibration. The production run simulations were performed for 2 ns with time step 1 fs. The data for analysis were collected every 0.1 ps.

Calculations of solvation free energies (SFEs) ΔG_{sol} of phenolic acids in supercritical media were carried out by Bennett’s acceptance ratio (BAR) method [41] realized in Gromacs-5.0.7 [31]. In the present study SFEs were calculated for one thermodynamic point (T = 323 K and P = 20 MPa). For each SFE calculation we performed a series of 11 independent NPT-MD simulations differing from each other by the value of a coupling parameter λ . The coupling parameter λ is changed from 0 to 1 with step of 0.1 (“fep-lambdas” keyword, see [31]) which characterizes fully decoupled and coupled solute-solvent interaction, correspondingly. Stochastic leap-frog integrator with 2 fs time step was used. Constant pressure of 200 bar was maintained by Parrinello-Rahman barostat [42] with compressibility of fluid $7.8 \cdot 10^{-4} \text{ bar}^{-1}$ [43]. For each simulation of the BAR series equilibration in NPT ensemble was performed during 200 ps (initial configurations of ternary systems were taken from previously described NVT MD simulations). The product simulation time was 2 ns. The energy differences were collected every 0.2 ps.

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