Squeezing Oil into Water under Pressure: Inverting the Hydrophobic Effect

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ABSTRACT: The molecular structure of dense homogeneous fluid water–methane mixtures has been determined for the first time using high-pressure neutron-scattering techniques at 1.7 and 2.2 GPa. A mixed state with a fully H-bonded water network is revealed. The hydration shell of the methane molecules is, however, revealed to be pressure-dependent with an increase in the water coordination between 1.7 and 2.2 GPa. In parallel, ab initio molecular dynamics simulations have been performed to provide insight into the microscopic mechanisms associated with the phenomenon of mixing. These calculations reproduce the observed phase change from phase separation to mixing with increasing pressure. The calculations also reproduce the experimentally observed structural properties. Unexpectedly, the simulations show mixing is accompanied by a subtle enhancement of the polarization of methane. Our results highlight the key role played by fine electronic effects on miscibility and the need to readjust our fundamental understanding of hydrophobicity to account for these.

Common experience tells us that oil and water are not miscible.1 The separation of oil and water is the cornerstone of the hydrophobic effect.2 Methane is the shortest hydrocarbon and is insoluble in water under ambient conditions1 (0.006 mol % solubility at 100 °C and 10 MPa). In this regard, the thermodynamics associated with the interaction of methane with water forms a classic textbook problem. Hydrophobic interactions are a fundamental and ubiquitous phenomenon because they underpin many crucial life-enabling processes such as protein folding and cell-membrane formation.1 Hydrophobicity also plays a central role in chemical engineering problems, for example, in the food industry.3

The evolution of hydrophobic interactions under different thermodynamic conditions is relevant to a wide range of science ranging from Earth and planetary sciences to biology and is consequently a longstanding active field of research.4,5 Methane–water mixtures are present at the bottom of oceans, where compression leads to the formation of solid methane hydrates,7 they are also major constituents of the middle layers of the ice giants Neptune and Uranus8 and icy satellites like Titan and Triton.9 Combinations of water, ammonia, and methane are predicted to be widely present in the recently observed exoplanets, which have most commonly been of Neptune-like proportions,10−14 and are likely to exist as either liquids or solids.15−18 A microscopic understanding of how extreme pressures modulate the solubility of methane–water mixtures is thus critical to develop realistic models of the interior of planets.19

Hydrophobic interactions are central in the underlying architecture of biological machinery. Over half a century ago, several different experiments showed the effects of pressure on biochemical processes such as protein folding and later on in chemical reactions.6 It is now well established, for example, that the phase diagram of proteins is very sensitive to pressure.20−22 Specifically, single-chained proteins are known to denature at pressures of ~100 MPa. Protein unfolding and denaturation have been generally linked to a pressure-induced weakening of hydrophobic interactions,23 but the molecular mechanisms associated with these phenomena remain poorly understood.

Methane generally shows a sublinear tendency of solubility increase with pressure in the range up to ~1 GPa so that the maximum solubility remains significantly below 1 mol %.24,25 However, it was shown recently that starting at 1.3 GPa, the solubility of methane in water begins to dramatically increase and eventually saturates at a maximum of 44(3) mol % at 1.9 GPa and 373 K.26 The microscopic origin of the increased solubility observed in these experiments is not clear. Chandler proposed that enhanced pressures would result in a disruption
of the hydrogen-bond network, leading to increased solubility. However, the extent to which hydrophobic molecules disrupt the hydrogen-bond network has been challenged by a combination of both simulations and experiment, which find that a fully H-bonded network is maintained to high pressure. Moreover attempts to obtain a microscopic understanding failed because standard intermolecular potentials, with sufficiently large unit cells, do not give a mixed state.

Here we report combined experimental and theoretical studies that reveal how the hydrophobic effect is inverted under pressure in methane–water mixtures. Our neutron scattering experiments reveal the local structure of the mixed fluid in the pressure range 1.7 to 2.2 GPa. A/b initio molecular-dynamics simulations of the methane–water mixtures confirm the experimental observables and show an enhancement of interactions between the methane and water molecules due to a subtle increase in the methane dipole moment. These effects were not captured by standard classical potentials, which failed at reproducing pressure-induced enhanced solubility.

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Experimental Details. Both measurements of the fluid structure were performed on the PEARL beamline at the ISIS Neutron Spallation Source, Rutherford-Appleton Laboratory, U.K. Samples of fully occupied methane hydrate I (MH-I, 5.75:1 water/methane content) were cryoloaded in a Paris-Etching high-volume press. A liquid-nitrogen-cooled TiZr gasket was filled with the sample and then placed in precooled anvils, and a 5 tonne sealing load was applied. The samples were compressed to the desired pressures and warmed to 413 K (where no crystalline content could be detected). Data were collected for 48 h for each run, followed by a 24 h collection of background and a 24 h collection of vanadium needed for normalization. Data analysis was performed using the EPSR (empirical potential software refinement) package having 1000 molecules simulation boxes with the same composition as the samples. The density of the fluid mixture was estimated using a linear combination of the known equations of state for fluid water and methane. After equilibration and fitting, the individual pair distribution functions were sampled over 10 000 accumulations. For the initial setup of the simulation box, the molecules were defined using the TIP3P parameters for water (for OH bond lengths and dihedral angle) and the OPLS-AA parameters for methane, as described by Kaminski et al.

Computational Details. The AIMD simulations were performed with the CP2K package using Quickstep. The wave function was expanded using both a TZVP Gaussian basis set and a plane-wave representation using a cutoff of 300 Ry. The Becke, Lee, Yang, and Parr (BLYP) exchange-correlation was used together with the Grimme D3 empirical corrections for the van der Waals interactions. Norm-conserving Goedecker–Teter–Hutter (GTH) pseudo-potentials were used for treating the core electrons. The AIMD simulations were integrated with a time step of 0.5 fs within the NVT ensemble using the canonical sampling through velocity rescaling (CSVR) thermostat, thermomixing the system at 413 K. Mixture boxes with 300 molecules had sizes at low pressure of 45.0 \times 15.0 \times 15.0 \text{ Å} corresponding to a density of 870 kg/cm$^3$ and a pressure of 0.2 GPa, where high-pressure size refers to pressures of 1.2 and 2.3 GPa. (See the SI.) Initial conditions for mixed systems were created from the experimental \(S(q)\) fitting and then expanded into a 311 orthorhombic box. Demixed systems were created from classical potential simulations, which favor this demixing. To reveal whether phase separation or mixing occurred, long simulations of up to 250 ps were performed. Figure 1a shows the pair (or radial) distribution functions (PDFs) obtained from neutron scattering data. The total-scattering patterns (see the SI) obtained showed a few clearly distinguishable peaks from the water scattering background and a 24 h collection of background and a 24 h collection of vanadium needed for normalization. Data analysis was performed using the EPSR (empirical potential software refinement) package having 1000 molecules simulation boxes with the same composition as the samples. The density of the fluid mixture was estimated using a linear combination of the known equations of state for fluid water and methane. After equilibration and fitting, the individual pair distribution functions were sampled over 10 000 accumulations. For the initial setup of the simulation box, the molecules were defined using the TIP3P parameters for water (for OH bond lengths and dihedral angle) and the OPLS-AA parameters for methane, as described by Kaminski et al.

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localized broad peaks with no sign of heterogeneity, ruling out
the possibility of an emulsion. Molecular-level homogeneous
mixing is supported by the further analysis: High-quality
fits did not require methane or water clustering or cluster-size
rescaling, as commonly encountered in emulsions.42 The
extracted PDFs are all smooth and monotonically decaying, as
expected for simple
fluids.43 By contrast, more complex
systems that present bonding and local ordering or clustering
tend to yield signifi-
cantly more feature-rich distribution
functions, such as SiO2 melts.44 The total scattering data
showed an increase in CH4−H2O coordination with increasing
pressure (Figure 1b), and a simultaneous decrease in CH4−
CH4 coordination is seen in Figure 3. This is accompanied by
very little change in the structure of water, which tends to
maintain its normal coordination and H-bonding structure
(Figure 1c). Conversely, the decreased methane−methane
coordination is accompanied by increased water coordination.
(See Figure 1b,d.) Both the C−O and C−H2O partial \( g(r) \)
values show clear increases in the height of the first peak at 2.2
GPa. Integration of these curves out to the first minimum
shows an increase in water coordination of \( \sim \)0.6 molecules.
Furthermore, the first coordination shell sharpens so that the
coordination out to 4.38 \( \text{Å} \) increases by almost two water
molecules.

Using EPSR’s built-in capabilities to calculate spatial
correlation functions, especially spatial distribution functions
and dipole moment orientations, we found that water’s dipole
moment points away from the methane molecules (see the SI),
similar to the situation reported at lower pressure by Koh et
al.45 during hydrate formation. Moreover, Buchanan et al.46
found that at 180 bar and 18 \( ^\circ \text{C} \), the presence of dissolved
methane in water causes a compression of the second shell of
water, similar to but smaller than the effect of high pressure on
pure water. We notice a significantly more collapsed second
shell due to the combination of both higher pressure and over
an order of magnitude more methane being present in the
mixture (14.8 mol % in our case, 0.3 mol % in Buchanan’s).
The authors also noted that there are 16 \pm 1 water molecules

Figure 2. (Top) PDFs showing demixing at 0.2 GPa as CC grows and CO reduces over time, forming the slab seen below. (Bottom) Initial and
final (150 ps) snapshots at 0.2 GPa, where the mixed system begins to phase-separate into a slab.

Figure 3. (Left) PDFs and inset running coordination numbers \( \langle c_n \rangle \) from AIMD (blue line, 1.2 GPa) compared with experimental results (dashed
black line, 1.7 GPa) and those of pure phases from AIMD (dotted gray lines). A fluctuation confidence window is included, indicated by a blue
shaded region. (Right) All \( \langle c_n \rangle \) values from integrating up to the first minima of PDFs for neutron data (dashed lines) and \textit{ab initio} data (solid lines).
Top panel shows the maximal solubility as a function of pressure, as reported by Pruteanu et al.26 Pure systems are included for reference, and
symbols match the type of atom pair. Whereas there are few data points, there is strong overlap between experiment and simulation, which are
likely probing the very same liquid.
coordinating a given methane molecule, whereas we find slightly fewer than and greater than 13 water molecules for 1.7 and 2.2 GPa, respectively. The number of neighboring water molecules is expected to decrease in a solution having a significantly higher methane content despite also being at much higher pressure (which naturally tends to increase the number of neighbors at a given fixed distance).

To provide more insights into the molecular origins of the pressure-induced mixing, we performed a series of \textit{ab initio} molecular dynamics simulations. \textit{Ab initio} simulations, while more accurate than classical simulations because they explicitly include the electronic degrees of freedom, are computationally more intensive and thus require prudent choice of system sizes and simulation times. A series of different initial conditions were constructed to study the mixing/demixing at 0.2, 1.2, and 2.3 GPa. Specifically, we began with two limiting cases: a mixed configuration obtained from the EPSR refinement at 1.7 GPa and a slab-like geometry corresponding to an initial demixed state. (See the Methods.)

Figure 2 highlights some of the key initial findings of our simulations that confirm the experimental observations. Initial and final snapshots obtained from a 130 ps trajectory at 0.2 GPa clearly illustrate that the system irreversibly demixes to a slab-like geometry. This is also quantified in the time-dependent PDFs shown at the top of Figure 2 reporting an increase in the methane coordination and a decrease in the solvent exposure of the methane molecules over time.

This phenomenon is distinct from the interfacial mixing previously observed at ambient pressure\cite{47,48,49} and shows that our simulations are able to mix and demix the system on \textit{ab initio} time scales.

Initial and final configurations that were obtained from the simulations at 1.2 GPa starting from a slab geometry are shown in the SI. Interestingly, over a time scale of 30–50 ps, we observe water molecules penetrating into the slab, which results in methane molecules breaking away from the cluster. The time scales associated with the mixing are very slow, and the simulations (200 ps at 1.2 GPa) are not long enough to capture the kinetics associated with this process required to generate fully mixed configurations. After 200 ps at 1.2 GPa and 250 ps at 2.3 GPa, respectively, the mixing process is evident yet slower than the demixing at 0.2 GPa.

To assess the quality of the mixed methane–water simulations, we show in Figure 3 the pair distribution functions and associated coordination numbers for the mixture at 1.2 GPa. The differences observed between the experimental and simulation PDFs are largely due to the different pressures of 1.2 and 1.7 GPa and are reflected more in the $g(r)_{CC}$. These differences can also be attributed to the simulation’s sensitivity to equilibration, differences in the mixing concentration (14 vs 14.8%), the possibility of having small emulsions in the sample, the EPSR CH bond length and the OPLSS-AA methane potential, and the \textit{ab initio} simulations lacking a perfect physical description of interactions. Better agreement could be made if the initial conditions were closer to the $g(r)$ distributions that EPSR converged upon. (See the SI.) The fact that the pure CH\textsubscript{4} $g(r)_{CC}$ is not hugely different from that of the mixture implies that CH\textsubscript{4}–CH\textsubscript{4} distances are similar but with much lower CC $c_6$ in the mixture. The pressure evolution of the coordination numbers and a comparison with the pure phases of water and methane, respectively, are shown in Figure 3. Consistent with the PDFs previously reported, there is a clear increase with pressure in the number of oxygen atoms within the first shell ($c_6$) of a given methane molecule, accompanied by a similar decrease in the number of neighboring methane molecules. The structure of solvated water molecules (water molecules neighboring other water molecules) also increases but remains lower than that of pure water due to the excluded-volume effect owing to the presence of methane. Computed spatial distribution functions from AIMD reinforce this (see the SI) and are in good agreement with those calculated by EPSR. One can also notice that at ~2 GPa, the number of water molecules within the first shell of a methane molecule in the mixture equals that...
of all neighboring molecules in the pure phase. The effect of solvating methane we observe here is akin to previous simulations by Hummer and coworkers, which examined the potential of mean force using classical potentials between two methane molecules in water as a function of pressure. An increase in pressure appears to destabilize the contact minimum between two methane molecules and stabilize the solvent-separated state.

The combined experimental and simulation results up to this point show that an increase in pressure leads to suppression of the hydrophobic effect. To understand better the microscopic origin of this phenomenon, we next examine the thermodynamic signatures associated with mixing. It is beyond the scope of the current calculations to compute the free energies of mixing/demixing. However, mixing is always entropically favored, and, in this particular case, the entropy of mixing is found to be close to that of an ideal random mixture, at both 1.2 and 2.3 GPa (calculated using the same method as in Pruteanu et al.; see the SI). We will therefore focus on the evolution of the internal energy on mixing. In the left panel of Figure 4, the internal energies of mixed and unmixed simulations are shown at 0.2, 1.2, and 2.3 GPa. At 0.2 GPa, U was calculated before the system starts to phase separate. Interestingly, at both 1.2 and 2.3 GPa, the mixed simulation of methane and water is lower in energy, by \( \sim 10 \text{ meV/molecule} \). At 0.2 GPa, where the methane molecules cluster together, the slab conditions are lower in energy compared with the mixed state. The stabilization of the methane–water interactions at high pressure thus correspond to \( \sim 12 \text{ meV/molecule} \), roughly 5% of the cohesive energy for a water molecule dimer. This suggests that internal energy is strongly influencing the mixing driving force and importantly turns over from not favoring to favoring mixing with pressure.

Previously, we stated that previously performed classical molecular dynamics simulations failed, even qualitatively, to reproduce the trends observed in the experiments. One possible origin of this failure is that the increase in pressure leads to subtle changes in the electronic properties of both methane and water, which cannot be captured by the TIP3P, TIP4P, SPCE, and OPLS-AA potentials, for example, in the molecular polarization. Previous theoretical studies have also suggested the importance of methane polarization in methane hydrates. To assess the role of polarization in our simulations, we examined the molecular dipole distributions of pure, mixed, and slab-like systems. The dipole moment was calculated using maximally localized Wannier functions (WCs). The total molecular dipole is given by \( D_{\text{tot}} = -\sum_i 2e r_i + \sum_i Q_i R_i \) where \( R_i \) is the position of the ion center, \( r_i \) is the position of the Wannier center, and \( Q_i \) is the ionic charge.

The dipole moments are shown for water and methane molecules in the top and bottom panels, respectively. Overall, the increase in pressure results in an increase in the dipole moment of water by 0.13 D at 2.3 GPa: the dipole moments in pure water at ambient pressure and 2.3 GPa are 2.97 ± 0.08 and 3.10 ± 0.09 D, respectively. For methane in the mixture, the change is quite remarkable. At just 1.2 GPa, the dipole moment increases to roughly 0.3 D and remains almost the same at 2.3 GPa. For reference, methane molecules in the pure phase are nonpolar and are characterized by a very small and pressure-independent dipole moment and fluctuations (calculated here to be 0.1 D). For the 0.2 GPa mixed system, the snapshots were taken from the first part of the simulation before the system had demixed. The increased dipole moments of the methane molecules we observe are consistent with previous \textit{ab initio} simulations that were performed at much higher temperatures and pressures, yet here they occur at much lower pressures and temperatures.

It is well appreciated the inclusion of dispersion interactions is critical for reproducing both the structural and dynamical properties of aqueous systems with density functional theory.
Although we have included dispersion interactions using the empirical Grimme correction, we wanted to assess the sensitivity of some of our results to the choice of using more accurate nonlocal dispersion functionals. For this reason, we performed simulations using both DRSLL and rV10 functionals for the methane-water mixtures at 1.2 GPa and for 20 ps. The dipole moment distributions are consistently reproduced by all of these functionals.

Methane in the gas phase would, due to symmetry, have no permanent dipole. The nonzero methane dipole seen in our simulations arises from fluctuation-induced symmetry breaking. This is a feature that appears to be enhanced at high pressure relative to ambient conditions. At high pressure, the presence of a large fluctuating dipole has already been observed in previous first-principles simulations.17 We find that the magnitude of the fluctuating dipole of methane is not short-lived (see SI Figure 34), which shows the dipole moment for a single methane molecule as a function of time. The magnitude of the dipole fluctuates between 0.05 and 0.7 D on the time scales of picoseconds, whereas the average of the magnitude of the dipole moments of all CH₄ molecules is roughly constant at 0.3 D. As expected, the average of each component of the dipole vector of methane is zero; however, the fluctuations away from zero are roughly twice as large in the mixture at 1.2 GPa compared with the pure methane system. It is these strong fluctuations of the vector from zero that boost the magnitude of the dipole moment for methane.

The enhanced dipole moment of methane under pressure does not imply that it has a permanent dipole moment, but a finite dipole arises from enhanced fluctuations of the three components of the dipole vector. In SI Figure 32, we observe that all three components of the dipole are well approximated by Gaussian distributions, with the same spread implying no symmetry breaking. However, under pressure, the enhanced fluctuations of all three components leads to an increase in methane’s dipole moment, which is consistent with previous studies.17

The increase in interactions between the methane molecules and water has a rather subtle effect on the water hydrogen-bond network. We first examined the number of hydrogen bonds formed between water molecules both in pure water up to 3 GPa and in the methane-water mixtures, which is shown in Figure 5. Hydrogen bonds were determined by using a geometrical criterion developed by Luzar and Chandler.55 Interestingly, we observe that the water hydrogen-bond network retains its integrity in the mixture. We find that the mixed system contains 97% of H bonds found in the pure water system at both 1.2 and 2.3 GPa. Although there are slightly fewer hydrogen bonds, they tend to be slightly stronger than in pure water: The bond angle and bond distance distributions are slightly smaller, with greater weight at smaller angles and distances, in the mixture. (See the SI.) Our results are thus fully consistent with some recent experiments and simulations by Grad dolnik et al.69 that found a tendency for pure hydrophobic solutes to strengthen and enhance hydrogen bonding rather than weaken it. It is likely that increased methane content (>14%) reduces the local dipole field of the water molecules, and this may limit the solubility of methane to the observed value of 44% at 3 GPa.

To examine the structural effects of methane mixing at high pressure on the topology of the hydrogen-bond network, we examined the distribution of closed rings made up of hydrogen-bonded water molecules in the different systems. Ring distributions have been used in several previous studies to provide insight into the changes on the hydrogen-bond network of water in the presence of solutes.56–59 The ring statistics are shown in Figure 5c for three different systems: the mixed methane-water system, the demixed slab system, and pure water at 1.5 GPa. We observe that all three systems are dominated by the presence of five-membered rings. However, the number of five-membered rings is highest for the pure water system and lowest for the methane mixture. Furthermore, the presence of water molecules interspersed by methane also results in an increase in the number of larger rings, as seen in the fatty tail of rings with six members or greater.

The presence of 4/5/6/8-membered rings has also been observed in low-pressure methane clathrates,50,61 indicated in Figure 5. The mixture exhibits a greater number of rings, with a greater difference for six-membered, consistent with MH-III (stable above 1.9 GPa), implying a similar clathrate-like structure in the mixed liquid but with greater flexibility for defects in the ring networks. Comparing liquid dipoles with MH-III, the mixture has greater fluctuations in both water and methane molecules. The methane dipole in the mixed liquid is stronger than that in MH-III, partly due to the difference in methane content (0.14 vs 0.33) and due to the geometry restrictions of MH-III where methane molecules exist as pairs. However, methane dipoles in MH-I at 1.5 GPa reveal a distribution closer to that of pure methane, even though the MH-I methane content is 14%, as in the mixed liquid. In the solid hydrates, increasing pressure shows a tendency to increase the methane dipole moment, but we find this effect to be much stronger in the liquid.

The combined experimental and ab initio modeling studies have revealed the structure of the pressure-mixed methane–water fluid. It has a fully hydrogen-bonded water network without significant broken hydrogen bonds and increasing water to methane coordination with increasing pressure and a reduction in the width of the hydration shell. The modeling provides insight into what is changing at the onset of mixing. At a macroscopic level, mixing appears to be driven by a change with pressure in the enthalpy of mixing rather than a change in the entropy of mixing. Mixing is also accompanied by a change in the ring connectivity of the water network with a trend to larger rings than pure water.

Our results begin to understand the importance of electronic polarization on hydrophobic effects in soft-matter systems. Protein–water interactions, for example, will clearly be affected by subtle changes in the polarizability, in particular, under pressure, and play an important role in tuning the phase diagram of protein stability. This opens up interesting challenges for the development of empirical force fields for biological systems under extreme pressures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpcl.0c01410. Simulation snapshots; polarization and Wannier centers; methane hydrate dipoles; vibrational density of states; table of simulation details; pressure temperature phase diagram; equation of state and pressure determination; structure factors; angular distribution functions; entropy of mixing; orientation dynamics; methane hydrate pair

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distribution functions; fluid mixture pair distribution functions; spatial density functions and dipole moment orientations; and dispersion, XC, and dipoles (PDF)

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**Notes**

The authors declare no competing financial interest.

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