

Use of molecular dynamics simulations to estimate the solubility of menadione in supercritical CO₂ using Chrastil's model



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ABSTRACT

The binary system of menadione in explicit supercritical carbon dioxide (SC-CO₂) was studied using molecular dynamics (MD) simulations, with the objective to understand the nature of interactions between menadione and SC-CO₂ at different temperatures and pressures in order to complement experimental solubility measurements. A force field was developed for menadione and tested by comparing computed and experimental monoclinic crystal structures at 283 K and 0.01 MPa. Lattice parameters obtained from anisotropic isothermal-isobaric MD simulations agreed reasonably well with experimental values, with an average absolute relative deviation (AARD%) less than 7%. A previously validated force field for SC-CO₂ was used, and simple mixing rules were used to describe cross interactions. Canonical ensemble MD simulations were used to estimate the association number for CO₂ about menadione and the enthalpy required to form a SC-CO₂ solvate complex with menadione as a function of temperature and CO₂ density. Spatial distribution functions were computed to better understand the nature of the molecular-level interactions between menadione and SC-CO₂ as well as between associating menadione molecules. This work is the first part of a study that uses MD simulations as the main tool to represent a binary system. The MD methodologies of this work will be applied to represent our future studies of menadione derivatives in SC-CO₂.

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1. Introduction

Supercritical carbon dioxide (SC-CO₂) is used as a solvent in the chemical [1], pharmaceutical [2] and food [3] industries. SC-CO₂ has good solvation and transport properties because it combines a liquid-like density with gas-like viscosity and diffusion. Moreover, small fluctuations in system temperature and pressure can produce significant changes in thermodynamic and transport properties. Furthermore, its low critical temperature ($T_c = 4$ K) prevents damage of thermally labile solutes [4,5] in comparison to conventional extraction, where the solvent must be removed by evaporation and steam distillation. In addition, SC-CO₂ is an inert, non-toxic, non-corrosive, non-flammable solvent, that can be removed easily from the extract using simple depressurization [6].

Menadione (2-methyl-1,4-naphthoquinone or vitamin K₃) is a synthetic compound whose chemical structure is shown in Fig. 1. Menadione displays blood-clotting [7] and anti-cancer mammalian

activity [8,9], and has been used to treat bone disease [10] in humans. In addition, menadione is involved in the transformation of vitamin K to menaquinone-4, which is commonly located in the human brain [11], and can be used in promising anti-cancer drugs [9].

The knowledge of the solubility of different compounds such as menadione in SC-CO₂ is important in any practical application of SC-CO₂. Ideally, one would like to determine solubilities with minimal experimental effort in order to minimize raw material and operational costs. In our previous work [12], Quantitative Structure-Property Relationships (QSPRs) were used to build a model that could predict the parameters of the Chrastil equation [13,14].

$$\log(w_2) = \log(w_2^0) + (k-1) \log\left(\frac{\rho_1}{\rho_1^0}\right) - \frac{\Delta H}{2.3R} \left(\frac{1}{T} - \frac{1}{T^0}\right), \quad (1)$$

where ρ_1^0 is the density of CO₂ (component 1) at the reference conditions (p^0 and T^0), w_2^0 is the reference solubility of the solute (mg kg⁻¹ solute/CO₂, component 2) at pressure p^0 and temperature

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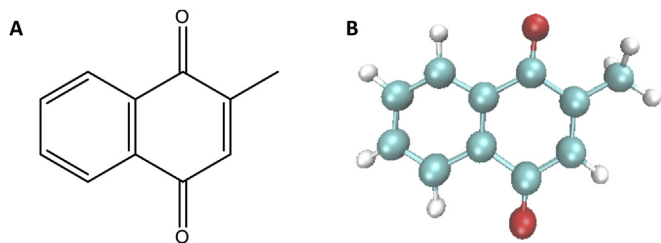


Fig. 1. Chemical structure of menadione corresponding to (A) 2D rendering, and (B) a 3D rendering, where cyan is carbon, red is oxygen and white is hydrogen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

T^0 , k is an association number corresponding to the number of CO_2 molecules surrounding a single solute, ΔH (kJ mol^{-1}) is the energy required to form a solute-solvent complex (vaporization and dissolution), and R is the universal gas constant. The Chrastil equation has been used widely to estimate solubilities in SC-CO_2 due to its simplicity and excellent correlative ability. To construct the QSPR model, molecular descriptors were estimated from the three-dimensional chemical structures of the compounds, which were minimized in implicit SC-CO_2 using molecular dynamics (MD) simulations. Then, one model for each Chrastil parameter was built using the most significant set of calculated descriptors (i.e., 5 for $\log(w_2^0)$, 9 for $(k-1)$, and 7 for $0.434 \Delta H/R$), and were correlated using artificial neural networks. Each resulting model predicted the Chrastil parameters with a root mean squared error of 0.49 for $\log(w_2^0)$, 0.35 for $(k-1)$, and 0.51 for $0.434 \Delta H/R$ for the test set of compounds, respectively. A drawback of the QSPR methodology is that it requires a large number of compounds with similar chemical structure and their respective solubility data to build a representative model. It would be desirable to have methods that are more predictive and do not require extensive experimental data [15].

MD simulation is a powerful technique that can model, represent, and help to understand the behavior of a system at an atomic level using classical mechanics [16]. In previous work, Zhou et al. [17] used MD simulation to estimate the infinite dilution diffusion coefficient of 38 organic compounds, including menadione, in SC-CO_2 . Canonical (NVT) ensemble simulations were carried out at 313.15 K and 16.0 MPa using a simple Lennard-Jones (LJ) potential model. The corresponding state [18] was used to calculate LJ potential parameters (ϵ , σ) for pure compounds, whereas an empirical mixing rule was applied to estimate non-bonded interaction for the solute-solvent complex (ϵ_{ij} , σ_{ij}). These simulations were able to estimate the diffusion coefficient with an absolute average relative deviation (AARD%) of 27.80% in comparison with experimental data obtained from the literature [19]. The authors did not examine other temperatures or pressures, nor were other properties such as solubility computed.

We are involved in a large project that studies the effect of chemical structure on the solubility in SC-CO_2 . The project entails chemical synthesis, solubility measurements, and molecular simulations of different derivative compounds of menadione. This paper defines the procedure to obtain the force field of menadione, and also the methodology to represent the binary system of menadione in SC-CO_2 , where both strategies will be used as a reference in the long-term project to represent the menadione derivatives in SC-CO_2 . The objective of the present work is to use MD simulation to estimate the parameters of the semiempirical Chrastil equation as a function of the number of CO_2 molecules and their residence time in the first solvation shell, with the ultimate goal of reducing experimental effort for solubility determination of related compounds. A secondary goal is to explore the interaction between the chemical structure of menadione and the CO_2

molecules, and the interaction with itself.

2. Computational methods

2.1. Force fields

CO_2 was modeled with a rigid three-site potential developed by Zhang and Duan [20]. This model has been shown to yield very accurate thermodynamic properties for pure CO_2 [21]. Menadione was modeled using a traditional class I force field of the following form [22]:

$$V_{\text{total}} = \sum_{\text{bonds}} k_r (r - r_0)^2 + \sum_{\text{bonds}} k_\theta (\theta - \theta_0)^2 + \sum_{\text{torsions}} k_\phi \left[1 + \cos(n\phi - \gamma) \right] + \sum_{i=1}^{N-1} \sum_{j>i}^N \left\{ 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right\} \quad (2)$$

where k_r , k_θ , and k_ϕ are force constants of bonded interaction, r_0 is the nominal bond length, θ_0 is the nominal bond angle, n is the periodicity parameter, ϕ is the torsional angle, and γ is the phase parameter. The torsion expression includes dihedral and improper dihedral angles present in the molecule. The Lennard-Jones and intramolecular parameters of menadione were taken from the General AMBER Force Field (GAFF) [23]. The partial charges were computed from a gas phase quantum calculation using a method developed by Zhang et al. [24]. Non-bonded interactions between different atoms were calculated using the Lorentz-Berthelot (LB) mixing rule [22]. A complete listing of all force field parameters is given in the [Supplementary Data section](#).

2.2. MD simulations of the solvate complex menadione and CO_2

The cumulative coordination number [25] was used to estimate the association number (k) in Eqn. (1) and was computed via the following expression

$$k = 4\pi\rho_{1,N} \int_0^r g(r) r^2 dr \quad (3)$$

where $\rho_{1,N}$ is the average number density of component 1 (CO_2), $g(r)$ is the radial distribution function (RDF) for CO_2 about the center-of-mass of a central menadione molecule, and r is the distance of the first minimum of the RDF.

To estimate ΔH in Eqn. (1), the following procedure was used. Impey et al. [26] introduced the concept of the residence time (τ) to describe the motion of water molecules in the hydration shell of different ions. In this work, τ was used to describe the behavior of CO_2 molecules in the first solvation shell of one molecule of menadione. Formally, τ is defined as the time it takes for CO_2 molecules to leave the first solvation shell and was computed from the following expression

$$\tau = \int_0^\infty R(t) dt \quad (4)$$

where $R(t)$ is the residence time correction function, computed via [26].

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