

Solubility of menadione and dichlone in supercritical carbon dioxide



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ABSTRACT

This work reports the solubility of menadione (2-methyl-1,4-naphthoquinone) and dichlone (2,3-dichloro-1,4-naphthoquinone) in SuperCritical (SC) carbon dioxide (CO₂) at 313, 323, and 333 K and (7.1–33) MPa. A Gibbs-Duhem test was applied to assess the thermodynamic consistency of experimental data using the Peng–Robinson equation of state with Wong–Sandler mixing rule to represent the solubility, and the non-random two-liquid model to compute Gibbs' excess free energy. In addition, the solubility of menadione and dichlone in SC-CO₂ at 313 K and 9.5 MPa, a solubility correction by a change in the density of SC-CO₂ as compared to this reference condition (580 kg/m³), and a solubility correction by a change in absolute temperature compared to 313 K were estimated using Chrastil's equation. The solubility of menadione at the reference conditions was 8.3 times higher than that of dichlone (3095 versus 375 mg kg⁻¹ solute/CO₂). However, both CO₂ density and system absolute temperature had anomalously smaller effects on the solubility of menadione than dichlone, so that menadione was only 4.2 time more soluble in SC-CO₂ than dichlone at the extreme conditions of 333 K and 33 MPa (3460 versus 831 mg kg⁻¹ solute/CO₂) for which $\rho = 851.1 \text{ kg/m}^3$. The anomalous behavior of the solubility of menadione in SC-CO₂ was imputed to experimental difficulties (solute precipitation resulting in tube blocking, saturation of HPLC detector signal) associated with high solubility values ($\geq 0.5 \times 10^{-3}$ M fraction) that may have been also responsible for thermodynamically inconsistent results reported by others in literature. We compared the solubilities in SC-CO₂ of menadione and dichlone with those for several solutes sharing the same molecule core (1,4-naphthoquinone) and concluded they are negatively impacted by polar and non-polar substituents, but that these negative steric and polarity effects could be partially compensated by a non-polar olefin substituent, or ameliorated by distancing substitutions from the carbonyl groups.

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1. Introduction

There exist a wide range of quinone derivatives [1] that have demonstrated biological activity, mainly as antioxidants [2–4]. The positive effect on human health of menadione (2-methyl-1,4-naphthoquinone or vitamin K₃, Fig. 1) has prompted its study by the pharmaceutical industry. Menadione is a fat-soluble vitamin that is used as an antihemorrhagic factor [5], a precursor of vitamin K that is transformed to menaquinone-4 and deposited in brain tissue [6], and a promising oncogenic agent against mammalian

cancer [7,8]. Menadione can be synthesized by the oxidation of 2-methylnaphthalene or 2-methyl-1-naphthol using conventional organic solvents, and supercritical carbon dioxide [9–12].

Supercritical (SC) carbon dioxide (CO₂) is commonly used as solvent in biological (e.g., extraction of antioxidants from natural matrices) and pharmaceutical (e.g., chromatographic purification) processes at near-critical temperature ($T_c = 304.85 \text{ K}$, in the case of CO₂ [13]), due to its interesting liquid-like density and solvent power, and gas-like transport properties (low viscosity and high diffusivity). Prevention of thermal damage to compounds dissolved in the gaseous phase at near-environmental temperature, ease precipitation of dissolved solutes by simple depressurization, and convenient chemical properties (e.g. nontoxicity, nonflammability) make SC-CO₂ an excellent alternative to conventional organic

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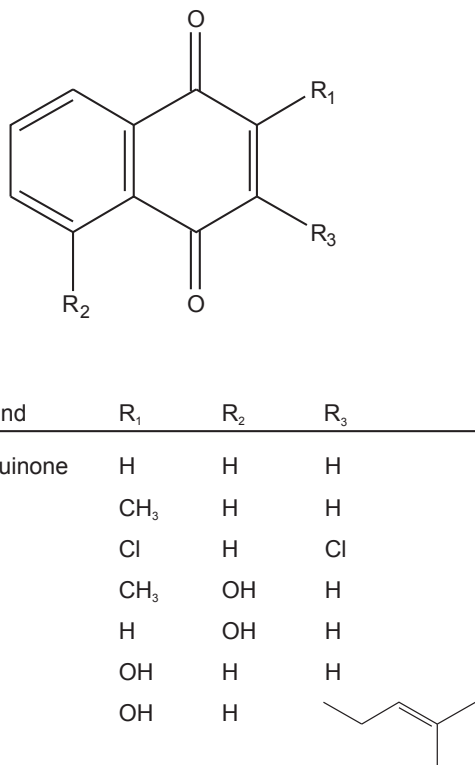


Fig. 1. Chemical structure of 1,4-naphthoquinone and derivatives analyzed in this manuscript.

solvents [13]. There are two previous studies on the solubility of menadione in SC-CO₂. Johannsen and Brunner [14] measured its solubility at 313 K and 22–32 MPa as part of a study on the solubility of fat-soluble vitamins in SC-CO₂. Knez and Skerget [15] reported solubility isotherms at 313, 333, and 353 K and 8–30 MPa as part of a comparative study on the solubility of vitamins D₂, D₃, and K₃ in supercritical CO₂ and propane. As discussed later, results of these two studies are contradictory. Valderrama and Zavaleta [16] proposed a methodology to discern good from questionable experimental data on solute solubility in SC-CO₂ that will be applied in this study. Their thermodynamic consistency test uses the Gibbs-Duhem equation for solid-gas phase equilibria [17], and requires the fugacity coefficient of the solid solute in the gaseous phase as a function of system pressure, system temperature, and the solubility of the solute in the CO₂-rich phase. The method was previously applied to analyze the consistency of experimental data for the solubility of another fat-soluble vitamin (β -carotene) in SC-CO₂ [18].

We are embarked in a long-term project to study the effect of small structural changes in chemicals on the solubility in SC-CO₂ that will demand chemical synthesis, solubility measurements, and molecular simulations. In its first stages, the project will use menadione and dichlone (2,3-dichloro-1,4-naphthoquinone, Fig. 1) as base structures to which different substituents will be attached. These chemical changes will alter the size, polarity, and halogen content of the molecules. To establish a baseline for solubilities, this work will measure and model the solubility of menadione and dichlone in SC-CO₂ at 313, 323, and 333 K, and 7–33 MPa.

2. Material and methods

2.1. Materials

Table 1 summarizes the source and purity of the solutes and solvent used in solubility measurements, and of solvents used in chromatographic analysis. Menadione, dichlone, and CO₂ were used in tests without further purification.

2.2. Measuring the solubility of menadione and dichlone in CO₂

The solubility of menadione or dichlone in SC-CO₂ was measured using the experimental equipment and dynamic-analytical method of Araus et al. [19]. The experimental system consists of a 50-cm³, stirred, high-pressure view-cell (Thar-Tech, Pittsburgh, PA) placed in a temperature-controlled air bath, a syringe pump (Teledyne ISCO 260D, Lincoln, NE) to load CO₂ into the system and adjust system pressure, and a gear pump (GAH-T23, Eurotechnica, Bargteheide, Germany) to recirculate the CO₂-rich phase, aid system equilibration, and feed samples of the CO₂-rich phase to the HPLC system coupled to the equilibration system. The HPLC system consists of a L-7100 pump, L-7350 oven, and L-7455 photodiode array detector from Hitachi LaChrom (Tokyo, Japan). To determine solute solubility in SC-CO₂, the equilibrium cell is loaded with approximately 2 g of menadione or dichlone, residual air is evacuated with a vacuum pump (Welch Vacuum, Skokie, IL), CO₂ is loaded using the high-pressure syringe pump, and temperature and pressure are adjusted to the required initial values. With the solute and CO₂ loaded in the equilibrium cell, the magnetic stirring (bar) and recirculation of the CO₂-rich phase were activated up to reaching equilibrium. After reaching equilibrium, a two-way, six-port injection valve Rheodyne 7010 (Rohnert Park, CA) equipped with a sampling loop of $V_i = 20 \mu\text{L}$ that interfaced the equilibration system with the HPLC apparatus, was used to sample the CO₂-rich phase. The molar fraction of solute (component 2) in the CO₂ (component 1) phase was estimated using Eq. (1):

$$y_2 = \left(\frac{A_i}{A_S}\right) \cdot \left(\frac{V_C}{V_i}\right) \cdot \left(\frac{MW_1}{\rho_1}\right) \cdot C_S, \quad (1)$$

where A_i is the chromatographic area for the tested sample, V_C and V_i are the volumes of sampling loops of the injection valves of the HPLC and high-pressure view-cell, respectively, MW_1 is the molecular weight of CO₂ (44.01 g/mol), ρ_1 is the density of CO₂ at equilibration temperature and pressure (calculated using NIST [20] database), and C_S is the concentration of the standard solution used to calibrate the HPLC (chromatographic area A_S). The solubility isotherm was completed by adding CO₂ to the cell to increase the pressure and attaining new equilibrium conditions up to reaching the required final pressure. Additional isotherms were obtained repeating this procedure using another initial temperature.

The isocratic HPLC method of by Hu et al. [21] with small modifications was used to determine the solute content in SC-CO₂. Separation was carried out 30 °C in a reverse-phase 2-mm (inner diameter) wide, 25-cm long, RP-18 HPLC column from Merck KGaA (Darmstadt, Germany) packed with 5- μm (diameter) adsorbent beads, using 1 cm³/min of a 70/30 (v/v) mixture of methanol and water as the mobile phase. Solute was detected at a wavelength of 300 nm. Solutions containing $C_S = 0.1 \text{ mg/cm}^3$ of menadione or dichlone in methanol were prepared and injected for calibration.

Five measurements of solubility data in SC-CO₂ were made at 313, 323, or 333 K and 7.1–32.6 MPa. Combined standard uncertainties were calculated using the methodology of Araus et al. [19], which included the relative inherent error associated to independent variables such as pressure, temperature, and others. In

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