Historical perspective

On the thermodynamics and kinetics of superheated fluorocarbon phase-change agents

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ABSTRACT

Superheated nanodrops are a new class of submicron-diameter liquid emulsion particles comprising perfluoropropane (C_3F_8), perfluorobutane (C_4F_{10}) and perfluoropentane (C_5F_{12}) that are being developed for ultrasound imaging and therapy. They can be formed by condensation of precursor lipid-coated, gas-filled microbubbles. Application of ultrasound or laser energy triggers the phase transformation back to a vapor bubble, and this process can be exploited for certain biomedical applications. The nanodrops are remarkably metastable in the liquid state under physiological conditions, even though they are highly superheated. In prior work, it was suggested that a high Laplace pressure in the lipid-coated nanodrop is responsible for its stability in the superheated state. Recent work by our group, however, points to the energy barrier for homogeneous nucleation as a more likely explanation. The purpose of this article is to review and discuss this mechanism in greater detail. We start with a brief description of basic fluorocarbon intermolecular forces. We then use the van der Waals equation of state to construct equilibrium phase diagrams and saturation curves. The effect of droplet Laplace pressure is superimposed onto these curves and compared to experimental data, where a poor correlation is observed. It is also shown that nanodrops with Laplace pressure are unstable to dissolution. The mechanism of homogeneous nucleation is then offered as an alternative explanation for the metastability of superheated nanodrops, with calculations that show good agreement with experimental data.

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1. Introduction

Phase-change agents are liquid droplets that can be converted on-demand into gas bubbles. Such agents typically comprise a fluorocarbon core and lipid, protein or polymer shell to maintain stability in an aqueous medium [1–5]. Conventional, low-superheat phase-change agents comprising a liquid perfluoropentane core (boiling point of 29 °C) can be formulated by conventional techniques, such as homogenization, sonication and extrusion [6]. The liquid droplet is 0.2 to 2.0 μm diameter and is transformed by the application of thermal, mechanical or electromagnetic energy into a 1–10 μm diameter bubble [7–14]. The liquid-to-gas phase transformation emits an acoustic pulse, and the resultant microbubble is highly echogenic, so these particles may be imaged by ultrasound or photoacoustic systems [15–22]. Additionally, the phase-change agent can deliver a therapeutic dose of thermo-mechanical energy and/or a drug [4,8,23–29]. This ability to provide both an imaging signal and a therapeutic effect makes these particles highly attractive for theranostic applications.

One of the most important innovations for phase-change agents was the recent advent of microbubble condensation methods to generate highly superheated droplets [30]. In this method, one starts with a suspension of microbubbles of a specific size and composition, and then condenses them with pressurization and cooling into nanodrops. The nanodrops are remarkably stable when brought back to room or physiological conditions, yet they may be easily converted back into microbubbles by the application of a relatively small amount of energy. For example, the mechanical index for acoustic droplet vaporization at 37 °C is reduced from 1.1 to 0.04 when comparing perfluoropentane (C_5F_{12}) droplets formed by conventional emulsification to perfluoropropane (C_3F_8) droplets produced by the microbubble-condensation method [31,32]. Likewise, the optical fluence for photo-thermal vaporization at 22 °C is reduced from 95 to 10 mJ cm^{-2} when comparing C_5F_{12} to C_3F_8 droplets [33].

The success of the microbubble-condensation method to generate droplets of extremely high superheat (e.g., 74 °C for a C_3F_8 droplet at physiological temperature) has required us to challenge the conventional view that superheated droplets are stabilized simply by boiling point elevation through the Laplace pressure, which manifests from the fluorocarbon/water interfacial tension [34–36]. In fact, as we show below, the high supercooling observed during microbubble condensation directly contradicts the Laplace-pressure hypothesis. Instead, a more satisfactory hypothesis involving the kinetics of homogeneous nucleation is provided to explain the high degrees of supercooling and superheating observed during condensation and vaporization, respectively.

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The review is organized to first consider fluorocarbon intermolecular forces and construction of the equilibrium phase diagram. We then show how Laplace pressure modifies the vapor–liquid equilibrium for fluorocarbon-in-water nanodrops, and the discrepancy with current experimental data. Laplace pressure is also shown to destabilize the nanodrop emulsion by promoting dissolution. Homogeneous nucleation theory for condensation and vaporization is then reviewed and verified by experimental data. Finally, we discuss limitations of this approach and suggest future research to help complete our understanding of the thermodynamics of fluorocarbon phase-change agents.

2. Intermolecular forces

Condensation and vaporization are phase transitions governed by the balance of molecular kinetic energy (heat) with intermolecular pair potentials [37]. In order to move molecules from a more organized liquid state to a more chaotic vapor state, the momentum transfer during molecular collisions must be strong enough to overcome the attractive van der Waals forces [38]. In this section, we consider the attractive and repulsive forces between two fluorocarbon molecules. First, we take a "bottom-up" approach using previously published Mie potentials between the C_3F_8 and C_4F_{10} fluorocarbon groups to determine intermolecular pair potentials for the fluorocarbon molecules positioned with parallel and anti-parallel orientations. We then compare the two intermolecular potentials for both orientations to gain a better understanding of fluorocarbon–fluorocarbon interactions. We then take a "top-down" approach by starting with measured thermodynamic properties and backing out the intermolecular force constants. A comparison provides interesting insight into the effects of molecular size and orientation.

2.1. "Bottom-up" approach: intermolecular forces to thermodynamic properties

Potoff and Bernard-Brunel recently published results from Monte Carlo simulations, in which intramolecular and intermolecular force field parameters for various hydrocarbons and fluorocarbons were fit to match experimental values of liquid density, vapor pressure and enthalpy of vaporization [39]. In this work, the intermolecular pair potential between fluorocarbon groups (i and j) on adjacent molecules was described by a general 6-m Mie potential (w_{ij}):

$$w_{ij}(r) = C_{ij}\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{m_{ij}} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^6\right] \qquad (1)$$

where the exponent m on the repulsive term between i and j is given as:

$$m_{ij} = \left(\frac{m_{ii} + m_{jj}}{2}\right). \qquad (2)$$

C_{ij} is an interaction constant dependent on the exponent m_{ij}:

$$C_{ij} = \left(\frac{m_{ij}}{m_{ij}-6}\right)\left(\frac{m_{ij}}{6}\right)^{6/(m_{ij}-6)}. \qquad (3)$$

Also in Eq. (1), ε is the depth of the potential energy well, r is the distance between the centers of the groups and σ is the van der Waals diameter, i.e., the distance between the groups where the potential equals zero. These parameters are determined for each group combination by the following combining relations:

$$\sigma_{ij} = \left(\frac{\sigma_{ii} + \sigma_{jj}}{2}\right) \qquad (4a)$$

$$\varepsilon_{ij} = \sqrt{\varepsilon_{ii}\varepsilon_{jj}}. \qquad (4a)$$

The values of these parameters for fluorocarbons are given in Table 1.

Table 1
Parameters for intermolecular interactions from [39].

Group	ε (K)	σ (Å)	m_{ii}
CF_3	155.75	4.475	36
CF_2	74.2	4.75	44

Note that the CF_2 group provides greater steric repulsion and hence lower dispersion energy than its CF_3 counterpart. The distance between fluorocarbon groups on the chain is taken as $l = 0.154$ nm [39]. The total intermolecular pair potential is then determined as a sum of the group combinations:

$$W(r) = \sum_i \sum_j w_{ij}(r). \qquad (5)$$

The "strength" of the intermolecular interaction depends on the conformation of each molecule and the orientation. The thermodynamic behavior is best determined by computer simulation, e.g., using Monte Carlo or Molecular Dynamics methods. However, we can simplify the analysis to get an approximation by exploring the interaction analytically. Consider the molecules are straight chains in either parallel or anti-parallel orientation. Fig. 1 shows the intermolecular pair potentials between C_3F_8 and C_4F_{10} molecules in these two orientations. The van der Waals diameter between C_3F_8 and C_4F_{10} molecules in the parallel orientation is 0.45 nm, with corresponding potential energy wells of 1.1×10^{-20} J ($\varepsilon = 797$ K) and 1.6×10^{-20} J ($\varepsilon = 1160$ K) at $r = 0.48$ and 0.49 nm, respectively. The potential energy wells for the anti-parallel orientation are 3.6×10^{-21} J ($\varepsilon = 260$ K) and 3.8×10^{-21} J ($\varepsilon = 275$ K) at $r = 0.63$ and 0.93 nm for C_3F_8 and C_4F_{10}, respectively. The parallel orientation is the most ideal interaction, as it provides the shortest distance between all fluorocarbon groups. The difference between these orientations is more severe for C_4F_{10} than for C_3F_8. Many other orientations are possible owing to conformational changes, molecular rotation and variations in approach angle and speed.

The intermolecular forces can be used to predict gas-phase thermodynamic behavior [40], and vice versa. To do so, we first convert the intermolecular pair potential to a self-energy by summing over all such interactions in the gas phase.

$$\mu_{gas}^i = \frac{1}{2}\int_\sigma^\infty W(r)\rho 4\pi r^2 dr \qquad (6)$$

We next insert a general London dispersion pair potential for the total intermolecular interaction.

$$W(r) = \frac{-C}{r^6} \qquad (7)$$

For a 6–12 Lennard–Jones potential, C is equal to $4\varepsilon\sigma^6$. Now the self-energy is given as:

$$\mu_{gas}^i = \frac{2\pi\rho C}{3\sigma^3} \qquad (8)$$

where ρ is the molecular density in the gas phase. The chemical potential is given by a combination of the self-energy and molecular entropy:

$$\mu_{gas} = \mu_{gas}^i + kT\ln\left(\frac{\rho}{1-X\rho}\right) \qquad (9)$$

where X is the molecular excluded volume, k is the Boltzmann constant and T (K) is temperature. We then employ Maxwell's relation to relate pressure to chemical potential.