Classical and ab initio molecular dynamics simulation of p-coumaric acid in methanol-modified supercritical carbon dioxide

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Abstract. Classical and ab initio molecular dynamics simulation of p-coumaric acid in methanol-modified supercritical carbon dioxide has been performed. Structural properties such as radial distribution functions, coordination numbers, and average numbers of hydrogen bonds were obtained. Vibration density of states was calculated from velocity autocorrelation functions. The redshift in the frequency of the OH stretching mode for hydroxyl and carboxyl groups of the solute in fluid compared with the same values for the p-coumaric acid in gas phase is an evidence for H-bond formation. Analysis of the hydrogen bond lifetimes indicates that p-coumaric acid forms stable hydrogen bonds with methanol through hydroxyl and carboxyl protons. At the same time, the longest period of the absence of hydrogen bond is observed for carbonyl oxygen.

1. Introduction
The p-coumaric acid (pCA) is a representative of a wide class of phenolic compounds, namely, hydroxycinnamic acids. pCA exhibits such useful activities as antioxidant, anti-inflammatory, antiplatelet, anti-melanogenic and so on. Due to its high physiological activity p-coumaric acid has a great potential for biomedical and industrial applications. It was shown that pCA can be extracted from plant sources by means of supercritical (SC) fluid extraction process with CO2 as a solvent [1]. The solubility of pCA in SC CO2 is very low [2] that is why using a small amount of a polar cosolvent (such as alcohol or acetone) is a common practice. The reasons for increasing the solubility of bioactive molecules in modified SC CO2 are probably related to intermolecular interactions between the solute and the cosolvent [3, 4]. In order to study in details intermolecular interactions in such systems the classical and ab initio molecular dynamics simulation of triple mixtures (pCA-methanol-SC CO2) has been performed.

2. Simulation details
Classical molecular dynamics (MD) simulation was carried out with Gromacs-5.0.7 software package (GPU-accelerated) [5]. NVT cubic box with periodic boundary condition contains 10342 CO2 molecules, 320 methanol molecules, and 1 pCA molecule (due to the low solubility of the acid). The OPLSAA force field [6] 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 CO$_2$ we utilized potential model which reproduces CO$_2$ critical parameters in the best way [7]. The combined Lennard-Jones parameters between atoms of different molecules were calculated as geometric means of the corresponding parameters. Verlet algorithm [8] was adopted to integrate the equations of motion. Modified Ewald summation method [9,10] was used to account for corrections of the long-range electrostatic interactions. Constraints were implemented using the LINCS algorithm [11]. Constant temperature 328 K was maintained by Nosé-Hoover thermostat [12,13], box length was 10.0045 nm which corresponded to a system density of 772 kg/m$^3$ and experimental pressure of 21.3 MPa. After the equilibration, a production time was $5 \text{ ns}$ with a time step 0.1 fs and collecting time each 0.1 ps.

Based on the classical MD data we have chosen an initial configuration of the first solvation shell for further simulation by ab initio Car-Parrinello molecular dynamics (CPMD). The CPMD method was proposed by R. Car and M. Parrinello in 1985 [14]. It is a type of molecular dynamics, usually employing Hohenberg–Kohn–Parrinello molecular dynamics [15] in NVT ensemble (1 solute, 6 molecule of methanol, 50 CO$_2$ molecules, $T=328$ K). The BLYP functional [16, 17] 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 [18] with a plane-wave cutoff of 25 Ry. The Brillouin zone was sampled at the $\Gamma$–point only. Fictitious electronic mass was set up to 600 a.u. The production time was 20 ps with time step 0.121 fs and collecting time every 1.21 fs.

3. Results and discussions

Statistical analysis of the data obtained by means of classical MD allowed defining the structure of the ternary system. Based on the radial distribution functions of a center of mass of the system components relative to each other it was obtained the coordination numbers of CO$_2$ and methanol around the solute (Table 1). In order to estimate the degree of selective solvation the local mole fraction $x_{loc}(r)$ of methanol around pCA was carried out using the relationship:

$$x_{loc}^{pCA-MeOH} = \frac{N^{pCA-MeOH}(r)}{(N^{pCA-MeOH}(r) + N^{pCA-CO_2}(r))},$$

where $N(r)$ are the numbers of methanol (MeOH) and carbon dioxide molecules whose centers of mass are at a distance $\leq r$ from the center of mass of the pCA molecule. Preferential solvation of pCA by methanol molecules was observed, namely, the local mole fraction of methanol around the solute $x_{loc}=0.15$ significantly exceeds the average mole fraction in solution $x_{bulk}=0.03$. The distribution for the number of methanol molecules in clusters containing the solute was calculated with the “g_clustsize” tool of Gromacs-5.0.7 [5]. Methanol molecules forming hydrogen bonds with the pCA show a much greater propensity to associate with each other than the molecules in the bulk. If the last are distributed as monomers and as a small amount of dimers and trimers, the methanol molecules solvating the solute are associated in clusters containing up to 8 molecules of methanol.

In details, the structure of the first solvation shell was considered by using ab initio molecular dynamics method (CPMD). Atom-atom radial distribution functions (RDFs) pCA-cosolvent and corresponding coordination numbers are shown in Figure 1. The H$_2$O-MeOH, H$_2$O-MeOH and OH-MeOH RDFs shown on figure 1a -1c point out that pCA hydroxyl and carboxyl hydrogen atoms, carbonyl oxygen atom can form H-bonds with methanol molecules. Moreover, the probability to find the methanol molecule near the carboxyl hydrogen is the greatest.

Utilizing Fourier transforms of the respective velocity auto-correlation functions (VACF) [19, 20], we calculated vibrational densities of states of pCA (Figure 2). The peak positions were compared with the peak positions of IR spectrum presented in the literature [21-24] for pCA in gas phase (Table 2). The redshift in the frequency of the OH stretching mode for hydroxyl and carboxyl groups of pCA involved in H-bonds with methanol was observed and is an evidence for H-bond formation.
Figure 1. Atom-atom radial distribution functions pCA-methanol (a, b, c) and corresponding coordination numbers (d, e, f) obtained from CPMD simulation, and the most probable structure of the H-bonded complex solute-cosolvent with the designations of the atoms (g).

Table 1. Structural and dynamic characteristics of pCA in methanol-modified SC CO₂ according to the classical and Car-Parrinello molecular dynamics.

|          | pCA-MeOH (MD) | pCA-CO₂ (MD) | <n_HB> pCA-MeOH (MD) | <n_HB> MeOH-MeOH (MD) | τ pCA-MeOH, ps | τ MeOH-MeOH, ps |
|----------|---------------|---------------|----------------------|------------------------|---------------|---------------|
| N         | 3.1           | 13.4          | 2.04                 | 0.21                   | 2.25          | 0.66          |
| <n_HB> pCA-MeOH | (CPMD)        | <n_HB> MeOH-MeOH (CPMD) | τ_Hp-MeOH (τ), ps | τ O-MeOH (τ), ps | τ Hc-MeOH (τ), ps | τ MeOH-MeOH (τ), ps |
|          | 1.86          | 0.75          | 0.123 (0.023)        | 0.039 (0.184)          | 0.077 (0.025) | 0.067 (0.025) |

Figure 2. Vibrational spectrum of pCA obtained as the Fourier transform of VACF from the CPMD trajectory:
1 – the spectra of the O₆-H₆ stretching mode of pCA in SC CO₂–methanol
2 – the spectra of the O₆-H₆ stretching mode of pCA in SC CO₂–methanol
3 – the spectra of the O₆-H₆ stretching mode of pCA in gas phase
4 – the spectra of the O₆-H₆ stretching mode of pCA in gas phase

Table 2. The peak positions of IR spectrum presented in the literature [21-24] for pCA in gas phase and the frequency of the OH stretching mode obtained by CPMD.

|          | Experiment [21-23] | HF [24] | DFT [24] | CPMD (gas phase) | CPMD (SC CO₂–methanol) |
|----------|-------------------|---------|----------|------------------|------------------------|
| ν(O₆-H₆) | 3651              | 3656    | 3596     | 3660             | ≈3350                  |
| ν(O₆-H₆) | 3582              | 3606    | 3545     | 3595             | ≈3250                  |
Based on the geometric criterion of H-bond ($R_{O \cdot \cdot O} \leq 3.5 \text{ Å}, R_{O \cdot \cdot H} \leq 2.6 \text{ Å}, \angle (H - O \cdot \cdot O) \leq 30^\circ$) we calculated an average number of H-bonds $p$CA – methanol per solute molecule $<n_{HH}>_{p\text{CA-MeOH}}$ (Table 1). The average number of H-bonds obtained from CPMD is slightly less than from MD simulations which may be explained by the smaller size of the ensemble and the production time. The contributions of the individual atoms of the pCA in the total $<n_{HH}>_{p\text{CA-MeOH}}$ were also determined. The results confirm that the carboxylic and hydroxyl protons form more H-bonds ($<n_{HH}>_{\text{H-Car-MeOH}}=0.84$ and $<n_{HH}>_{\text{H-OH-MeOH}}=0.85$, $<n_{HH}>_{\text{H-MeOH-MeOH}}=0.66$ and $<n_{HH}>_{\text{H-pMeOH-MeOH}}=0.88$, CPMD and MD results respectively) than carbonyl oxygen atom (0.17 and 0.44, CPMD and MD results respectively).

In order to evaluate the stability of solvation structures the average continuous (that is, up to the first violation of geometric criterion) lifetime, $\tau$, of H-bonds through different atoms was calculated. It indicates that H-bond formed by $H_p$ atom of pCA is the most stable. At the same time the longest period of the absence of H-bond, $\tau^*$, is observed for carbonyl oxygen. In general total H-bond lifetime $\tau_{p\text{CA-MeOH}}$ equals 2.25 ps for classical MD and 0.416 ps for Car-Parrinello MD. Ab initio molecular dynamics gives the H-bond lifetime less than classical MD which is explained by the smaller step of integration of Newton's equations in CPMD.

In general, it can be concluded that the two methods, supplementing each other, provide detailed information on the behavior of p-coumaric acid in methanol-modified supercritical carbon dioxide.

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