

# From Water Under Confinement to Understanding Life at Subzero Temperatures

Yang Yao\*

**Abstract:** Water in confined geometries is highly relevant to biology, geology, and other fields where the function and properties of materials are significantly influenced by the presence and behavior of water in these environments. The structure and dynamics of confined water are strongly dependent on the confining geometry and its interaction with the interfaces. This review provides a brief overview of water under nano-sized hard and soft confinement, as well as water in living cells and in the hydration shells around biomolecules. Confined water exhibits distinct characteristics compared to bulk water, particularly in terms of nucleation, crystallization, molecular dynamics, and hydrogen bond network. In nano-sized confinements, water can remain in liquid state at extremely low temperatures (from  $-45\text{ }^{\circ}\text{C}$  to  $-120\text{ }^{\circ}\text{C}$ , at atmospheric pressure), offering insights into the fundamental physics of water and potentially enhancing our understanding of life in subzero temperature environments.

**Keywords:** Crystallization · Hydration shell · Lipidic mesophase · Molecular dynamics · Nano-sized confinement



**Yang Yao** obtained her Bachelor's and Master's degrees in Materials Science from Beijing University of Chemical Technology (China) in 2008 and 2012, respectively. She then moved to Mainz, Germany, to pursue her PhD at the Max Planck Institute for Polymer Research under the supervision of Prof. Hans-Jürgen Butt and Prof. George Floudas. She earned her PhD (magna cum laude) in 2018 with the dissertation entitled

*'Imbibition, Crystallization, and Dynamics of Polymers and Water under Nanometer Confinement'*. In 2019, Yang joined ETH Zürich as a postdoctoral researcher in the lab of Prof. Raffaele Mezzenga. She was promoted to senior scientist in early 2022. Later that year, she was awarded an ERC Starting Grant subsidized by SERI to study water in biological systems. Since January 2024, Yang has been an assistant professor and leading her research group as a Principal Investigator in the Department of Chemistry at the University of Basel.

## 1. Introduction

Water is the most ubiquitous and essential liquid on Earth's surface, fundamental to geoscience and the existence of all known life forms. A water molecule consists of two hydrogen atoms bonded to one oxygen atom and typically forms hydrogen bonds with four other water molecules in a tetrahedral arrangement (Fig. 1). Despite its simple structure, water exhibits rich physical behaviors and various physico-chemical anomalies originating from the hydrogen bonds between water molecules.<sup>[1–4]</sup> These anomalies include the well-known density maximum at  $4\text{ }^{\circ}\text{C}$ , volume increase on crystallization to ice (ice floats on water), high surface tension, decreased viscosity under pressure and many more. Many of these unusual properties of water sustain life. For instance, the floating ice on top of liquid water creates an insulating layer that protects the liquid water underneath from further freezing, enabling aquatic life to survive during winter. In other words, it is questionable whether life on Earth could have developed if water did not behave anomalously.<sup>[5,6]</sup>

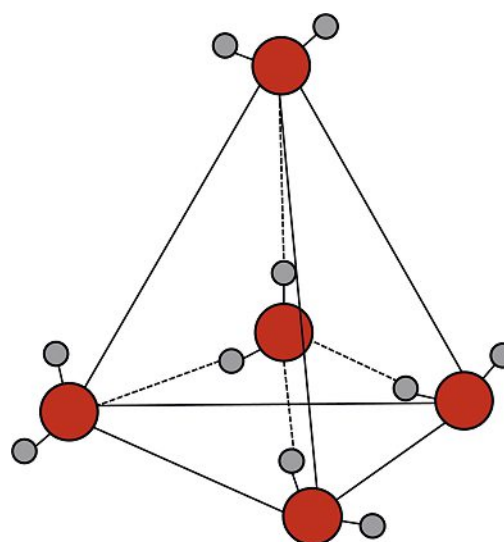


Fig. 1. Schematics of tetrahedral arrangement of hydrogen bonds between water molecules.

In nature, water often exists under nano-sized confinement, both in geological environments and biological systems. Most geological environments, such as the interlayer spaces of clay minerals, porous rocks, and zeolites, can be considered as hard confining media for water.<sup>[7]</sup> These confining space sizes range from a few nanometers to a few tens of nanometers.<sup>[8]</sup> The hard confined water plays important roles in geological and environmental sciences. Biological systems primarily contain water in soft confining media, such as protein channels and cell membranes.<sup>[9,10]</sup> Additionally, many biological processes occur in crowded aqueous environments where water can be considered as soft confined. The dimensions of such confinement range from 1 to 100 nm, with water being no more than about  $5\text{ \AA}$  from other biomolecules, such as lipids, proteins, and amino acids.<sup>[11]</sup> This soft confined water preserves the structure and the function of biomolecules, making it essential for life.<sup>[12,13]</sup>

Understanding the physical behaviors of confined water is crucial not only for addressing geological problems and applications but also for advancing bioengineering and life sciences. This

\*Correspondence: Prof. Y. Yao, E-mail: yang.yao@unibas.ch  
Department of Chemistry, University of Basel, CH-4058 Basel, Switzerland

knowledge is particularly important for uncovering the mechanisms of the survival of life at subzero temperatures in cold environments, such as permafrost, glaciers, and polar regions. For decades, researchers have been studying water under various confining media and have discovered that it exhibits different physical properties compared to bulk water, in aspects such as nucleation, crystallization, molecular dynamics, and the hydrogen bond network. Our purpose in writing this short review is to provide a general overview of studies on water under both hard and soft confinement at subzero temperatures. Additionally, we will touch upon the current understanding of the role of water in biological environments. Beyond the current understanding, there is still much to explore. Therefore, we seek to capture the interest of researchers, especially PhD students and postdocs in physics, chemistry, and biology, in this topic. By collectively deepening our comprehension of confined water, we aim to advance our understanding of the mechanisms behind the survival of life at subzero temperatures.

## 2. Water Under Hard Confinement

Hard confinement refers to systems with rigid pores. Various hard confining media, both hydrophilic and hydrophobic,<sup>[14,15]</sup> have been employed to investigate the physical properties of water. In this review, we will focus on hydrophilic confinement, specifically in nano-porous alumina (AAO), hollow silica spheres, and mesoporous silica nanoparticles (MCM/SBA). These systems exhibit different confining sizes and geometries, offering insights into water's behavior under different conditions.

Nano-sized confinement influences the physical properties of water, particularly its nucleation, melting, crystallization, and molecular dynamics. In terms of nucleation, unlike bulk water which crystallizes through heterogeneous nucleation, Suzuki *et al.*<sup>[16]</sup> observed a transition from heterogeneous nucleation ( $d > 200$  nm) to homogeneous nucleation ( $d \leq 65$  nm) with decreasing pore diameter in self-ordered AAO. In contrast, Yao *et al.*<sup>[17]</sup> found that water confined within larger hollow silica spheres, with diameters ranging from 190 to 640 nm, still crystallizes *via* homogeneous nucleation (at  $-38$  °C). In the hollow silica sphere studies, water molecules are infiltrated in the silica shell through small pores approximately 3 nm in size. This process filters out all the heterogeneities larger than this size, leaving homogeneous nucleation as the only nucleation mechanism for water confined inside the spheres.

The melting and crystallization of confined water has a pore diameter dependence (Fig. 2), which can be explained by a modified Gibbs-Thomson equation that takes into account a layer of non-freezable water (with thickness of  $t$ ) in contact with the pore wall:

$$T_m = T_m^\infty \left( 1 - \frac{2\sigma}{\rho\Delta H R - t} \right) \quad (1)$$

where  $T_m$  is the melting temperature,  $T_m^\infty$  is the melting temperature of bulk ice,  $\sigma$  is the interfacial free energy,  $\rho$  is water density,  $\Delta H$  is the heat of fusion, and  $R$  is the pore radius. If we use the  $T_m$  values for water in nano-sized pores with a broad range of diameters, it suggests a value of  $t \approx 0.21$  nm, indicating a monolayer liquid water next to the pore wall. Apart from melting, both heterogeneous and homogeneous nucleation temperatures have a linear dependence on pore diameter. The two lines converge at a pore diameter of approximately 2.6 nm, below which the crystallization of confined water is suppressed.<sup>[18–20]</sup>

The *molecular dynamics* of confined water has been studied through different techniques, including broadband dielectric spectroscopy (BDS), solid-state nuclear magnetic resonance (NMR), and quasi-elastic neutron scattering (QENS). In mesoporous silica nanopores, two dynamically different fractions of liquid water have been detected using a combination of BDS and NMR. These

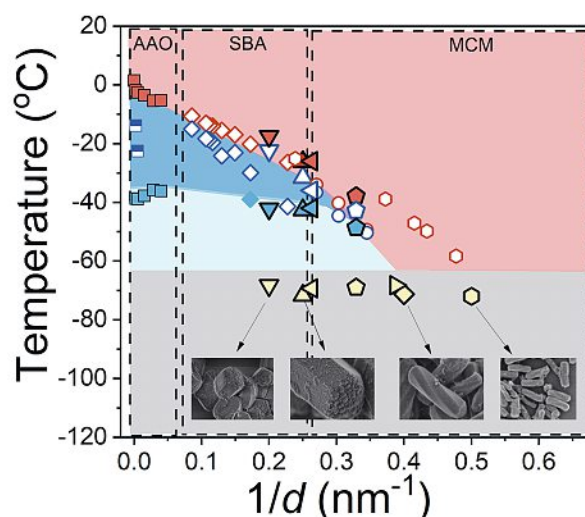


Fig. 2. Melting and crystallization temperatures of confined water located inside different systems (self-ordered AAO, and SBA/MCM nanopores) as a function of pore diameter ( $d$ ). Cyan and blue areas correspond to water crystallization *via* homogeneous and heterogeneous nucleation, respectively. Fig. adapted from ref. [18].

fractions are attributed to a slower interfacial water and a faster confined water in the pore interior.<sup>[18]</sup>

In addition to distinguishing between bound and confined water, researchers have been investigating the physical properties of water in the so-called ‘no man’s land’ region<sup>[3,21]</sup> (ranging from  $-45$  °C to  $-120$  °C, at atmospheric pressure) by studying water in nano-sized confinement. It is well known that we can lower the crystallization temperature of bulk water from 0 °C by adding third components, such as salt and sugar. However, when the temperature reaches  $-38$  °C, bulk water will inevitably form homogeneous nuclei as water molecules gather, leading to ice crystal growth. Below  $-45$  °C, liquid water cannot sustain itself due to the freezing from homogeneous nucleation.<sup>[22]</sup> Nonetheless, temperatures lower than  $-140$  °C can be reached through ultrafast cooling of water droplets, resulting in the formation of solid water without crystallization, known as amorphous ice. Researchers have identified two types of amorphous ice with different densities: low-density amorphous ice (LDA) and high-density amorphous ice (HDA). This phenomenon, known as polyamorphism, indicates that a pure material can exist in more than one amorphous states. Corresponding to water’s polyamorphism (LDA and HDA), it has been hypothesized that water also has two liquid states with different densities.<sup>[23,24]</sup> This hypothesized liquid-to-liquid transition, associated with the so-called fragile-to-strong transition, occurs in the ‘no man’s land’ region, which is inaccessible under ambient conditions (Fig. 3).<sup>[25]</sup> Therefore, nano-sized confinement has been used as a method to suppress water crystallization, allowing researchers to explore this temperature region through the molecular dynamics of liquid water.<sup>[26–28]</sup> Additionally, it is worth noting that the liquid-to-liquid transition of water is also studied under pressure.<sup>[29]</sup>

## 3. Water Under Soft Confinement of Lipidic Mesophase

Unlike the rigid porous structure found in hard confinement, soft confinement refers to the systems with soft and flexible interfaces, such as water-in-oil emulsions,<sup>[30–32]</sup> hydrogels,<sup>[33–35]</sup> and self-assembled structures like lipidic mesophases. These confining media are particularly relevant to biological systems. Water mixed with solutes (such as salts, sugars, ionic liquids, polymers) at high concentration can also be considered under soft confinement.<sup>[26,36,37]</sup> In these soft confining systems, both the hydrogen

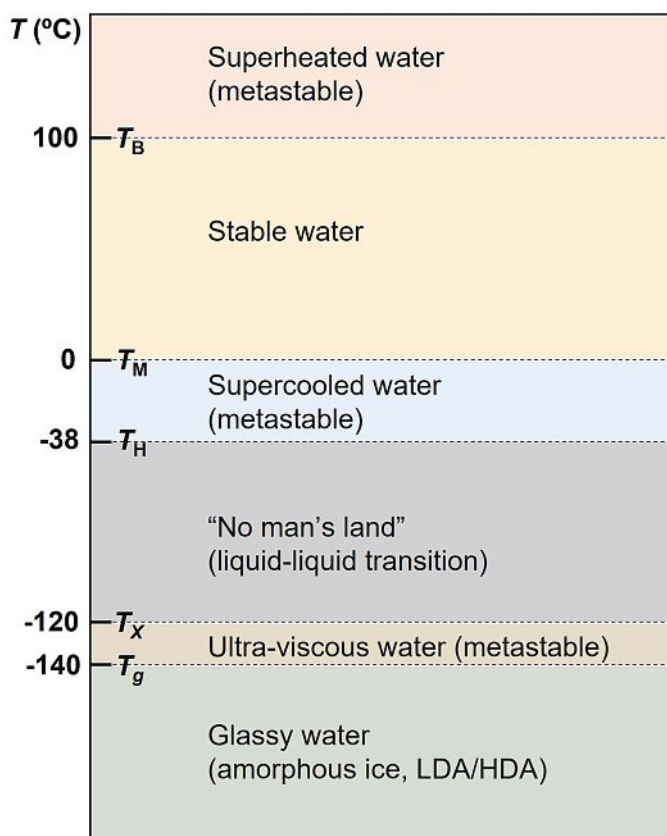


Fig. 3. Schematics of different temperature domains of water at atmospheric pressure. The temperature range from  $-45\text{ }^{\circ}\text{C}$  to  $-120\text{ }^{\circ}\text{C}$  is known as 'no man's land'. Adapted from refs [3,20].

bond network and molecular dynamics of water are significantly influenced by the strong interactions with the soft interfaces. Experimentally, studying water dynamics in soft confinement presents additional challenges, as the confining media itself is mobile. Here we will summarize our findings on water confined in a model soft confining medium: lipidic mesophase.

Lipidic mesophases (LMPs) are formed by mixing lipids with water and are an ideal platform to study water under soft nanoconfinement. Lipids are amphiphilic molecules with hydrophobic tails and a hydrophilic headgroups. The amphiphilic property of lipids enables them to self-assemble into nano-sized ordered structures in water. The most common types of mesophase structures observed in lipid-water systems are reverse micelle, lamellar phase, reverse hexagonal phase, and bicontinuous cubic phases.<sup>[38–41]</sup> In all the structures, water, as a minority phase, is softly confined between lipid molecules. Due to their structural features and biocompatibility, LMPs are widely used in drug delivery,<sup>[42,43]</sup> membrane biology,<sup>[44,45]</sup> bio-device fabrication,<sup>[46]</sup> and enzymatic reactions.<sup>[47–49]</sup>

Among the various phase structures of LMPs, bicontinuous cubic phases and lamellar phases present lipidic bilayer structures that mimic native membranes *in vivo*. To study the state of water at subzero temperatures, an unfrozen lipid is crucial, as most common lipids crystallize below room temperature and phase-separate from water. A synthetic lipid that remains unfrozen at subzero temperatures has been developed, but its complex and low-yield organic synthesis process limits its practical application.<sup>[50]</sup> Recently, we discovered that the commercially available lipid, phytantriol, forms a stable lamellar phase in water at subzero temperatures.<sup>[48]</sup> Using differential scanning calorimetry (DSC) and BDS, we investigated the crystallization and molecular dynamics of water confined in this soft lamellar phase. Below 9.5 wt%, water remains in a liquid state down to  $-120\text{ }^{\circ}\text{C}$ . With higher

water content, confined liquid water coexists with ice. Additionally, the confined water divides into two dynamically different fractions: slower bound water near the lipid headgroup and faster interstitial water (Fig. 4). The dynamics of lipid, bound water, interstitial water, and ice depend on the diameter of the water channels (obtained by small-angle X-ray scattering, SAXS). The presence of confined liquid water in the lamellar phase at subzero temperatures facilitates cryo-enzymatic reactions, where water serves as both medium and substrate. It was demonstrated that the model horseradish peroxidase oxidation reaction was successfully conducted, with the free-radical product stabilized at  $-20\text{ }^{\circ}\text{C}$ . Moreover, a cascade reaction and a lipase reaction with both hydrophobic and hydrophilic substrates were also successfully carried out.<sup>[48]</sup> The mechanism of preserved enzyme activity in LMPs was investigated using Fourier-transform infrared spectroscopy (FTIR). Analysis of the fractions of different secondary structures ( $\alpha$ -helix,  $\beta$ -sheet,  $\beta$ -turn, and random coil) revealed that these structures remain stable in LMPs regardless of temperature changes, while in bulk solution, they change significantly, leading to enzyme denaturation at low temperatures.<sup>[51]</sup>

The state of water is significantly influenced by the geometry of the host LMP. In our study, we examined the phase transition from cubic to reverse hexagonal ( $H_{II}$ ) phase (Fig. 5) by analyzing the static and dynamic states of water and lipids using a combination of techniques.<sup>[52]</sup> SAXS confirmed the phase transition temperature, and BDS identified three lipid processes in the monolinolein-water mesophase: headgroup association, interaction of polar headgroups with the mesophase matrix, and global dynamics. The lipid headgroups in the  $H_{II}$  phase exhibited slower dynamics compared to the cubic phase due to the topological differences. For confined water, two dynamically distinct fractions were found in both phases *via* high frequency BDS, both slower than bulk water. Dielectric intensity indicated a higher ratio of bound to interstitial water in the  $H_{II}$  phase, a finding supported by FTIR results showing stronger disruption of the water hydrogen-bond network. These observations are explained by the larger specific interfacial area in the  $H_{II}$  phase, promoting more water binding to lipid heads.<sup>[52]</sup> Additionally, we studied the effect of excess water on the lipid-water interaction during the same phase transition from cubic to  $H_{II}$  phase. The FTIR results indicate that the excess water molecules penetrate the interface between headgroups and tails, forming additional hydrogen bonds with the carbonyl group at the lipid interface. This accumulation of water molecules at the interface results in less dense packing of headgroups and faster dynamics in the lipidic mesophase.<sup>[53]</sup>

#### 4. Water in Biological Systems

Intracellular water constitutes a substantial portion, approximately 80% in mass, of the cellular composition in most living organisms.<sup>[54]</sup> Beyond its conventional function as a solvent facilitating biochemical reactions and participating as a substrate, water profoundly influences the conformation and functionality of biomolecules, notably in processes like protein folding. Since the middle of the last century, extensive research efforts have been directed towards unraveling the intricate properties of *water within living cells*.<sup>[55,56]</sup> The cellular environment is highly crowded, primarily attributed to the presence of biomacromolecules, which imposes unique dynamics on intracellular water. This crowding effect is evidenced by the cytoplasm's viscosity, which is nearly 106 times higher than that of bulk water.<sup>[57]</sup> Understanding how this crowding phenomenon influences intracellular water dynamics stands as an important question in biology. Various techniques have been employed to probe the dynamics of intracellular water in living systems, spanning bacteria, yeast, and spores. Among these techniques are THz<sup>[58]</sup> and Kerr-effect spectroscopy,<sup>[59]</sup> as well as BDS<sup>[60]</sup> and NMR,<sup>[61,62]</sup> Through these methodologies, researchers have unveiled a slower dynamic of intracellular water

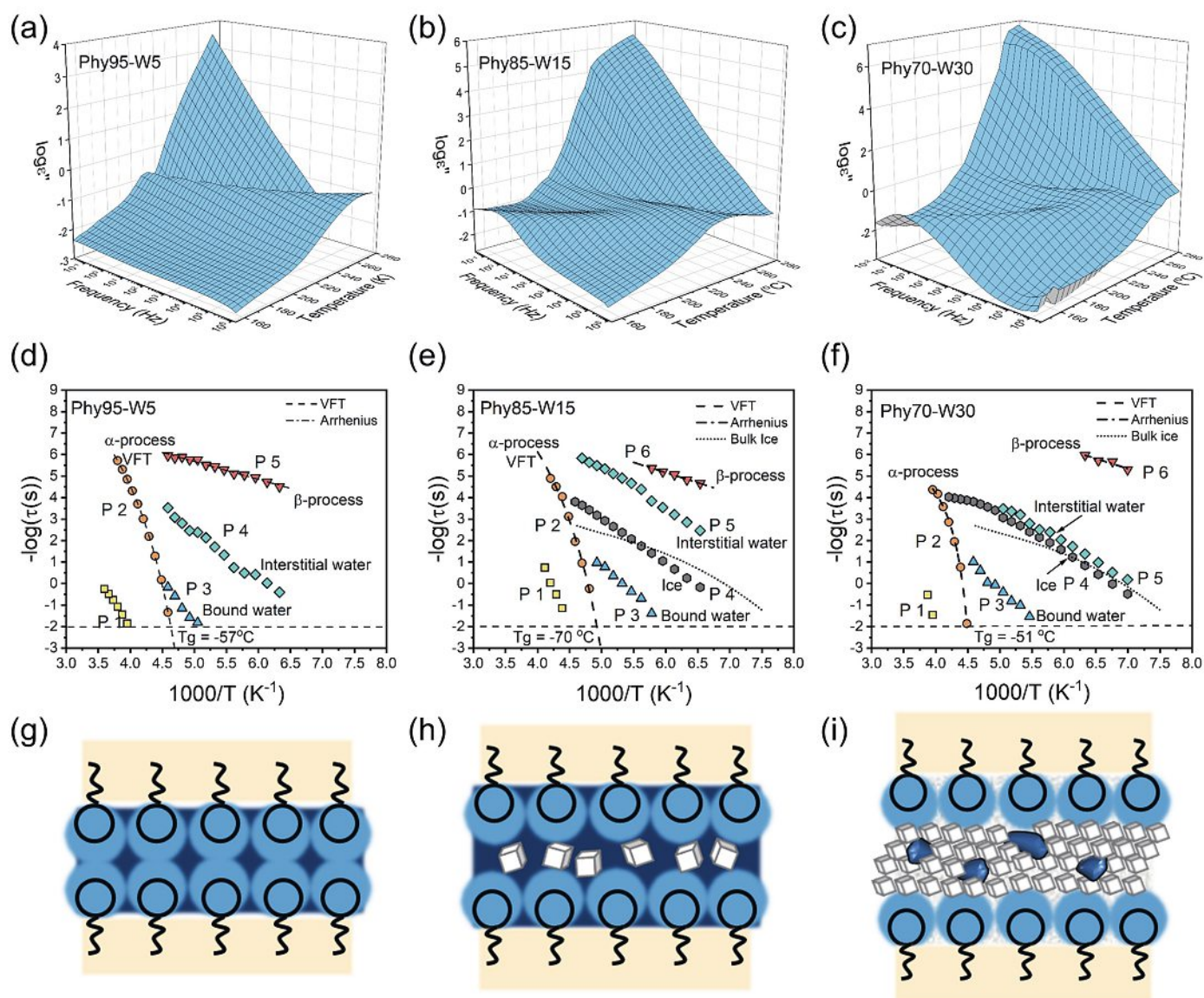


Fig. 4. 3D plots of dielectric loss as a function of frequency measured across a range of temperatures for (a) Phy95-W5, (b) Phy85-W15, and (c) Phy70-W30. Panels (d)–(f) summarize the relaxation times of lipids and water for the corresponding samples. Panels (g)–(i) provide schematics of water confinement in (g) Phy95-W5, (h) Phy85-W15, and (i) Phy70-W30, illustrating three states of water: bound water (light blue), interstitial water (dark blue), and ice (grey cubes). Adapted from ref. [48].

compared to that in bulk, shedding light on the intricate behavior of water within the cellular milieu.

In addition to studying the collective dynamics of water in living cells, significant efforts have been dedicated to investigating the localized dynamics of *water in the hydration shells of biomolecules*, such as proteins<sup>[63,64]</sup> DNA,<sup>[65]</sup> and phospholipids.<sup>[66]</sup> The state of water near biomolecules with diverse structures and properties is strongly influenced by the electric, steric, and other boundary conditions imposed by the bio-

molecule. These influences are similar to those observed when water is in contact with polymers, ions, or small solutes. Recent theoretical, numerical, and experimental approaches have significantly enhanced our understanding of water dynamics around biomolecules in recent decades. Several key features of water structure and dynamics in the hydration shell have been identified: (a) the arrangement of the first layer of water molecules is strongly influenced by the heterogeneous geometric and chemical properties of the biomolecular surface; (b) beyond the first layer, the hydration shell gradually adopts a structure similar to bulk water within fewer than five layers; (c) the hydration shell acts as a heat sink for excess energy released from biomolecules, with energy transfer occurring in picosecond timescales.<sup>[67]</sup>

## 5. Conclusion and Outlook

We briefly reviewed the current understanding of water in various environments: hard confinement, soft confinement, and complex biological systems. In each of these contexts, water exhibits behavior distinct from that in bulk form, particularly in terms of nucleation, crystallization, molecular dynamics, and hydrogen bond networks.

Biocontinuous cubic phase ( $Pn3m$ )    Reverse hexagonal phase ( $H_{II}$ )

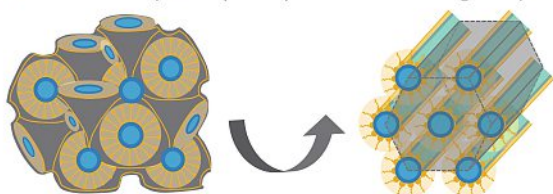


Fig. 5. Schematics illustrating the phase transition from a diamond bicontinuous cubic phase ( $Pn3m$ ) to a reverse hexagonal phase ( $H_{II}$ ). Adapted from ref. [52].

In hard confinement, water's relaxation behavior in the 'no man's land' region can provide insights into its physical nature. However, the effects of surface interactions and geometric confinement must be considered. In soft confinement, such as lipidic mesophases, cryo-enzymatic reactions have been successfully conducted, with lipidic mesophases stabilizing enzyme secondary structures and preserving their activities despite temperature changes. Given that water remains liquid down to  $-120\text{ }^{\circ}\text{C}$  in these systems, it is worth investigating the low-temperature limits for enzymatic reactions, including the potential for conducting reactions within the 'no man's land' region, such as at  $-80\text{ }^{\circ}\text{C}$ .

Intracellular water, influenced by the crowded cytoplasm, displays slower dynamics compared to bulk water. Detailed studies using theoretical, numerical, and optical approaches have focused on water in the hydration shells of biomolecules. To advance our understanding of water's role in life survival mechanisms, particularly at subzero temperatures, a combination of structural and dynamic techniques is required. These techniques must also be suitable for subzero temperature studies to capture the water state in these extreme conditions.

While significant progress has been made in understanding water in confined geometries, several intriguing questions and mysteries remain. Here are some key questions for future research:

1. *Hydrogen bond network*: how does the hydrogen bond network of water in various confining geometry differ from that in bulk water?
2. *Nanoconfinement and the 'no man's land'*: can we gain more insights into the physical nature of water in the 'no man's land' region through nanoconfinement?
3. *Structure and dynamical properties*: how do the structural and dynamical properties of water change under confinement or on the surface of biomolecules?
4. *Biochemical functions*: Relating water structure and dynamics to biochemical functions remains an emerging yet challenging field. How do perturbed hydration dynamics affect biomolecular functions in biochemical reactions?

By addressing these questions, future research can deepen our understanding of confined water and its unique properties. This, in turn, could lead to breakthroughs in various scientific fields and practical applications, enhancing our ability to utilize confined water in novel ways.

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