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Morphologies Observed in Ultraflexible Microemulsions with and without the Presence of a Strong Acid

Tobias Lopian,†‡ Sebastian Schöttl,§ Sylvain Prévost,§ Stéphane Pellet-Rostaing,‡ Dominik Horinek,†‡ Werner Kunz,†§ and Thomas Zemb†

†Institut de Chimie Séparative de Marcoule, UMR 5257(CEA/CNRS/UM2/ENCSM), 30207 Bagnols sur Cèze, France
‡Institute of Physical and Theoretical Chemistry, University of Regensburg, 93040 Regensburg, Germany
§ESRF—the European Synchrotron Radiation Facility, 38000 Grenoble, France

ABSTRACT: We show that three different morphologies exist near the two-phase boundary of ternary systems containing a hydrotropic cosolvent. Based on synchrotron small- and wide-angle X-ray scattering combined with molecular dynamics, we rationalize the specific scattering signature of direct, bicontinuous, and reverse mesoscale solubilization. Surprisingly, these mesostructures are resilient toward strong acids, which are required in industrial applications. However, on a macroscopic scale, the phase boundary shifts in salting-in and salting-out in the direct and respectively reverse regime, leading to a crossing of the binodals.

INTRODUCTION

Water and octan-1-ol (for simplicity referred to as octanol) are essentially nonmiscible, but upon addition of ethanol, the miscibility gap can be closed. The formation of organized aggregates was observed in the monophasic region of the phase diagram close to the phase boundary using light scattering techniques, and was referred to as the pre-Ouzo effect,¹ which has also been described as "mesoscale solubilization".² To ensure that this is not simply a critical effect, this phenomenon was further investigated by small-angle X-ray and neutron scattering experiments.³ Variation of the contrast allowed detecting an accumulation of ethanol at the interface. These results have been confirmed by molecular dynamics simulations, which demonstrated that ethanol is present in both phases and is enriched at the interface.⁴ Moreover, it was possible to show that the pre-Ouzo aggregates have preferable sizes, which is unusual for critical effects. Thus, the presence of well-defined, swollen micelle-like aggregates with weak intermolecular interactions has been proven. They are composed of mainly octanol, ethanol, and, to a lesser extent, water.

The pre-Ouzo effect is a quite general phenomenon that was also observed in alternative aqueous systems with fragrances,⁵ insect repellents,⁶ or green organic solvents⁷ as organic counterparts. Thus, a generalization for the occurrence of the effect has been formulated: the pre-Ouzo phenomenon is observed in systems containing two solvents, "A" and "B", that are mutually not miscible and a third one, "C", that is miscible with both.⁸ The term detergentless microemulsions has been introduced as concluded from their large solubilization power, which makes them even suitable as media for enzymatic reactions,⁹ and from moderate resistance toward ultracentrifugation, leading to a Winsor-III type of phase separation.¹⁰ Recently, the term ultraflexible microemulsions has been coined and a theoretical framework based on a balance of entropy and hydration forces has been developed.¹¹,¹²

Since the interfacial film is enriched by hydrotrope molecules, any ion present at the interface can be a "perturbing" ion, but also ions in the aqueous pseudophases, as explained with a general concept introduced recently.¹³ Combined X-ray, neutron, and light scattering studies have shown that the microstructuring can transform gradually into aggregates resembling "ordinary" microemulsions, by adding so-called antagonistic salts.¹³

The formation of mesoscopic structures in neat and wet octanol, the most studied solvent for ultraflexible microemulsions (UFME) so far, has been a long-time discussion when it comes to understanding the success and efficiency of the log(Kp) model:¹⁴ the partition of a solute between water and 1-octanol, to determine its affinity toward organic or aqueous phases. In this context it has been revealed by direct (X-ray scattering/diffraction¹⁵) and indirect¹⁶−¹⁸ structure analysis methods that spherical reverse aggregates with tail-to-tail arrangement of octanol molecules are present in wet 1-octanol. With the help of molecular dynamics,¹⁹−²¹ it was

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shown that the actual mesoscopic inhomogeneities in wet octanol are more complicated, since there are many different shapes and sizes of aggregates present. However, Chen and Siepmann demonstrated that spherical aggregates with aggregation numbers from 4 to 6 dominate the statistical distribution in wet 1-octanol, which thus confirms the outcome of the experimental results.21

Based on conductivity measurements, it was postulated that not only one but possibly four different types of regions are present in the monophasic domain of the ternary phase system 1-octanol/ethanol/water at different compositions.22 In the two phase domain of the phase triangle, we use the term phase for compositions at the edge of the equilibrium state. If spontaneous emulsification takes place, we refer to compositions after slight centrifugation (at approximately 1000 rpm). In a macroscopically homogeneous single phase domain, we consider the aggregates and the external medium as pseudophases, as was done for the case of micelles and bilayers by Charles Tanford23 and quantitatively developed by Israelachvili, Mitchell, and Ninham for classical surfactants.24 In this picture, the nonhomogeneous distribution of ethanol in the core or close to the w/o interface is simply averaged.25 Besides a molecular solution and the direct pre-Ouzo clusters, the possible presence of bicontinuous and reverse structures was reported. However, electrical conductivity data only allows a macroscopic interpretation of results, and a hypothesis on structuring on a molecular scale was thus ambiguous. It is worth noting that, to our knowledge, the region on the octanol-rich side of the phase diagram has not been studied yet by X-ray, so no structural reference was known before the present study.

For the first part of this work, two fundamental questions were raised: First, does the structuring of 1-octanol/water mixtures remain present when a component, here ethanol, which closes the miscibility gap between water and octanol, is added? The second question raised was: In case of a stable structuring in the presence of a hydrotrope, is there a transition of the continuous phase via bicontinuous structures in the gap between the direct pre-Ouzo regime and the reverse regime?

We use as model system octan-1-ol/ethanol/water mixtures, since thermodynamic data as well as the solubility of many added solutes are available.26–28 We want to extend the previous analysis to regions all around the phase transition border, using a comparative experimental and theoretical approach. To do this, small and wide-angle X-ray scattering experiments (SWAXS) have been performed to reveal the structuring of the yet uninvestigated part of the phase diagram. To avoid ambiguity on the interpretation of the spectra, complementary molecular dynamics simulations (MD) have been performed.

Morphological transitions of weak aggregates induce the emergence of new properties in complex fluids. For instance, weak aggregates of extractants can be ordered or less ordered, where weak aggregation is defined as any morphological transformation that is linked to less than 1 k_BT per molecule.29 Moreover, it has been shown very recently that mesoscale ordering of weak aggregates originates from attractive interactions already on a molecular level.30 In this work, a comparative analysis of MD simulations, theoretical predictions from electrostatic theory, and experimental SWAXS have been brought together to explain the correlation of attractive interactions between supramolecular structures and the molecular organization of the weak aggregate.

From a more practical point of view, phase separation and the structuring in the phases is crucial for extraction and recycling processes of metals as salts or nonelectrolytes. Therefore, in the second part of this work, we investigate how UFME are modified in their microstructure and properties in the presence of a further additive: sulfuric acid. This acid not only is of industrial interest but also is an example of a system containing a divalent ion, for which colloidal long-range interactions beyond the first neighbors32 have been identified.33 In this context, we focus on the following questions in the second part of this work: How is the miscibility gap modified in the presence of sulfuric acid, and what are the weak molecular interactions behind the variation of the liquid–liquid phase separation observed? Further: How does the addition of an electrolyte influence the microstructuring near the phase boundary? To answer these questions, the pseudoternary phase diagrams have been determined with varying amounts of added sulfuric acid, and SWAXS with and without sulfuric acid has been performed.

RESULTS AND DISCUSSION

Reverse Aggregation on the Octanol-Rich Part of the Phase Diagram. The primary subject of our study was the analysis of the mesoscopic structuring around the binodal for the ternary system 1-octanol/ethanol/water. X-ray scattering techniques are among the few suited methods for probing structure transitions in surfactant-free microemulsions. SWAXS is particularly appropriate, as it yields information from the atomic scale (high Q-values) up to the nano- and mesoscopic scale (low Q-values).

In Figure 1, five different experimental SWAXS spectra are shown for 1-octanol with and without the presence of water and/or ethanol. In the WAXS regime, above 7 nm⁻¹, the curves converge and two peaks are visible. These correspond to the aliphatic and aqueous structure factors of molecular packing, with an intense signal to be found at 14.7 nm⁻¹ and a less pronounced peak at 28 nm⁻¹.

In the small-angle regime below 7 nm⁻¹, all spectra show a characteristic peak, around ~3.5 nm⁻¹ (focused inside the small box of Figure 1), which, according to Franks et al., is a pair...
correlation between hydroxyl groups, since OH groups possess a higher electronic density than the aliphatic bulk (which is predominantly CH₂).\(^ {15,21}\) As mentioned before, alcohol moieties tend to group together, forming nodes of a hydrogen-bond network in dry octanol.\(^ {21}\) Comparing wet (black dashed curve) to dry octanol (dashed in red), the peak shows a higher intensity and shifts slightly toward lower Q-values, which can be related to the accumulation of water at the center of the nodes, causing them to swell. Considering that water reorients octanol molecules to form reverse aggregates, the polar cores exhibit a higher electron density than the aliphatic bulk region, which leads to a higher amplitude. Furthermore, the displacement of the peak toward lower Q-values reflects that the distance between the electron-dense clusters is slightly increasing (from 4.1 nm\(^{-1}\) to 3.5 nm\(^{-1}\), corresponding to real space distances of 1.5 to 1.8 nm).

Adding ethanol to a partially water containing octanol phase leads always to a displacement of the peak toward lower Q-values, compared to dry octanol. At 20 wt % (cyan curve) and 26 wt % ethanol (blue curve) the position of the peak is at even smaller Q-values than wet octanol (3.3 nm\(^{-1}\) and 3.15 nm\(^{-1}\) respectively), implying that, by adding ethanol, the average distance between the swollen nodes can be even further increased. It should further be noticed that the intensities in the small-angle regime for wet and dry octanol, as well as for the sample with 6.7 wt % ethanol, are similar and the peak is shifted to very low Q. In contrast, for higher concentrations of hydrotrope, the signal at very low Q-values gradually increases. This is related to an increase of the compressibility of the solution, which is thermodynamically connected to the S(0)-value of the structure factor.\(^ {34}\)

Thus, from a qualitative analysis of the SWAXS spectra, it can be concluded that, by adding ethanol, the reverse aggregates remain present after introduction of a hydrotrope to the system.

**Comparative Experimental and Theoretical Analysis**

**To Evaluate the Structuration along the Phase Transition beyond the Pre-Ouzo Domain.** As illustrated in Figure 2ii, three experimental SWAXS spectra were collected for octan-1-ol/ethanol/water at different compositions, depicted in Figure 2i. As in Figure 1, the curves converge in the WAXS regime, above 7 nm\(^{-1}\). While the aliphatic correlation peak of ethanol and octanol can be found around 14 nm\(^{-1}\), the signature peak of water is localized at 20 nm\(^{-1}\) (see Figure S1: spectra of the pure solvents). Therefore, the position of the peak of sample (a) is slightly shifted toward higher Q-values (Q\(_{1}\) = 17.8 nm\(^{-1}\)), due to the higher water content. For sample (c), the opposite is found: The position of the peak remains at Q = 14.7 nm\(^{-1}\) as in Figure 1, due to the low amount of water in the solution. With an intermediate intensity, sample (b) shows a signal between the two extremes, where the position of the peak is at Q = 15.1 nm\(^{-1}\). Indeed, Diat et al. demonstrated that the WAXS signal for mixtures of three solvents can be approximately estimated by superposition of the pure solvent spectra.\(^ {3}\)

The spectrum of sample (a) in Figure 2ii shows by far the highest intensity at low Q-values. The composition of the sample was chosen to be in the previously reported pre-Ouzo regime and is not directly situated at the phase border, but several weight percent of ethanol above the binodal.\(^ {8}\) The signal indicates the formation of agglomerates in the nanometer scale. In order to estimate the size of these aggregates, the Ornstein–Zernike equation was applied. We obtain a value \(I_{Q_{0}} = 0.019\) mm\(^{-1}\) for the zero-angle intensity, and a value of \(\xi = 0.8\) nm for the correlation length, which is a measure for the size of the aggregates. This result is in good agreement with reports in previous works\(^ {1,4,13}\) and proves the presence of mesoscopic objects.

A similar slope is found for the spectrum in the intermediate regime (sample (b)) between 3 nm\(^{-1}\) and 6 nm\(^{-1}\). However, at lower Q-values, a plateau appears with an intensity that is much lower than for the pre-Ouzo spectrum. Concerning the intermediate spectrum, similar SAXS profiles were reported for bicontinuous microemulsions, where no correlation peak was found at low Q-values. Such systems have been called “flexible bicontinuous microemulsions”.\(^ {35}\) Thus, our result supports the hypothesis of such a bicontinuity also in the present case, which has also been inferred from recent conductivity data, which were measured in the same regime of the phase diagram.\(^ {22}\) Finally, the intensity at low Q angles is very low for samples in the region with supposed reverse
aggregates, represented by sample (c), with a similar shape of the intensity as demonstrated in the previous paragraph.

Complementary to experimental X-ray scattering, atomistic molecular dynamics simulations have been conducted with systems of the same composition as the experimental ones. The calculated X-ray scattering intensities are illustrated in Figure 2ii. Scattering spectra represent the signal of the totality of aggregates in solution, and, in case of polydispersity, interpretations become scarce.

The theoretical wide-angle regime shows the same tendencies as the experimental results, with the correlation peaks for aliphatic chains and water at the same Q-values. For sample (a), the peak is shifted to $Q = 18$ nm$^{-1}$ as well, due to the higher water content, while it stays around $Q = 14.7$ nm$^{-1}$ for samples (b) and (c). In the small-angle regime, the three spectra show once again profiles very similar to the experimental ones.

Sample (a) shows a typical Ornstein–Zernike behavior, while sample (c) shows a slightly sharper structure peak at $Q = 3$ nm$^{-1}$. The intermediate spectrum shows the same tendencies at low Q-values, with the indication of a peak at 2.1 nm$^{-1}$ and the formation of a plateau at lower angles. Note that simulation predictions of $I(Q)$ for even smaller angles are not feasible, due to the necessity of bigger simulation boxes.

However, it is quite remarkable that all three scattering length density profiles regarding structuring in the mesoscale domain are overlapping to a large degree. This is shown in detail in the Supporting Information, where a detailed comparison of experimental and calculated intensity spectra can be found (Figures S2-A and -B and Tables S1-A and -B).

In agreement with the experimental data set, the theoretical spectra demonstrate the presence of three different types of mesoscopic structures: direct micelle-like pre-Ouzo aggregates, bicontinuous structures, and swollen reverse water pools, surrounded by 1-octanol and ethanol headgroups.

We now analyze the structural differences between the three regimes on a molecular level. Figure 3 depicts representative renderings of 2 nm slices through the simulation boxes for octanol, ethanol, and water, respectively. In the pre-Ouzo region, one finds several small clusters of octanol along with a few monomers that show up as holes in the excess water domain. Ethanol is essentially distributed uniformly throughout the system.

Besides forming an interfacial film, it is also present inside the octanol aggregates. In the octanol-rich region of the ternary phase diagram, the situation is inverted: holes in the octanol domain correspond to numerous agglomerates of water molecules. Ethanol is also absent in some areas of the system, because most of it is accumulated at the octanol/water interface. This is supported by the picture given in Figure S3, showing a surface representation of water and all the hydroxyl groups in the segment, which characterizes these water agglomerates as reverse aggregates, swollen by ethanol. Between these two regimes of aggregation we find a bicontinuous region, in analogy to observations in classical water–oil–surfactant systems.

In the bicontinuous region of the phase diagram, water and octanol each form a sponge-like interwinded network. Similar to the pre-Ouzo regime, ethanol is distributed evenly in the simulation box. The probability of finding an infinite aggregate of octanol, judged by finding an aggregate that extends continuously through the whole simulation box, is 1, and therefore the system is continuous in octanol. For a characterization of the water domain, we employ commonly used criteria denoting percolation in three dimensions (with a corresponding plot in Figure S4):$^{37–39}$ (1) the probability of finding an infinite cluster is above 50%, (2) the cluster size histogram follows a power law with exponent $-2.19$, and (3) the infinite cluster is a fractal object with dimension $d_f > 2.53$. Our analysis shows a probability of the spanning cluster of 89.5%, a power-law exponent of $-2.09$ in reasonable agreement with the theoretical value $-2.19$, and a dimensionality of the infinite cluster of $d_f = 2.78$. The composition is thus well beyond the percolation threshold of water, resulting in continuity both in octanol and in water.

To conclude the first part of the presented work, the combined experimental and theoretical analysis allowed us to confirm that direct micelle-like aggregates are present in the pre-Ouzo regime. Furthermore, the simulations give proof that reverse aggregates are still present on the water-rich side of the phase diagram. The gap between these two regimes is closed by a bicontinuous regime, where phase inversion from a water-continuous to octanol-continuous system occurs. This allows us to define a new mapping of the phases, which is depicted in Figure 4. The structures are the more defined the closer the composition is situated to the phase boundary. With increasing addition of ethanol the aggregation develops more and more into a molecular solution, which is indicated by a color gradient in Figure 4. Note that, in addition to the data shown here, other compositions were investigated with the help of SWAXS experiments along two dilution lines. The results and discussion of these data are given in Figures S5-A and -B.

Miscibility Gap Influenced by the Presence of Sulfuric Acid: Crossing of the Binodals. One quite stunning discovery is the change in the phase transition borders of the pseudoternary system and of the tie lines, when adding sulfuric acid to water. As depicted in Figure S1 (phase diagram in mass fractions), the monophasic region is increasing on the water-rich side of the diagram with increasing acidic concentration, ranging from 0 M to 4 M. On the other hand, the area of the
The progression of the binodal lines is thus the result of the two opposing features, the additional stabilization of pre-Ouzo structures (salting-in) in the water-rich region and the salting-out of water out of octanol in the octanol-rich region. Note also that the partition of ethanol is significantly shifted toward a higher ethanol concentration in the aqueous phase. This can be seen by the change in the slope of the tie lines, as represented in Figure 6.

To check whether the aggregates are still present after addition of sulfuric acid, SWAXS spectra have been recorded in each of the three regimes. A thorough qualitative analysis is neglected here, since our objective is merely to qualitatively assess whether the structures survive such high concentrations of sulfuric acid or if they experience serious structural rearrangements. The compositions of the spectra are shown in the phase diagram of Figure 6, where the amount of water (in wt %) is replaced by the same amount of aqueous sulfuric acid solution (also in wt %). It should be noted that the significant amount of sulfuric acid slightly changes the density, which would lead to different points in diagrams based on volume or mole fractions. As depicted in Figure 7 the shape of the spectra remains roughly the same and thus confirms that the aggregates are still present at 2 M sulfuric acid. All three

Figure 4. Schematic view of the mesoscopic structuring in the ternary phase diagram 1-octanol/ethanol/water. The region around the phase transition border is dominated by 3 different regimes, which are less pronounced, the more the system is diluted with ethanol. The black lines are the experimentally determined tie lines.

Figure 5. Phase diagram of 1-octanol/ethanol/aqueous sulfuric acid in (i) wt % and (ii) mol %, at different acidic concentrations and at 25 °C; the “aqueous phase” takes into account both water and sulfuric acid, for weight and mole fraction calculations. The blue line is the binodal line for 0 M, the light blue one for 0.5 M, the green one for 1 M, the orange one for 2 M, and the red one for 4 M. See Figure S6 for alternative pseudoternary interpretation.
spectra have higher intensity in the low-angle scattering regime, compared to the ternary systems without acid. The introduction of the electron-dense sulfur enhances the scattering contrast, which leads to an increase of intensity.

### CONCLUSION AND OUTLOOK

By performing SWAXS experiments on different monophasic water–ethanol–octanol mixtures along the miscibility gap in the phase diagram, we observe fundamental changes in the nanostructuring of the system: the pattern evolves from a typical Ornstein–Zernike behavior in the water-rich pre-Ouzo domain to a bicontinuous region with a characteristic plateau at low $Q$ and finally to the octanol-rich domain, for which more or less connected w/o domains predominate in a way similar to reverse connected w/o aggregations. Thus, we can draw an analogy toward the morphology transitions in microemulsions containing surfactants. A yet open question is the phase-transition mechanism, which will be the focus of interest for future works. In the pre-Ouzo region, the single-phase domain is enlarged by the addition of sulfuric acid, due to an additional hydration force repulsion, caused by the presence of the electrolyte.

By contrast, in the octanol-rich domain of the phase diagram, the monophasic region is reduced, because sulfuric acid reduces the amount of water dissolved in octanol in equilibrium with the aqueous solution.

These different structures and their modifications in the presence of a significant amount of electrolytes may have significant consequences on various applications. As already shown, they influence biochemical reactions as well as extraction processes. Probably, even chemical reactions can be optimized by a proper tuning of these highly dynamic nanoconfinements, but this will be the topic of future research.

### EXPERIMENTAL SECTION

**Materials.** Octan-1-ol (purity >99%, for simplicity referred to as “octanol”) was purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). Ethanol (purity >99.5%) and sulfuric acid (96 wt %) were provided by Carlo Erba Reagents (Cornaredo, Italy). All samples were prepared with deionized water, with a conductivity of 6.5–12.3 μS·cm$^{-1}$. The solvents were used without any further purification steps. The term dry octanol is attributed to noncontacted octanol, without any drying procedures. The water content from contact with the environment was found to be 452 ppm and determined by coulometric Karl Fischer titration.

**Phase Diagrams.** All phase diagrams were determined with the cloud point method, by initially mixing ethanol with one of the other two solvents, then adding the third one until the clear solution becomes turbid. The initial diagrams were determined in mass fractions $\omega_i$. To obtain the phase diagram in volume fractions $\Phi_i$ the densities of the pure solvents were used, assuming ideal mixing behavior. To obtain the phase diagrams in molar fractions $x_i$, the molar masses of the pure solvents were used. All diagrams were determined at 25 °C.

**SAXS Measurements.** Small and wide angle X-ray scattering (SWAXS) data were acquired at the ID02 beamline at the European Synchrotron Radiation Facility (ESRF, Grenoble, France). A wavelength of 12.46 keV ($\lambda = 0.0995$ nm) was chosen. Two CCD detectors from Rayonix were used (MX170-HS and LX170-HS respectively for SAXS and WAXS), with a geometry allowing simultaneous acquisition with an overlap in $Q$, the magnitude of the wavevector,

Figure 6. Pseudoternary phase diagram of sulfuric acid/ethanol/1-octanol in wt %. The phase transition for pure water is given in blue, for 2 M sulfuric acid in red. Two tie lines are given for each case (blue tie lines for pure water and red tie lines for 2 M acid, respectively. The composition of the three samples, for which SAXS spectra have been recorded, is also indicated.

Figure 7. SWAXS spectra in the presence (blue spectra) and absence (orange spectra) of sulfuric acid in the three designated regions: (i) direct pre-Ouzo, (ii) bicontinuous, and (iii) reverse aggregates.
where $\theta$ is the scattering angle as commonly defined. This configuration requires an air gap of ca. 15 cm, causing an increased signal mostly corrected by subsequent background subtraction. The sample-to-detector distances were 1.5 m for the SAXS detector and 0.13 m for the WAXS, as calibrated by the Bragg peaks of $p$-bromobenzoic acid (SAXS and WAXS), silicon (WAXS), and silver behenate (SAXS). Samples were inserted in a thermalized flow-through quartz capillary of inner diameter 1.7 mm. The data were corrected for the dark current, the flat field, and the transmitted beam as measured by a PIN diode on the beam stop; note that effects from the beam polarization and the sample geometry were not taken into account during data reduction. An absolute scale was obtained using the low-$Q$ intensity level of water (at $1.63 \times 10^{-3}$ mm$^{-1}$ at 25 °C). The scattering from the empty capillary was subtracted. At low $Q$, a significant part of the scattering comes from surface roughness of the quartz capillary, and is therefore poorly corrected, as the inner interfaces of the capillary have different contrasts depending on the capillary filling. This often results in a small upturn or downturn of the intensity as seen in the various spectra presented hereafter.

**SAXS Fit Functions.** To determine the correlation length and radii of the pre-Ouzo aggregates, the Ornstein–Zernike (OZ) equation was used as a model, given by

$$ I(Q) = \frac{I_0}{1 + \xi^2 Q^2} = \frac{I_0}{1 + \frac{R_g^2 Q^2}{3}} $$

with the correlation length $\xi$, the radius of gyration $R_g$, the scattering vector $Q$, and the intensity $I_0$ for $Q = 0$. Full fitting of the spectra using refined expressions is out of the scope of this paper.

**Molecular Dynamics.** The simulations were performed using the software GROMACS 4.6. The systems are sampled as cubic boxes of variable edge lengths (controlled by temperature and pressure coupling, see below) with periodic boundary conditions applied in all directions.

**System Compilation.** Simulation boxes of 11 to 12 nm edge lengths were filled with the three components, octanol, ethanol, and water, inserting new molecules at random. The system chosen to represent the pre-Ouzo regime contains 224 molecules of octanol, 6366 molecules of ethanol, and 25380 water molecules. The intermediate system consists of 2088 octanol, 5608 ethanol, and 8303 water molecules. The system on the water-poor side of the phase diagram is filled with 3000 octanol, 3600 ethanol, and 5400 water molecules.

First, excessive forces in the systems were eliminated applying a steepest descent algorithm. The resulting configurations were then equilibrated for 100 000 steps at 3 fs/step using the parameters for the production run described in the next paragraph but employing a Berendsen barostat.

**Simulation Parameter.** We employed the TIP4P/2005 model for water and the OPLS all-atom force field for ethanol and octanol. For octanol, special torsional parameters for long hydrocarbons were used. van der Waals interactions were described by a Lennard-Jones potential with a 1 nm cutoff. Electrostatic interactions were calculated according to the smooth particle mesh Ewald (PME) algorithm. The temperature was set to 300 K applying the velocity rescaling algorithm while the pressure was held at 1.0 bar by means of a Parrinello–Rahman barostat. The time constant for both procedures was 1 ps, and a compressibility of $4.5 \times 10^{-5}$ bar$^{-1}$ was assumed for the barostat. Bond lengths were constrained to their equilibrium positions using the LINCS algorithm, and hydrogen atoms were represented by virtual interaction sites. The leapfrog scheme was employed as an integration method, using a time step of 5 fs.

The water-rich system was sampled for 700 ns while the intermediate and octanol-rich regimes were both simulated for 200 ns.

**Analysis.** The program nMOLDYN was used to calculate the partial static coherent structure factors from MD trajectories. The partial intensities were derived using the relation $I(Q) \sim S(Q)f_1(Q)f_2(Q)$, where $f_1(Q)$ are the atomic form factors of the scattering particles. These partial intensities were normalized and summed up to obtain the overall intensity.

A distance criterion is used to identify molecular clusters of water or of octanol. For water, an O–O distance of 0.35 nm was used as a cutoff. In the case of octanol, the carbon and hydroxyl group atoms are considered and the cutoff was set to 0.478 nm, the first distinct minimum in the radial distribution function of this subset in bulk octanol. Other values for these cutoffs lead to slightly different results, but the general observations are qualitatively not influenced.

**NOTE ADDED AFTER ASAP PUBLICATION**

Due to a production error, this article published July 11, 2016 with an incorrect version of Figure 2. The correct version published July 27, 2016.