

Chemically Dependent Transport in a Cross-linked H_{II} Phase Lyotropic Liquid Crystal Membrane

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Abstract

The uniform size and complex chemical topology of the pores that constitute cross-linked inverted hexagonal (H_{II}) phase lyotropic liquid crystal (LLC) membranes make them promising for selective separations. In this work, we observe transport of water, sodium ions and 20 small polar solutes within the pores of an LLC membrane using atomistic molecular simulations. We found that the transport rate of a species is dependent not only on molecular size, but on chemical functionality as well. The membrane’s inhomogeneous composition gives rise to radially dependent transport mechanisms with respect to the pore centers. In general, we observed that all solutes perform intermittent hops between lengthy periods of entrapment. Three different trapping mechanisms are responsible for this behavior. First, solutes that drift out of the pore can become entangled among the dense monomer tails. Second, solutes can donate hydrogen bonds to the monomer head groups. Third, solutes can coordinate with sodium counter ions. The degree to which a solute is affected by each mechanism is dependent on the chemical functionality of the solute. Using the insights developed in this study, we can begin to think about how to redesign existing LLC membranes in order to perform solute-specific separations.

1 Introduction

Membranes capable of separating nm-sized solutes with high selectivity and permeability are highly desirable for a number of applications. For example, separation of salt from seawater or other briny sources can yield potable drinking water.¹ Removal of organic micropollutants, such as personal care products, pesticides and pharmaceuticals, from surface and groundwaters, can have large benefits for public health.² Finally, one can purify and recover dissolved species present in complex hydraulic fracturing flowback water waste streams which would help mitigate the effects of deep well injection and generate value.³

All of these separations are possible with current commercial membrane separation tech-

niques but suffer from serious drawbacks. Currently, reverse osmosis (RO) and nanofiltration (NF) dominate commercial membrane separations of small molecules.⁴ RO membranes are typically dense polymer matrices that separate solutes based on differences in their solubility and permeability in the membrane material.¹ Although they can perform highly selective separations, high feed pressures, and thus large amounts of energy, are necessary in order to generate a useful permeate flux.⁵ NF membranes have well-defined nm-sized pores which can give the same permeate flux as RO with lower applied pressure.⁶ However, the pores are not uniform in size, limiting selectivity.⁷

Cross-linked H_{II} phase lyotropic liquid crystal (LLC) membranes are nanostructured membranes that may be able to achieve the selectivity of RO membranes while maintaining the high permeability of NF membranes.⁸ The H_{II} LLC phase is formed when LLC monomers self-assemble into hexagonally packed and uniform-sized pores.⁹ Alignment and subsequent cross-linking of the hexagonal mesophases yields a mechanically strong membrane.^{10,11} The uniform-sized pores enforce a strict molecular-size cut-off while the hexagonal geometry is ideal for high permeability.⁸ Additionally, because the LLC monomers are salts, Donnan exclusion plays a role in rejection of charged molecules upon pore entry.¹²

In addition to geometric factors which make H_{II} membranes ideal for selective separations, they have the potential to further disrupt conventional membrane separation techniques by being selective based not only on solute size and charge, but on chemical functionality as well. The functional LLC monomer head groups that occupy the pore region of the membrane can interact with solutes. Dischinger et al. studied the performance of a Q_I phase LLC membrane, which has a similar pore topology to the H_{II} phase, but a more tortuous geometry, and observed a range of selectivities dependent on the anion coordinated to the LLC monomer.¹³ Intelligent design of LLC monomers can help us tailor membranes for solute-specific separations.

While H_{II} membranes have been synthesized and characterized in a lab setting, there is a limit to the level of detail that can be obtained from experiment. The separation performance

of these membranes has been primarily characterized with size-exclusion experiments which emphasizes selectivity based on the ability to enter a given pore.⁸ While size-exclusion is a useful separation, it cannot reliably purify a solution where the solute size is on the same order as water. Therefore, it is important to take advantage of material properties other than pore size. Unfortunately, the complexity of LLC Membranes has obscured the interpretation of experimental transport studies.¹³

Molecular dynamics (MD) simulations can give us mechanistic insights with atomistic resolution so that we can directly observe small solute transport within LLC membrane nanopores and intelligently design new membranes for solute-specific separations.

In our previous work, we used MD simulations to determine the most likely structure of the hexagonal phase formed by the monomer Na-GA3C11, expanding upon the most recent experimental characterization.^{11,14} We developed techniques for equilibrating the hexagonal phase formed by neat monomer as well as with varying amounts of water in the pores.

In this work, we have studied the transport mechanisms exhibited by 20 uncharged polar solutes with varying size, chemical functionality and hydrophilic character. We have listed the solutes studied along with the abbreviations that we will use in the charts for the remainder of this paper in Table 1.

First, we will comment on the membrane’s structure. Previously, we have studied dry membrane systems and some systems with low water content. We will observe how the radial density of monomer components and water change based on membrane water content.

Then we will present our efforts to understand how small molecules, including water, partition within the pores. From a macroscopic perspective, it is straightforward to hypothesize that the water and polar solutes spend their time exclusively in the tube-like hydrophilic pore region. Our previous work showed that there is a gradual compositional transition from the hydrophilic to the hydrophobic region which means that solutes may not necessarily stay confined to the centers of the pores or even within the pore region. We will study the gradient in composition of solutes and water and any resultant influence it might have on mechanistic

Table 1

Solute Names and Their Abbreviations	
Name	Abbreviation
Acetic Acid	ACH
Acetamide	ACN
Acetone	ATO
Butanol	BUT
Dimethyl Formamide	DMF
2,3-Dimercapto-1-propanol	DMP
Dimethyl Sulfoxide	DMSO
Ethyl Acetate	EAC
Ethanol	ETH
Ethylene Glycol	GCL
Glycerol	GLY
Methanol	MET
Propylene Carbonate	PCB
Propylene Glycol	PG
Propanol	PR
Ribose	RIB
Mercaptoethanol	SOH
Tetrose	TET
Tetrahydrofuran	THF
Urea	URE

properties.

Finally, and for the bulk of this work, we will present our observations and explanations of the observed transport mechanisms exhibited by water and solutes. Given that the pores will restrict motion of the solutes, we anticipate that transport will be hindered in some way. We want to understand the differences in solute motion, specifically its mean squared displacement (MSD), based on a solute’s size, shape and chemical functionality. We will study the interactions between solutes, the membrane, and water in order to determine which mechanism or mechanisms dominate.

There are also a couple of points that this study is not intended to address. First, we will not study the concentration dependence of the observed transport rates. Although the average MSD might change with concentration, we are focused on the underlying solute-membrane interactions that lead to the observed transport mechanisms which we conjecture will be the same regardless of concentration. Second, we will not study the chemical potential of solutes in the pores, which could give us a better understanding of equilibrium solute partitioning. This information will not greatly enhance our understanding of mechanistic details in various membrane regions. Both of the above points will add unnecessary levels of complexity which can be left for a future study. This work is a simple starting point meant for observing the types of interactions which occur between isolated solutes and the membrane.

2 Methods

Python scripts used to set up systems and conduct post-simulation trajectory analysis are available online at https://github.com/shirtsgroup/LLC_Membranes. The appropriate scripts to use for the subsequent calculations are summarized in Table S1 of the Supporting Information.

We ran all molecular dynamics simulations and energy minimizations using GROMACS

2.1 System Setup

Stable H_{II} phases, assembled with Na-GA3C11, can be formed using a broad range of water concentrations. In the literature, the system studied in this work is typically synthesized with close to 10 wt % water.^{9,19} However, Resel et al. noted that the system is likely fully hydrated with less than 7 wt % water.²⁰ Excess water fills space between hexagonal mesophases. We decided to test systems with two different water contents: 5 and 10 wt %.

We observed that water partitions into the distal tail region of our system and therefore built our initial configurations with water in both regions, close to the expected equilibrium partition. We define the distal tail region to be ca. 1.5 nm from the pore center based on the minimum in the radial distribution of water (see Section 2.10). The amount of water present in the distal tail region may or may not be experimentally consistent but it is necessary for our results to be thermodynamically consistent. We iteratively adjusted the pore radius in our systems until the appropriate amount of water fit in the pores after running the GROMACS command `gmx solvate`. We placed water molecules in the distal tail region one at a time in random locations with a short energy minimization between each insertion. When studying transport of water in the pores, we limited the calculations to water molecules that spent greater than 95 % of their time outside of the distal tail region.

We equilibrated an initial solvated configuration before adding solutes. First, we equilibrated the initial configuration using the ‘wet’ equilibration procedure described in our previous work. Then we cross-linked the equilibrated solvated configuration using the cross-linking procedure also described in our previous work.²¹

To study a given solute, we added 6, equally spaced in z , solute molecules to the center of each pore of the equilibrated cross-linked configuration. Our choice of 6 solutes per pore provided a balance of a useful amount of data for generating statistics and a low degree of interaction between solutes (see Section S3 of the Supporting Information). At each insertion

point we placed a randomly oriented solute molecule then ran a short energy minimization. We allowed the solutes to equilibrate for 5 ns using berendsen pressure control then collected transport data over the course of 1 μ s MD simulations.

2.2 Solute Parameterization

We parameterized the interaction potential for the monomer and solutes using the Generalized AMBER Force Field (GAFF)²² with the Antechamber package²³ shipped with AmberTools16.²⁴ We use GAFF since it has been parameterized for use with organic molecules. We assigned atomic charges using the am1bccsym method of `molcharge` included with QUACPAC from Openeye Scientific Software.

2.3 Mean Squared Displacement

We measured the time-averaged z -direction mean squared displacement (MSD) of the centers of mass (COM) of each solute over the course of 1 μ s MD simulations using Equation 1:

$$\overline{z^2(\tau)} = \frac{1}{T - \tau} \int_0^{T-\tau} (z(t + \tau) - z(t))^2 dt \quad (1)$$

where τ is the time lag and T is the length of the trajectory.²⁵ Generally, the MSD grows according to Equation 2:

$$\langle z^2(t) \rangle = K_\alpha t^\alpha \quad (2)$$

where α is the anomalous exponent and K_α is the generalized diffusion coefficient. A value of $\alpha < 1$ indicates a subdiffusive process, while a value of $\alpha = 1$ and $\alpha > 1$ is characteristic of Brownian and superdiffusive motion respectively. In practice, α corresponds to the growth of the *ensemble* MSD given by Equation 3:²⁵

$$\langle z^2(t) \rangle = \langle z(t) - z(0) \rangle \quad (3)$$

Since the ensemble MSD is calculated with respect to a reference position, it carries some dependence on its starting point. The time-averaged MSD averages over all possible time lags of a given length, effectively eliminating any initial configuration dependence and generating an increased number of observations. For ergodic systems, both types of MSDs will be equal. Since we have a small number of solutes with which to generate statistics and because we are not calculating values of α for this particular study, we will only use the time-averaged MSD.

We fixed the length of each simulated trajectory so that we could compare the total MSD between different solutes without the influence of the ageing phenomenon. In systems such as ours where solutes show hopping behavior between long periods of immobility, ageing is defined by the tendency of the average slope of an MSD curve to decrease as the length of trajectories are increased.²⁶ Since the maximum measured dwell time can be no longer than the total length of a simulated trajectory, longer dwell times are incorporated into the calculation as measurement time or trajectory length is increased, lowering the average MSD. Because the solute MSDs are non-linear and because of the ageing phenomenon, we did not attempt to calculate a diffusion constant as one might for a Brownian particle with a linear MSD. Instead, the reported MSD values represent the average MSD for a given solute after a 400 ns time lag. Our results are shown to be insensitive to our choice of time lag in Section S4 of the Supporting Information.

The z -direction MSD of water in the 10 wt % system is linear. Therefore, for the purpose of comparison, we calculated its diffusion constant by fitting a line to the linear region of the MSD curve.²⁷ The diffusion constant is then equal to $m/2$ where m is the slope of the linear fit. The slope is divided by 2 (rather than 6) because we only measured the diffusion coefficient in one dimension.

2.4 Molecular Size Determination

In order to determine an effective radius for each solute, we divided in half the maximum pairwise distance between atoms of each solute over the course of a 2.5 ns simulation of solutes dissolved in a cubic box of water. Each box consisted of about 2100 water molecules and 6 solutes. Although there exist more involved methods for determining the hydrodynamic radius,²⁸ we chose to use a simpler and more intuitive metric since we are only interested in observing trends in the solute mean squared displacement as a function of solute size.

2.5 The Stokes-Einstein Relationship

The Stokes-Einstein relationship expresses the diffusion coefficient of a hard spherical particle as a function that is inversely related to the particle’s radius:

$$D = \frac{k_b T}{6\pi\eta f r} \quad (4)$$

where k_b and T are the Boltzmann constant and the system temperature respectively and η is the system’s viscosity. Here we have also included the microfriction correction factor, f , introduced by Gierer and Wirtz^{29,30} for when solute size becomes on the order of solvent size since the solute can no longer be treated as a non-interacting hard sphere. f is defined in terms of the ratio of r_1 and r_2 , the radii of the solute and solvent molecules respectively:

$$f = \left(1.5 \frac{r_2}{r_1} + \frac{1}{1 + \frac{r_2}{r_1}} \right)^{-1} \quad (5)$$

For consistency with the presentation of our results, rather than calculate trends in D , we will apply Equation 4 in order to analyze trends in solute MSDs, which is only valid because all trajectories are of the same length.

Since we will be using this equation for primarily qualitative observations, we made a number of simplifying assumptions so that it could easily be used for comparison between

systems. First, we assume that all systems’ viscosities are equal since we only make minor changes to the membrane’s composition and accurately assessing the viscosity in a complex and inhomogeneous system such as ours is a challenge by itself. Second, we assume all particles are approximately spherical, neglecting the effect of solute shape on mobility. Chan et al. showed that the difference in diffusion constants of differently shaped particles, with constant molecular volume, did not differ by more than 25 % with most deviating by less than 10 %.³¹ Third, we assume that the ratio of solute and solvent radii as calculated using the methodology of Section 2.4, is equivalent to the the ratio of hydrodynamic radii. For similarly shaped molecules, it has been shown that one can relate the hydrodynamic radius and radius of gyration (R_g) using a constant scaling factor.^{32–34} Assuming that our end-to-end distance reasonably approximates R_g for our small, relatively inflexible molecules, we believe this assumption is justified for qualitative demonstrations relevant to this study.

In order to make qualitative comparisons, we fit Equation 4 so that it passed through the highest solute MSD. We assumed that the solute with the highest MSD behaved the most “Stokes-like” and therefore could set a rough boundary between subdiffusive, Brownian and superdiffusive MSDs. As a lower bound to our approximation, we also plotted the uncorrected version of Equation 4 ($f=1$), requiring it to converge to the same value as the corrected curve for large radii.

2.6 Hop Detection

In order to measure the length of hops, we first needed to detect when they occurred. We used an off-line change point detection algorithm, implemented in the python package **ruptures**,³⁵ in order to determine at which points hops occurred in the time series of each solutes’ COM. We used the 3 dimensional COM positions of each solute, rather than just the z -direction, in order to detect lateral hops. However, hop lengths are reported as their displacement the z -direction.

2.7 Identification of Hydrogen Bonds

Based on the geometric criteria proposed by Luzar and Chandler,³⁶ we determined a hydrogen bond to exist if the distance between the donor, D, and acceptor, A, atoms is less than 3.5 Å and the angle formed by D–H · · · A is less than 30°. Attempts to describe a hydrogen bond in the context of molecular simulations has yielded a number of definitions with no true consensus³⁷ especially since the geometry of hydrogen bonds has some dependence on the system being studied. The definition of Luzar and Chandler is easily visualized for trajectories using the `hbonds` representation of the Visual Molecular Dynamics (VMD) software package which allows us to directly check the validity of identified hydrogen bonds. In Section S6 of the Supporting Information, we show that our conclusions are insensitive to this definition within a reasonable range.

2.8 Coordination Number

We quantified the coordination of solute constituent atoms with sodium ions. For each frame, we counted the number of coordinated molecules to a given solute atom based on a distance cut-off. Using four different methods, Rowley and Roux observed peaks in the radial distribution function for sodium coordinated with water at an O–Na distance of between 2.3 and 2.5 Å.³⁸ We used 2.5 Å as the distance cut-off. We found that this approach is more useful than calculating the 3D spherical radial distribution function because it gives detailed frame-by-frame information rather than an average.

Using our procedure we found that sodium ions in a solution of tip3p water coordinate with an average of 3.6 water molecules. We created a 4 x 4 x 4 nm cubic box of water with the GROMACS tool, `gmx solvate`. We used `gmx genion` to replace water molecules with sodium and chloride ions in order to create a 0.1 M NaCl solution. We let the system simulate for 5 ns and reported the average number of coordinated water molecules per frame after discarding the first nanosecond of simulation.

2.9 Association Lifetimes

We quantified the length that two species stay associated via hydrogen bonding or coordination. For each unique pair, we measured the number of consecutive frames in which they stayed associated. We considered pairs that disassociated for a single time step and reformed on the next time step as a single continuous association event. We compiled the length of these events into a distribution of association lifetimes.

We found that the distributions best fit a power law / exponential distribution.

2.10 Radial Distribution Functions

We measured the average radial distance of each solute of interest from the pore centers. We binned the radial distances and then normalized by the volume of the annulus defined by the bin edges. Although the pores are often described as straight, they have a small degree of tortuosity which disrupts the RDF calculation. We tried to mitigate the effects of tortuosity by calculating the RDF with respect to splines that run through the pore centers. See Section S5 of the Supporting Information for a graphical illustration. Each spline consists of 10 points, equally spaced in the z -direction, whose (x, y) coordinates are defined based on the center of mass of all head groups closest, in z , to the given point. When calculating RDFs, the radial distance from the pore center is based on the distance between the solute center-of-mass and the linearly interpolated (x, y) coordinates of the pore center calculated based on the closest two spline points. Using the splines, we calculated the tortuosity of the pores by calculating the ratio $\frac{L}{Z}$ where L is the length of the spline and Z is the length of the unit cell in the z -direction. The average tortuosity of each pore is 1.03 ± 0.01 and 1.07 ± 0.02 in the 5 and 10 wt % water systems respectively.

In all RDF plots, we include the average RDF of the head groups as a reference. The head group RDF shown is the average of the head group RDFs for each solute system in the plot. We generated 95 % confidence intervals by bootstrapping the RDF of each individual head group. For each head group, we obtained an RDF averaged over the entire simulation

trajectory. We randomly chose head group RDFs with replacement and averaged them for each bootstrap trial. This approach assumes that head group positions are uncorrelated.

3 Results and Discussion

3.1 Structure of Membrane Constituents

Before beginning the analysis of transport behavior, it is important to elucidate the topology of the membrane pores in solvated systems.

In contrast to our previous work with a dry version of this membrane, the pore region of the 5 and 10 wt % water systems are primarily filled with water and sodium ions. We define the pore region based on the average COM position of the monomer head groups' carboxylate oxygen atoms. Figure 1 plots the RDF of each membrane constituent in the dry system as well as the 5 and 10 wt % water systems. In dry systems, the pore center is densely filled with sodium ions and head groups. The peak head group density occurs within 0.25 nm of the pore center. In hydrated systems, water occupies, and is densest, at the center of each pore. The density of sodium ions is somewhat uniform in the pore center of the 5 wt % water system while it shows a maximum closer to the head groups in the 10 wt % water system. The peak density of sodium ions is not at the pore center in the 10 wt % water system likely because they are still loosely associated with the monomer's carboxylate head groups.

Pores in the 10 wt% water system are wider and less crowded by monomers than those in the 5 wt% water system. The peak head group density of 10 wt% water systems is about 0.2 nm further from the pore center than the 5 wt% water system. Based on these observations, we expect solute transport to be fastest in the 10 wt % water system.

There is an appreciable amount of water that partitions into the distal tail region of both systems. 28 % and 31 % of the total water is present in the tail regions of the 5 and 10 wt% water systems respectively. See Section S2 of the Supporting Information for more details.

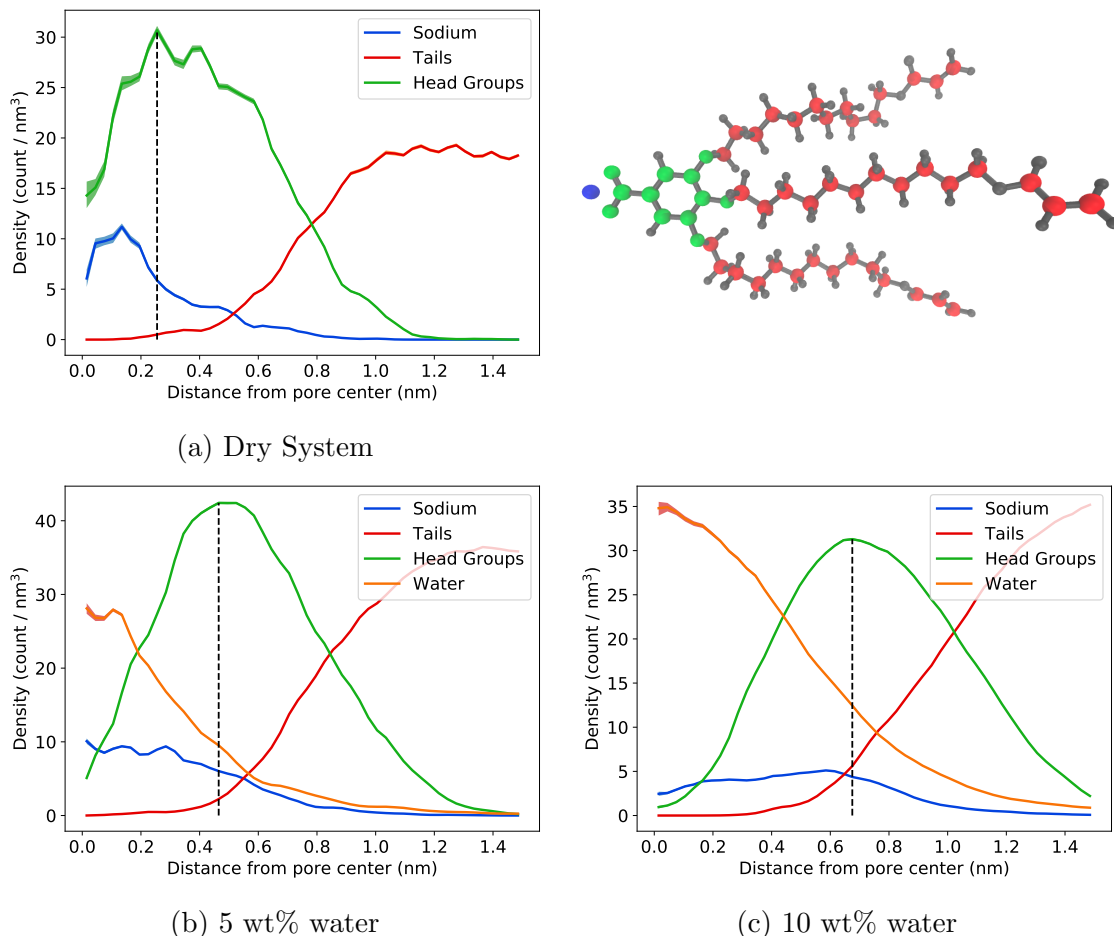


Figure 1: The radial densities of various monomer components paint a picture of the pore topology where the pore centers are primarily composed of water and sodium ions. The monomer groups labeled in each plot correspond to the color-coded monomer pictured in the upper right corner of the figure. All RDFs represent the number of atoms located at a given distance from the pore center normalized by the volume of the annular bin to which they belong. (a) In the dry system, the density of head groups and sodium ions are highest within 0.25 nm of the pore center. (b) In the 5 wt % system, monomer head groups retreat about 0.2 nm radially in order to make room for water molecules. (c) Monomers in the 10 wt % system retreat an additional 0.2 nm to make room for more water.

This result is due to a combination of the lower density of the tail region as well as oxygen atoms at the ends of each monomer tail which can further stabilize water molecules. See Figure S9 of the Supporting Information for a graphical illustration of this point.

3.2 Mechanisms Governing Small Solute Transport

We observed transport of sodium, water and 20 other small polar solutes inside the membrane nanopores. First, we will comment on transport of the membrane constituents, water and sodium, in a system absent of any additional solutes. Then we will present the general trends that we observe among the set of solutes studied.

3.2.1 Water and Sodium Ions

Water and sodium's mobilities increase in larger and less crowded pores. In the 10 wt% water system, the MSD of water is about 51 times higher and the MSD of sodium is about 49 times higher compared to the 5 wt % water system. In the 10 wt % water system, water moves about 51 times faster than sodium and in the 5 wt % system, water moves about 49 times faster than sodium. Assuming long timescale Brownian behavior of water in the 10 wt % system, we measured its diffusivity to be $7.45\text{e-}07\text{ cm}^2/\text{s}$ which is only 1.4 % that of bulk tip3p water.³⁹

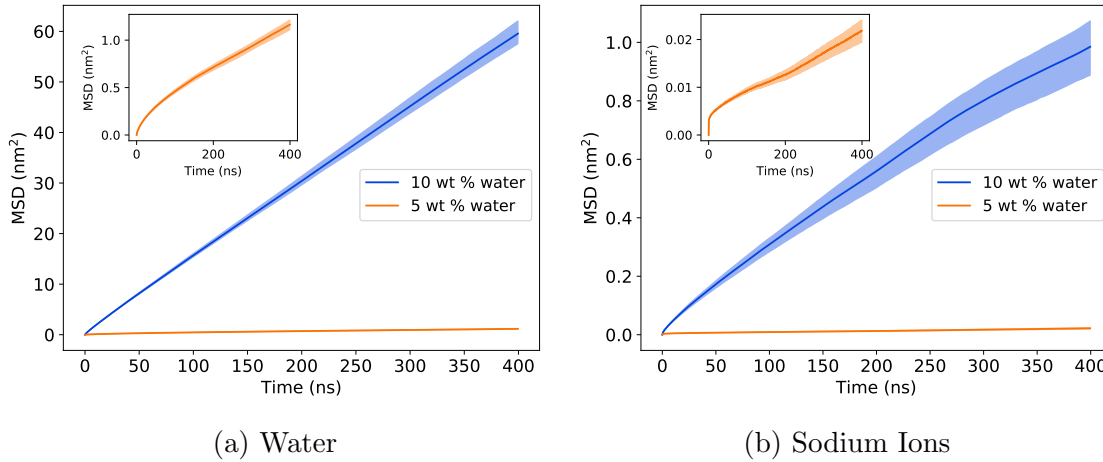


Figure 2: (a) The MSD of water in the 10 wt % water system is about 51 times higher than water in the 5 wt % water system. (b) The MSD of sodium in the 10 wt % water system is about 49 times higher than sodium in the 5 wt % water system.

Sodium coordinates with far less water molecules than it does in bulk solution. Compared to 3.4 coordinated water molecules in bulk solution (see Section 2.8), sodium ions in our

system, on average, coordinate with about 1.7 water molecules in the 10 wt % system and 1.2 water molecules in the 5 wt% system. However, the sodium ions are not undercoordinated since they frequently pair with negatively charged carboxylate head groups. On average, sodium ions coordinate with 1 carboxylate group in the 10 wt % water system and 0.8 carboxylate groups in the 5 wt % water system.

3.2.2 Transport of Small Polar Solutes

We observe trends in transport properties that are dependent on the chemical environment within the nanopores rather than just solute size. Polar solutes are slowed by interactions between monomer functional groups and ions. Solutes with hydrophobic character partition out of the pore and are slowed by densely packed organic monomer components. A thorough understanding of these interactions will help us to create monomer design principles. We will begin our analysis by considering the collective trends observed across all systems and then focus on subsets of similar molecules.

Like water and sodium above, the MSDs of the solutes studied in this work are significantly larger in the 10 wt % system than those in the 5 wt % water system (Figure 3). The fastest moving solute in both cases, methanol, has an MSD about 175 times larger in the 10 wt % versus the 5 wt % water system. Clearly the equilibrium water content of a given LLC system will determine its viability for real separations.

The MSDs are not solely a function of solute size. We plotted each solute’s radius against their MSD in Figures 3c and 3d. Of all the solutes, we believe methanol is subject to the least hindrance by the membrane due its small size. Therefore we fit Equation 4 so that it intersected methanol’s MSD. The uncorrected version of Equation 4 is plotted and converges to the same value as the corrected form for large radii (see Section 2.5). Although both curves are approximations, they illustrate that the majority of solutes in our study show lower than expected MSDs. In most cases, the predicted MSDs even fall below the conservative uncorrected Stokes-Einstein estimate. It is clear that more complex mechanisms

determine the MSDs of these solutes.

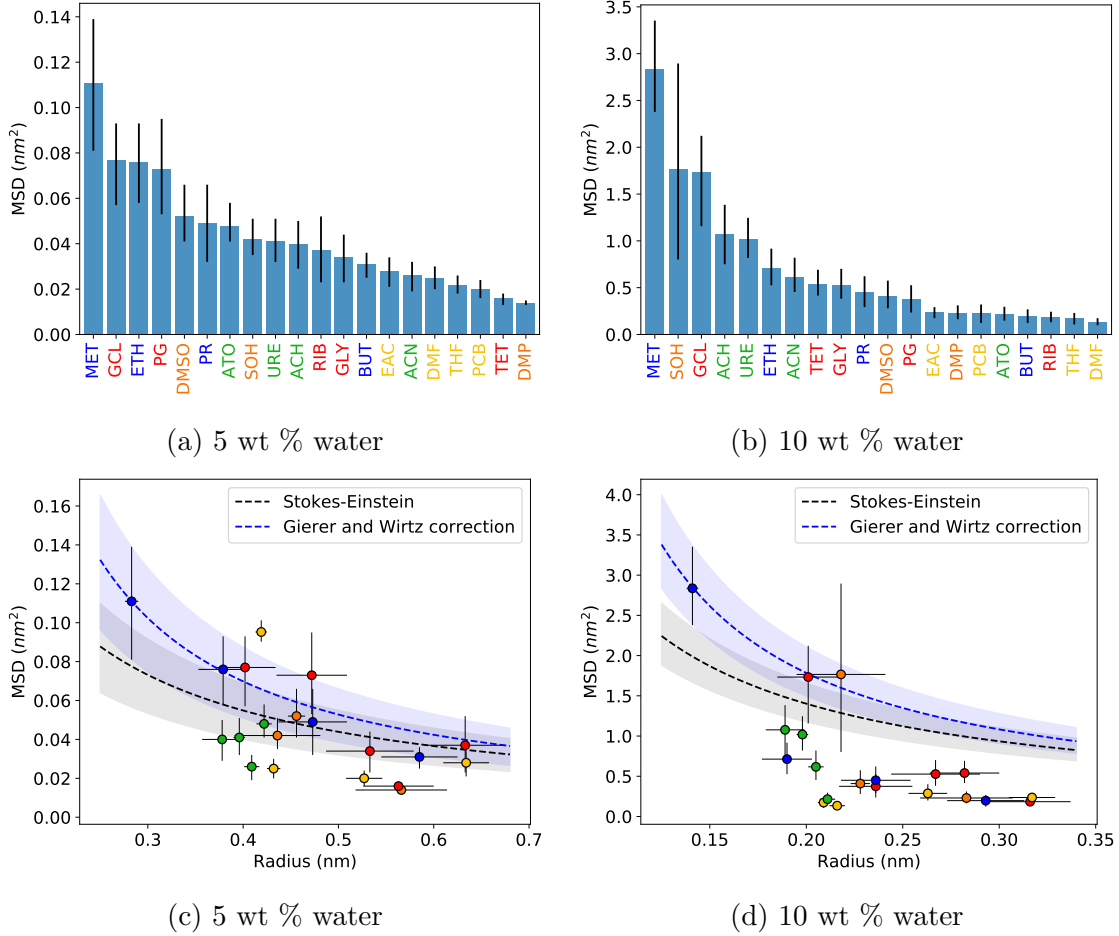


Figure 3: The MSDs of solutes in the 5 wt % water system (a) are significantly smaller than those of the solutes in the 10 wt % water system (b). The MSDs are not a monotonic function of molecular size (c and d). A significant number of solute MSDs fall below the theoretical lines predicted by the Stokes-Einstein equation and Gierer and Wirtz’ corrected Stokes-Einstein equation.

On the timescales simulated in our study, solutes exhibit subdiffusive behavior. Figure 4a plots the z -coordinate versus time of 3 representative ethanol centers of mass in the 10 wt % water system. There are clear periods of entrapment separated by relatively large hops. The MSD calculated based on all ethanol molecules is plotted in Figure 4b and its shape is sublinear. The long periods of entrapment lead, in part, to this sublinear, and thus subdiffusive, behavior.

The complex and non-homogeneous structure of the membrane leads to radially depen-

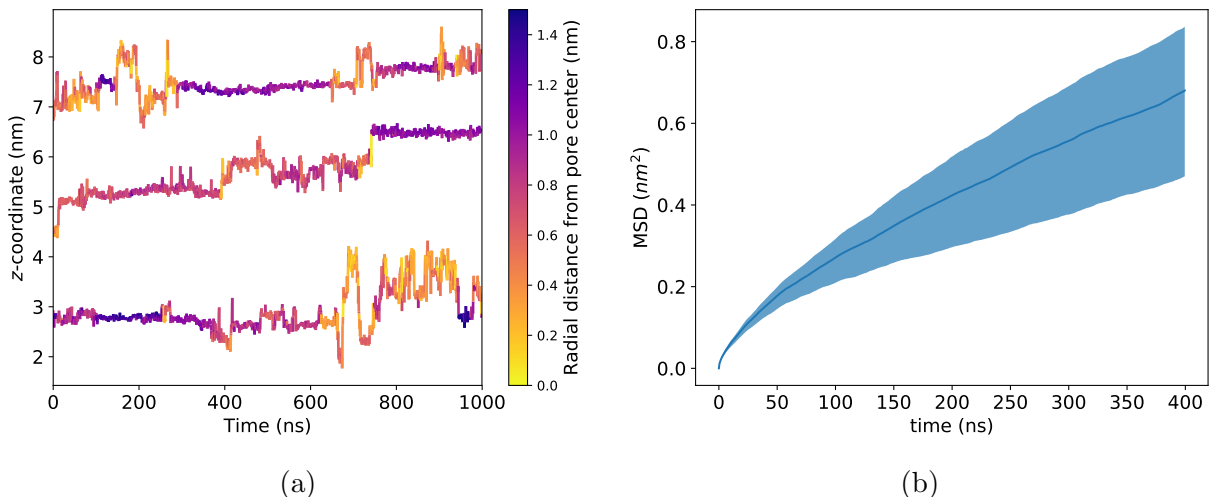


Figure 4: All solutes show subdiffusive transport behavior inside the membrane’s nanopores, similar to that exhibited by ethanol. (a) The z -coordinate trace of 3 representative ethanol COMs shows clear periods of entrapment separated by hops. In general, the longest dwell times occur when solutes are situated far from the pore center and the hops occur when solutes are close to the pore center. (b) The time-averaged MSD of ethanol is sub-linear which suggests transport is governed by an anomalous subdiffusion process.

dent transport mechanisms. In general, we observed that hops made in the pore region are about 45 % larger than those made outside the pore region (See Figure 5a). There is a high resistance to movement in the alkane-dense head group and tail regions while, in the pore region, solutes can move relatively freely since it is primarily composed of water molecules. However, time spent in the pore region does not necessarily lead to more frequent hopping. The largest solutes in this study spend the most time in the pore region (see Figure 5b), but many hop with a below-average frequency (see Figure 5c). Therefore, trapping mechanisms controlled by membrane properties other than density must be prevalent.

In addition to solute trapping in dense monomer regions, we observe a second trapping mechanism caused by preferential hydrogen bonding between hydrogen bond donor solutes and monomer head groups. To continue with our ethanol example, we observe that 64 % of ethanol molecules donate hydrogen bonds and 3 % of ethanol molecules accept hydrogen bonds each frame. On average, 40 % of hydrogen bonds donated by ethanol go to carboxylate head groups, 25 % go to the ether linkages between the tails and the head groups and the

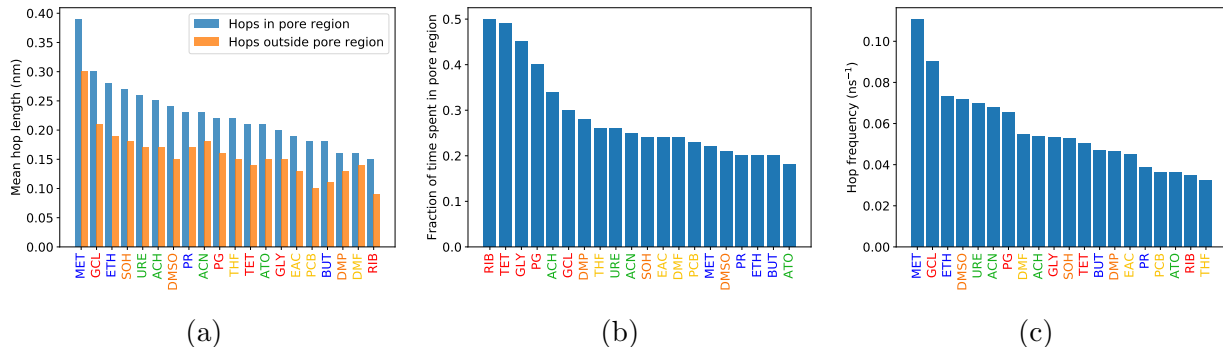


Figure 5: (a) Hops made in the pore region of the 10 wt % water system are, on average, 45 % larger than those made outside the pore region. The trend in hop lengths is similar to the trend in MSDs shown in Figure 3b implying that solutes which make consistently larger hops have higher MSDs. The fraction of time spent by a solute in the pore region (b) does not necessarily lead to more frequent hopping (c). For example, ribose spends the largest fraction of time in the pore region, yet performs the the second lowest number of hops.

remaining 35 % to water. There are about 46 % less carboxylate oxygen atoms in the pore than there are water molecules yet more hydrogen bonds are donated to them. The stability of hydrogen bonds with carboxylate oxygen atoms is high because they have a negative charge with no neutralizing positive charges nearby. Additionally, on average, each sodium ion is coordinated to 1.7 water molecules meaning an appreciable fraction of the water molecules occupying the pore region are usually coordinated to a sodium ion which decreases their availability to accept hydrogen bonds from solutes.

The lifetime of hydrogen bonds between solutes and monomer head groups tends to be longer for solutes that hydrogen bond more frequently. In Figure 6 we see nearly the same ordering of the percentage of solutes hydrogen bonded to monomer head groups and the mean hydrogen bond lifetime. Solutes with multiple hydroxyl groups donate hydrogen bonds most frequently and tend to stay hydrogen bonded longer. Hydrogen bonds donated by nitrogen are far less common and tend to be short-lived as supported by acetamide and urea.

Finally, we observe slowing or immobilization of solutes that associate with sodium counterions. Much like water, the polarity of the solutes creates regions of high electron density, modeled using partial negative charges, which are stabilized through electrostatic interactions with sodium ions. In Figure 7, we’ve plotted the percentage of sodium ions coordinated

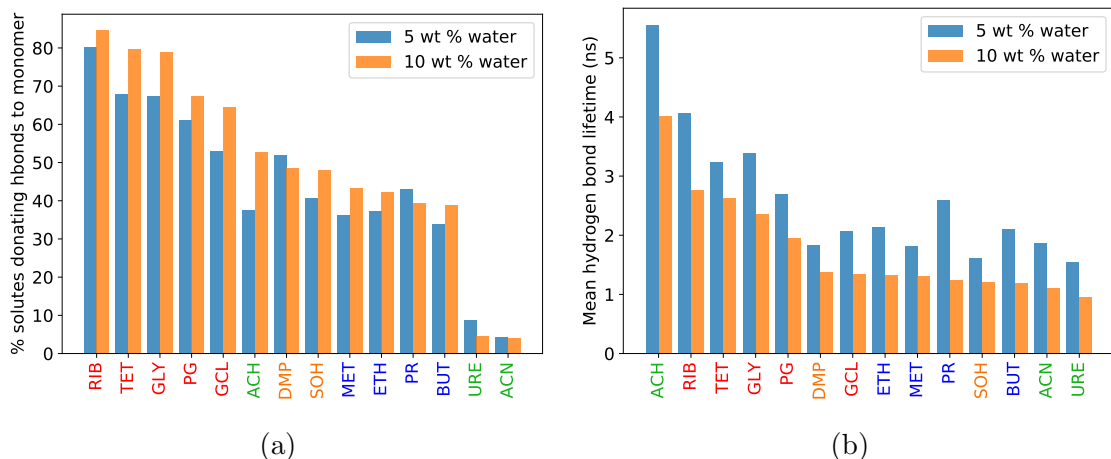


Figure 6: (a) Solutes capable of donating hydrogen bonds to monomer head groups do so to varying degrees. The reported percentages represent unique solute-monomer hydrogen bonds. Individual solutes that hydrogen bond with multiple head groups simultaneously are only counted once. (b) The lifetime of individual hydrogen bonds appears correlated to the percentage of solutes involved in hydrogen bond interactions. Hydrogen bond lifetimes tend to be longer for solutes that hydrogen bond frequently. Note that solutes incapable of donating hydrogen bonds are omitted from this figure.

to the oxygen atoms of each solute as well as the average length of time that pairs stay coordinated. The degree and length of coordination between solutes and sodium in the 5 wt % water system is higher in all cases than that in the 10 wt % water systems. The crowded pores of the 5 wt % water system forces sodium ions in close proximity to solutes. The 5 highest coordinated solutes, which also have the longest coordinated dwell times, all contain carbonyl groups (except for dimethyl sulfoxide which has an analogous sulfinyl group) which leaves a highly electron-dense oxygen atom exposed and ready to interact with sodium. The dwell times are power law distributed, which means that while many of these interactions are fleeting, there is still a chance for very long periods of association to occur. For example, the longest period of coordination between acetone and sodium was 110 ns.

Coordination of ions with oxygen has been observed in a variety of systems. Carvajal et al. noted that Na^+ coordinated with four tetrahydrofuran molecules when they dissolved a sodium salt in the solvent.⁴⁰ Wu et al. observed coordination of Na^+ with the carbonyl group of a molecule used to design an organic electrode.⁴¹ Finally, Shinoda et al. observed

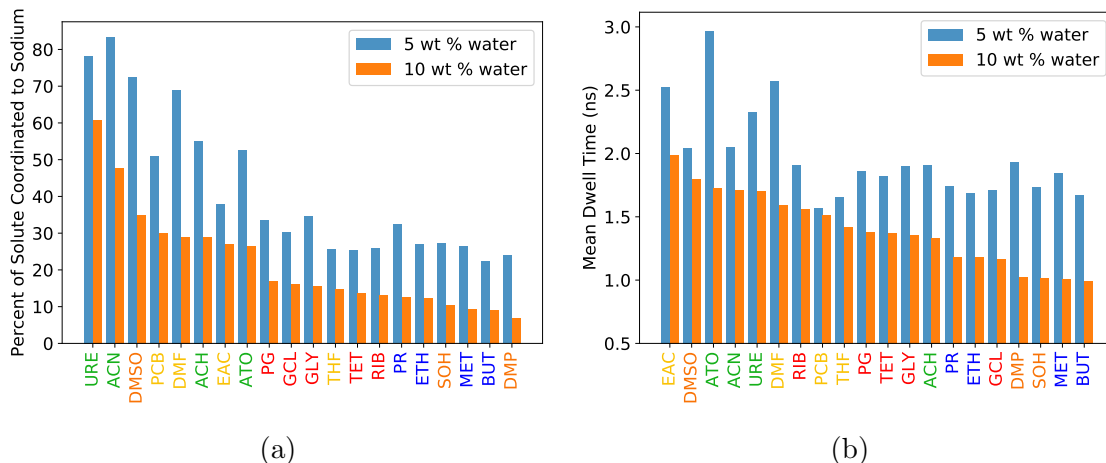


Figure 7: (a) Solutes, especially those with carbonyl groups, spend a significant fraction of time coordinated to sodium ions. (b) The length of time a solute-sodium pairs spends associated tends to be higher for pairs that associate more frequently.

K^+ ions coordinated with the carbonyl and hydroxyl groups of carboxy-terminal groups in crystallized ATPase.⁴²

Overall, the transport behavior exhibited by solutes in the 5 wt % water systems is similar to that shown by those in the 10 wt % system however the timescales are much longer. We observe subdiffusive behavior with intermittent hopping between periods of entrapment and evidence of the same three trapping mechanisms. The frequency and length of hops are both diminished in the 5 wt % system. Since there are only 24 solute molecules in each system, in order to obtain better time-averaged descriptions of solute transport mechanisms, we will focus the remainder of our analysis on transport in the 10 wt % water systems.

We will revisit our observations in the the context of specific groups of molecules in the discussion that follows.

3.3 Transport of Simple Alcohols

The MSDs of methanol, ethanol, propanol and butanol descend in order of their size. Using methanol as a reference, the larger alcohols move slower than expected according to both the pure Stokes-Einstein relationship and the corrected relationship (See Figure 8a).

Methanol has the highest MSD of all solutes because it makes the most frequent and longest hops (see Figure 5). Somewhat counterintuitively, methanol, along with the other simple alcohols, spends a smaller fraction of its time in the pore region than most other solutes. However, even outside the pore region, hops made by methanol are larger than those by any other solute. The small size of methanol allows it to move relatively unhindered.

The RDFs of longer chain alcohols show a sharp peak near the head groups (see Figure 8b). On average, the density of methanol in the pore center is only slightly less than its density near the head groups while all other alcohol molecules are most concentrated near the head groups.

All simple alcohols participate in a similar number of hydrogen bonding interactions with the monomer head groups, but with varying preference towards hydrogen bonds with the monomer carboxylate oxygen atoms over the ether oxygen atoms that connect the tails to the head groups (see Figure 8c). If all 5 hydrogen bonding acceptor sites on the monomer head groups were equal, we would expect the ratio of the number of hydrogen bonds between solutes and the two carboxylate oxygen atoms to the number of hydrogen bonds between solutes and the three ether groups to be $2/3$. There is a clear preference towards hydrogen bonding with the carboxylate oxygen atoms for all simple alcohols. This is largely due to the large net charge of the carboxylate groups as well as the more highly crowded environment surrounding the ether oxygen atoms. Butanol shows the largest preference towards hydrogen bonds with carboxylate head groups. The radial distribution function of atoms located at opposite ends of butanol shows that, on average, oxygen atoms are situated closer to the pore centers than the most distal carbon atoms. This suggests that alcohols tend to orient themselves like the liquid crystal monomers, with hydrophilic components directed towards the pore centers.

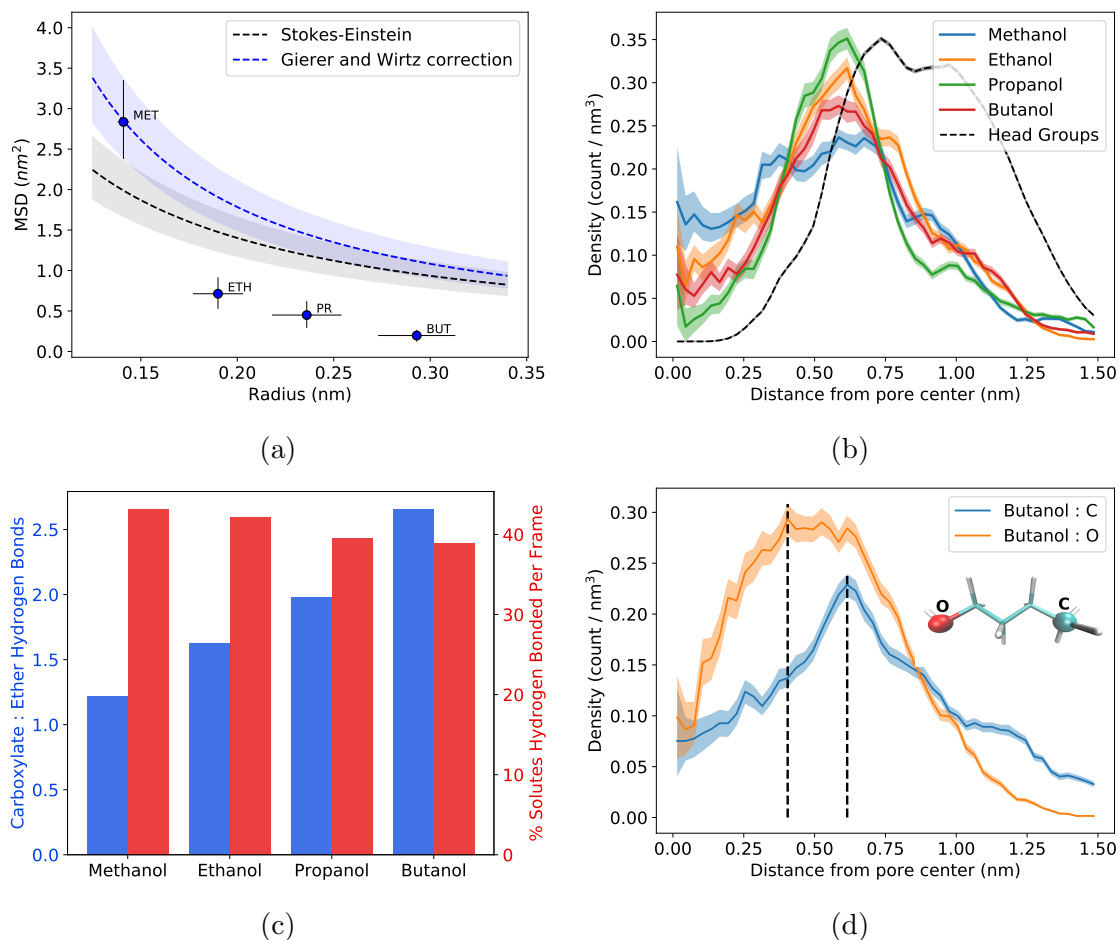


Figure 8: (a) The MSD of the simple alcohols decrease as a function of the solute size, however the MSDs of ethanol, propanol and butanol are considerably lower than expected based on the Stokes-Einstein equation. (b) The radial distribution functions of each simple alcohol shows a maximum close to the highest density of monomer head groups (normalized based on propanol’s maximum density for easier visual comparison). Methanol spends the largest proportion of time, relative to the other alcohols, near the pore center, which may help explain its fast dynamics. (c) Despite relatively little difference in the total number of solutes actively participating in a hydrogen bond each frame, a given alcohol’s preference towards hydrogen bonds with the carboxylate groups of ether linkages increases with molecule size. (d) The average location of butanol’s oxygen atom is closer to the pore center than its most distal carbon atom, suggesting that the molecule is oriented with hydrophobic tails pointing away from the pore center.

3.4 Transport of Diols, Triols and Sugars

The order of the MSDs of solutes in this grouping are roughly consistent with their size, however propylene glycol moves exceptionally slow (see Figure 9a). Ethylene glycol has the

highest MSD followed by tetrose and glycerol, whose MSDs are similar, propylene glycol, the second smallest solute of this set, and finally ribose.

Transport is both facilitated and hindered by additional solute hydroxyl groups due to their influence on radial density and hydrogen bond frequency. Extra hydroxyl groups cause solutes to favor the water-rich pore region where there is the least hindrance to movement (See Figure 9b). Tetrose, ribose and glycerol are densest close to the pore center. They spend a greater fraction of their time in the pore region than any other solute (see Figure 5b) This is likely a consequence of both their hydrophilicity and large size which prevents them from partitioning into the head group region. However, these extra hydroxyl groups facilitate a larger number of hydrogen bond interactions that work to hold solutes in place (see Figure 9). It has been observed that hydrogen bonding in a system will generally reduce diffusivity.⁴³

The number of hydrogen bonding interactions between solutes and head groups increases with the number of solute hydroxyl groups. These solutes frequently undergo simultaneous hydrogen bond interactions as shown in Figure 9. For example, both hydroxyl groups of ethylene glycol can undergo hydrogen bonds with different hydrogen bond acceptors at the same time. In some cases, all 4 hydroxyl groups of ribose hydrogen bond to monomer head groups simultaneously. As a consequence, hydrogen bond lifetimes in these cases tend to be longer (see Figure 6b) since the solute positions are stabilized by multiple interactions. When one hydrogen bond is broken, the remaining unbroken hydrogen bonds keep the molecule in place and allow the previously broken bond to reform. Proximity to the pore center partially compensates for this effect in the cases of glycerol and tetrose, causing them to have relatively high MSDs for their size.

Of the two diols, ethylene glycol moves significantly faster than propylene glycol due to propylene glycol's affinity for the monomer head groups. Combined with an increase in size, the addition of a single methyl group to ethylene glycol increases propylene glycol's hydrophobic character and causes it to favor positions near monomer head groups. Both diols have comparable densities close to the pore center, however propylene glycol's density

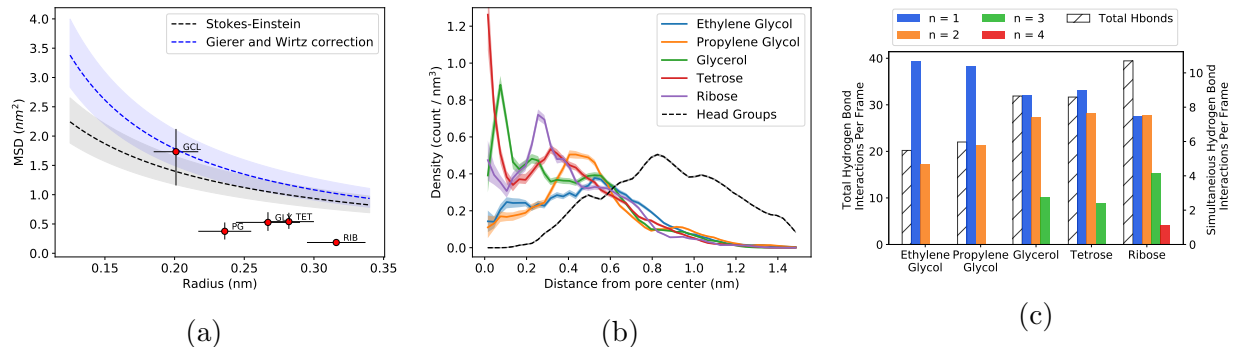


Figure 9: (a) The MSDs of the solutes in this set descend in order of their size, except for propylene glycol which moves exceptionally slow. The MSD of ethylene glycol is in close agreement with the theoretical lines, implying that the solute is subject to a similar amount of hindrance as methanol, the solute to which the theoretical lines were fit. (b) Glycerol, tetrose and ribose have high densities close to the pore center because they have a high number of hydrophilic groups and are relatively large. Ethylene glycol and propylene glycol are densest close to the head group region. (c) The number of hydrogen bond interactions between solutes and monomers increases as solutes gain additional hydroxyl groups. The number of hydrogen bonds made by a single solute in different locations simultaneously, n , also increases with the number of hydroxyl groups. In the most extreme case, all four hydroxyl groups of Ribose ($n = 4$) are involved in a hydrogen bond interaction at the same time.

has a large peak near the monomer head groups relative to ethylene glycol. Propylene glycol can form more highly stabilized hydrogen bonds with carboxylate groups, explaining the slightly higher incidence of hydrogen bonds shown in Figure 9. The average hydrogen bond lifetime of propylene glycol with monomers is 1.95 ns compared to 1.34 ns for ethylene glycol. Somewhat counterintuitively, there is a relatively high density of ethylene glycol molecules beyond the head group region probably due to its relatively small size. This likely contributes to the somewhat large error bars on its MSD in Figure 3.

3.5 Transport of Ketones and Amides

The 4 ketone-like molecules tested show a surprising range of transport behaviors. Urea, acetic acid, acetamide and acetone are all characterized by a carbonyl group with two attached heavy atoms. All are similar in size and are planar molecules due to the sp² hybridization of their carbonyl group. The fastest solutes of this grouping, acetic acid and

urea, move about 3 times faster than the slowest, acetone.

The amides, urea and acetamide, hydrogen bond with head groups relatively infrequently, but regularly coordinate with sodium ions (see Figure 10). In an average frame, over 50 % of acetic acid molecules participate in hydrogen bonds with monomer head groups while less than 10 % of urea and acetamide molecules hydrogen bond with head groups. Urea and acetamide both have hydrogen bond donating nitrogen atoms, however nitrogen is a weaker hydrogen bond donor than oxygen due to its lower electronegativity.⁴⁴ Given their lower propensity to hydrogen bond, one might expect amides to partition out of the pore and/or to move through the pore quickly, perhaps faster than methanol. However, both RDFs contain sharp peaks situated between the pore center and the head groups, but closer to the pore center than other solutes that hydrogen bond with carboxylate groups. Solute that hydrogen bond frequently tend to show peaks in their RDFs near 0.5-0.6 nm from the pore center (see Figure 8b, for example) and those that coordinate with sodium ions more frequently tend to show peaks in their RDFs near 0.2-0.4 nm from the pore center. Both solutes spend about half of their time with their carbonyl oxygen atom coordinated to a sodium ion which restrains the solutes to within the pore region

Among the solutes in this set, only the carbonyl oxygen atoms coordinate with sodium ions. The nitrogen atoms do not coordinate at all despite a similar negative partial charge because the attached hydrogen atoms shield this interaction by making the NH_2 group approximately neutral.

Acetone has the lowest MSD of this set because it either coordinates with sodium or stays trapped near and behind the head groups. Acetone spends the smallest fraction of time in the pore region out of all solutes in this study (see Figure 5b). On average, acetone coordinates with sodium with the same frequency as acetic acid which is manifested as a peak in its RDF about 0.2 nm from the pore center. Acetic acid and the amides have other, unoccupied, hydrophilic groups while bound to sodium ions which increases their stability in the pore.

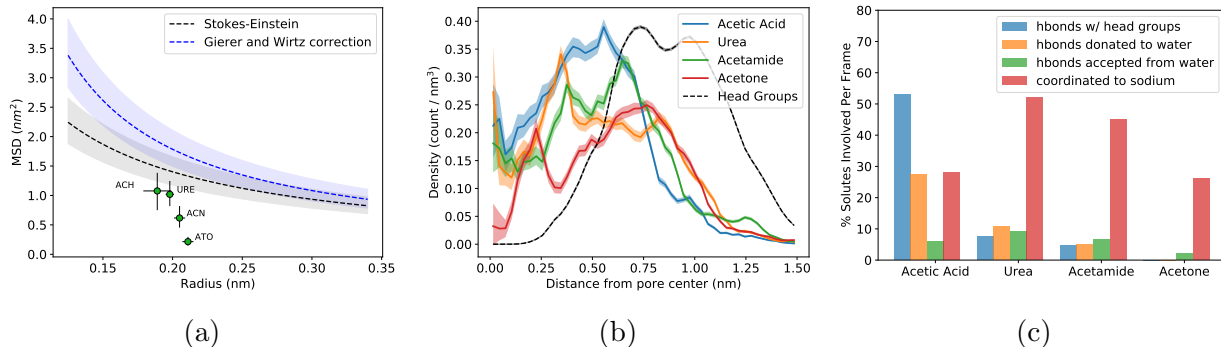


Figure 10: (a) The MSD of the solutes decreases and the deviation from Stokes-Einstein predicted behavior increases as with molecular size increases. (b) The radial density near the pore center ($r = 0$) decreases with decreasing solute MSD. Peaks in the RDFs of urea, acetamide and acetone that appear 0.2 - 0.4 nm from the pore center are likely due to coordination with sodium ions. (c) The amides hydrogen bond with water far less than acetic acid, however they tend to coordinate with sodium ions more frequently. Acetone coordinates with sodium with same frequency as acetic acid.

3.6 Transport of Thiols

We also studied the transport properties of sulfur analogs of glycerol, ethylene glycol and acetone. We replaced all but one oxygen atom of ethylene glycol and glycerol with sulfur atoms to create dimercaptoethanol and 2,3-dimercapto-1-propanol. We replaced the carbonyl carbon of acetone with sulfur in order to create DMSO. Sulfur-containing compounds form weaker hydrogen bonds than nitrogen and oxygen-containing compounds due to their low electronegativity.⁴⁴ For this reason, thiols are less soluble in water than their hydroxyl group analogs.

Mercaptoethanol has a similar average MSD and RDF to ethylene glycol. There is a much larger uncertainty associated with mercaptoethanol's MSD. The range of behaviors shown by mercaptoethanol help explain the large variance of its MSD. Some can be accounted for by the higher density of mercaptoethanol molecules outside the pore region, where transport is inherently slower. Mercaptoethanol spends 20 % less time in the pore region than ethylene glycol. Conversely, mercaptoethanol hydrogen bonds with head groups about 40 % less frequently, which is less than expected if equal amounts of both solutes occupied the pore region. Consequently, shorter hydrogen bond lifetimes within the pore region may yield some

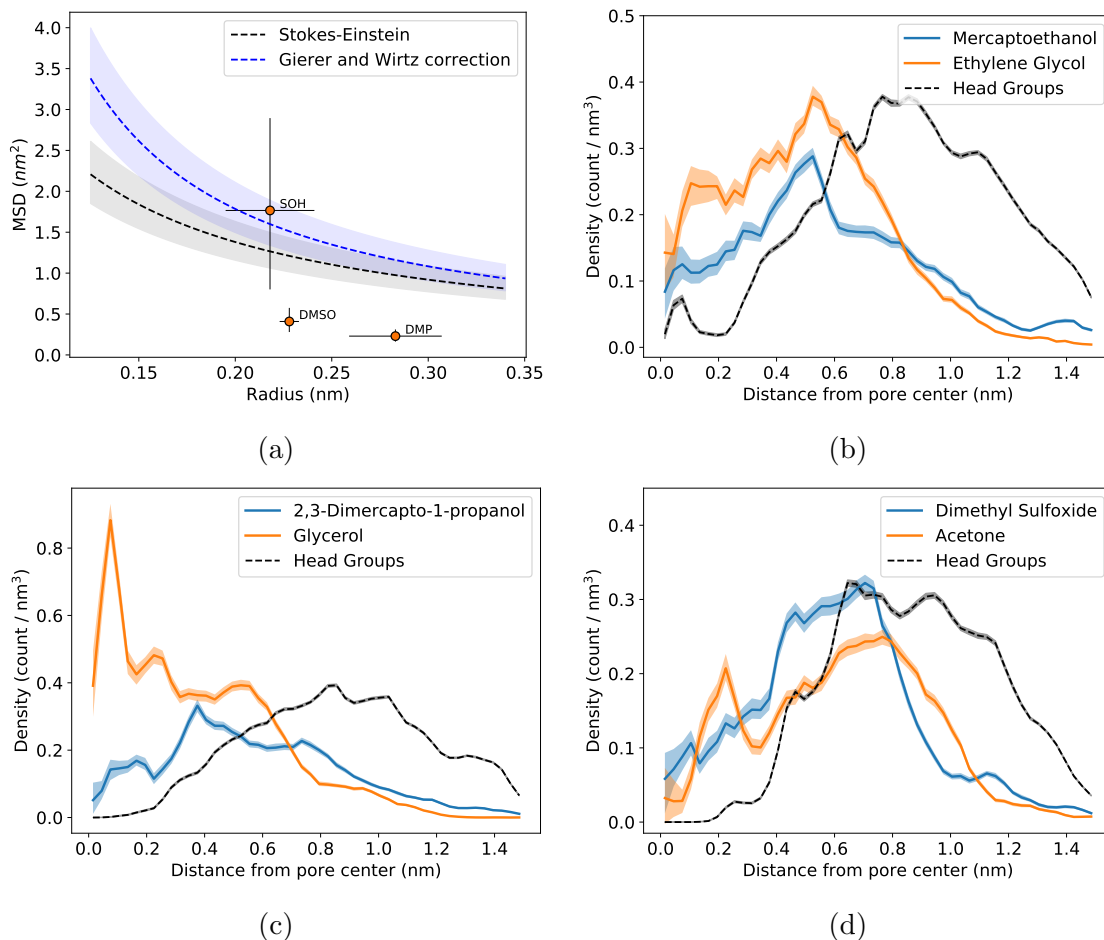


Figure 11: (a) The RDF of mercaptoethanol is similar to ethylene glycol except for its higher density in the tail region and consequently lower density in the pore region. (b) 2,3-dimercapto-1-propanol is densest near the head groups, unlike glycerol whose density is very high close to the pore center. (c) Overall, dimethylsulfoxide has a higher density than acetone within the pore region which may in part explain its marginally larger MSD.

high MSD trajectories.

2,3-dimercapto-1-propanol exhibits slower transport than glycerol because more of it partitions into the tail region. 2,3-dimercapto-1-propanol spends 38% less time in the pore region than glycerol. Glycerol participates in about 2.5 times as many hydrogen bonds as 2,3-dimercapto-1-propanol. Only 22 % of the hydrogen bond interactions of 2,3-dimercapto-1-propanol involve sulfur. Because sulfur can only weakly hydrogen bond, 2,3-dimercapto-1-propanol is less soluble than glycerol in the water-filled pores and more readily partitions into the tail region.

DMSO has a comparable if not larger MSD than acetone even though it is a slightly larger molecule. DMSO spends 17 % more time in the pore than acetone. On average, 35 % of DMSO molecules are coordinated to a sodium ion each frame compared with 26 % of acetone molecules. The pyramidal structure of DMSO may force it to spend more time closer to the pore center which increases its interaction with sodium ions. The tendency of DMSO to stay in the pore region counterbalances the sodium ion interactions to give it a higher MSD than acetone.

3.7 Hydrogen Bond Acceptors

The slowest set of molecules we studied can accept hydrogen bonds, but cannot donate them. Among this set are the two slowest solutes in our study: tetrahydrofuran and dimethyl formamide. The MSDs of ethyl acetate, propylene carbonate and acetone are only marginally larger.

The solutes in this set have small hop lengths. 3 of the bottom 6 mean hop lengths are associated with ethyl acetate, propylene carbonate and dimethyl formamide (Figure 5a). Acetone and tetrahydrofuran perform slightly larger hops but have the third and first lowest hop frequencies respectively (see Figure 5c).

The radial density of solutes near the pore center in this set is surprisingly high as shown in Figure 12b. Propylene carbonate and ethyl acetate are among the largest solutes in this study. Their size prevents them from easily entering the tail region and consequently leads to faster transport properties. However, this is not a hard rule. When a solute does overcome the barrier of entry beyond the head group region, it can become trapped. All solutes in this set show at least a small peak ≥ 0.9 nm from the pore center which is likely caused by solutes that get trapped in the tail region for significant periods of time.

Carbonyl groups continue to show high degrees of association with sodium ions. Between 25 and 30 % of propylene carbonate, dimethyl formamide and ethyl acetate molecules are coordinated with sodium ions for a given frame which is consistent with the coordination

exhibited by acetone (see Figure 12c). The carbonyl group of the amides studied in the previous section associate with sodium nearly twice as frequently as compounds that don't contain nitrogen (see Figure 10c). Association between sodium and solutes in this set are also among the longest, only beat by other solutes with carbonyl groups and ribose.

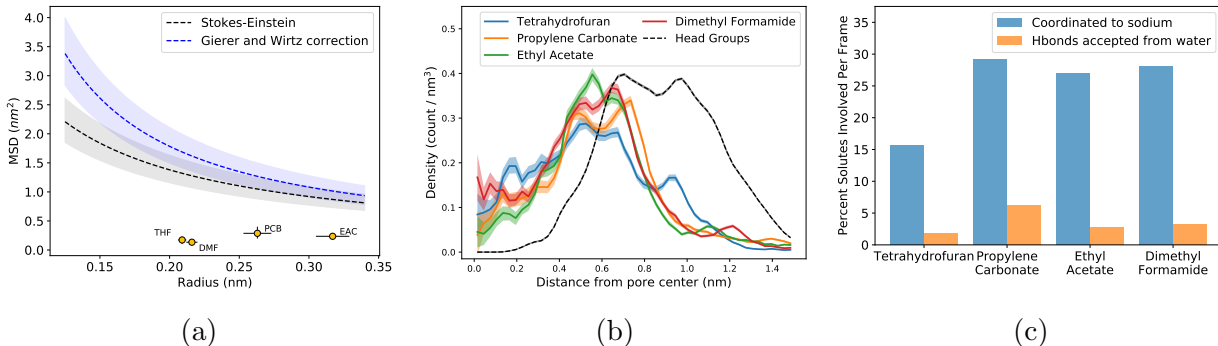


Figure 12: (a) The MSDs of solutes that can only receive hydrogen bonds are significantly lower than expected. (b) The solutes' radial density is surprisingly high in the pore region, but is balanced by an appreciable amount of solute trapped in the tails. (c) The low MSDs exhibited by each of these solutes is due to a combination of entrapment within the tail region and a high degree of coordination with sodium ions.

4 Conclusion

We have examined the transport characteristics of a series of small polar molecules in our model of the H_{II} phase formed by the liquid crystal monomer Na-GA3C11.

We learned that the MSD of solutes, water and counter ions are highly dependent on LLC membrane water content. The MSD of these components is about 2 orders of magnitude larger in the 10 wt % system than in the 5 wt % system. As more water is added to the system, the pores become less crowded with monomer components. The amount of water in the pores deserves special attention when screening new monomers.

We observed three mechanisms of solute entrapment.

1. A solute can become stuck among monomer tails.
2. A solute can donate hydrogen bonds to immobile monomers.

3. A solute can associate with a bound counterion.

Based on these trapping mechanisms, we can suggest modifications that can be made to monomers in order to mitigate or enhance their effect on solute MSDs. Since solutes move slowly while entangled among the monomer tails, one can try to design monomers that better control the partition of solutes between the pore and tail region. For example, removal of the ether linkages between the head groups and the monomer tails will decrease the stability of polar molecules near the head groups. Alternatively, one can focus on designing head groups with varying hydrogen bonding capabilities. One can increase the number of hydrogen bonding sites on the head groups in order to trap more solutes, or decrease the number of hydrogen bond sites to trap less. Finally, one can attempt to control the degree to which solutes coordinate with counterions. Changing the size and valence of the counterion may offer some interesting behavior.

5 Supporting Information

Detailed explanations and expansions upon the results and procedures mentioned in the main text are described in the Supporting Information. This information is available free of charge via the Internet at <http://pubs.acs.org>.

6 Acknowledgements

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