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Inhibiting Gas Hydrate Formation Using Small Molecule Ice Recrystallization Inhibitors

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Gas hydrates are ice-like solids containing gas molecules (usually methane) within molecular cavities. Formation of these structures is problematic in high-pressure environments such as gas pipelines and deep-sea drilling operations. In these environments polyvinylpyrrolidone (PVP 10) is used to inhibit gas hydrate formation and break-up gas hydrate deposits. Herein, we demonstrate several recently developed small molecule ice recrystallization inhibitors (IRIs) capable of inhibiting the formation of gas hydrates. These small molecule IRIs are cheaper and in many cases, more effective than PVP 10.

Introduction

Gas hydrates are ice-like solids containing gases within a highly ordered network of water molecules. These hydrates can be found in large quantities in nature but they can also be formed in a laboratory under carefully controlled conditions.[1] There are many different forms of gas hydrates[2-5] but those containing a single molecule of methane contained within a "cage" of water molecules are known as sI hydrates.[6] Hydrates are problematic in the petroleum industry[7] as they tend to accumulate in pipelines posing significant dangers as the build-up of solid material leads to blockages in the pipeline reducing flow and ultimately causing a rupture.[8] Furthermore, subterranean gas hydrates are often associated with deep-sea oil and natural gas deposits making it difficult to access these precious natural resources.[9, 10]

Gas hydrate formation is prevented using additives that affect a colligative freezing point depression. Compounds of this nature are referred to as thermodynamic hydrate inhibitors (THI) and these are often used in oil pipelines.[11] Methanol is a common THI however, its flammability and toxic nature, in addition to the large volumes often required are not ideal.[12] Consequently, low dosage hydrate inhibitors (LDHIs) are beneficial as they are environmentally friendly and cost effective.[5, 13-16] There are two classes of LDHIs: the kinetic gas hydrate inhibitors (KHIs) and anti-agglomeration agents (AAs). KHIs inhibit the nucleation of gas hydrates while AAs reduce the propensity of gas hydrates to aggregate and form blockages in pipelines.[8] Polyvinylpyrrolidone (PVP 10) is an example of a commercial KHI.[8] Recent work has led to the discovery that polyvinylcaprolactam and various branched polyester amides can also function as KHIs.[5, 8] Relative to KHIs, AAs require continual agitation for optimal effectiveness ultimately limiting their use.[17] While LDHIs offer many advantages over THIs, the

mechanism by which they inhibit gas hydrate formation is not fully understood.[5]

Antifreeze proteins (AFPs) are found in many organisms that inhabit sub-zero environments.[18] These proteins protect organisms from cryoinjury by selectively depressing the freezing point below that of the melting point, a phenomenon known as thermal hysteresis (TH).[19-21] AFPs are also potent inhibitors of ice recrystallization.[22] It has recently been demonstrated that these proteins also inhibit the growth of gas hydrates and that TH activity was not necessary for this.[23] While AFPs inhibit gas hydrate formation, the difficulties associated with obtaining large quantities of these compounds prevent their use on a commercial scale. Consequently, we investigated whether small molecule inhibitors of ice recrystallization (molecular weights < 300 g/mole) could also inhibit the nucleation of gas hydrates much like the AFPs. In contrast to the AFPs, small molecule ice recrystallization inhibitors (IRIs) are easy to prepare in large quantities. In this paper, we demonstrate that small molecule IRIs inhibit gas hydrate nucleation and that several of these molecules are superior to commercially utilized PVP 10 at significantly lower weight percent concentrations.

Results and Discussion

Quantifying Gas Hydrate Nucleation and its Inhibition

To quantify the effectiveness of small molecule IRIs to inhibit gas hydrate nucleation, differential scanning calorimetric (DSC) analysis was utilized. This approach has been shown to be an effective method to quantify gas hydrate formation. In this technique, the output of heat correlates to individual gas hydrate nucleation events.[23-28] Fig. 1 is representative of this isothermal analysis using PVP 10 (1 mM, 10,000 g/mol on average) at -12°C. Twelve individual samples of a 1 mM PVP 10 solution (confined in silica) were placed in

borosilicate capillary tubes. Silica gel was chosen because it increases the area of water-gas interfaces and facilitates gas hydrate nucleation and growth.[23, 29] These samples were placed under 100 bar of pure methane gas and allowed to stand prior to the experiment to ensure the aqueous phase is saturated. We have assumed the formation of a sI gas hydrate under an atmosphere of pure methane gas. This assumption is based upon literature precedent with this technique[23] and the fact that sI gas hydrate is the predominant gas hydrate in the presence of methane.[6] The exothermic peaks resulting from gas hydrate nucleation upon cooling are represented by the blue line. The position of the peaks represents nucleation events while the area under the peak represents growth.[23] The pink line represents the temperature profile. As multiple nucleation events are possible in a single sample, the number of exothermic peaks is often larger than twelve. Trials containing fewer than twelve exothermic peaks represent instances where nucleation did not occur in some samples.[23] During the warming phase, a "negative peak" corresponding to a melting event is observed. It is important to note that only a single gas hydrate dissociation peak is observed suggesting that hydrate nucleation is a homogeneous process. Furthermore, no DSC peak representing ice melting was observed.[23, 25, 28]
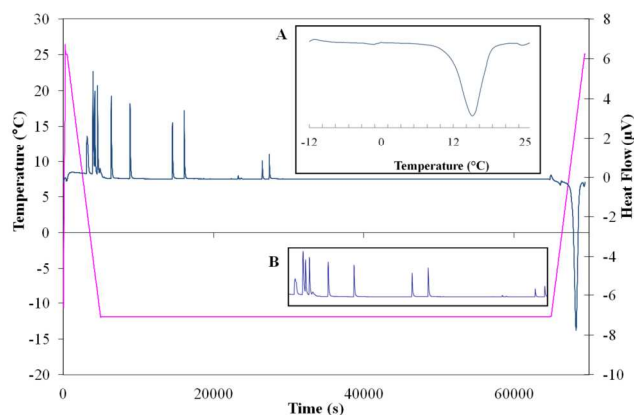

Fig. 1 DSC curve (blue line) representative of a test run for an isothermal temperature experiment (-12 °C, pink line) with 1 mM PVP 10. Inset A magnifies the observed melting event and inset B magnifies the observed nucleation events.

Each experiment was repeated three times representing a total of 36 trials for each sample. The areas under each exothermic peak were used to generate a total cumulative heat of reaction for each compound. Curves were plotted using the integrated averages of all 36 trials. The cumulative heat of reaction correlates directly to gas hydrate nucleation and the time to the first nucleation event indicates the degree to which gas hydrate nucleation is delayed.[23] This metric was utilized to quantify the effectiveness of the small molecule IRIs.

Inhibiting the Formation of Gas Hydrates using *n*-octyl-β-D-Pyranosides

n-Octyl-β-D-pyranosides **1** and **2** (Fig. 2) are anti-agglomeration agents (AAs)[30] and our laboratory has quantified the IRI activity of **1** and **2** and demonstrated that only *n*-octyl-β-D-galactopyranoside (**2**) was an effective inhibitor of ice recrystallization.[31] As stated in the previous section, the ability of AFPs to inhibit the formation of gas hydrates is independent of their TH activity.[23] However, **1** and **2** (as well as other novel small molecule IRIs discovered by our laboratory) do not exhibit TH activity [31] suggesting that some of the structural properties necessary for IRI activity may also be important for inhibiting gas hydrate nucleation. Thus, the small molecule IRIs reported by our laboratory represent ideal molecules to investigate whether a correlation between the ability to inhibit ice recrystallization and inhibition of gas hydrate formation exists.

Inhibition of gas hydrate nucleation was measured for both **1** and **2**. PVP 10 (1 mM, 10,000 g/mol) and water were used as negative and positive controls respectively, for gas hydrate nucleation (Fig. 2). Initial experiments used **1** and **2** at 1 mM[23] concentration. From the data presented in Fig. 2, **1** and **2** are significantly better inhibitors of gas hydrate nucleation than PVP 10. Based upon the relative areas under each curve, the inhibition is approximately ten times better with **1** and **2** than the commercial inhibitor PVP. It should be noted that t = 0 minutes represents the start of the cooling phase. Thus, the time at which the first positive value for cumulative heat of reaction is observed represents the onset time for nucleation.[8, 32] In the presence of a gas hydrate nucleation inhibitor delays in the nucleation of individual samples would be expected. The degree of inhibition is very impressive, especially when one takes into account the lower molecular masses associated with **1** and **2** (< 300 g/mol) versus PVP 10 (10,000 g/mol on average). A 1 mM solution of PVP 10 corresponds to a 1% w/v solution (10 mg/mL), whereas 1 mM of **1** or **2** corresponds to a 0.03% w/v solution (0.29 mg/mL).
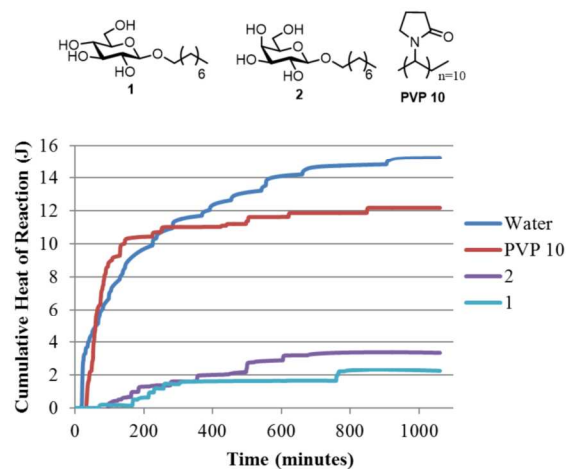

Fig. 2 Cumulative heat of reaction of gas hydrate inhibitor PVP 10 and anti-agglomeration agents **1** and **2** at 1 mM. The result for each compound is based

on the integrated average of 36 trials at -12 °C. Time = 0 minutes represents the start of the cooling phase.

Interestingly, there is very little difference in the degree to which **1** (a D-glucose analogue) and **2** (a D-galactose analogue) inhibit gas hydrate nucleation. This was surprising, as we have has previously shown that the D-galactose analogue **2** was a significantly better inhibitor of ice recrystallization than the D-glucose analogue **1**.[31] This suggests that the structural requirements for IRI activity are not the same as those for the inhibition of gas hydrate nucleation.

Small Molecule IRIs as Inhibitors for Gas Hydrate Formation

Our previous work investigating the IRI activity of *n*-octyl-β-D-pyranosides has indicated that the presence of a long alkyl chain is important for IRI activity.[31] This has also been demonstrated with *C*-linked D-galactose derivatives and lysine-based derivatives.[33, 34] Consequently, we chose to investigate the following: a) the relationship between hydrophobic alkyl chains of different lengths and IRI activity and b) whether small molecule IRIs would also inhibit the nucleation of gas hydrates. Consequently D-glucose-based alditol derivatives **3-5** and aza-sugar derivatives **6-8** (Fig. 3) were prepared and assessed for IRI activity and the ability to inhibit gas hydrate formation (Figs. 4 and 5).

Compounds **3** and **4** exhibited very potent IRI activity at concentrations as low as 0.5 mM. [31] It should be noted that the term "potent" is defined as mean grain size (MGS) values < 25% of phosphate-buffered saline (PBS). Compounds **3** and **4** (0.5 mM and 22 mM, respectively) are significantly more active than the 1 mM PVP 10 but both derivatives have comparable IRI activity to a 22 mM solution of PVP 10. It was not possible to test **3** at concentrations higher than 0.5 mM as it was insoluble. However, the importance of a long hydrocarbon chain is apparent as **5** possesses only half the number of carbons in its alkyl chain relative to **4** and has very little IRI activity. More recently, we have discovered that various aza-sugars (**6** and **7**) are IRI active (Fig. 4). Compounds **6** and **7** exhibit IRI activity similar to compounds **2**, **3** and **4** but the *N*-methyl derivative of **6** is inactive.
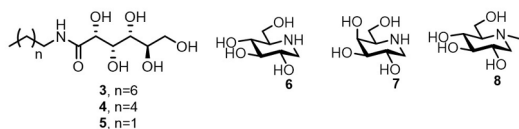

Fig. 3 Structures of *N*-alkyl-D-gluconamides (**3-5**) and aza-sugar derivatives (**6-8**).
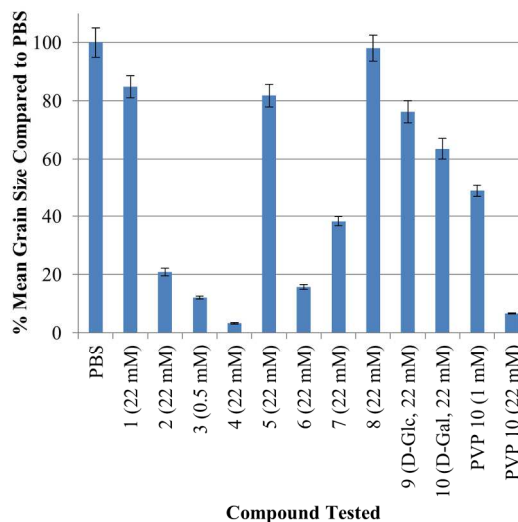

Fig. 4 IRI activity of compounds **1-10**. Activity is represented as % MGS (mean grain size) relative to PBS (phosphate-buffered saline).[31, 35]

Having assessed the IRI activity of *N*-alkyl-D-gluconoamides **3-5** and aza-sugar derivatives **6-8**, we investigated the ability of these compounds to inhibit gas hydrate formation. Firstly, we examined alditol derivatives **3-5** containing alkyl chains of different lengths (Fig. 5).
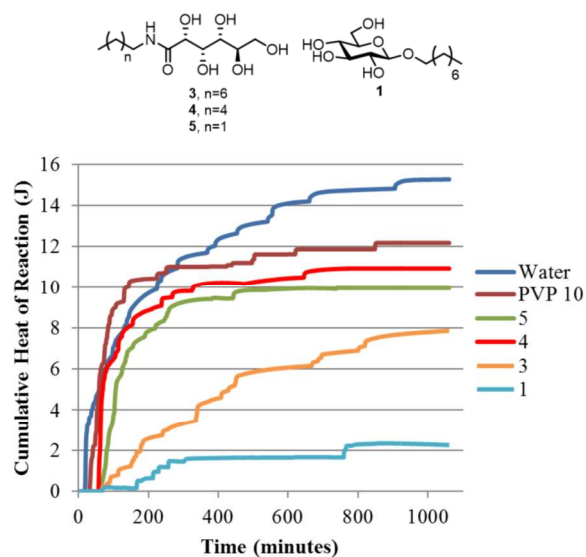

Fig. 5 Cumulative heat of reaction of compounds **1-5** at 1 mM. Water and PVP 10 (1 mM) are included as representative controls. The result for each compound is based on the integrated average of 36 trials at -12 °C. Time = 0 minutes represents the start of the cooling phase.

Compounds **4** and **5** were comparable to commercial additive PVP 10 in their ability to inhibit gas hydrate formation. Compound **3**, possessing the longest alkyl chain (eight carbons), showed an improvement relative to **4** and **5**. While this result suggests that a long alkyl chain is important, it is clear that a pyranose ring is more important because compound **1** possessing both the pyranose ring and an eight carbon alkyl chain is a much better inhibitor of gas hydrate nucleation.

Our laboratory has previously demonstrated that simple monosaccharide reducing sugars exhibit varying degrees of IRI activity.[35] D-Glucose (**9**) and D-galactose (**10**) are the most IRI active reducing sugars when tested at 22 mM. The IRI activity of **2** (an anti-agglomeration agent) at 11 and 22 and 44 mM was significantly better than 22 mM D-galactose.[31] But, D-glucose has IRI activity similar to **1** suggesting that simple monosaccharides lacking long alkyl chains at the C1 carbon might be effective inhibitors of gas hydrate nucleation. Thus, we examined the ability of D-glucose (**9**), D-galactose (**10**) and aza-sugar derivatives **6-8** to inhibit gas hydrate nucleation (Fig. 6).
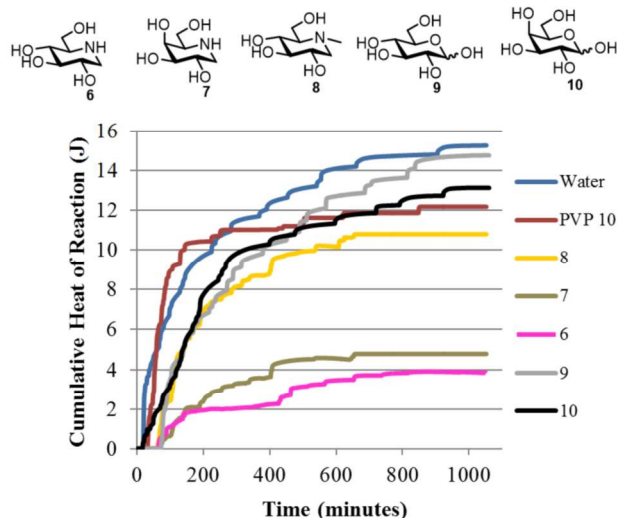

Fig. 6 Cumulative heat of reaction of **6-10** at 1 mM. Water and PVP 10 (1 mM) are shown are representative controls. The result for each compound is based on the integrated average of 36 trials at -12 °C. Time = 0 minutes represents the start of the cooling phase.

Reducing sugars **9** and **10** failed to inhibit gas hydrate formation and were significantly less effective than PVP 10. Compound **8** is only marginally more effective than commercial gas hydrate inhibitor PVP 10. However, aza-sugars **6** and **7** were very effective inhibitors of gas hydrate nucleation with activity profiles comparable to **1** and **2** at equimolar concentrations. Most of small molecule IRIs examined in this study inhibits ice recrystallization to some degree. However, given that not all of these molecules were effective inhibitors of gas hydrate nucleation, we correlated IRI activity to inhibition of gas hydrate nucleation.
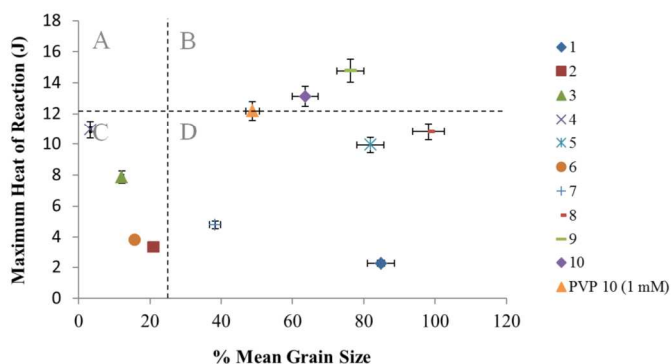

Fig. 7 Correlating IRI activity (%MGS relative to PBS) with the ability to inhibit gas hydrate nucleation (maximum heat of reaction) for compounds **1-10**.

Fig. 7 shows the IRI activity (percent mean grain size (% MGS) relative to PBS) and the maximum heat of reaction for nucleation of gas hydrates of all compounds examined in this study. Potent IRI activity is defined as < 25% mean grain size and an effective inhibitor of gas hydrate nucleation is defined as any compound that is comparable or better in activity to commercial inhibitor PVP 10 (< 12 J). These thresholds define four distinct quadrants in Fig. 7. Quadrant C is the most relevant as it represents compounds that are potent inhibitors of ice recrystallization and very effective inhibitors of gas hydrate nucleation (much better than PVP 10). There are only four compounds in this quadrant; alditiol derivatives **3** and **4**, pyranose derivative **2** (*n*-octyl-β-D-galactose) and aza-sugar **6**. However, analysis of the data from Fig. 7 clearly indicates that a compound exhibiting potent IRI activity does not necessarily inhibit gas hydrate nucleation. For instance, compounds **1** (*n*-octyl-β-D-glucose) and **2** (*n*-octyl-β-D-galactose) are equally effective at inhibiting gas hydrate nucleation (<4 J) at equimolar concentrations but **2** is a very effective inhibitor of ice recrystallization and **1** is not. Similarly, alditol derivative **5** possessing the shortest hydrocarbon chain (3 carbons) and aza-sugar derivative **8** (the *N*-methyl version of **6**) are poor inhibitors of ice recrystallization but are just as effective at inhibiting gas hydrate nucleation as PVP 10. It is especially interesting to note that while the presence of the *N*-methyl substituent in **8** results in a compound that has no IRI activity, this compound still inhibits gas hydrate nucleation, albeit less so than aza-sugar **6**. Finally, the IRI activity of alditol **5** and *n*-octyl-β-D-pyranoside **1** is approximately the same (80% MGS relative to PBS). While both compounds inhibit gas hydrate nucleation, **1** is a superior inhibitor and is as effective as **2** yet the IRI activities of **1** and **2** are very different. Out of the ten compounds tested for IRI activity and inhibition of gas hydrate nucleation, only four of the ten are effective inhibitors of both processes (quadrant C), eight of the ten are effective inhibitors of gas hydrate nucleation but only four of these ten are potent inhibitors of ice recrystallization.

Thermal Hysteresis and Inhibition of Gas Hydrate Nucleation

It is well known that AFPs generally exhibit both TH and IRI activity. TH activity refers to the ability to selectively

depress the freezing point of a solution below that of the melting point [19, 21] and arises from the ability to adsorb onto the ice crystal surface.[21] Previous work has shown that AFPs have the ability to adsorb onto the surface of ice and it has been suggested that they may behave similarly with gas hydrates but that TH activity did not correlate well to the ability of a compound to inhibit gas hydrate formation.[23] Thus, we assessed whether compounds **1**, **2**, **6** and **7** exhibited TH activity and possessed the ability to bind to ice. TH activity was assessed using a nanoliter osmometry.[36] Typically a compound capable of interacting with the ice lattice will show dynamic ice shaping (DIS) and alter the habit of the ice crystal. Single ice crystals grown in the presence of molecules that do not interact with the ice crystal surface are "disk-like". TH measurements and single ice crystal morphologies are shown in Fig. 8.
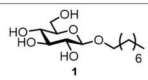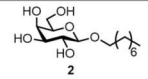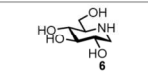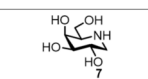
Compound	Melting Point (°C)	Freezing Point (°C)	Ice Crystal Habit
1	-0.09	-0.09	
2	-0.05	-0.05	
6	-0.24	-0.24	
7	-0.33	-0.33	

Fig. 8 Ice crystal habit in the presence of **1**, **2** at 1 mg/mL and **6** and **7** at 10 mg/mL.

The TH activity and DIS capabilities of **1** and **2** have previously been reported by our laboratory.[31] As can be seen from Fig. 8, **1**, **2**, **6** and **7** do not interact with the ice surface. Based upon this it is likely these compounds are not directly interacting with the surface of gas hydrates. As expected, these compounds also failed to have any TH activity.

Conclusions

We have demonstrated the use of small, carbohydrate-based molecules to inhibit gas hydrate nucleation. This may have potential applications in the petroleum industry. Some of these small molecules are significantly better inhibitors of gas hydrate nucleation than the currently utilized inhibitor PVP 10. The low molecular weights of these small molecules, easy synthesis and potency make them excellent alternatives to PVP 10. Amongst these molecules certain structural features such as a six membered ring containing an oxygen or nitrogen heteroatom appear to be essential to inhibit gas hydrate nucleation but, unlike molecules that are highly IRI active, the presence of an alkyl chain was not necessary. In conclusion, while some of the structural features in the ten molecules may be amenable to both activities, it seems that the ability to inhibit

ice recrystallization is not a good indicator of the ability to inhibit gas hydrate nucleation. Overall, these small molecules must be acting as gas hydrate inhibitors via a different mechanism of action than an ice recrystallization inhibitor and further studies are required to elucidate this mechanism.

Acknowledgements

Notes and references

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