Clathrate Hydrates: Recent Advances on CH₄ and CO₂ Hydrates, and Possible New Frontiers

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Abstract

Gas hydrates continue to attract enormous attention throughout the energy industry, as both a hindrance in conventional production and a substantial unconventional resource. Scientists continue to be fascinated by hydrates because of their peculiar properties, including the ability of sequestering large amounts of hydrophobic gases, unusual thermal transport properties, and unique molecular structures. From a technological point of view, clathrate hydrates offer potential advantages in applications as diverse as natural gas production, carbon sequestration, water desalination and natural gas storage. The communities interested in hydrates span traditional academic disciplines, including earth science, physical chemistry, and petroleum engineering. The studies on this field are equally diverse, including field expeditions to attempt the production of natural gas from hydrate deposits accumulated naturally on the seafloor, to lab-scale studies to attempt to exchange CO₂ for the CH₄ present in hydrate deposits; from the scale up of water desalination plants to the testing of compounds used to prevent the formation of large hydrate plugs in pipelines; from theoretical studies to understand the stability of hydrates depending on the guest molecules, to molecular simulations to probe nucleation mechanisms. This review highlights a few fundamental questions faced by the research community, with focus on knowledge gaps representing some of the barriers that must be addressed to enable growth in the practical applications of hydrate technology, including natural gas storage, water desalination, CO₂ – CH₄ exchange in hydrate deposits, and prevention of hydrate plugs in conventional energy transportation.

Keywords: Gas storage, Nucleation, Anti-Agglomerants, Promoters, Molecular simulations
1. Introduction: Fundamental Features of Clathrate Hydrates

Sir Humphrey Davy identified water clathrate hydrates (also known as gas hydrates) in 1811.\(^1\) In clathrate hydrates, guest gas molecules (e.g., methane and CO\(_2\)) stabilize crystalline hydrogen-bonded water cages, the most common of which are sI, sII, and sH.\(^2\) Other, less common, structures have also been reported, e.g., a trigonal structure in the presence of dimethyl ether.\(^2,3\) Gas hydrates exhibit many unique thermophysical and transport properties. In liquid water, CH\(_4\) solubility is approximately 1 molecule for every 4,000 waters, while in hydrates the same amount of water holds more than 600 CH\(_4\) molecules. The thermal conductivity of hydrates is five to twenty times lower than that of ice,\(^4\) and it depends on temperature in a way that resembles glasses above 100 K.\(^5,6\) Many hydrate phase diagrams have been reported in the literature, depending on the guest gas species.\(^6,9\) Under limited conditions, theoretical models enable reasonable predictions of the hydrate phase boundary.\(^7,9\) Molecular simulations have contributed to understanding some of these unique hydrate properties,\(^19\) including the enhanced stability of CO\(_2\) hydrates relative to CH\(_4\) ones.\(^20\) However, several of the fundamental properties of clathrate hydrates remain elusive, including their formation mechanism.\(^21\)

In this short review we first provide an overview of recent advancements along four main technological areas in which clathrate hydrates promise great advantages, focusing primarily on experimental observations. We then summarise selected advancements accomplished through the implementation of molecular simulations. The combined overview of experimental and simulation studies allows us to identify a few key fundamental questions that we believe remain open. We conclude by suggesting possible research activities that could be implemented to tackle such questions.

2. Selected Promising Technological Applications of Gas Hydrates

2.1. Producing CH\(_4\) and sequestering CO\(_2\) in hydrates

It has been estimated that the energy dormant in natural gas hydrates worldwide is at least twice that of all conventional fossil fuels combined.\(^9,22-24\) However, reviewing approximately 40 years of research, Boswell and Collett,\(^25\) pointed out that technical and economical limitations inhibit the transformation of hydrate deposits into reserves. To probe whether the large deposits can become resources, approximately 25 major field explorations have been initiated since 1995 worldwide,\(^26\) including those in Japan,\(^27\) Gulf of Mexico,\(^28\) Alaska,\(^29\) the Barents Sea,\(^30\) and Hong Kong.\(^31\) However, Boswell and Collett\(^25\) pointed out that current technology is not ready for safe industrial-scale economic production of natural gas from hydrates. The ‘mature’ technologies include depressurization, thermal stimulation, and inhibitor injection, while CO\(_2)/CH\(_4\) gas exchange and microwave are being developed.\(^32-36\)

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Phase boundaries for methane (left) and CO\(_2\) (right) hydrates. The red circle indicates similar P&T conditions in the two diagrams: CO\(_2\) hydrates are stable, while CH\(_4\) ones are not at these conditions. The red arrows indicate the effect of adding tert-butyl alcohol (TBA) to the systems: the CH\(_4\) hydrates increase their stability while the CO\(_2\) ones become less stable. Figure adapted with permission from Kim et al.\(^{41}\) Copyright (2016) Elsevier.
While developing hydrate deposits is not yet attractive, the economic landscape depends on local market forces. Environmental motivations are also important and often justify field studies. Because CO₂ hydrates are more stable than CH₄ hydrates, one could extract CH₄ from naturally occurring hydrates, and simultaneously store industrially emitted CO₂ and CH₄, as well as their mixtures, forming hydrates. Lee et al. used C NMR to assess the equilibrium composition of mixed CO₂/CH₄ hydrates and the kinetics of conversion. They found that (a) for gas compositions between 10 and 70% CO₂, hydrates show significant enrichment in CO₂, and (b) the kinetics of CO₂/CH₄ replacement when a CH₄ hydrate is exposed to CO₂ is ~6 times faster than the kinetics of both CO₂ and CH₄ hydrate formation from ice. Several approaches could be attempted to enable the CO₂-CH₄ swap in hydrates. For example, laboratory investigations on a 60 L reactor quantified advantages and disadvantages of heating the system while CO₂/CH₄ swap occurs. The results show that the efficiency of the process strongly depends on factors such as hydrate saturation and heating rate. An analysis of the carbon balance at moderate heating rates suggested “a substantially negative carbon footprint”. The Alaska field study seeks to assess the feasibility of exchanging CO₂ for CH₄ in naturally occurring hydrate reservoirs. The results are promising, although it has been reported that “the nature, extent, and efficiency of the exchange reaction [is] uncertain”. Laboratory studies have been able to explain why CO₂ can replace CH₄ (Figure 1), identify some of the rate-limiting steps for hydrates growth, and quantify the conversion rate dependence on hydrate surface area, nucleation and diffusion barriers. Many studies, including field campaigns, continue to be conducted to determine the optimal operation conditions (T, P, addition of liquid vs. gaseous CO₂) to enhance CH₄ removal from hydrates. Because it is a very aggressive hydrate former, H₂S is proposed as an additive for this application, and it could help improving the kinetics of the CO₂/CH₄ swap process.

![Figure 2](image-url) Experimental amount of CH₄ gas replaced by CO₂ during CO₂/CH₄ swap. The transition from fast replacement to slow, diffusion-limited process is identified by the dark band. Figure reproduced with permission from Zhao et al. Copyright 2015 American Chemical Society.

Although analysis of experimental studies often reveals unexpected phenomena, kinetics barriers have been shown to be very important in the exploitation of natural hydrate deposits. For example, Zhao et al. showed that CH₄ production from hydrates is fast when the experiment starts; however, after 5 hours, the production rate decreases (Figure 2). The initial production of CH₄, and its slow decay at short times, can be described by models which are able to account for the reduction in driving force (i.e., CO₂ pressure) as CH₄ hydrates are destabilised and CO₂ hydrates are formed. The following slow CH₄ production is thought to be due to strong barriers to diffusion that appear because of the formation of CO₂ hydrates on the surface of a particle. Among models developed to describe such observations, the shrinking-core one seems able to account for the observed slow CH₄ production because it can account for barriers to diffusion. Salamatin et al. developed a phenomenological model to describe the shrinking-core stage achieving predictions that are semi-quantitative with respect to experiments. Because hydrate formation is exothermic, the formation of CO₂ hydrate releases heat that could melt CH₄ hydrates. Baig et al. developed a model based on non-equilibrium thermodynamics, which highlighted the effect of heat-transport on the kinetics of CO₂/CH₄
swap, and suggested that it might be beneficial to have a layer of free water around the hydrate particle. This appears somewhat surprising, as the water layer implies some distance between the growing CO\textsubscript{2}-CH\textsubscript{4} hydrate and the dissolving CH\textsubscript{4} hydrate, which could delay heat transfer. The CO\textsubscript{2}/CH\textsubscript{4} swap could lead to structural reorganisations, which could be monitored using Raman spectroscopy.\textsuperscript{58} For example, Lee et al.\textsuperscript{58} studied the structural transition from hydrate sH to sI as CO\textsubscript{2} replaces CH\textsubscript{4}. The results suggested that in CO\textsubscript{2}-rich conditions, CO\textsubscript{2} functions as a co-guest in sH hydrates. Approximately 88\% of CH\textsubscript{4} was recovered during those experiments. The dissociation of sH hydrates, followed by the formation of sI hydrates was confirmed by calorimetry.

To directly observe the kinetics of hydrate formation, Daniel-David et al.\textsuperscript{60} reported a simple, yet insightful set of data, summarised in Figure 3. They studied hydrate growth, seeded by a hydrate fragment, on a sessile water droplet exposed to CH\textsubscript{4} and/or CO\textsubscript{2}. The authors observed rapid hydrate growth on the surface of the droplet. When the droplet surface was covered by hydrate, the growth decreased significantly. Hydrate growth was much faster when at least 75\% of the gas was CO\textsubscript{2}. When the gas was CO\textsubscript{2}-rich, adding surfactants had a negligible effect on the growth rate; conversely, hydrate growth in a CH\textsubscript{4}-rich gas system was enhanced by ionic surfactants (e.g., SDS and AOT), while non-ionic surfactants (e.g., Tweens and Pluronics) had no effect on the growth rate.

Ionic surfactants also affect the morphology of the resultant hydrate particle, suggesting that a capillary-driven pattern occurs during hydrate growth when the gas is CH\textsubscript{4} and SDS or AOT are present, while a rapid growth of a non-permeable hydrate ‘skin’ grows in the other cases. The results summarised are consistent with previous observations,\textsuperscript{61 - 63} including those reported by Dicharry et al.,\textsuperscript{64} who studied hydrate formation triggered by tetrahydrofuran (THF), where the effect of the alkyl chain length of sodium alkyl sulfates (from 8 to 18 carbon atoms) was studied explicitly. It has been argued that surfactants are not effective in CO\textsubscript{2}-rich systems because of a competitive adsorption between CO\textsubscript{2} and the surfactants at the water-gas interface.\textsuperscript{63} Alberti et al.\textsuperscript{65} suggested a different explanation. Using MD simulations, they found that CO\textsubscript{2} dissolved in water orients neighbouring water molecules in a hydrate-like structure. When SDS is present, CO\textsubscript{2} preferentially interacts with SDS, thus reducing its effect on re-structuring water molecules. The simulations were however too short to observe nucleation.
2.2. Preventing hydrate plugs formation in pipelines

Since 1934, gas hydrates have been regarded as a hindrance in oil and gas pipelines, as they can result in blockages that fully occlude flow.66 These plugs can (1) decrease the mechanical integrity of the pipeline during remediation, increasing the risk of pipeline rupture with the connected environmental consequences; (2) negatively affect the safety of operators; or (3) interrupt production, with economic losses due to reduced productivity and compromised well integrity. The conceptual model for hydrate blockage formation in gas-water pipelines is presented in Figure 4.67 Most attention concerns CH₄ hydrates because in oil and gas pipelines, water and methane are at contact, sometimes at high pressure and low temperature conditions. CO₂ hydrates in pipelines have received attention as a pure species due to their sequestration potential,68 but it could also be important to quantify how polar species (CO₂ and H₂S) affect mixed hydrate phase boundary and growth kinetics. In fact, both quantifying accurately the thermodynamic conditions at which hydrates could form, and the kinetics of their growth are important for ensuring pipelines integrity, which is the goal of the industrial sector known as ‘flow assurance’.

![Figure 4. Conceptual model of hydrate plug formation in a pipeline. Figure reproduced with permission from Joshi et al.67 Copyright (2013) Elsevier.](image)

Conventional flow assurance approaches includes the addition of thermodynamic hydrate inhibitors (THIs), such as methanol, to fully suppress the hydrate equilibrium condition.69 Unfortunately, for this approach to be effective, some fields may require methanol dosages in excess of 50 wt% with respect to the aqueous phase, which causes severe limitations both in terms of economics and environmental footprint. Alternatives are needed to reduce costs and carbon emissions, including the development of low dosage hydrate inhibitors (LDHIs), which are injected at concentrations as low as 0.5 wt% with respect to the aqueous phase.2,70

Current LDHI classes include both kinetic hydrate inhibitors (KHI) and anti-agglomerants (AAs).70 KHIIs are thought to inhibit hydrate nucleation and growth, perhaps by perturbing the water structure or interfering with the formation of a critical hydrate nucleus. Nature inspired the development of KHIIs, as some aquatic species (e.g., the winter flounder) survive in sub-zero waters via specialised proteins.71 KHIIs are usually polymers, such as poly(N-vinyl pyrrolidone), PVP; polyvinyl-caprolactam, PVCap; polydiethylacrylamide; or co-polymers of DEAMA or PVCap that exhibit improved biodegradability. The presence of caprolactam or pyrrolidone rings has been shown to significantly enhance KHI performance. Pendant alkyl groups should interact with cavities on the hydrate surface, and carbonyl groups form hydrogen bonds with water. Kelland72 showed that PVP, PVCap, PolyNIPMAM, and Polyesteramide are equally effective in preventing cyclopentane hydrates at 100 ppm; note that cyclopentane hydrates form at atmospheric pressures and temperatures below 7.7°C, and they can be easily formed in the laboratory at conditions where ice is not stable while maintaining the same hydrate structure (sill) that is found in most industrial pipelines.

The other common class of LDHIs are AAs, which are typically ionic surfactants.70 The best performing AAs are based on quaternary ammonium salts. The leading hypothesis for their active mechanisms involves the generation of stable water-in-oil emulsions, whereby the AA can adsorb to the hydrate-oil surface following crystallisation of the water droplets into hydrates. Aman et al.73 developed the micromechanical force (MMF) apparatus to quantify the adhesion between hydrate particles, demonstrating that both ionic and non-ionic surfactants can adsorb to the hydrate-oil interface reducing adhesion forces and, by extension, particle aggregation potential. At present, the
standard characterisation test for AAs involves trial-and-error methods, such as rocking cells, although it is often preferred to assess the AAs performance on flow loops, which are expensive to operate and maintain.

Several phenomena are important and should be considered to completely understand how hydrate plugs form in pipelines. Such phenomena include, but are probably not limited to, the adhesion between two hydrate particles and that between hydrates and the pipe, the diffusion of gases across the interface between water and hydrocarbons, the adhesion between water droplets covered by anti-agglomerants, the effect of impurities on both the nucleation and growth of hydrate particles, etc. Aman and Koh recently studied the formation of hydrates from either pure methane gas, or a ternary gas mixture containing CH₄, CO₂ and C₃H₆. They found that CO₂ hydrates adhere to the vessel surfaces much more strongly than CH₄ ones. Sojoudi et al. considered the adhesion of cyclopentane hydrates on polymeric coatings. A clear understanding of the adhesion mechanisms in hydrates is needed for securing progress in this field. Along these lines, Aman et al. employed the MMF to measure adhesion, both between two cyclopentane hydrate particles, and between one hydrate and a surface. Among the adhesion mechanisms proposed is the formation of a capillary bridge followed by sintering.

### 2.3. High-tech applications: Natural gas storage and water desalination

From a different technological perspective, the controlled formation of gas hydrates promises to boost high-tech applications such as natural gas storage ("solidified natural gas offers the safest, cleanest and the most compact mode of storage") and seawater desalination, among others. The success of these applications depends strongly on our ability to control hydrates nucleation and growth.

The experimental investigation of hydrates nucleation is extremely difficult because of the need to probe nucleation events, which are stochastic by nature. Neutron diffraction data suggest that the structure of water around methane does not change substantially during hydrate formation, but it is dramatically different once the hydrate has formed. NMR data suggested that 20 water molecules are present in the methane hydration shell during hydrate formation. Because additives often promote the formation of hydrates, it becomes of fundamental and practical interest to quantify how they affect hydrates. Among interesting results available in the literature, Luo et al. showed that although dimethyl sulfoxide (DMSO) increases the solubility of CO₂ in water, it reduces the range of stability of CO₂ hydrates. On the other hand, tetra-n-butyl ammonium bromide (TBAB) is an environmentally friendly additive often used to apply hydrates in gas storage applications because its hydrates form at atmospheric pressures. 83-84 increases the stability of the CO₂ hydrate. Kim et al. employed 13C NMR, Raman spectroscopy, and X ray diffraction to investigate the effect of tert-butyl alcohol, TBA, in CO₂, CH₄ and N₂ hydrates. For CH₄ and N₂ hydrates, TBA increases the range of thermodynamic stability (lower P and constant T, or higher T at constant P), while it destabilised CO₂ hydrates (see Figure 1). This is in part surprising, because in both CH₄ and CO₂ hydrates, TBA causes a transition from sI hydrate (the stable form for the pure hydrates) to sII, and it preferentially occupies the large cage in the sII hydrate. These observations are consistent with others suggesting that large guests stabilise hydrates, unless hydrogen bonds or other preferential interactions between guest and water molecules perturb the cages. Tetramethylammonium hydroxide, e.g., reduces the stability region of both CH₄ and CO₂ hydrates due to its strong electronegative interactions with water.

THF is a widely studied promoter of hydrate nucleation. Because THF hydrates are stable at near-ambient conditions, mixed THF-CH₄ hydrates could be useful for long-term energy storage. Linga and his group showed that THF has both a thermodynamic and a kinetic effect on CH₄ hydrates. It would be helpful to develop a quantifiable molecular mechanism that explains these observations.

When hydrates are used for desalination, it becomes important to understand and control the effect of salt on the properties of hydrates. Linga and his group studied formation and dissociation of CO₂ hydrates in the presence of NaCl, up to seawater concentration. NaCl has a thermodynamic inhibition effect during hydrate formation, as expected, but not a kinetic one. Not much effect was observed on the dissociation. Yagasaki et al. conducted molecular dynamics (MD) simulations for CH₄ hydrate dissociation in the presence of NaCl. They found two competing phenomena: NaCl slightly slows the early stage of hydrate dissociation, before the formation of a methane bubble, but it decreases CH₄ solubility in water, which causes the formation of methane bubbles. It could be that experimental
data see little effect of NaCl on hydrate dissociation because these two effects cancel each other out. It remains to be tested whether the effect of NaCl on CH₄ hydrate dissociation is different than that on CO₂ hydrates.

3. Some advancements in the understanding of clathrate hydrates enabled by molecular simulations

Among the pioneers in the use of molecular simulations for better understanding the fundamental properties of hydrates a note of tribute goes to the late Prof. Rodger. He and his group studied hydrate formation at water-methane interfaces,¹¹²,¹¹³ the phase transition between structures sl and sII, hydrate melting, among other fundamental topics related to the subject.¹¹⁴-¹¹⁶

One of the fundamental properties of gas hydrates that remain highly debated concerns their nucleation. Because molecular dynamics simulations (MD) follow the trajectory of individual molecules, they have been used to address this topic.¹¹²,¹¹⁷-¹¹³ Walsh et al.¹²⁴ were the first to report microsecond-long simulations successful in observing hydrates nucleation: the critical step for homogeneous nucleation was found to be the arrangement of methane molecules in a bowl-like structure interspersed by water. Both hydrate sl and sII formed, stabilised by uncommon S¹¹⁶ cages that prevented energetically unfavourable interfaces. This group quantified effects due to methane concentration, system size, and simulation ensembles.¹²⁵,¹²⁶ Sarupria and Debenedetti also conducted microsecond-long MD simulations.¹²⁷ Their results show the formation of subcritical clusters of water and methane structures, dynamic in nature, that undergo continuous rearrangements, until they aggregate yielding the critical nucleus. These two results summarise the two mechanisms proposed for hydrate nucleation: (i) the ‘labile cluster hypothesis’,¹²⁸,¹²⁹ consistent with the results reported by Sarupria and Debenedetti and with the coarse-grained simulations of Molinero et al.,¹³⁰ according to which isolated hydrate cages form independently and agglomerate to yield the critical nucleus; and (ii) the ‘local structure hypothesis’,¹³¹ consistent with the results reported by Walsh et al.,¹²⁴ according to which the guest molecules pre-arrange in a structure to yield a very small hydrate critical nucleus. Knott et al.¹³² also simulated hydrate nucleation. This contribution is important because the Authors extracted from the simulations parameters to be applied to the classical nucleation theory. They obtained a nucleation rate of ~ 10⁻¹¹¹ nuclei cm⁻³s⁻¹ at 273 K and 900 atm. He et al. simulated the nucleation of CO₂/CH₄ mixed hydrates.¹³³ The results show that the difference in hydrophobicity between CH₄ and CO₂ affects the stability of gas nano-bubbles, that high CO₂ content accelerates hydrate formation, and that CH₄ and CO₂ preferentially adsorb in cages that are consistent with their sizes, and that multiple pathways lead to hydrate formation. These simulations are important because in many practical conditions gas mixtures are present, rather than pure gases.

Concerning the nucleation of hydrates, an important question that is being addressed by the community concerns the effect on the nucleation rate due to the proximity of mineral surfaces and the presence of impurities. Recently, Cox et al.¹³⁴ combined atomistic MD simulations with neutron scattering experiments to address this question and reported no effect on hydrate nucleation due to the presence of a wide variety of nanoparticles. These results seem to be consistent with coarse-grained simulations by DeFever and Sarupria,¹³⁵ who showed that even in proximity of an interface nucleation follows a bulk-like mechanism. However, DeFever and Sarupria also suggested that an interface could lead to enhanced concentrations of the hydrate-forming solute, which could affect nucleation rates, and therefore it is possible that confinement yields a measurable effect on hydrates nucleation. For example, Phan et al.¹³⁶ reported evidence of short-lived hydrates when water-methane systems were confined in narrow slit-shaped pores carved out of silica. It is likely that these effects are strongly dependent on the chemical nature of the solid surface, as well as on pressure-temperature-composition conditions. Borchardt et al.¹³⁷ recently reviewed experimental, theoretical and simulations studies conducted on the topic of hydrates formation in confined spaces.

Molecular simulations were used to study hydrate dissociation. English et al.¹³⁸ found that the diffusion of methane away from the dissolving hydrate is the rate-limiting step in this process. These simulations were consistent with those of Baez and Clancy,¹³⁹ who showed that even hydrate dissociation, not only hydrate nucleation, is stochastic, and those of others confirming the importance of the transport of guest gases away from the hydrate.¹¹¹,¹³⁸ The occupancy of the hydrate affects the rate of dissociation,¹³⁷,¹³⁸ as well as the size of the guest molecules and their interactions with the water molecules in the cage.¹⁴⁰ Adiabatic MD simulations showed that, because the hydrate dissociation is endothermic, it is possible that the local temperature decreases upon dissociation, regenerating hydrate cages from the melt.¹³⁸,¹⁴¹,¹⁴² Thermodynamic inhibitors such as NaCl and CH₃OH promote the formation of nano-bubbles, which deplete the surrounding water of gas molecules, enhancing hydrate dissociation. NaCl reduces CH₄ solubility in water,
while \( \text{CH}_3\text{OH} \) reduces the gas-liquid interfacial tension.\textsuperscript{143} The presence of \( \text{CO}_2 \) in the large cages stabilises \( \text{CO}_2\text{-CH}_4 \) mixed hydrates, and hydrate dissociation does not follow a regular layer-by-layer process.\textsuperscript{144}

Simulations attempted to address how a \( \text{CH}_4 \) hydrate transforms into a \( \text{CO}_2 \) one. It is crucial for the stability of the mixed hydrate that \( \text{CH}_4 \) occupies the small cages, and that \( \text{CO}_2 \) occupies the large ones.\textsuperscript{145,146} Liu et al.\textsuperscript{147,148} considered the stable structures of \( \text{CO}_2, \text{N}_2, \text{CH}_4 \) and mixed hydrates and computed structural and thermal fluctuations. Their results suggest that to recover most \( \text{CH}_4 \) from methane hydrates, \( \text{CO}_2 \) should occupy the larger cages and \( \text{N}_2 \) the smaller ones. While useful, these results stop short at revealing the mechanism of \( \text{CO}_2/\text{CH}_4 \) swapping. Muromachi et al.\textsuperscript{149} studied the occupancy of \( \text{CO}_2 \) and \( \text{CH}_4 \) within the cages of mixed hydrates to interpret experimental XRD data: TBAB generated an elongated distorted cage within the hydrate structure. While \( \text{CO}_2 \) preferentially adsorbed within this elongated cage, \( \text{CH}_4 \) did not.

Simulations quantified the diffusion of guest gas molecules, since experimental measurements are problematic.\textsuperscript{150} Burnham et al.\textsuperscript{151} considered diffusion of \( \text{H}_2 \) in sI hydrates. The lowest energy barrier was found to be the one between adjacent cages that share one hexagonal face. To quantify the free energy barriers they employed the umbrella sampling method,\textsuperscript{152} and they calculated iso-surface energy profiles as a function of \( \text{H}_2 \) loading.\textsuperscript{153} The results were presented for 50, 100 and 200 K. As \( T \) increases the energy barrier also increases, which is at odds with expectations and with the results by Trinh et al.,\textsuperscript{154} perhaps because of entropic effects.\textsuperscript{151} Peters et al.\textsuperscript{155} studied \( \text{CH}_4 \) diffusion, and Demurov et al.\textsuperscript{156} reported the rates of hopping events for \( \text{CO}_2 \) molecules. The approach by Peters et al.,\textsuperscript{155} is particularly instructive. They employed the equilibrium path sampling method\textsuperscript{157} to compute the free energy landscape as \( \text{CH}_4 \) diffuses across neighbouring cages in a structure I hydrate. They then employed a kinetic Monte Carlo formalism\textsuperscript{158} to estimate the self-diffusion coefficient of \( \text{CH}_4 \) within the hydrate. The estimated self-diffusion coefficient was found to be \( \sim 10^{-15} \text{ m}^2/\text{s} \), depending on the degree of occupancy. This data-point is a few orders of magnitude faster than \( \text{CH}_4 \) diffusion in ice, and a few orders of magnitude slower than that through polycrystalline ice and hydrate layers.\textsuperscript{159-161} Thus methane diffusion in hydrates preferentially occurs along grain boundaries, which can be quantified using the technique proposed by Klapp et al.\textsuperscript{162} Lo et al.\textsuperscript{163} conducted equilibrium MD simulations in a periodic system within which they had introduced water vacancies. The estimated \( \text{CO}_2 \) diffusivities are \( 3.6 \times 10^{-15} \text{ m}^2/\text{s} \) at 273 K and \( 1.1 \times 10^{-15} \text{ m}^2/\text{s} \) at 288 K, while the water vacancy defect was found to diffuse with \( \sim 10^{-12} \text{ m}^2/\text{s} \). Futera et al.\textsuperscript{164} combined experimental Raman spectroscopy and MD to determine the vibrational modes of hydrogen molecules confined in structure II hydrates.\textsuperscript{165,166} The simulations agreed qualitatively with the experimental Raman spectra. The ability of reproducing vibrational spectra is key for predicting thermal conductivities in systems that show many interfaces.\textsuperscript{167}

Simulations helped better understand the thermal conductivity of hydrates.\textsuperscript{168-170} English et al.\textsuperscript{171,172} employed classic MD to predict the thermal conductivity of methane hydrates (sI, sII and sH). Following others,\textsuperscript{173-175} the thermal conductivity was extracted by the Green-Kubo linear response theory\textsuperscript{176} via the heat flux auto-correlation function. The results are in good agreement with experiments not only with respect to the thermal conductivity, but also with respect to its changes with \( T \). The thermal conductivity of the \( \text{CH}_4 \) sI hydrate at 30 K (\( \sim 1.05 \text{ Wm}^{-1}\text{K}^{-1} \)) is lower than that of ice at the same \( T (1.79 \text{ Wm}^{-1}\text{K}^{-1}) \) but also that of the hydrate with no \( \text{CH}_4 \) (1.41 \text{ Wm}^{-1}\text{K}^{-1}).\textsuperscript{172}

Simulations shed light on the mechanism by which LDHIs function. Available studies report the strength of adsorption of a short polymer and a hydrate:\textsuperscript{177} those compounds that adsorb more strongly and perturb the interfacial water more effectively are possible LDHIs candidates.\textsuperscript{177} Trout and his group recently reported similar simulations for single AAs.\textsuperscript{178} Jimenez-Angel and Firozaabadi, after studying hydrate nucleation and the hydrate-methane interface,\textsuperscript{179-181} focused on the adsorption of individual AA molecules on a hydrate surface.\textsuperscript{182} On a related footprint, some recent simulations attempted to quantify the collective features of AAs at hydrate-hydrocarbon interfaces. The importance of these contributions is predicated on the models of hydrate growth:\textsuperscript{9} hydrates form in droplets dispersed within oil. Hydrates form on the droplet surface, and grow towards its centre. For the hydrate particle to complete, it is necessary that \( \text{CH}_4 \) diffuse from the oil to the droplet core. Bui et al.\textsuperscript{183} simulated various AAs at the hydrate-hydrocarbon interface changing systematically the AAs concentration, their molecular features, and also the composition of the hydrocarbon phase. The MD results suggest that those AAs effective at preventing hydrate plugs yield ordered films, reminiscent of the ‘interfacial freezing’ phenomenon reported for surfactants at oil-water interfaces.\textsuperscript{184} Some hydrocarbon chains were found to penetrate the AAs film, in qualitative agreement with experimental data by Tokiwa et al.\textsuperscript{185} These results also provide a new hypothesis for the mechanism by which AAs function: when the AAs form an ordered film, they could prevent methane transport across the interface.\textsuperscript{186}
4. Some Open Fundamental Multidisciplinary Questions

The overview provided above considers explicitly four multi-disciplinary advanced applications: (a) CH₄ production from hydrate deposits and simultaneously sequester CO₂, via swapping CO₂ for CH₄; (b) reduce the likelihood of hydrates formation in pipelines; and (c) control hydrate formation to advance gas storage and water desalination. While diverse, these applications share several fundamental principles, and their further development depends on the community ability to answer a few fundamental questions, such as: (1) Why are H₂S and tetrahydrofuran (THF) effective promoters of hydrates nucleation? (2) How do TBA, dimethylsulfoxide (DMSO) and tetra-n-butyl/ammonium bromide (TBAB) affect hydrates stability, and why do they have different effects on different hydrates? (3) Can inclusions or co-adsorbrates modulate the diffusion of guest molecules in hydrates? (4) Why is the growth of CO₂-rich hydrates faster than that of CH₄-rich hydrates? (5) Why do ionic surfactants such as sodium dodecyl sulphate (SDS) speed up the growth of CH₄ hydrates, but are ineffective for CO₂-rich hydrates? (6) What are the mechanisms by which LDHIs function? (7) Are the mitigation strategies effective for preventing CH₄ hydrate plugs effective for other hydrates? (8) Why do CO₂ hydrates adhere more strongly to surfaces than CH₄ ones?

To answer these, and other questions, and to quantify their effects at the large scale, it is necessary to implement comprehensive multi-scale quantitative models that link different molecular phenomena, sometimes synergistically and other times antagonistically, to macroscopic observables. To develop such understanding, advanced experiments, high-end simulations and theoretical approaches are required, and care should be placed in combining synergistically their results. Progress requires reconciling observations obtained from a variety of experiments (e.g., spectroscopy and micromechanical forces), perhaps using state-of-the-art molecular simulations. For example, the literature shows that chemical promoters and inhibitors can both facilitate and impede the formation of hydrates. The critical missing link is a comprehensive understanding of how these compounds work: do they affect the nucleation of hydrates, their growth, their agglomeration, are they synergistic or antagonistic? Practical progress will then require translating such understanding into macroscopic observables via the implementation of meso-scale approaches. At a minimum, three steps should be attempted:

1. Discover new molecular mechanisms;
2. Quantify how molecular mechanisms affect macroscopic observables;
3. Verify all theoretical predictions via experimental observations.

Within this over-arching framework, possible activities along these outlines include:

Discover new molecular mechanisms. Perhaps, massive molecular dynamics simulations and advanced experiments could be combined to address, for example: (a) growth of CO₂ & CH₄ hydrates, and effects of surfactants on the growth rate; (b) hydrates nucleation promoters, with emphasis on THF, H₂S and caprolactone rings (the latter, a critical component of LDHIs, is expected to delay nucleation, while THF and H₂S are very effective promoters); (c) guest diffusion in hydrates, with emphasis on the effect of chemical additives; (d) the effect of chemical additives on CO₂/CH₄ swap, with emphasis on TBAB, DMSO and TBA. These, and other studies will yield a detailed understanding of the underlying molecular mechanisms, which is essential to promote progress, but also to quantify time constants and parameters that could be used in meso-scale models (e.g., hydrates nucleation rate, growth kinetics, etc.)

Quantitative multi-scale considerations. Meso-scale models are needed to quantify the practical meaning of molecular discoveries such as those just listed. This proposition is complicated because multiple phenomena occur simultaneously and affect each other. For example, in the case of swapping CO₂ for CH₄ in hydrates, it will be critical to consider the kinetics of CH₄ hydrates dissociation, with the respective heat released, the CO₂ hydrate formation and the correspondent heat adsorbed, heat dissipations, and, perhaps more importantly, the transport of CH₄ out of, and that of CO₂ into the hydrate particle. Perhaps, stochastic approaches such as kinetic Monte Carlo (KMC) could be successful to identify the true rate-limiting steps, therefore allowing the community to design strategies to optimise various practical applications. KMC has been successfully applied to catalysis, where a number of chemical reactions can occur simultaneously to transform reactants and intermediates into a variety of products, to describe transport in porous networks, as well as in many other applications. ⑧⑨ ⑩
Experimental validation. It is necessary to validate the quantitative understanding achieved via fundamental research. Relevant laboratory experiments include those conducted with an autoclave to study the kinetics of hydrates growth under various conditions, and with a rocking cell to quantify the effect of, e.g., AAs on the formation of hydrate plugs. Other experiments of relevance include micromechanical force measurements, kinetics of CH₄ production from hydrates, as well as calorimetric and spectroscopic measurements. It remains to be demonstrated that laboratory-scale experiments are representative of large-scale applications in the area of hydrates. For example, in flow assurance it is necessary to test models on flow loops, of which only few are available in academic laboratories, and to quantify the feasibility and sustainability of CO₂-CH₄ swaps in hydrate deposits field campaigns are essential.

Acknowledgments

This work was supported, in part, by the EPSRC, via grant number EP/N007123/1. The Author is grateful to Prof. Zach Aman of the University of Western Australia, for providing critical feedback for an early version of this review, and to the members of his research group for frequent stimulating discussions, and in particular to Dr Anh Phan for critically editing an early version of this manuscript.

This article is dedicated to Prof. Peter T. Cummings of Vanderbilt University, whose vision on the ability of molecular simulations to interpret, understand and eventually guide experimental explorations has been transformative, and has been extremely influential at the early crucial stages of the author’s career.

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