Molecular Clustering in Formaldehyde–Methanol–Water Mixtures Revealed by High-Intensity, High-q Small-Angle Neutron Scattering

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ABSTRACT: Methanol–Water (mw) mixtures, with or without a solute, display a nonideal thermodynamic behavior, typically attributed to the structure of the microphase. However, experimental observation of the microphase structures at the molecular length scale has been a challenge. We report the presence of molecular clusters in mw and formaldehyde–methanol–water (fmw) mixtures using small-angle neutron scattering (SANS) experiments and molecular dynamics (MD) simulations. Hydrophobic clusters of methanol in mw and formaldehyde–methanol in fmw mixtures were observed at low methanol compositions ($x_m \leq 0.3$). A three-dimensional hydrogen-bonded network of water with the solute is observed at $x_m = 0.5$. Linear chains of methanol surrounding the formaldehyde and water molecules were observed at high methanol compositions ($x_m \geq 0.7$). The calculated size of the molecular clusters ($r \approx 0.5$ nm, spherical) from the SANS data and their volume fraction closely matched the MD simulation results.

The composition of methanol–water (mw) mixtures affect the mixture's thermodynamic properties, including the enthalpy of mixing, free energy of solvation, and the excess molar volume, which do not vary linearly. This anomalous thermodynamic behavior is attributed to the dynamic structures at a molecular length scale, referred to as the "microphase". The formation of microphase structures is due to trade-offs between the enthalpic gains and the entropic penalties, which eventually stabilize the system. In the midst of ongoing contradicting views, the common understanding is that methanol forms hydrophobic clusters at low methanol compositions, a bipercolating mixture near equimolar compositions, and linear chains of methanol at high methanol compositions, in which the water molecule is either caged or exists in a free form within the mixture. To understand the structure of the microphase, researchers explored experimental techniques such as neutron diffraction, X-ray techniques, Raman spectroscopy, and classical molecular dynamics simulations. We also used to simulate the microphase structure and complement the experimental observations. However, a quantitative analysis of the presence of microphase structures as a function of solvent composition is yet to be established.

Recently, we showed that syngas and CO$_2$ can be hydrogenated into formaldehyde in methanol–water mixtures and that the concentration of methanol has a significant impact on the product yield. It is known that, when a small organic compound is solvated in mw mixtures, the chemical and physical behaviors of the solute are distinct at different mixture compositions. For example, the equilibrium of heterogeneous catalysis reactions are greatly affected by the mw mixture composition. The solvation structure plays a central role in explaining most of these phenomena.

Formaldehyde hydrates in the presence of water and exists in its metastable form, methanediol (md). At higher formaldehyde concentrations (>3 wt %), dimers and trimers of formaldehyde start forming, and as formaldehyde concentrations increase further, a precipitate of paraformaldehyde (pFa) is obtained. Addition of methanol prevents the oligomerization of formaldehyde, and such formaldehyde–methanol–water (fmw) mixtures are commonly known as formalin solutions. In the presence of methanol, formaldehyde mostly remains in its metastable monomeric form, methoxymethanol (mm). The ability of the metastable monomers (md and mm) to react or adsorb/desorb on to the catalytic surface is likely to be affected by their solvation environment. For example, Magnai et al. reported a cage-like solvation structure around formaldehyde in water, which hindered the translation and rotation of the formaldehyde and thus affected its hydration. Moreover, mm is solvated by a ring/chain structure of 8–10 methanol molecules, which is reported to be the reason for the high catalytic yield of formaldehyde in the presence of methanol. However, the stability and the solvation environment of mm in the mw mixtures remains poorly understood. Our recent molecular dynamics (MD) work predicted the presence of methanol around the hydrophobic sites of mm and methanol at low methanol concentrations.

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experimental study reports the solvation structure of formaldehyde in mw mixtures.

Hitherto, small-angle neutron scattering (SANS) has not been explored to resolve the microphase structure of liquid mixtures such as fmw. In the present work, we demonstrate molecular dynamics simulations to guide the background subtraction and formulate a method to identify the molecular clusters at a high-\(q\) range. Recent advancements in the experimental infrastructure, specifically the improved performance of the detector, facilitate the meaningful collection of scattering data at a high-\(q\) range for such liquid mixtures. The neutron scattering data at a high-\(q\) range, when fitted with the cluster models such as Guinier, Sphere, and Ellipsoid, resolves any cluster formed at a molecular length scale. Understanding these molecular clusters may pave a path to optimize the liquid-phase catalytic reaction mechanisms to produce formaldehyde. Moreover, we believe that this work can be extended to investigate the topology of other liquid mixtures of a similar nature, which is not possible otherwise.

We observed small (<1 nm) molecular clusters in liquid mixtures using a SANS experiment, which could only be possible because of (a) enhanced contrast between hydrogenated clusters and deuterated solvent and (b) the measurement of high-\(q\), high-intensity SANS, which was enabled by a significantly higher count rate detector installed at the Australian Nuclear Science and Technology Organisation (ANSTO) in 2019.

The detailed experimental methods are provided in the Supporting Information, but briefly, the methods are described below.

**Classical Molecular Dynamics Simulations.** Classical MD simulations were performed using the GROMACS simulation package, and the Visual Molecular Dynamics (VMD) software package \(^{33}\) was used for visualization. The all-atom optimized potentials for liquid simulations (OPLS-AA) force field \(^{29,32}\) was used to define the interaction parameters of methanol, mm, and md, while the SPC/E \(^{33}\) model was used for water.

**Preparation of Liquid Mixtures for SANS Experiments.** We prepared three sets of mixtures with formaldehyde (fa) mole fractions \(x_{fa}\) of 0, 0.01, and 0.02. Each set was comprised of seven methanol (m)-water (w) compositions (\(x_m = 0, 0.1, 0.3, 0.5, 0.7, 0.9, \text{and } 1\)). Formaldehyde–methanol–water mixtures are denoted as \(x_m-(\text{mole}\%fa)\_\text{fmw}\); for example, \(0.1-1\_\text{fmw}\) means 1 mol % formaldehyde in mw mixture with \(x_m = 0.1\), and \(0.3\_\text{mw}\) means mw mixture with \(x_m = 0.3\), without any formaldehyde. To achieve a contrast between the molecular clusters and the free solvent, fmw mixtures were prepared such that normal methanol (m) and deuterated-water (d-w) were used when the volume fraction of methanol \(V_{fm}\) was less than or equal to 0.5 (i.e., \(x_m = 0, 0.1, \text{and } 0.3\)), and deuterated-methanol (d-m) and normal water (w) was used when \(V_{fm} \geq 0.5\) (i.e., \(x_m \geq 0.5\)). All the mixture compositions and their \(V_f\) values are given in the Supporting Information (Table S2).

The molecular clusters in the present study are defined as the solvent molecules within the first solvation shell of the solute, including the solute. For example, at a low \(x_{fa}\) of an fmw mixture, mm and methanol molecules within the first solvation shell of mm are considered as a cluster.

**SANS Experiments and Data Fitting.** The prepared liquid mixtures were subjected to high-intensity, high-\(q\) (scattering vector) SANS experiments at the Quokka beamline of the

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**Figure 1.** MD snapshot and scattering curves for mw mixtures where (a) MD snapshot for 0.1-mw, (b) scattering curve and model fit for 0.1-mw, (c) MD snapshot for 0.3-mw, and (d) scattering curve and model fit for 0.3-mw.
The liquid mixtures, prepared in a Hellma cell of 1 or 2 mm thickness, were kept at 4 °C during measurements. We used the data modeling program SASview to fit the SANS data. The data were fitted with sphere, ellipsoid, and sticky-hard-sphere (SHS) models. The first two models did not account for the interparticle interactions that arise from the hydrophilic and the hydrophobic interactions between the solute molecules. Therefore, a structure factor was introduced via the SHS model. More details about the SHS model are provided in the Supporting Information, Section 1e.

The background-subtracted scattering intensity $I(q)$ was fitted with various models to reveal the presence of clusters in mixtures with $x_m \leq 0.5$. No meaningful clustering was observed for mixtures with $x_m \geq 0.5$ (Supporting Information, Section 2). In the subsequent sections, we discuss our observations for mw mixtures at low, equimolar, and high methanol concentrations. The $V_f$ of the clusters obtained by fitting the scattering data shows similar trends to the $V_f$ calculated from MD simulations, as discussed in the Supporting Information, Section 2.

Molecular Clustering in a Methanol−Water Mixture. It is well-established, via soft X-ray absorption spectroscopy, that, at low methanol concentrations ($x_m \approx 0.05$), the three-dimensional (3-D) hydrogen-bonding network of water is not affected and that methanol is hydrated by a shell of water. At $x_m \approx 0.27$, hydrophobic clusters of methanol were reported. However, it is unclear if the tendency of forming these hydrophobic clusters gradually increases on increasing the methanol concentration and if the formation of a hydrophobic cluster within the hydration shell of water is possible at low methanol concentrations (0 < $x_m < 0.27$). Figure 1a shows a snapshot of a cluster of four methanol molecules from the MD trajectory of the 0.1-mw mixture. The hydrophobic tails of methanol orientate toward each other. The coordination number of methanol-methanol molecules is 2.2, as calculated by the center of the mass radial pair distribution function ($g(r)$-com$_{md}$). Figure 1b shows the SANS curve for a 0.1-mw mixture, with Sphere and SHS-Sphere model fits. A sphere with a radius of 2.67 Å, as predicted by the SHS-sphere fits on SANS data; and $g(r)$-com of md-md and md-w, and the potential of mean force (PMF) for md-md interaction in (d–g) 0.1−1fmw mixture and (h–k) 0.3−1fmw mixture.

Figure 2. (a) MD snapshot, (b) SANS data with Sphere and SHS-Sphere fitting curves and (c) $g(r)$-com of md-md and md-w, and the potential of mean force (PMF) for md-md interaction in 0.0−1fmw sample, showing md clustered in water. MD snapshot; SANS data with Sphere and SHS-Sphere fitting curves; centroids of molecules in the cluster, superimposed by a sphere of radius predicted by the SHS-sphere fits on SANS data; and $g(r)$-com of md-md and md-w, and the potential of mean force (PMF) for md-md interaction in (d–g) 0.1−1fmw mixture and (h–k) 0.3−1fmw mixture.
formation of a hydrophobic cluster was gradual at dilute methanol concentrations, thus increasing the possibility of an interaction of the hydration spheres of methanol molecules. This observation concurs with the previously reported MD study, which showed that hydrophobic clustering increases at low concentration ranges and at higher temperatures, where it is easier to break the hydrogen-bonding network of water.34

Solvation Shell Structure of Formaldehyde—Methanol—Water at Low Methanol Concentrations. The metastable form of formaldehyde in water is md, which has a CH2− group attached to two −OH groups. Therefore, the molecule tends to form hydrophobic clusters. Simultaneously, it has a large surface available for hydrophilic interactions due to the presence of two −OH groups on one carbon. Figure 2a shows a snapshot from the MD trajectory of the 0.0−1fmw mixture, where two md molecules are in proximity of each other. The sphere drawn in Figure 2a is centered at the centroid of the cluster with a radius of 3.27 Å, which was obtained by fitting the SHS-Sphere model on the 0.0−1fmw SANS curve (Figure 2b). This cluster’s formation is likely due to the inherent tendency of water to preserve its 3-D hydrogen-bonding network, like in the low-concentration mw mixtures. Moreover, the g(r)-com md (Figure 2c) shows two peaks in the 3−5 Å range, which is due to the hydrophilic (at ~4 Å) and hydrophobic (at ~5 Å) interaction within the hydration sphere. Assuming no more than two molecules form a cluster, the coordination number of ~0.5 between md-md from the g(r)-com md-md (Figure 2c) suggests that ~67% of the md molecules in the liquid mixture are clustered, whereas the remaining are free md molecules.

The dominant metastable form of formaldehyde in all fmw mixtures, with $x_m \geq 0.1$, is mm,24,29 whose details are described in the Supporting Information, Section 1a. The mm molecule has a CH3− and a CH2− group. Therefore, the formation of hydrophobic clusters with methanol is expected. Figure 2d shows the MD simulation snapshot for a 0.1−1fmw mixture, where the hydrophobic tails of three methanol molecules are oriented toward the mm molecule’s hydrophobic sites. The coordination number of methanol around mm in the first solvation shell (g(r)-com mm-mm) is 3.12 (Figure 2g). The Sphere model fit on the scattering data predicted a radius of 2.74 Å, whereas the SHS-Sphere model predicted a radius of 3.53 Å (Figure 2e). Figure 2f shows a sphere with a radius of 3.53 Å as predicted by the SHS-Sphere model, centered at the centroid of the MD snapshot cluster shown in Figure 2d. The sphere in Figure 2f encapsulates all molecular centroids of the cluster, which shows excellent agreement between the simulation and the experiment. Figure 2g shows the center of the mass radial pair distribution function (g(r)-com) between mm-mm, mm-w, and mm-m molecules. The g(r)-com mm-mm shows a single broad peak in the range of 4−6 Å, contrary to the 0.0−1fmw mixture (Figure 2c). Moreover, the lower peak height signifies that only the hydrophobic interaction is dominant between the mm molecules, and the strength of the interaction between two mm molecules is less than that of two md molecules. This observation also supports that, upon addition of methanol, the formation of dimers and trimers of formaldehyde is reduced.

When the methanol concentration is increased to $x_m = 0.3$ (0.3−1fmw), the number of methanol molecules inside the solvation shell of mm increases. Figure 2h shows a snapshot from the MD trajectory, where six methanol molecules are present around one molecule of mm. The g(r)-com mm-mm (Figure 2k) integrates to a coordination number of 7.9 until the first minimum. Similar to the 0.1−1fmw mixture, the hydrophobic tails of methanol molecules are oriented toward the hydrophobic sites of mm. Figure 2i shows the Sphere and the SHS-Sphere model fit. The former model fit results in a sphere with a radius of 2.29 Å, whereas the latter gives a radius of 3.53 Å.
of 4.96 Å. Figure 2j shows a sphere of radius 4.96 Å, drawn from the centroid of the cluster and it encapsulates all the molecular centroids. Because of the specific orientation of the methanol molecules around mm, the shape is closer to an ellipsoid. When the scattering curve was fitted with the SHS-Ellipsoid model (see Supporting Information, Table S6), an equatorial radius of 6.18 Å is observed when the polar radius is fixed at 3 Å. Figure 2k shows the g(r)-com between mm-mm, mm-m, and mm-w molecules. The relative strength of the interaction between mm-mm and mm-m increases compared to the 0.1−1fmw mixture, an effect of which is also manifested in the scattering curve. Because of the increased interparticle (mm-mm) interactions, introducing a structure factor for the 0.3−1fmw mixture is necessary and is apparent in the scattering curve (Figure 2i). This result also supports the argument that, in dilute concentrations, the formation of a hydrophobic cluster is likely and that the 3-D network of water is fragmented.

To confirm that the methanol molecules are hydrophobically oriented around methanol at low methanol concentrations, we compared the g(r) between C1_{mm}-C_m and C1_{mm}-O_m and between C2_{mm}-C_m and C2_{mm}-O_m (Figure 3). The C1_{mm} originates from the formaldehyde carbon and C2_{mm} from the methanol’s carbon, which makes up the methoxymethanol molecule. For a hydrophilic interaction between mm and methanol, we would expect the g(r) to show the O_m-C_{mm} distance to be shorter than that of C_m-C_{mm}. Conversely, for a hydrophobic interaction, we would expect the g(r) to show the C_m-C_{mm} distance to be shorter than that of O_m-C_{mm}. The first peak in the g(r) between C(1 or 2)_{mm}-O_m is due to the methanol molecules present around methoxymethanol, a result of the hydrophilic interactions. However, most of the methanol molecules contributing to the second peak are due to hydrophobic interactions. In contrast, the first peak of C(1 or 2)_{mm}-C_m is due to hydrophobic interactions between methanol and mm. For x_m = 0.1 and 0.3, the height of the first peak of the C(1 or 2)_{mm}-C_m g(r) is higher than the first peak of C(1 or 2)_{mm}-O_m g(r), which shows that the strength of interaction is more significant for the hydrophobic interactions. Figure 3a shows that the coordination number is low (<0.2), until the first minimum of the C(1 or 2)_{mm}-O_m and increases to ~1 for the first minima of C(1 or 2)_{mm}-C_m, indicating that more methanol molecules are hydrophobically oriented and their oxygen is counted in the second peak of C_{mm}-O_m g(r). The difference between the first peak of C(1 or 2)_{mm}-C_m and the second peak of C(1 or 2)_{mm}-O_m is ~1.5 Å, which supports our observation that the molecules contributing to the first peak of C(1 or 2)_{mm}-C_m g(r) and the second peak of C(1 or 2)_{mm}-O_m g(r) are largely the same. Therefore, the g(r) in Figure 3a,b reveals that methanol molecules are hydrophobically oriented toward the hydrophobic ends of the mm molecule at low methanol concentrations. However, this is not the case for x_m ≥ 0.5 mixtures (Figure 3c−e); the strength of hydrophilic interactions between C1_{mm}-O_m increases and is more prominent for higher methanol concentration mixtures. This orientation changes on further increasing the x_m. The coordination number for the first peak of C(1 or 2)_{mm}-O_m indicates more hydrophilic interactions between methanol and mm. This is also due to a greater number of methanol molecules in the mixture. However, the greater increase in the coordination of C(1 or 2)_{mm}-O_m than C(1 or 2)_{mm}-C_m at lower distances shows that fewer molecules of methanol are hydrophobically interacting with mm. This gap in coordination number fades after the first minima of C(1 or 2)_{mm}-O_m.

**Figure 4.** (a) MD snapshot of the solvation environment, (b) the background-subtracted scattering curve, and (c) the g(r) for the 0.5−1fmw mixture. The MD snapshot of the solvation environment is shown for the (d) 0.7−1fmw and (e) 1−1fmw mixtures (radius = 4.96 Å).
an MD snapshot. A fragmented network of water molecules hydrogen-bonded to each other was observed at the mm molecule’s hydrophilic site. The scattering curve with SHS-Sphere fit (Figure 4b) resulted in a cluster with a radius of 4.32 Å, which is smaller than that of the cluster observed for 0.3–1fmw. This is confirmed by the g(r)-com of mm-w shown in Figure 4c. The smaller size of the cluster is due to the small size of water molecules forming this cluster and because of the strong hydrogen bonds between the water molecules and mm (i.e., shorter bond lengths). At higher x_m (i.e., ≥0.7), the mm was mostly surrounded by methanol molecules. Water is present at the mm molecules’ hydrophilic sites; however, a network of hydrogen-bonded water was not observed. In such cases, no meaningful scattering data could be resolved after the background subtraction. This can be attributed to the fact that methanol forms linear chains and mostly surrounds the mm molecule. For 0.7 methanol forms linear chains and mostly surrounds the mm molecule in pure methanol surrounded by water present around one molecule of mm, and hence cluster formation is unlikely. In 1–1fmw, mm is surrounded by a linear chain structure of methanol molecules, as shown in Figure 4e. The mm molecule in pure methanol surrounded by a ring structure of 8–10 methanol molecules was reported in our earlier ab initio MD study. Guo et al. also showed that water is expected to exist in free form or trapped in methanol chains at high x_m methanol–water mixtures.

In summary, the solvation environment of methanol in water and formaldehyde in methanol–water mixtures was studied via small-angle neutron scattering at a high-intensity and high-q range, and MD simulations guided the background subtraction. Sphere, Ellipsoid, SHS-Sphere, and SHS-Ellipsoid models were fitted against the scattering data to analyze the size and shape of the molecular clusters. The SHS-Sphere and SHS-Ellipsoid models provided the best fit as the SHS model captures the interparticle interactions between molecular clusters. The cluster size and Vf calculated by experiments matched the simulation results. At low methanol concentration (x_m = 0.1 and 0.3), a hydrophobic cluster of methanol was observed. The size of the cluster increased from 3.53 to 4.96 Å for x_m = 0.1 and 0.3, respectively. In a formaldehyde–water (x_m = 0.0) mixture, formaldehyde clusters formed in a hydration shell. When methanol was added (x_m = 0.1 and x_m = 0.3), the tendency of formaldehyde to form clusters became weaker, and methanol oriented itself hydrophobically around methoxymethanol. At an equimolar mixture composition, a fragmented network of hydrogen-bonded water molecules was observed around the hydrophilic site of formaldehyde. No meaningful clustering could be resolved at compositions x_m ≥ 0.7 due to methanol forming a linear chain structure and solvating the methoxymethanol and water.

**ASSOCIATED CONTENT**

1. Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpcl.0c03515.

A detailed description of computational and experimental methodology, background-subtracted scattering data, and volume fraction results (PDF)

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**ABBREVIATIONS**

mm, methoxymethanol; md, methanoldiol; m, methanol; w, water; g(r)-com, center of mass radial pair distribution function; fmw, formaldehyde–methanol–water mixture; mw, methanol–water mixture

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