# Size, Shape and Functionality Dependence of Solute Transport Mechanisms in a Cross-linked $H_{II}$ Phase Lyotropic Liquid Crystal Membrane

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February 25, 2019

## 1 Introduction

We need highly selective membranes in order to perform efficient separations.

$H_{II}$ phase lyotropic liquid crystals have densely packed, uniform sized pores and have the potential to disrupt conventional membrane separation techniques by being selective based not only on size and charge, but on chemical functionality as well.

We can only learn so much from experiment. MD can give us mechanistic insights with atomistic resolution so that we can intelligently design new membranes for solute-specific separations.

In previous work, we determined the most likely structure of the hexagonal phase formed by the monomer Na-GA3C11.

- We developed techniques for equilibrating the hexagonal phase made 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 a number of polar solutes with varying size, chemical functionality and hydrophilic character.

- Many of the separations we are interested in involve polar organic compounds.

There are a number of questions we wish to address in order to characterize transport in this system.

1. What transport mechanisms do we observe?

   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.

2. How do 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 properties.

3. Can we describe the transport mechanisms using pre-existing mathematical models.

   A mathematical model may provide additional insight into the transport mechanisms and, in future work, can help relate performance on the timescales studied with MD to macroscopic timescales. We will use qualitative and semi-quantitative arguments in order to choose a governing model.

4. How can we modify the current monomers in order to enhance solute-specific separations?

   Most experimental characterization up to this point has been centered around the monomer, Na-GA3C11, studied here. The primary reason for conducting these simulations is to understand what chemical modifications can be made to this or similar liquid crystal molecules in order to enhance transport of desired species or restrict that of undesired species. We will use the insight gained from our mechanistic observations in order to suggest new monomer designs.

There are number of questions this study is not intended to answer.

- 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.
- We will not study the chemical potential of solutes in the pores, which could give us a better understanding of equilibrium solute partitioning. However, 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

## System Setup

Stable $H_{II}$ phases, assembled with Na-GA3C11, can be formed using a broad range of water concentrations.

- In the literature, this system is typically synthesized with close to 10 wt % water [1, 2]
- However, Resel et al. noted that the system is likely fully hydrated with less than 7 wt % water. [3]
- We decided to test two different levels of water content: 5 and 10 wt %

We observed that water partitions into the tail region of our system and therefore built our initial configurations with water in both regions close to the expected equilibrium value.

- There is about 2:1 water in the pores versus in the tails for the 10 wt % system.
- The amount of water present in the tails may or may not be experimentally consistent but if we don't put it in, the results will not be thermodynamically consistent, which will give issues with measurements and calculations.
- See supporting info for water equilibration simulation data.
- We adjusted the pore radius in our systems so that the right amount of water fits in the pores without any vacuum using `gmx solvate`.
- We placed water molecules in the tail region one at a time in random locations with short energy minimizations between insertions.

We equilibrated an initial solvated configuration before adding solutes.

- We equilibrated the initial configuration using the 'wet' equilibration procedure described in our previous work [4].
- We cross-linked the equilibrated solvated configuration using the cross-linking procedure described in our previous work.

We added 6 solute molecules to each pore of the equilibrated cross-linked configuration.

- We equally spaced each solute in the pore
- 6 solutes per pore provided a balance of a useful amount of data for generating statistics and a low degree of interaction between solutes (reference to supporting information to show low degree of interaction)
- 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
- We collected transport data using 1 $\mu$s simulations

### Mean Squared Displacment

### 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 calcuation
- We obtain the best RDF by constructing splines that run through the pore centers.
- We construct the splines by dividing the membrane into 20 slices in the $z$-direction. Within each slice, we calculate the location of the pore centers based on the average location of the aromatic rings that make up the monomer head groups.
- When calculating the RDF, the radial distance from the pore center is based on the distance between the solute center-of-mass and the ($x$, $y$) coordinates of appropriate point on the spline.

### Coordination number

We quantified the coordination of solutes with surrounding molecules.

- For each frame, we counted the identities and number of coordinated molecules to a given solute based on a 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.

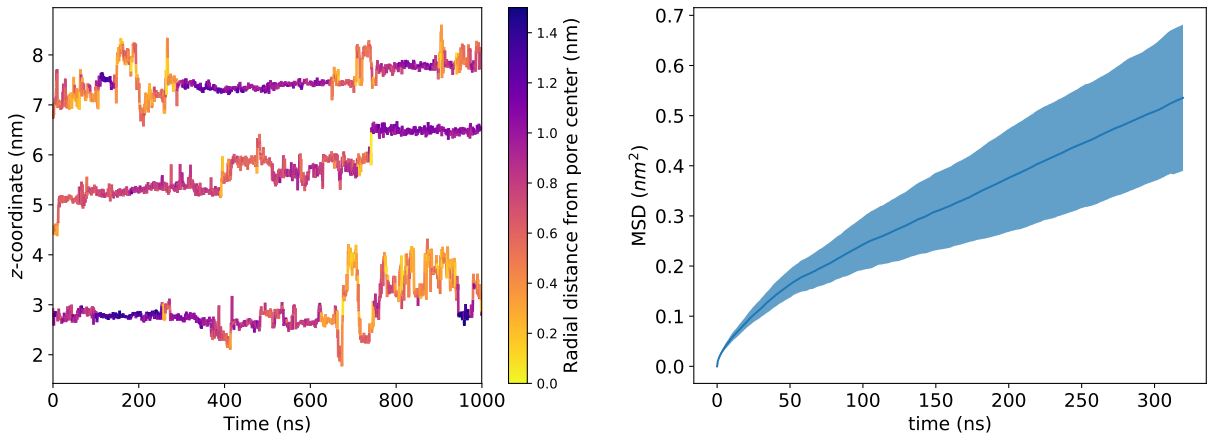
## 3 Results and Discussion

### Governing Mechanisms

We have gained a clearer picture of the general transport properties exhibited by this system through the collective study of all solutes. We will first answer the questions posed in the introduction in a general sense before addressing them with respect to specific molecules where exceptions occur.

On the timescales simulated in our study, we observe subdiffusive behavior.

- Figure 1b plots the $z$-coordinate versus time of 3 representative ethanol centers of mass.
- There are clear periods of entrapment separated by relatively large hops.
- The MSD calculated based on all ethanol molecules is plotted in Figure 1a and is sublinear.




(a) (b)

Figure 1

- The long periods of entrapment likely lead to this sublinear, and thus subdiffusive, behavior.

Mathematical modeling All solutes exhibit hop diffusion, characteristic of a continuous time random walk.

- The length of entrapment follows a power law distribution (Figure 1c) and the distribution of hop lengths can be described with a Gaussian distribution (Figure 1d).
- Power law distributed dwell times are responsible for the ageing phenomenon which causes the MSD curve to decrease with increasing measurement time as longer dwell times get sampled.

The direction of each hop is anti-correlated to the direction of the previous hop.

- Figure 1e shows the autocovariance function of ethanol step vectors.
- The negative autocovariance at low values of k indicates anti-correlation between steps.
- If solutes followed a pure CTRW mechanism, the autocovariance function would decay to zero immediately.
- Although the autocovariance function is relatively noise, due to the somewhat small number of hops observed over the course of each solute trajectory, there is the least uncertainty at k=1, the most insightful data point. This behavior is consistent across all solutes molecules.
- Therefore, we believe transport can be described as subordinated fractional Brownian motion where the leading process is a CTRW with hops that are dictated by the parent process, FBM.
- Future publications will focus on modeling the solute's transport characteristics with an sFBM model

We calculated the time-averaged MSD of each solute in the set over the course of 1 $\mu$s MD simulations.

- Because the 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 MSD values plotted in Figure 2 represent the average MSD of each solute after a 400 ns time lag.

The MSDs are not a monotonic function of solute molecular weight.

- We plotted the solute molecular weights alongside their MSDs in Figure 2.

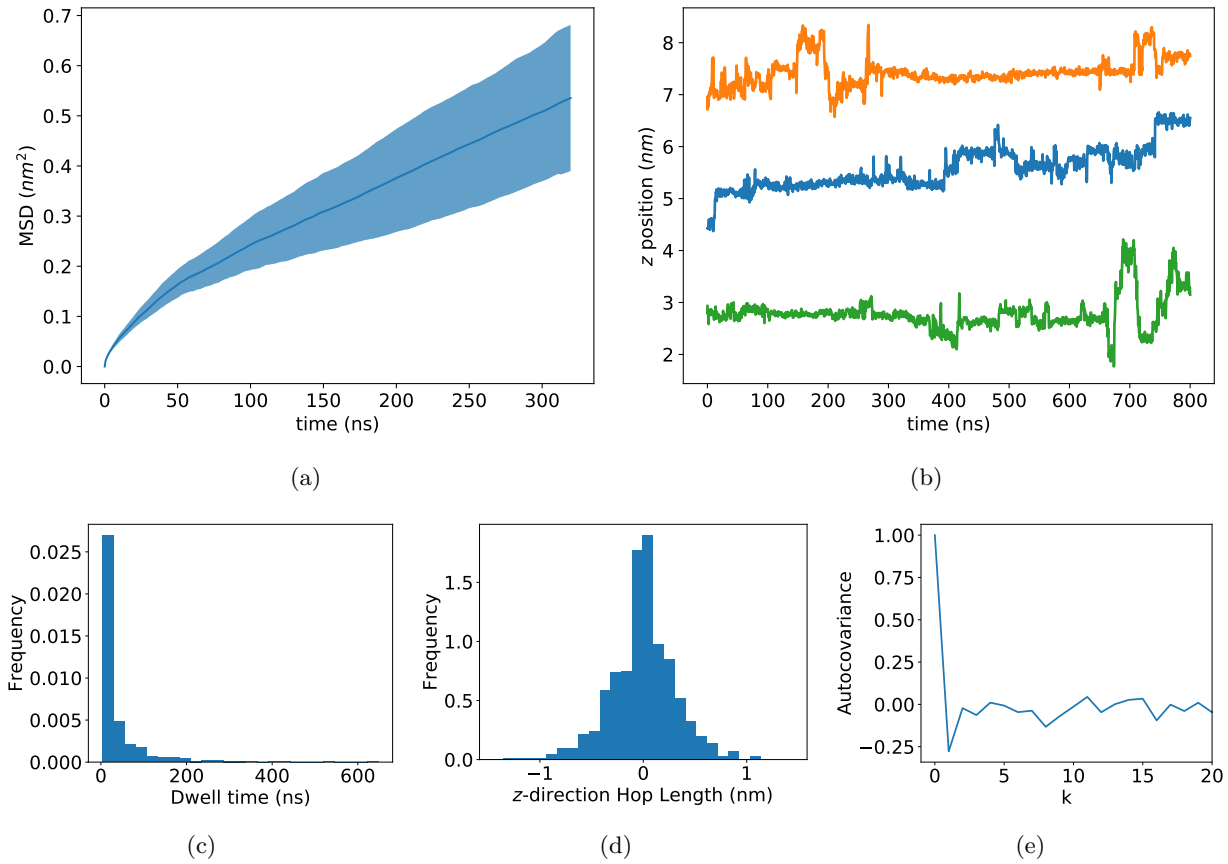



Figure 2: All solutes show subdiffusive transport behavior inside the membrane's nanopores, similar to that exhibited by ethanol. (a) The time-averaged MSD of ethanol is not linear which suggests transport is governed by an anomalous subdiffusion process. (b) The $z$-coordinate trace of 3 representative ethanol COMs shows clear periods of entrapment separated by hops. (c) The distribution of dwell times follows a power law. (d) The distribution of hop lengths appears Gaussian. (e) Hops are anti-correlated to their previous hop as indicated by the negative value of the autocovariance function at $k = 1$.

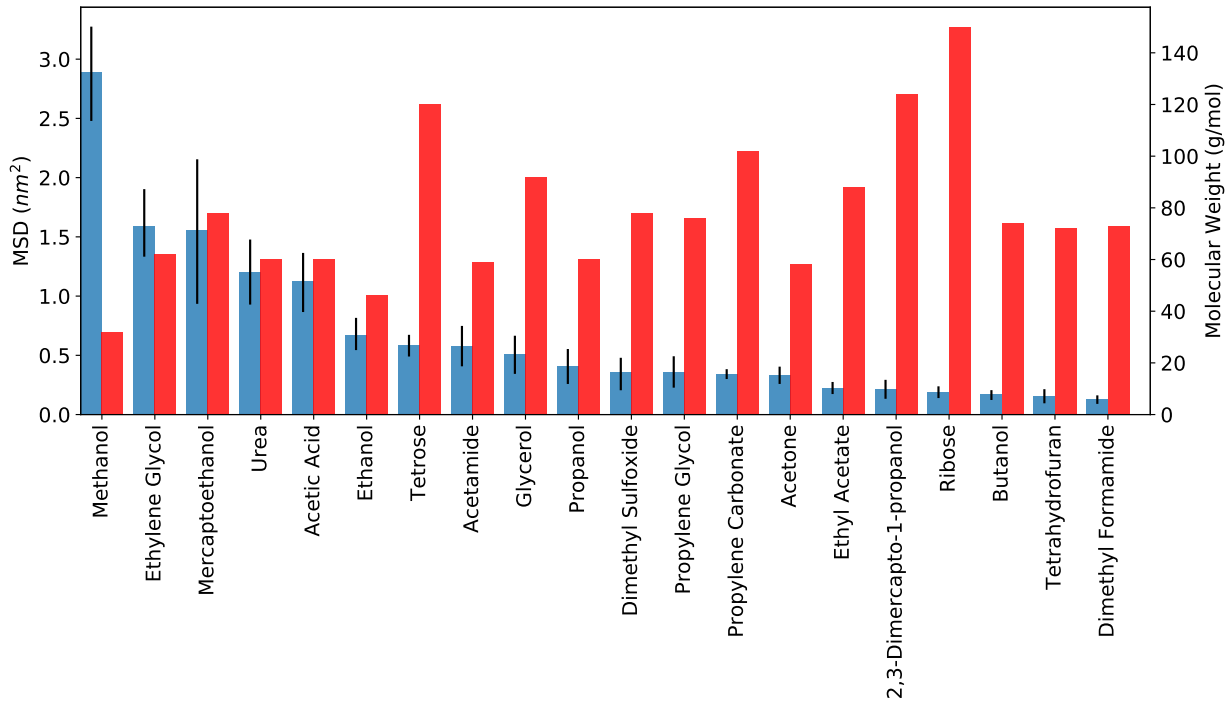



Figure 3

- Transport is clearly affected by factors other than molecular weight.
- Tetrose, our third heaviest solute, has an MSD higher than more than half of all solutes studied.
- The three slowest solutes have lower molecular weights than 8 faster solutes.

The MSDs in Figure 2 are a strong function of two solute trapping mechanisms.

- Solutes that are hydrogen bond donors can be stabilized through hydrogen bonds with one of the five oxygen atoms attached to each monomer head group.
- In a separate interaction, solutes can become kinetically trapped between or behind monomer head groups. These interactions likely lead to the observed anti-correlated hopping behavior.
- Generally, both mechanisms affect each solute to varying degrees.

The degree to which solutes are influenced by each entrapment mechanism is a complex function of a solute's size, shape, and polarity.

- In general, solutes can move fastest in the pore center, where there is comparatively little resistance to diffusion.
- The 5 fastest solutes in our study have a low molecular weight and spend a significant amount of time in the pore center. They are only slowed by hydrogen bonds with monomer carboxylate groups.
- Bulky solutes with many hydrogen bond donating groups, like glycerol, spend most of their time in the pore center, but their large size combined with a higher solute-head group hydrogen bond frequency, makes their dynamics slow.
- Solutes with high hydrophobic character tend to partition into the head group region where entrapment occurs.

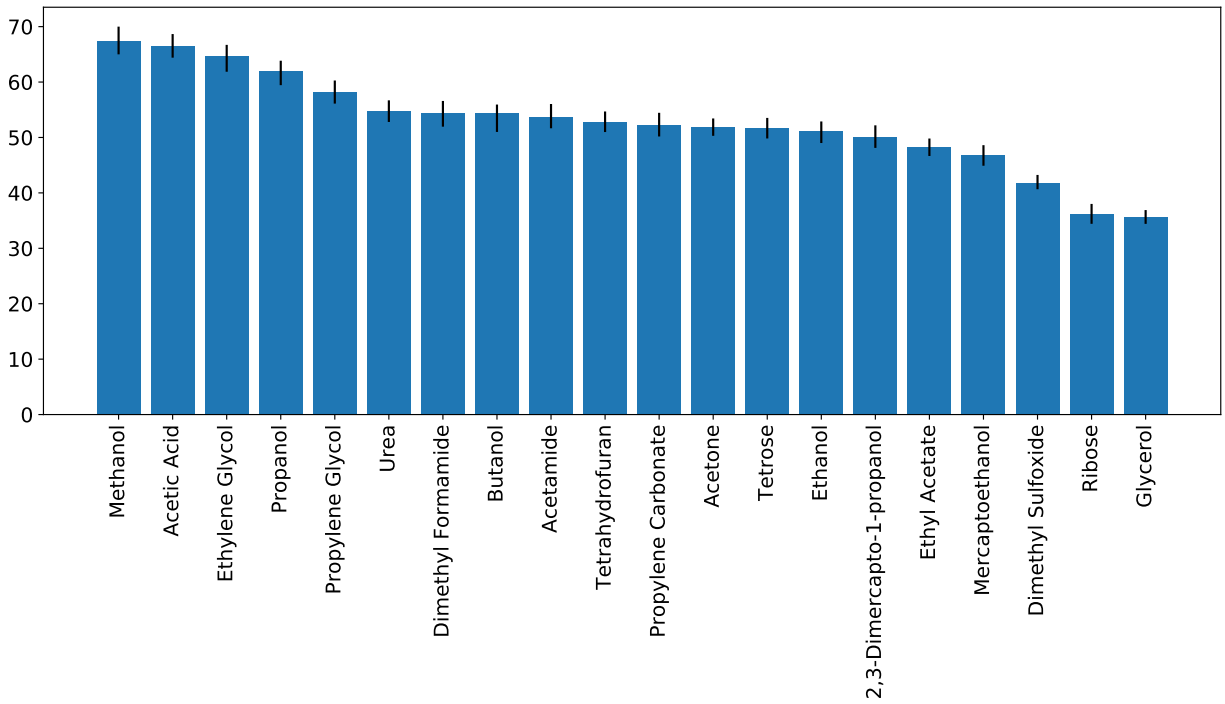



Figure 4

- We observe low MW solutes with lower-than-expected MSDs because they spend more time trapped between monomer head groups due to low water solubility.
- Small, planar molecules, without the ability to donate hydrogen bonds, like acetone, exhibit some of the slowest MSDs. Their flat geometry and small size makes it easy for them to get lodged deep between head groups.
- Overall solutes exhibit some degree of trapping, by one or a combination of the above mechanisms, with anticorrelated hops between each period of immobility due to obstructions.

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

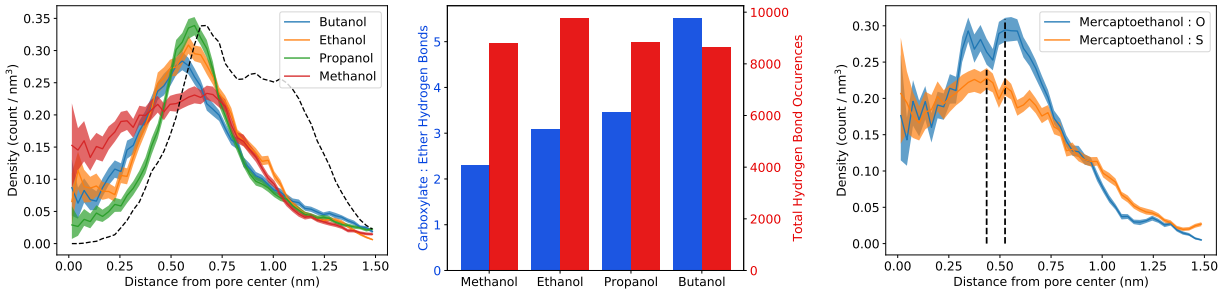
## Transport of Water

The MSD of water is a weak function of the solute residue disolved in the pores.

- Large molecules like glycerol and ribose obstruct the movement of water molecules forcing them to have lower MSDs
- I don't know why the MSD is fast in the fastest systems or why DMSO is slow.
- Sulfur containing compounds have slowest water transport
- How do 24 solute molecules have such a drastic effect on water motion

## Transport of Simple Alcohols

The MSD of methanol, ethanol, propanol and butanol descends in order of their molecular weight, however, methanol travels faster than expected.




(a) (b) (c)

Figure 5: (a) The radial distribution functions of each simple alcohol shows a maximum close to the highest density of monomer head groups (dashed line, normalized 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. (b) Despite relatively little difference in the total number of hydrogen bond occurences, a given alcohol's preference towards hydrogen bonds with the carboxylate groups increases with molecule size. (c) The average location of butanol's oxygen atom is significantly 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.

- The radial density as a function of distance from the pore center for each alcohol is plotted in Figure 4a.
- On average, the density of methanol in the pore center is only slightly less than the density near the head groups.
- All other alcohol molecules are most concentrated in the head group region.

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 (See Figure 4b).

- 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 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 0.25 nm closer to the pore centers than the distal carbon atoms.
- This suggests that alcohols tend to orient themselves like the liquid crystal monomers, with hydrophilic components point towards the pore centers.

## Transport of Diols, Triols and Sugars

Transport is both facilitated and hindered by additional solute hydroxyl groups.

- Extra hydroxyl groups cause solutes to favor the water-rich pore region. where there is the least hindrance to movement.
- However, these extra hydroxyl groups facilitate a larger number of hydrogen bond interactions that work to hold solutes in place (See Figure 5).

- At the same time, solute molecular weight increases, which inherently causes them to move more slowly.
- Ethylene glycol, the fastest solute in this grouping (and second fastest overall), obtains the best balance of both effects.

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 5.
- 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 are hydrogen bonded to monomer head groups simultaneously.

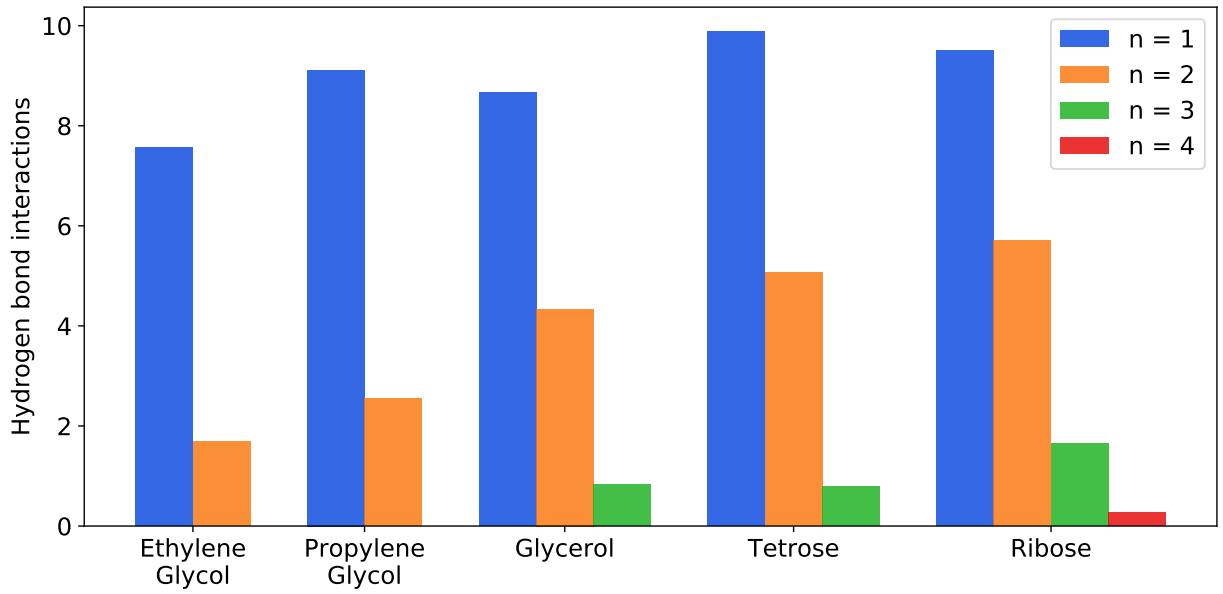



Figure 6: The number of hydrogen bond interactions between solutes and monomers increases as solutes gain additional hydroxyl groups. Multiple hydroxyl groups within a solute often hydrogen bond in different locations simultaneously. Occasionally, all four hydroxyl groups of Ribose (n = 4) are involved in a hydrogen bond interaction at the same time.

Between the two diols, ethylene glycol moves significantly faster than propylene glycol due to propylene glycol's affinty for the monomer head groups.

- The distribution of each solute's dwell time and hop length distributions shows that ethylene glycol has shorter dwell times and longer hop lengths, which combine to create a relatively fast MSD.
- Both diols have comparable densities close to the pore center, however propylene glycol's density has a large peak near the monomer head groups relative to ethylene glycol.
- Combined with an increase in molecular weight, the addition of a single methyl group increases the molecule's hydrophobic character and causes propylene glycol to favor positions near monomer head groups.
- This causes propylene glycol to form more highly stablized hydrogen bonds with carboxylate groups, explaining the higher incidence of hydrogen bonds shown in Figure 5.

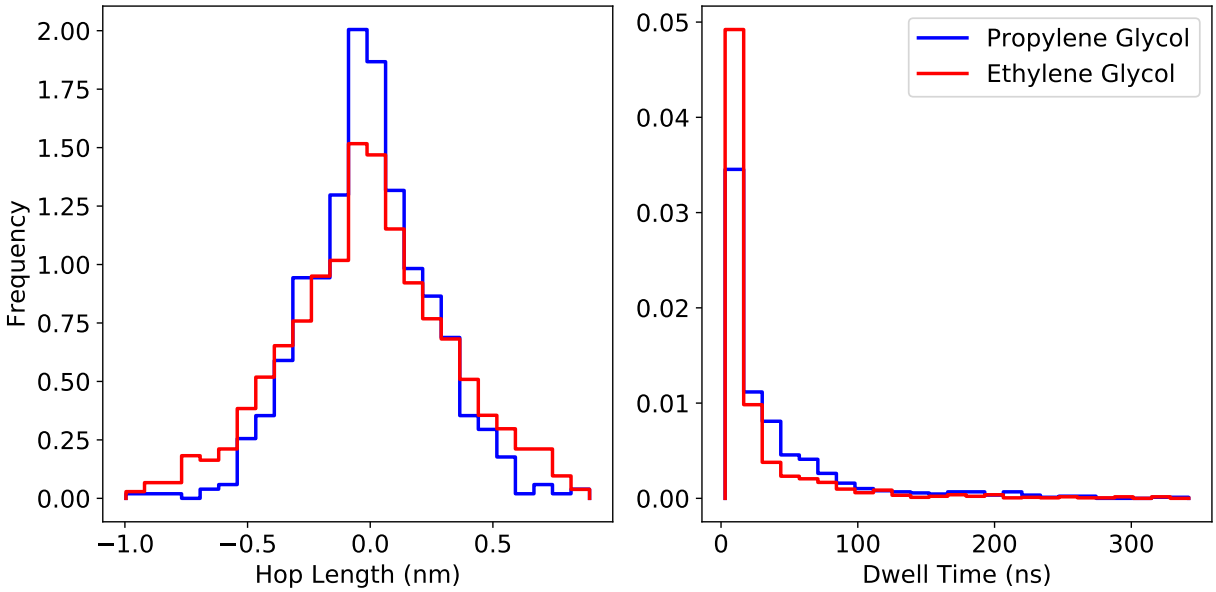



Figure 7

Solutes with three or more hydroxyl groups have the highest density at the pore center which contributes to overall faster than expected transport.

- These molecules are highly water soluble but relatively large
- They can easily hydrogen bond in multiple locations.
- Their large size and high hydrogen bonding capability prevents them from having larger MSDs.

## Transport of Ketones and Amides

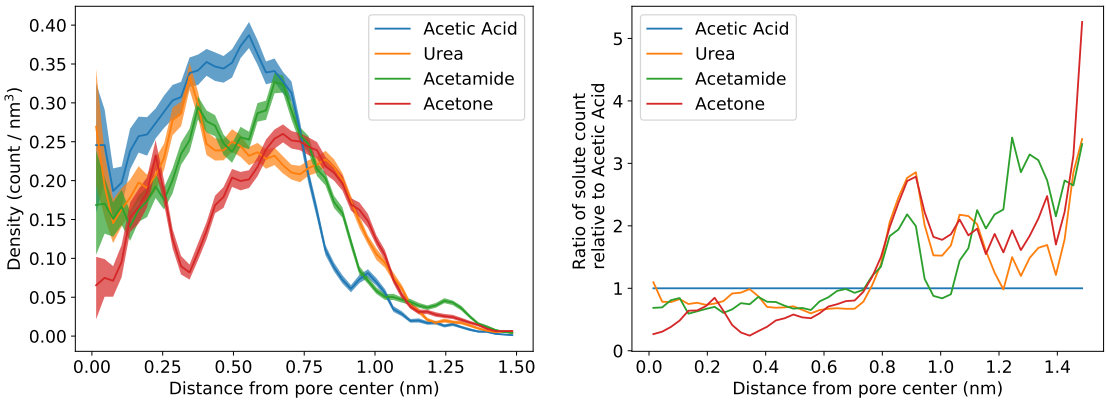
The 4 ketone-like molecules tested show a surprising range of transport behaviors.

- Urea, Acetic Acid, Acetamide and Acetone are all characterized by a carbonyl group with two attached heavy atoms.
- All have approximately the same molecular weight and are planar molecules due to the sp2 hybridization of the carbonyl group.
- The fastest solute of this grouping, Urea (comparable to Acetic Acid too), has an MSD comparable to that of ethylene glycol while the slowest, Acetone, has an MSD one third of that of Urea.

Once again, the trends in the MSD can in large part be explained by the solutes' preference for water.

- Urea, Acetic Acid and Acetamide are all capable of donating hydrogen bonds, while acetone is the first instance of a molecule in this study that can only accept hydrogen bonds. It follows that acetone has the slowest MSD of this grouping.
- 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.
- Hence, Acetic Acid donates the greatest number of hydrogen bonds and has the highest density throughout the pore region.
- All other solutes show a higher preference for the tail region where three dimensional confinement directly contributes to a lower MSD.

- Urea likely compensates for its loss of mobility in the head group region by making large hops upon escape into the pore region.
- Urea frequently moves between the head group and pore region because its planar shape makes it easier to transition between regions.
- As the solutes become less polar, their MSD decreases.
- Acetamide has one less amine group than Urea and a corresponding smaller MSD.
- Despite a peak in its density near the pore center due to its water solubility, Acetone is the least polar and spends the most time outside the tail group region leading to the lowest MSD.




(a) (b)

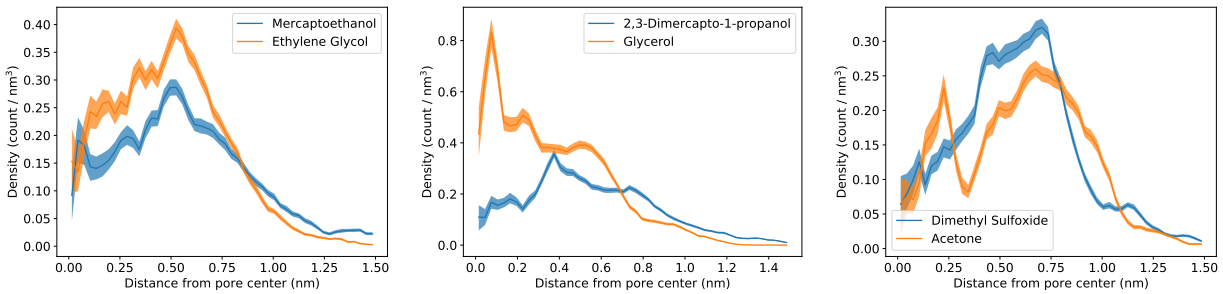
## Transport of Thiols

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 is unable to hydrogen bond, however it is soluble in water
- Comparisons of their RDFs are shown in Figure 8.

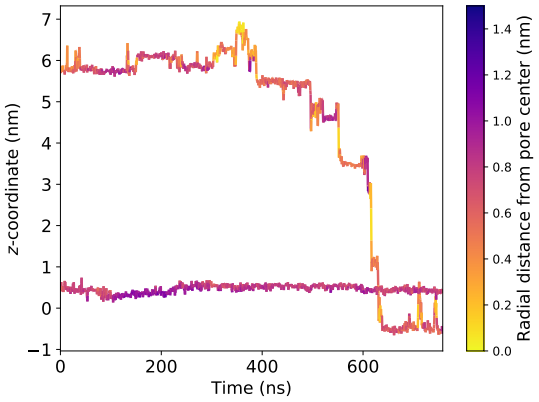
Mercaptoethanol has a similar average RDF and MSD to ethylene glycol.

- There is a much larger uncertainty associated with mercaptoethanol's MSD.
- It spends more time in the tail region than ethylene glycol, where transport is inherently slower, and may contribute to some slower MSDs.
- Conversely, Mercaptoethanol also exhibits some of the highest single solute MSDs
- It hydrogen bonds with head groups 6 times less frequently than ethylene glycol.
- This may lead to larger hops in the pore region.
- Some of this can be accounted for by the higher density of mercaptoethanol molecules in the head group / tail region. There are nearly 40 % more mercaptoethanol molecules than ethylene glycol molecules beyond 0.8 nm from the pore center.




(a) (b) (c)

Figure 9




(a)

Figure 10

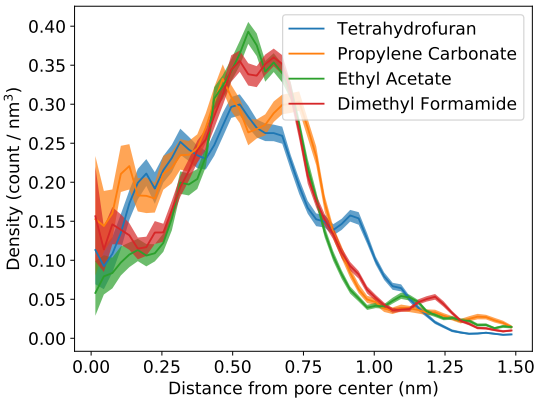



Figure 11

2,3-Dimercapto-1-propanol exhibits slower transport than glycerol because it spends more time near monomer head groups.

- Glycerol frequently hydrogen bonds with more than one head group at a time.
- It also hydrogen bonds with water molecules which increases its stability in the pore region.
- 2-3-Dimercapto-1-propanol preferentially hydrogen bonds with head groups so it gravitates towards the head group region.

DMSO has a comparable MSD to acetone even though its molecular weight is about 25 % larger.

- The pyramidal structure of DMSO may force it to spend more time closer to the pore center.
- There are 20 % more acetone than DMSO molecules in the region beyond 0.8 nm from the pore center.
- DMSO cannot as easily work its way in and out of the dense head group region.
- There is a peak in DMSO's radial density near 1.1 nm which may be a consequence of solute molecules that get stuck in the tails.

## Hydrogen bond acceptors

The final 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.
- Ethyl acetate and Propylene Carbonate are only marginally faster, however they are both larger molecules.

The radial density functions highlight the solutes' preference for the head group region.

- There are small peaks in the radial density greater than 1 nm from the pore center.
- The solutes become trapped in these regions where each step is highly anti-correlated to its previous step, leading to very low MSDs.
- The large size and nonplanar shapes of ethyl acetate and propylene carbonate may destabilize entrapment in the tail region more quickly, leading to slightly faster transport.
- Overall,

### Transport of Ions

Sodium ions coordinate with water molecules.

### 3.1 Design Principles

Water content affects pore size and strongly influence the MSD of both solutes and water. Experiments to understand how controllable this parameter is could be useful.

Monomers that cannot hydrogen bond.

Separate polar molecules by creating monomers with head group components designed to hydrogen bond.

- Hbond donors
- More incentive to dwell on walls.

## 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 Na-GA3C11.

We calculated the macroscopic diffusion coefficients of each solute as approximated by a CTRW model and validated our estimates using experimental DOSY NMR measurements.

We have studied the influence of water content on the diffusion coefficients.

We showed that hydrogen bonding between solutes and Na-GA3C11 monomers plays a major role in mechanism by which molecules traverse the nanopores.

We can use this intuition in order to modify our monomers for a specific separation.

- Increase number of h-bond sites to increase selectivity towards water over polar molecules

## 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.

## Acknowledgements

Molecular simulations were performed using the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number ACI-1548562. Specifically, it used the Bridges system, which is supported by NSF award number ACI-1445606, at the Pittsburgh Supercomputing Center (PSC). This work also utilized the RMACC Summit supercomputer, which is supported by the National Science Foundation (awards ACI-1532235 and ACI-1532236), the University of Colorado Boulder, and Colorado State University. The Summit supercomputer is a joint effort of the University of Colorado Boulder and Colorado State University.

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## TOC Graphic