Supporting Information

Pressure-Responsive, Surfactant-Free CO₂-Based Nanostructured Fluids

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Experimental determination of the ternary Gibbs diagrams using the cloud point method

The experimental set-up used for measuring the ternary Gibbs phase diagrams mixtures is shown in Figure S1. Worthy, for the system water-acetone-CO$_2$, only the locations where the CO$_2$-dilution-paths cross the bimodal have been measured experimentally, while for the mixture water-acetonitrile-CO$_2$ the ternary diagram has been measured experimentally and modeled by the SRK equation (see Table S1). The high-pressure variable volume view cell (HPVVVC) is made of stainless steel and is equipped with four borosilicate windows. It is surrounded by an also optically accessible oven used for the temperature conditioning of the chamber. The HPVVVC is equipped with a recirculation pump and a magnetic agitation, for achieving homogenization of the mixture. The pressure and the volume inside the HPVVVC can be fine-adjusted by either increasing or decreasing its volume with the moveable piston. The HPVVVC has been first cleaned and dried, and then warmed up to the working temperature. The binary mixture water/organic-solvent is loaded via an HPLC pump (Agilent) and the CO$_2$ is slowly added using an ISCO pump (Teledyne ISCO).
Figure S1: Schematic representation of the high-pressure variable volume view cell (HPVVVC) used for measuring the ternary Gibbs diagrams: (P) stainless steel piston, (H/C) heating/cooling air chamber, (P1) recirculation pump, (P2) CO$_2$ pump, (P3) solvent/solution pump, (PRV) pressure reducing valve, (PI) pressure indicator, (TT) temperature transducer, (PT) pressure transducer, (RD) rupture disc.\textsuperscript{1}

The location of the binodal curve within the ternary Gibbs diagrams was measured applying the cloud-point-method. In this case the composition of a homogeneous single-phase mixture is varied by the isobaric (10 MPa) and isothermal (298 K, 308 K, 328 K) addition of a certain amount of one of the involved compounds until the mixture becomes and remains turbid (cloud point). The cloud point indicates the emergence of a second phase and thus is assigned to one point of the binodal curve. This procedure has to be repeated several times driving various single-phase mixtures of different initial composition into the two-phase region. The line combining the compositions at which the cloud points were determined defines the binodal curve.
Table S1: Composition in molar fraction of the light and dense phases of the bimodal curve for the ternary mixture water/acetonitrile/CO\textsubscript{2} mixtures at 308 K and 10 MPa.

|         | Light Phase |            | Dense Phase |            |
|---------|-------------|------------|-------------|------------|
|         | x\textsubscript{H\textsubscript{2}O} | x\textsubscript{Acetonitrile} | x\textsubscript{CO\textsubscript{2}} | x\textsubscript{H\textsubscript{2}O} | x\textsubscript{Acetonitrile} | x\textsubscript{CO\textsubscript{2}} |
| 0.4012  | 0.4692      | 0.1296     | 0.7711      | 0.193      | 0.0359     |
| 0.2321  | 0.5465      | 0.2214     | 0.83238     | 0.13751    | 0.0301     |
| 0.1848  | 0.5425      | 0.2727     | 0.85091     | 0.11739    | 0.0317     |
| 0.1396  | 0.5097      | 0.3507     | 0.87459     | 0.09391    | 0.0315     |
| 0.0979  | 0.4557      | 0.4464     | 0.89181     | 0.07679    | 0.0314     |
| 0.068   | 0.3991      | 0.5329     | 0.90309     | 0.06511    | 0.0318     |
| 0.0488  | 0.33907     | 0.61214    | 0.9107      | 0.0568     | 0.0325     |
| 0.0382  | 0.2178      | 0.744      | 0.9309      | 0.0418     | 0.0273     |
| 0.2687  | 0.5482      | 0.1831     | 0.81788     | 0.15312    | 0.029      |

Experimental determination of the isothermal compressibility

The isothermal compressibility (κ) of the ternary mixture water/acetone/CO\textsubscript{2} was measured with the variable volume view cell shown in Figure S1. At a constant and known composition the ternary mixture inside the view cell can be compressed isothermally by moving the piston into to the cell. We analyzed the pressure $P$ as a function of the mass specific volume $v$ of the ternary mixture. For a mixture with a composition $x_{CO2} = 0.15$ and $x_{water} = x_{acetone} = 0.425$ the pressure-volume data and the resulting isothermal compressibility data are shown in Figure S2a.
The isothermal compressibility of CO₂ is also reported in Figure S2b as comparison.

\[ \kappa = -\frac{1}{V} \left( \frac{\partial V}{\partial P} \right)_T \]

Figure S2: (a) Specific volume and isothermal compressibility of a ternary water/acetone/CO₂ mixture (\( x_{CO₂} = 0.15 \) and \( x_{water} = x_{acetone} = 0.425 \)) as a function of pressure; (b) comparison between pure CO₂ isothermal compressibility and isothermal compressibility of a ternary water/acetone/CO₂ mixture (\( x_{CO₂} = 0.15 \) and \( x_{water} = x_{acetone} = 0.425 \)).
Experimental determination of the development of hydrogen bonds

Figure S3 shows a sketch of the experimental setup used for the determination of the development of hydrogen bonds in the ternary mixtures.

Figure S3: Sketch of the experimental setup used to acquire Raman spectra of the mixtures loaded inside the high pressure variable volume view cell. OS: organic solvent

An in-house built Raman sensor was used for the acquisition of the Raman spectra of the mixtures directly from the HPVVVC. The laser was guided via a glass fiber to the sensor system. At the fiber outlet a convex lens collimates the laser beam. A short pass filter (not included in Figure S3) blocks the wavelengths longer than 532 nm originating from light matter (SiO₂ and impurities) interactions inside the fiber. The collimated laser beam was then reflected with a dichroic mirror (DCM) and focused into the measuring chamber with a lens of 100 mm focal length. This achromatic lens also collimates the backscattered Raman
signals. The collimated signals were focused onto the entrance of a glass fiber bundle by means of an achromatic lens with a focal length of 200 mm. On the path to the fiber bundle the elastically scattered light is discriminated from the desired Raman signals firstly by the dichroic mirror and secondly by the Raman razor edge longpass filter with an overall optical density of more than 8. The fiber bundle guides the signals to a QE 65000 Ocean Optics spectrometer equipped with a high quantum efficiency back illuminated charge coupled device detector (CCD) array. A background corrected example spectrum of a ternary water/acetone/CO₂ mixture at 10 MPa and 308 K is shown in Figure S4. The composition of the mixture is defined by the molar fractions of water \( x_{\text{water}} = 0.45 \), of acetone \( x_{\text{acetone}} = 0.45 \) and of CO₂ \( x_{\text{CO₂}} = 0.1 \).

In order to isolate the symmetric stretch vibration Raman signal of water, from which the development of hydrogen bonds was derived, the mixture Raman spectrum had to be deconstructed into the Raman signal contributions of water, acetone and CO₂ using a Levenberg-Marquardt least squares optimization, as it is described in detail elsewhere.² The fitted contributions of water, acetone and CO₂ are also shown in Figure S4. Due to the development of hydrogen bonds between water molecules and between water and acetone molecules the water stretch vibration Raman signal is a broad band compared to the narrow peaks of the Raman signals of the other compounds. The symmetric stretch vibration Raman signal of water was resembled of 6 Gaussian shaped peaks.³⁵ In order to get acceptable fit results for all mixture compositions, for each peak a range was defined for the peak center wavenumber and for its full width at half maximum (FWHM) as listed in Table S2. The freedom with respect to the peak center wavenumber and the peak broadness considers the circumstance that during the dilution experiments the probability of possibly
occurring intermolecular interactions (water↔water, water↔acetone, water↔CO₂) changes. Thus, during the fit to the experimental mixture spectrum each peak had the freedom to move within the defined ranges for the peak center wavenumber and the peak FWHM. Only the height (peak intensity) of the Gaussian peak was not predefined and thus fitted completely.

Figure S4: Raman spectrum of a water/acetone/CO₂ mixture (x_{water} = 0.45, x_{acetone} = 0.45, x_{CO₂} = 0.1 in molar fraction) at 10 MPa and 308 K as black data points and its deconstruction into the Raman signal contributions of water (dark red), acetone (grey) and CO₂ (dashed black). The Raman signal of the symmetric stretch vibration of water itself is deconstructed into 6 Gaussian signal peaks (reddish). The summation of the deconstructed Raman signals is shown as the solid black fitted mixture spectrum.

\[
I_{water} = \sum_{i=1}^{6} I_{Peak,i}
\]
Table S2: Ranges in which the center position and the broadness of the six Gaussian peaks were adjustable for the obtainment of a fit to the mixture spectrum.

| Peak  | Central Wavenumber (min) / [cm⁻¹] | Central Wavenumber (max) / [cm⁻¹] | FWHM (min) / [cm⁻¹] | FWHM (max) / [cm⁻¹] |
|-------|----------------------------------|----------------------------------|---------------------|---------------------|
| Peak 1| 3200                             | 3230                             | 60                  | 85                  |
| Peak 2| 3220                             | 3310                             | 50                  | 80.5                |
| Peak 3| 3370                             | 3415                             | 50                  | 90                  |
| Peak 4| 3495                             | 3510                             | 50                  | 80.5                |
| Peak 5| 3569                             | 3619                             | 50                  | 80.5                |
| Peak 6| 3675                             | 3700                             | 8                   | 50                  |

Figure S5 shows the intensity normalized symmetric stretch vibration Raman signal of water isolated from different binary water/acetone-mixtures. It can be seen that the shape of the isolated symmetric water stretch vibration Raman signal is a function of the mixture composition, respectively a function of the development of hydrogen bonds. In the water concentrated mixture more hydrogen bonds develop than in the water less-concentrated mixture, what is represented by larger Raman signal intensities at small Raman shifts and smaller Raman signals at larger Raman shifts.
Figure S5: Symmetric water stretch vibration Raman band $I_{\text{water}}$ isolated from different binary mixtures of water and acetone at 10 MPa and 308 K. The compositions of the binary mixtures are expressed in water molar fractions $x_{\text{water}} = 0.9, 0.7, 0.5, 0.3, 0.1$.

In our previous work $^6$, where we analyzed the water/acetone/CO$_2$ mixtures in a rather limited range of mixture compositions, we obtained good fit results of the symmetric water stretch vibration Raman band with keeping the central peak wavenumbers and the peak broadness fixed. In this case we quantified the development of hydrogen bonds (or the shape of the symmetric water stretch vibration Raman signal) considering the equilibrium between strongly $[(H_2O)_{\text{shb}}]$ and weakly hydrogen bonded $[(H_2O)_{\text{whb}}]$ water molecules.

$$R_{\text{water}} = \frac{[(H_2O)_{\text{shb}}]}{[(H_2O)_{\text{whb}}]} \approx \frac{I_{\text{Peak1}} + I_{\text{Peak2}} + I_{\text{Peak3}}}{I_{\text{Peak4}} + I_{\text{Peak5}} + I_{\text{Peak6}}} = \frac{I_{\text{shb}}}{I_{\text{whb}}}$$

For the computation of this ratio the intensities of the six peaks we used before, for the isolation of the symmetric water stretch vibration, were required. At least for pure water there is a consensus in literature that the different peaks (peak 1 to peak 5) representing the hydrogen bonded water molecules can be further differentiated into contributions assignable
to strongly (shb) and weakly hydrogen bonded (whb) water molecules. Shb water molecules are represented by peaks 1 to 3 and can be assigned to those water molecules forming hydrogen bonds to three or more other water molecules. Whb water molecules are represented by peaks 4 and 5 and can be assigned to those water molecules forming hydrogen bonds to one or two other water molecules. Peak 6 represents the water stretch vibration of “free” water molecules, which do not interact via hydrogen bonds with any other molecule.\textsuperscript{3-7}

The approach applied in our previous work is not applicable for this study, as it covers a wide range of mixture compositions. For the wide range of compositions studied, we were not able to find a “composition-isosbestic-point”, which makes a clear differentiation between two states of hydrogen bonding in equilibrium with each other – namely shb and whb - impossible. Therefore, instead of computing the ratio $R_{\text{water}}$ (previous approach), we here computed the centroid of the isolated symmetric water stretch vibration Raman signal and considered the Raman shift of the centroid $\bar{\nu}_{\text{water}}$ for the quantification of the development of hydrogen bonds

$$
\bar{\nu}_{\text{water}} = \frac{1}{\int_{\bar{\nu}=2900cm^{-1}}^{3800cm^{-1}} I_{\text{water}}(\bar{\nu}) \cdot \bar{\nu} \, d\bar{\nu}}
$$

where $I_{\text{water}}(\bar{\nu})$ is the Raman signal intensity at a certain Raman shift $\bar{\nu}$. With increasing $\bar{\nu}_{\text{water}}$ the Raman signal intensities at large Raman shifts increase and the Raman signal intensities at small Raman shifts decrease. This implies that with increasing $\bar{\nu}_{\text{water}}$ the development of hydrogen bonds decreases. Figure S6 shows the Raman shift of the centroid
as a function of the water concentration in binary water/acetone mixtures at 10 MPa and 308 K. The more the water/acetone-mixture is diluted by the addition of more acetone ($c_{\text{Water}}$ decreases), the more the development of hydrogen bonds decreases ($\tilde{v}_{\text{water}}$ increases).

Figure S6: Raman shift of the centroid $\tilde{v}_{\text{water}}$ of the isolated symmetric water stretch vibration Raman signal as a function of the water concentration $c_{\text{Water}}$ in binary water/acetone mixtures at 10 MPa and 308 K. Data points and error bars are the mean value and the standard deviation of 300 single measurements, respectively.

Summarizing, for the measurement of the development of the hydrogen bonds in a wide range of compositions, the consideration of $\tilde{v}_{\text{water}}$ instead of $R_{\text{water}}$ is advantageous, as it does not rely on the existence of an isosbestic point.
Experimental determination of the correlation lengths of the structural heterogeneities using high-pressure small angle neutron scattering (hp-SANS)

High-pressure small angle neutron scattering (hp-SANS) measurements were performed at the Institut Laue-Langevin (ILL, Grenoble, France) (beamline D11). Data were collected using an incident neutron beam with a wavelength of 6 Å and 9% FWHM, and working at two different sample-detector distances (1.75 and 10 m); this setup allows reaching a momentum transfer range between 0.007 and 0.35 Å⁻¹. A high-pressure cell, previously described by Pütz et al. was utilized for the measurements. The temperature of the hp-SANS cell can be set to 308 K with an accuracy of 0.1 K by connecting a thermostat to the cell. All samples were prepared directly into the HP-SANS-cell. The mixture was homogenized using a magnetic stirrer. hp-SANS data were collected on different mixtures water/d₆-acetone/CO₂ at 308 K and 10 MPa, prepared individually, adding different amounts of CO₂ over an initial binary mixture water/acetone-deuterated (50/50 by amount of substance). Measurements at various pressures were also performed after the addition of CO₂ by adjusting the position of the tunable piston. The mixture was first compressed up to 30 MPa, by a progressive pressure increase of 4 MPa each time, and then expanded again down to 10 MPa. The normalization of the scattering intensities to an absolute scale was performed using the secondary calibration standard H₂O with 1mm path-length, cross-calibrated against h/d polymer blends. For 6 Å the differential scattering cross section for 1mm H₂O is 0.983 cm⁻¹ for beamline D11. The raw data treatment, masking and radial averaging to obtain a one dimensional scattering spectrum were performed using the standard reduction software LAMP available at the ILL, which also accounts for the dead time of the detector. All measurements were background corrected, subtracting a dark
current measurement and the measurement of the empty hp-cell. The hp-SANS data for the
ternary mixtures plotted in Figures 6 and 7 were modelled in terms of the Ornstein-Zernicke
model that is commonly used to describe density fluctuations leading to large scale
aggregates, e.g. when approaching critical demixing or phase separation.\textsuperscript{9-11}

The formalism used for the model is:

\[ I(Q) = \frac{I(0)}{1 + Q^2 \xi^2} + \text{bkg}; \]

Where \( I(0) \) is the coherent forward scattering amplitude, \( \xi \) is the correlation length
(providing an estimate for the characteristic size of structural heterogeneities) and bkg corresponds to an incoherent, featureless and flat background.

**Additional information on MD Simulations**

We performed molecular dynamics (MD) simulations of binary water/acetone and
ternary water/acetone/CO\textsubscript{2} mixtures. We first started with a MD simulation of a binary
mixture with 1000 water molecules and 1000 acetone molecules (so \( x_{\text{water}} = x_{\text{acetone}} \)). After
this simulation, we performed two different sets of simulations using this initial simulation
as starting point. In the first set of simulations, we added more acetone molecules to the
initial simulation, obtaining binary mixtures with decreasing molar fractions of water. In
particular, the binary mixture simulations correspond to molar fractions of acetone of 0.50,
0.54, 0.58 and 0.65. A second set of simulations was performed by adding increasing
numbers of CO\textsubscript{2} molecules to the water/acetone 50/50 mixture. In this way we obtained
simulations of ternary water/acetone/CO\textsubscript{2} mixtures with different amounts of CO\textsubscript{2} but
always with the same number of acetone and water molecules (so \( x_{\text{water}} = x_{\text{acetone}} \)). The
compositions of these ternary systems corresponded to $1-x_{\text{water}}=0.425, 0.52, 0.54, 0.575, 0.64$.

In all simulations we employed the same simulation protocol. The Newtonian equations of motion of the molecules were solved with a 2 fs time step. The temperature was kept constant at 308 K using the Langevin thermostat with a relaxation constant of 1 ps$^{-1}$. A constant pressure of 10 MPa was applied using an isotropic Nosé-HooverLangevin piston with standard NAMD parameters (oscillation period of 100 fs and decay time of 50 fs). Periodic boundary conditions in all directions were employed in all our simulations. Electrostatic interactions were computed using the particle mesh Ewald summation method (PME) with the standard settings in NAMD (1 Å spatial resolution and were updated each 2 time steps). Lennard-Jones interactions were truncated at 1.2 nm employing a switching function starting at 1.0 nm.

We performed an initial energy minimization followed by a 4 ns NPT simulation until the simulation box reached a stable, equilibrium size. Then, we performed a 16 ns production run. The snapshots of the simulations and the calculations of the radial distribution functions $g(r)$ were obtained from the MD trajectories by using the Visual Molecular Dynamics (VMD) software.$^{12}$ All other analysis from the MD trajectory were made using our own programs.

All the snapshots shown in the main paper, as well as the density profiles and correlation functions reported here correspond to the particular ternary simulation with 1000 water molecules, 1000 acetone molecules and 353 CO$_2$ molecules (molar fractions of $x_{\text{CO}_2} = 0.15$ and $x_{\text{water}} = x_{\text{acetone}} = 0.425$).
In Figure S7, we show the density profiles calculated across the system averaged over the production run of the MD simulations described in the main text. These profiles correspond to an arbitrary, particular axis of the simulation box (the \( z \) axis). Profiles calculated over \( x \) or \( y \) axes (not shown here) give identical results.

In Figure S8, we show radial pair correlation functions for water (water-water, water-acetone and water-CO\(_2\)) and CO\(_2\) (CO\(_2\)-CO\(_2\), acetone-CO\(_2\) and again water-CO\(_2\)) averaged over the production run of the MD simulations described in the main text. Note that acetone is able to make hydrogen bonds with water through the carbonyl group, as demonstrated by the sharp peak at 1.7 Å in the acetone-water correlation function (Figure S8, top panel). Acetone is also able to interact favorably with CO\(_2\) through the apolar methyl groups, as denoted also by a clear peak in the acetone-CO\(_2\) correlation function (Figure S8, bottom panel). As discussed in the main text, water molecules are found in hydrogen-bonded structures, evidenced by the sharp peak at 1.8 Å in Figure S8. Also, water tends to be anticorrelated with CO\(_2\); the correlation function reaches the value 1 (no correlation) only after distances of about 1 nm. On the other hand, the broad peaks in the CO\(_2\) radial correlation functions shown in Figure S8 (bottom panel) indicate that CO\(_2\) molecules tend to be coordinated both with other CO\(_2\) molecules and acetone molecules. The peak in the C-C distance between CO\(_2\) molecules is about 4 Å, and the peak in the acetone-CO\(_2\) separation is at 4.4 Å.
Figure S7: Density profiles (molecules (nm)$^{-3}$) from MD simulations of the water/acetone/CO$_2$ ternary mixture (10 MPa and 308 K, $x_{\text{CO}_2} = 0.15$, $x_{\text{H}_2\text{O}} = 0.425 = x_{\text{acetone}}$) (a) Water and acetone and (b) CO$_2$. We also show the average value expected for a homogeneous system obtained by dividing the number of molecules of a given species by the average volume of the simulation box. Note that both, acetone and CO$_2$, are homogeneously distributed in the system, but water presents inhomogeneities of nanometric size.
Figure S8: Radial distribution functions calculated from MD simulations of the ternary water/acetone/CO₂ mixture (10MPa and 308K, x_{CO₂}=0.15, x_{water}= x_{acetone}=0.425). Top panel: Correlations of water (H atom) with: O atoms from acetone (red dashed-dotted line), O atoms from water (solid black line) O atoms from CO₂ (blue dashed line). Bottom panel: Correlations of C atoms from CO₂ with C atoms from CO₂ (solid black line) or C atoms from Acetone (red dashed-dotted line). CO₂ –water correlations from the top panel are also
reproduced here. The insets show typical molecular configurations corresponding to the peaks indicated with arrows.

**Solubilization of ibuprofen in nanostructured water-acetone-CO₂ mixture** In this section, we describe in detail an experiment of solubilization of ibuprofen, non-water and non-CO₂ soluble molecule, in a pressurized ternary mixture water-acetone-CO₂. Referring to the Figure S9:

![Figure S9](image)

Figure S9: Schematic representation (1-5) of the dissolution of ibuprofen in the nanostructured fluids; (5-6) ibuprofen precipitation upon pressure change.

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1. Ibuprofen is fully dissolved in acetone due to its high solubility ($x_{\text{ibuprofen}} = 0.32$). An almost saturated solution is loaded to the HPVVC (see Figure S1) at 35°C.

2. Water is slowly added to the cell till a molar ratio of water to acetone 50:50 is reached. The temperature is kept at 308K and the pressure is 10 MPa.

3. As a consequence ibuprofen precipitates as water acts as an antisolvent, being the solubility of ibuprofen in water $x_{\text{ibuprofen}} = 1.9 \times 10^{-5}$.  

4. Compressed CO$_2$ is added to the system isothermally (308 K) and isobarically (10 MPa).

5. Unexpectedly, the precipitated ibuprofen dissolves in the mixture and the mixture gets transparent. Now all the ibuprofen is dissolved. Since we know that ibuprofen is neither soluble in water nor in pure CO$_2$ ($x_{\text{ibuprofen}} = 0.13 \times 10^{-2}$), but it is soluble in CO$_2$-expanded acetone ($x_{\text{ibuprofen}} = 0.4$), we can describe the behavior of this quaternary mixture in the light of the nanostructuration of the system. Ibuprofen is now dissolved in the water depleted regions, which are spread all around the nanostructured system and coexist with the water-rich regions (size of the order of 2 nm by SANS and MD simulation).

6. We increase the pressure at 308 K up to 30 MPa by a volume decrease keeping constant the overall mixture composition. Upon the pressure increase, we observe an increase in the turbidity corresponding to the ibuprofen precipitation. From SANS measurements we know that when the pressure is increased isothermally at constant mixture composition, the extent of the nanostructuration gets less: therefore the nanodomains that are separated from each other into water-rich and water-depleted (CO$_2$-expanded acetone) at 10 MPa (well developed nanostructuration), partially or completely mix with each other at 30 MPa (less developed nanostructuration). Thus with increasing
pressure more water gets in contact with ibuprofen and finally the antisolvent effect of water causes the precipitation of ibuprofen.

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