

Synthesis of Thermosensitive Poly(*N*-vinylamide) Derivatives Bearing Oligo Ethylene Glycol Chain for Kinetic Hydrate Inhibitor

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Abstract

Thermosensitive poly(*N*-vinylamide) derivatives bearing an oligo ethylene glycol (OEG) chain at the *N*-position were designed for development of a kinetic hydrate inhibitor (KHI). Novel *N*-vinylamide monomers bearing an OEG chain at the *N*-position were synthesized and copolymerized with *N*-vinylformamide (NVF) or methyl *N*-vinylacetamide (MNVA) by free radical polymerization. Then, thermosensitive behaviors, such as lower critical solution temperature (LCST), of the synthesized poly(*N*-vinylamide) derivatives were investigated by light transmittance and DSC measurement. The LCST values were observed over a wide temperature range from 45°C to 90°C, due to the ethoxy OEG chain at the *N*-position. Their phase transition properties were surmised to be coil-globule transition by DSC measurement. Furthermore, KHI values of the synthesized polymers were evaluated by the THF hydrate crystal growth method. On the basis of these results, it is expected that the polymers of synthesized poly(*N*-vinylamide) derivatives will gain a prominent position in the oil industry.

Keywords: Thermosensitive, Poly(*N*-vinylamide) derivatives, Kinetic hydrate inhibitor, LCST, amphiphilic polymers

Introduction

In gas pipelines at the bottom of the sea, the elevated pressure and low temperature environment cause natural gas to form gas hydrate by trapping low-molecular weight natural gas molecules in water.¹ It is well known that typical guest molecules are small gas molecules, such as methane, ethane and propane.²

Kinetic hydrate inhibitors (KHIs) are one of a class of low dosage hydrate inhibitors (LDHI), which have been used by the oil and gas industry in transportation operations for about 20 years.³ KHIs are water soluble polymers and are sometimes used with additional synergists to improve their performance. KHIs generally delay the hydrate nucleation at the first step of hydrate formation.⁴ They induce hydrate nuclei (clusters of water and gas) to generate under hydrate-stable temperature and pressure conditions. Hydrate nuclei then grow to the critical size for hydrate crystal growth.^{2, 5} KHI mechanisms have yet to be elucidated but some theories have been put forward.⁶⁻⁹ Above all, KHI polymers with amide groups show good KHI properties.^{10,11} Furthermore, KHI polymers usually have thermosensitive behaviors such as lower critical solution temperature (LCST).¹²⁻¹⁴ The LCST is a property of thermosensitive polymers in aqueous media that has been intensively investigated.¹⁵⁻²²

The thermosensitive behaviors of poly(*N*-vinylamide) derivatives have also been studied, such as poly(*N*-vinylpyrrolidone) (PNVP),²³⁻²⁵ poly(*N*-vinylcaprolactam) (PNVC),²⁶⁻³³ poly(*N*-vinylacetamide) (PNVA),³⁴⁻³⁸ and others.³⁹⁻⁴² Among them, *N*-vinylacetamide (NVA)⁴³ is a non-ring structure unlike *N*-vinylpyrrolidone (NVP) or *N*-vinylcaprolactam (NVC), into which any functional substituent can be freely introduced. *N*-vinylformamide (NVF) is also a non-ring structure and is more hydrophilic than NVA.^{38,41} In addition, it is known from other applications that poly(*N*-vinylformamide) (PNVF) and PNVA can change to cationic polyvinylamine by hydrolysis under acidic or alkali conditions.⁴¹ The stimuli-responsive amphiphilic polymers using PNVF and PNVA were originally investigated for use as biocompatible materials.⁴⁴⁻⁴⁶ Recently, PNVA and PNVF derivatives which were derived from amphiphilic polymers including amide groups have been reported to be good candidates for KHIs.^{10,11}

In addition, polyethylene glycols (PEGs) and other polyalkylene glycols have been investigated for their properties as anti-agglomerants. By themselves PEGs are poor KHIs.⁴⁷ PEG is also a weak synergist for PNVC.⁴⁸ Graft polymer of *N*-vinyl lactams onto a PEG backbone has been carried out.^{49,50} As mentioned in the previous section tyrosine was also investigated in blends with polyethyleneoxide (PEO) and polypropylene oxide

(PPO) in a mini-loop apparatus.⁵¹ Polyesteramides wherein the functionalized dendrimer comprises at least one polyalkylene glycol end group, have also been reported.⁵²

In our previous research, PNVA derivatives bearing an alkyl chain at the *N*-position and some amphiphilic polymers were studied for their potential use as KHIs.⁵³⁻⁵⁶ These poly(*N*-alkyl-*N*-vinylamide) derivatives exhibited a good KHI value which was almost the same as Luvicap 55W, a commercially available KHI supplied by BASF which is poly(NVP-*co*-NVC) (NVP:NVC=1:1) with a low molecular weight in water. On the other hand, their values were less than another commercially available KHI, Luvicap EG, which is also by BASF and is a PNVC with a low molecular weight in monoethylene glycol. In order to develop a high performance KHI, we were motivated to design modifications of the substituents of poly(*N*-vinylamide) derivatives at the *N*-position and to investigate their possible application as biocompatible materials. It was therefore necessary to design the functional groups at the *N*-position of poly(*N*-vinylamide) and to control their thermosensitive behavior for the development of poly(*N*-vinylamide) derivatives materials.

In this study, we synthesized poly(*N*-vinylamide) derivatives bearing an oligo ethylene glycol (OEG) chain at the *N*-position. The thermosensitive behavior and KHI properties of the synthesized polymers were investigated and evaluated for their performance as tetrahydrofuran hydrate crystal growth inhibitors.

EXPERIMENTAL

Copolymerization

Twelve polymers were synthesized according to the reference elsewhere. The typical procedure is selected for the radical copolymerization of NVF and **MOENVF**. Into a 20 mL glass tank, NVF (0.14 g, 2 mmol), **MOENVF** (1.0 g, 8 mmol), toluene (5 ml) and AIBN (0.044 g 0.25 mmol) were combined. The reactor was capped with septa, then N₂ bubbling was carried out for 2 min. The reaction mixture was heat up to 60 °C to start polymerization. After 24 hours, it was cooled down to room temperature, and the reaction mixture was poured into 10 mL of methanol. The polymer was twice washed by poor solvent of 500 ml diethyl ether and recovered by centrifugation. The obtained polymer was dried under vacuum at 30 °C over 12 hr. Other methods were written in Supporting Information.

THF hydrate crystal growth test

NaCl (26.28 g), THF (99.9%, 170 g), and distilled water were mixed to give a final volume of 900 mL. This ratio is a stoichiometrically correct molar composition for making structure II THF hydrate, $3\text{THF} \cdot 17\text{H}_2\text{O}$. The test procedure is as follows: (1) 80 mL of the mixture solution is added in a 100 mL glass beaker. (2) The polymer sample is dissolved in this solution at each concentration, such as, 0.32 g of polymer in 80 mL of solution gives a 0.4 wt% (4000 ppm) solution of the polymer. (3) The beaker is placed in a cooling bath preset to a temperature of -0.5°C . (4) The solution is stirred manually with a spatula every 5 min, without touching the glass beaker, while being cooled for 20 min. (5) A hollow glass tube with inner diameter 7 mm was filled at the end with ice crystals kept at -10°C . The ice crystals are used to initiate THF hydrate formation. (6) The glass tube was placed almost halfway down in the cooled polymer mixture solution after the solution had been cooled for 20 min. (7) THF hydrate crystals could be grown at the end of the glass tube for 60 min. (8) After this time, the tube was picked up, the THF hydrate crystals weighed, and the crystal growth rate in grams per 1 hour determined. The shape and morphology of the crystals both in the beaker (if any) and on the end of the glass tube were visually analyzed.

Results and Discussion

N-Vinylamide monomers bearing an OEG chain at the *N*-position (*N*-vinyl-*N*-methoxyethylformamide: **MOENVF**, *N*-vinyl-*N*-ethoxyethylformamide: **EOENVF**, *N*-vinyl-*N*-methoxyethoxyethylformamide: **2MOENVF**, and *N*-vinyl-*N*-ethoxyethoxyethylformamide: **2EOENVF**) were designed, which consisted of a commercial KHI⁵³ (Luvicap EG) and the products of our previous research⁵³⁻⁵⁶ of poly(*N*-vinylamide) derivatives bearing an alkyl chain at the *N*-position. Then, synthesized monomers and NVF or methyl *N*-vinylacetamide (MNVA) were copolymerized by free radical polymerization and 12 polymers were obtained (Figure 1). Further, the thermosensitive behaviors of the 12 polymers were investigated by light transmittance in 0.2 wt% aqueous solution and differential scanning calorimetry (DSC) measurement of the hydrate polymers. Finally, the KHI properties of the 12 polymers were evaluated by the THF hydrate crystal growth method.⁴⁴

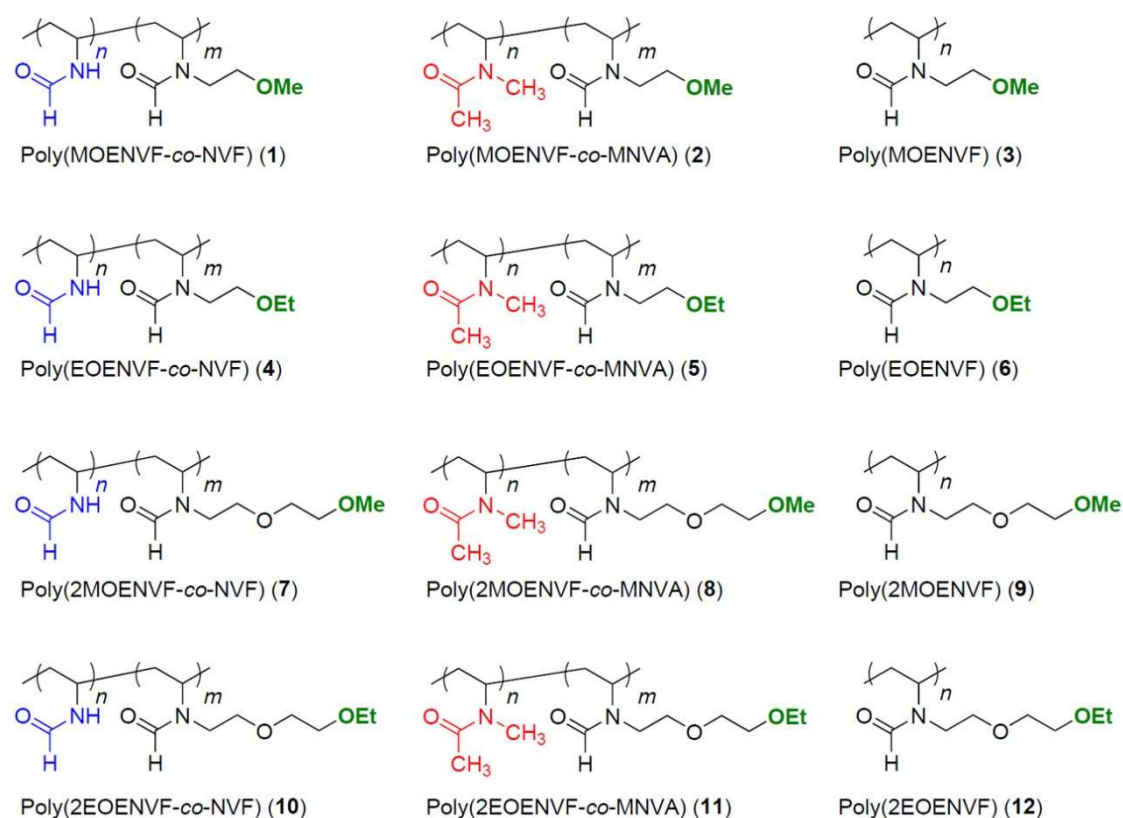


Figure 1. Chemical structures of poly(*N*-vinylamide) derivatives bearing an OEG chain at the *N*-position.

Table 1 shows analytical data for the synthesis of poly(*N*-vinylamide) derivatives. Yields of **7**, **8**, and **12** were low compared with the other polymers, probably because of their high solubility in poor solvent. Their polymers were purified by precipitation, then diethyl ether was used as poor solvent in order to clarify the difference of the solubility. All of the polymers were synthesized by free radical polymerization and then distributions of molecular weight were estimated to be in the range between 1.7 and 3.6. It was important to keep the molecular weights of the polymers fairly similar since molecular weight

Table 1. Analytical data of poly(*N*-vinylamide) derivatives. Characterization and composition^a.

Entry	Polymer	Concentration	Yield ^b	$M_n (\times 10^3)^c$	PDI ^c	<i>n:m</i> ^d
1	1	2M	59%	6.6	2.8	22:78
2	2	2M	71%	15.4	3.1	19:81
3	3	5M	89%	12.6	2.8	0:100
4	4	2M	75%	7.2	3.6	19:81
5	5	2M	74%	10.2	2.4	18:82
6	6	5M	85%	12.0	3.6	0:100
7	7	2M	22%	8.0	1.7	22:78
8	8	2M	16%	10.1	2.0	18:82
9	9	5M	58%	17.7	2.4	0:100
10	10	2M	53%	13.6	3.1	39:61
11	11	2M	55%	13.5	2.3	26:74
12	12	5M	19%	11.2	2.3	0:100

^a Solvent = toluene. Initiator = AIBN. Temp. = 60°C. Time = 24 hr. ^b Diethyl ether-insoluble part. ^c Determined by SEC with polystyrene standard in DMF. ^d Determined by ¹H NMR (400MHz, D₂O)

affects the performance as THF hydrate crystal growth inhibitors.³ Structural characterization and composition of polymers were determined by ¹H NMR in D₂O. The composition ratios in copolymers for almost all of the polymers were in good agreement with the feeding ratios of comonomers except for **10** and **11**. This is probably because OEG at the *N*-position for **10** and **11** was too long and sterically bulky to incorporate to the polymer main chain with the same ratio as the comonomers. This is also supported by the low yield of **12** bearing the same group as the *N*-position. This speculation was

supported by our previous research,⁴² in which the bulky side chain at the *N*-position influenced the polymerizability of *N*-vinylamide derivatives. All of the polymers were synthesized by free radical polymerization and should consist of the random copolymer sequences. The thermosensitive behaviors of these 12 polymers were investigated as shown in Table 2.

Table 2. Analytical data of poly(*N*-vinylamide) derivatives. Thermosensitive behavior.^a

Entry	Polymer	T_g (°C)	Phase Transition energy (W/g)	LCST ^b (°C)	LCST ^c (DSC) (°C)	Heat quantity ^c (J/g)	Polymer weight in water ^a (wt%)
1	1	-28.15	-0.06	N. D.	N. D.	N. D.	37.7
2	2	-31.00	-0.19	N. D.	N. D.	N. D.	46.5
3	3	-30.42	-0.12	N. D.	N. D.	N. D.	61.7
4	4	-27.40	-0.04	59	56	-0.45	39.0
5	5	-25.19	-0.14	68	65	-0.3	41.7
6	6	-26.54	-0.14	48	53	-0.45	38.2
7	7	-50.62	-0.06	N. D.	N. D.	N. D.	30.1
8	8	-48.81	-0.1	N. D.	N. D.	N. D.	32.4
9	9	-50.14	-0.1	N. D.	N. D.	N. D.	31.4
10	10	-40.91	-0.15	87	N. D.	N. D.	34.9
11	11	-48.60	-0.11	89	N. D.	N. D.	39.0
12	12	-42.33	-0.07	77	77	-0.63	39.7

^a The polymers were analyzed with water. The weight ratio of polymer in water suspended samples are shown as wt % in the right column. ^b Determined by transmittance using UV-vis spectrometer. ^c Determined by DSC measurement.

However, poly(*N*-vinylamide) derivatives including **MOENVF** units (**1**, **2** and **3**) dissolve in water at all temperatures. In other words, these polymers do not show LCST probably due to the hydrophilicity of the methoxy group at the *N*-position.

On the other hand, poly(*N*-vinylamide) derivatives include **EOENVF** units (**4**, **5** and **6**). Figure 2 shows the thermosensitive behaviors of poly(*N*-vinylamide) derivatives including **EOENVF** units. Aqueous solutions (0.2 wt%) of polymers were observed under UV light (500 nm) during heating or cooling ($\pm 2^\circ\text{C}/3$ min) (Table 2, entries 4, 5 and 6). The thermosensitive behaviors of poly(*N*-vinylamide) derivatives including **EOENVF** units were observed between 45°C and 70°C . The hysteresis between the heating and cooling process was not so different. The **EOENVF** units were more hydrophobic than NVF and MNVA. Therefore, the LCST of **6** was the lowest at about 50°C . Besides, the LCST of **4** was higher than **6** by about 10°C even though **4** only has 20% NVF. The LCST of **5** was also higher by about 20°C due to the inclusion of 20% MNVA units. This indicates that thermosensitive behaviors were influenced a great deal by the side chain effect of poly(*N*-vinylamide) derivatives at the *N*-position.

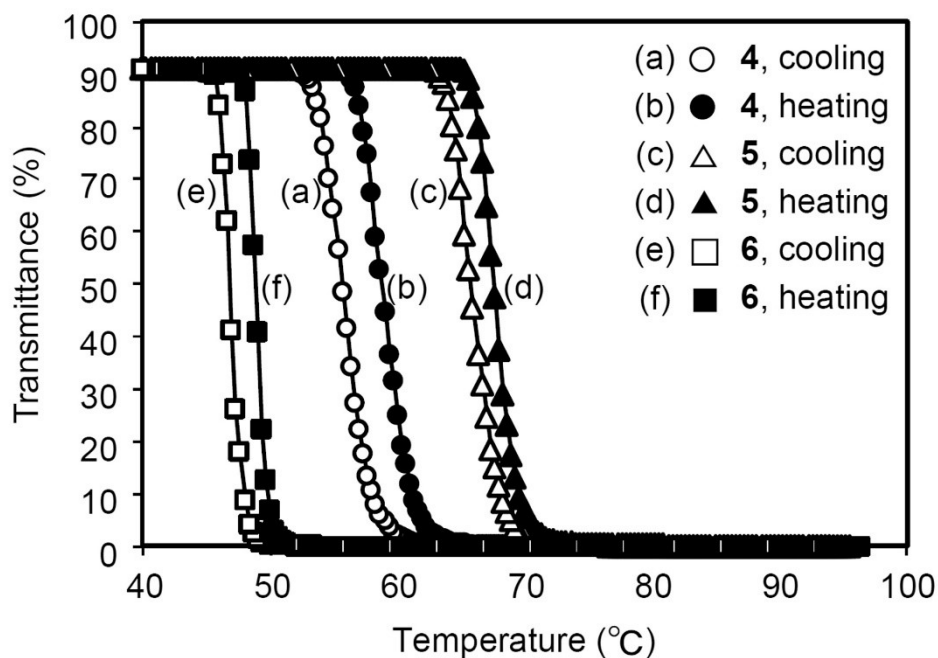


Figure 2. Temperature dependence on light transmittance of poly(*N*-vinylamide) derivatives including **EOENVF** unit polymers (**4**, **5** and **6**). (○) **4** during cooling (a). (●) **4** during heating (b). (△) **5** during cooling (c). (▲) **5** during heating (d). (□) **6** during cooling (e). (■) **6** during heating (f).

Poly(*N*-vinylamide) derivatives including **2MOENVF** units (**7**, **8** and **9**) also dissolved in water at every temperature, the same as for **MOENVF** unit polymers (**1**, **2** and **3**) and for the same reason. Figure 3 shows the thermosensitive behaviors of poly(*N*-vinylamide) derivatives including **2EOENVF** units (Table 2, entries 10, 11 and 12). The thermosensitive behaviors of poly(*N*-vinylamide) derivatives bearing **2EOENVF** units were observed between 70°C and 95°C. The LCST of these copolymers were higher than **EOENVF** unit polymers (**4**, **5** and **6**) because of a more elongated ethylene glycol chain. **2EOENVF** units were shown to be more hydrophilic than **EOENVF** units.

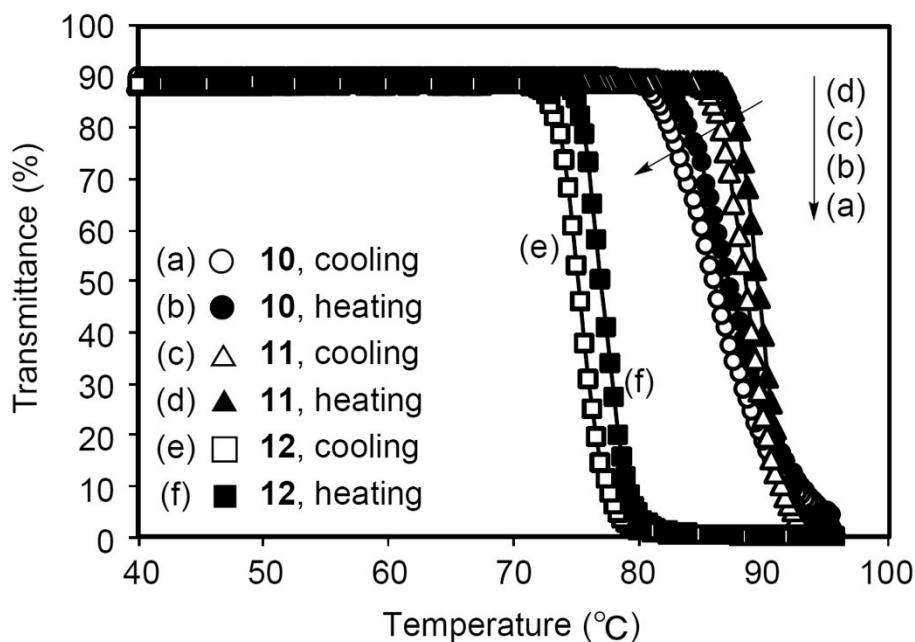


Figure 3. Temperature dependence on light transmittance of poly(*N*-vinylamide) derivatives including 2EOENVF unit polymers (**10**, **11** and **12**). (○) **10** during cooling (a). (●) **10** during heating (b). (△) **11** during cooling (c). (▲) **11** during heating (d). (□) **12** during cooling (e). (■) **12** during heating (f).

The LCST of poly(*N*-vinylamide) derivatives with 2EOENVF units (**10**, **11** and **12**) were higher than those with EOENVF units (**4**, **5** and **6**). The LCST of **12** was also the lowest of the three polymers including 2EOENVF units (**10**, **11** and **12**) in much the same case as **4**, **5** and **6** because of the more hydrophobic nature of the ethyl group at the end position than the methyl group. Interestingly, the range of transitional temperatures of 2EOENVF unit polymers were broader than that for the EOENVF unit polymers and it was surmised

that the range of transitional temperatures were affected according to side chain length at the *N*-position. Light transmittances of **4**, **5** and **6** were switched from a transparent to a clouded state within a range of about 5°C during heating and cooling. However, those of **10**, **11** and **12** were over a wider range of 10°C. This result indicates that the side chain effect of poly(*N*-vinylamide) derivatives at the *N*-position was increased by increasing the length of the OEG chain.

Table 2 shows the thermosensitive behaviors of poly(*N*-vinylamide) derivatives bearing an OEG chain as determined by DSC. The glass transition temperatures (T_g) of all polymers were observed in the range of -50°C and -25°C. **1**, **2** and **3** had almost the same T_g of about -30°C and methoxy group units, however, the T_g of **7**, **8** and **9** were about -50°C in spite of the methoxy group units. For the ethoxy group polymers also, **4**, **5** and **6** had almost the same T_g of about -25°C but the T_g of **10**, **11** and **12** were about -45°C. These results indicated that T_g were strongly influenced by chain length or number of oxygen atoms in the OEG unit. Furthermore, the difference between having a methoxy group or an ethoxy group at the chain end did not greatly influence T_g . The T_g of poly(*N*-vinylamide) derivatives bearing more elongated OEG chains tended to be lower than in short chain polymers. The peaktops of heat flow by DSC were observed at around the

same temperature as that determined by transmittance measurements. The temperature range was set to between -100° C and 95 °C in order to avoid water vapor leakage from the DSC pan. Therefore, heat quantity peaks of **10** and **11** could not be observed because of overlaps in energy increase around the upper limit temperature and the endothermic peaks of **10** and **11**. Actually, the LCST of **10** and **11** were about 90°C, determined by transmittance, so the LCST of those polymers should have been observed at around 90 degrees. Heat flow energy values of the polymers were slightly lower than that of poly(*N*-isopropylacrylamide) (PNIPAM)^{19,36,40}. In concrete terms, heat flow values of PNIPAMs were above 0.6 J/g and 4.8 kJ/mol¹⁹ or above 2.3 kJ/mol³⁶. On the other hand, the values for the OEG side chain poly(*N*-vinylamide) derivatives were 0.3 ~ 0.63 J/g which were not so different. In addition, the thermal properties of poly(*N*-vinylamide) derivatives have also already been investigated^{36,40} and the heat quantities were not so different from previous polymers³⁶ such as poly(*N*-vinylisobutylamide) and OEG side chain poly(*N*-vinylamide) derivatives.

Furthermore, thermosensitive behaviors of **6** was investigated by dynamic light scattering (DLS) and static light scattering (SLS) in detail. Under the dilute condition at 0.01 wt%, LCST values of **4-6** were elevated with the decreased transmittance

percentages, starting above 70°C in the case of **4** and **5** (Figure S17). Therefore, we selected only **6** for the further investigation. Firstly, the concentration of polymer **6** in aqueous media was decided at 0.004 wt% because transmittance is above 60% at every temperature. (Figure S18). Secondly, temperature dependence of hydrodynamic radius and light scattering intensity were measured by DLS (Figure S19). The result indicated that polymer **6** was assembled about 50°C by intermolecular interaction. Finally, the aggregation of **6** was analyzed by SLS at 70°C. The weight-average molecular weight (M_n) was calculated ($M_n = 1.08 \times 10^8$ g/mol) by SLS measurement (Figure S20). The association constant was also calculated (association constant = 2500) using molecular weight and PDI by SEC measurement (Table 1, entry 6: $M_n = 12.0 \times 10^3$, PDI = 3.6). These results suggest that the mechanisms of thermosensitive behaviors were different among **4**, **5**, and **6**. Probably, it will be important to clarify the aggregation mechanism among **4**, **5**, and **6** under diluted concentration.

Next, we move to the evaluation of possible KHI applications. Numerous approaches are known for the evaluation of gas hydrate inhibitors.⁵⁷ We selected the THF hydrate crystallization approach. THF hydrate forms a Structure II clathrate hydrate which is the same structure most commonly encountered in the field with natural gas mixtures. Our

method investigates crystal growth inhibition not nucleation of THF hydrates. Figure 4 shows the schematic view of the method of THF hydrate crystal growth (Figure 4a) and THF hydrate example (Figure 4b and 4c).

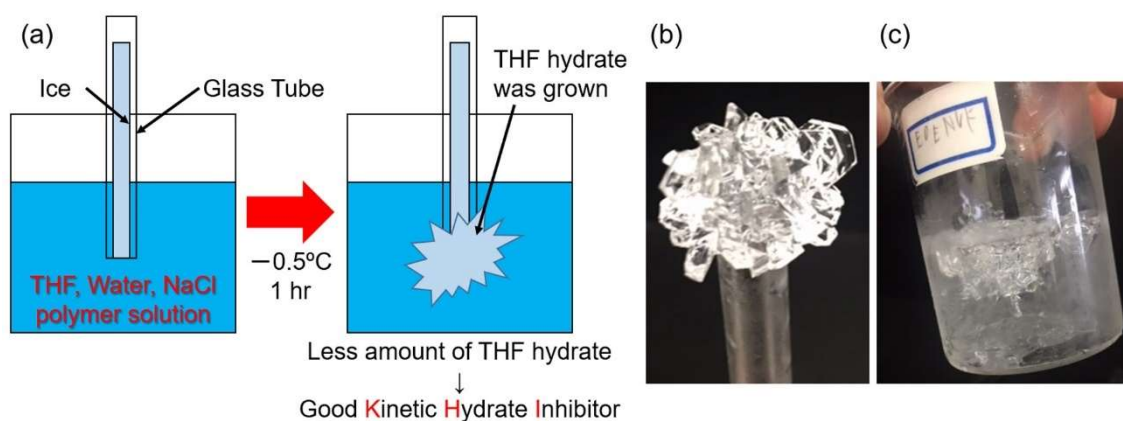


Figure 4. The method of THF hydrate crystal growth (a). The photo of small amount of THF hydrate on the glass tube (b) and large amount of THF hydrate in whole beaker (c).

These experiments were conducted according to previously reported methods.^{47,58-62}

Ammonium compounds with OEG have been also investigated, which are good reference to this study.⁶²

Table 3 shows results of the THF hydrate crystal growth. Under the condition without a polymer, THF hydrates were grown to a weight of up to 13.98 g (Table 3, entry 13).

Table 3. Result of THF hydrate crystal growth.

Entry	Polymer	Concentration (ppm)	THF hydrate (g)
1	1	4000	4.69 ± 2.20 ^a
2	2	4000	13.46 ± 1.88 ^a
3	3	4000	3.44 ± 2.26 ^a
4	4	4000	3.45 ± 2.01 ^a
5	5	4000	9.09 ^b
6	6	4000	2.03 ± 1.32 ^a
7	7	2000	4.78 ± 0.81 ^a
8	8	2000	3.18 ± 0.69 ^a
9	9	4000	2.11 ± 1.46 ^a
10	10	4000	4.74 ± 1.78 ^a
11	11	4000	5.56 ± 1.08 ^a
12	12	4000	4.15 ± 3.03 ^a
13	No Polymer	-	13.98 ± 1.40 ^a

^a*n* = 3. ^b*n* = 1.

On the other hand, except for in the polymer solution condition, weights of THF hydrate in each condition were decreased by more than 60% compared to the no polymer condition. Figure 5 summarized the THF hydrate generation under these conditions.

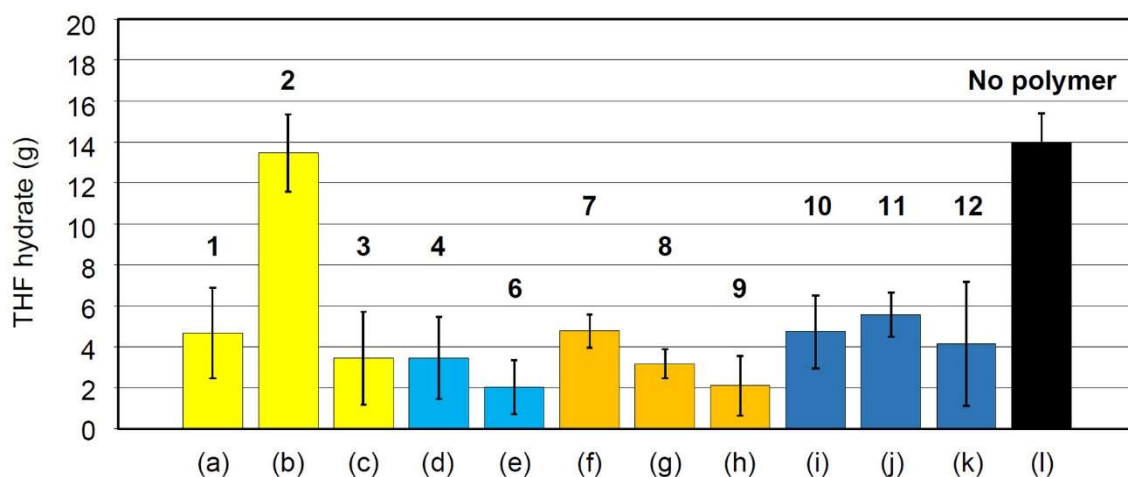


Figure 5. The weight of THF hydrate after crystal growth using **1** (a), **2** (b), **3** (c), **4** (d), **6** (e), **7**, (f), **8** (g), **9**, (h), **10**, (i), **11** (j), **12** (k), and no polymer as a control (l).

Therefore, nearly all synthesized polymers of poly(*N*-vinylamide) derivatives bearing an OEG chain at the *N*-position were expected to have KHI properties. However, compared with the conventional KHI, it is not so surprising result. For example, poly(*N*-vinylcaprolactum) (PNVC) is one of the most famous compounds for the prevention of THF hydrate crystal growth. PNVCs gives zero growth of THF hydrate crystal at 4000 ppm condition,⁴⁷ which possesses the better prevention ability than those of poly(*N*-vinylamide) derivatives bearing an OEG chain at the *N*-position in this study. This indicates the modest interactions between the hydrate surface and poly(*N*-vinylamide) derivatives bearing an OEG chain at the *N*-position.

In addition, compared to MOENVF unit polymers (**1**, **2** and **3**), EOENVF unit polymers (**4**, **5** and **6**), 2MOENVF unit polymers (**7**, **8** and **9**) and 2EOENVF unit polymers (**10**, **11** and **12**), the crystal growth speeds of THF hydrate were not so closely related to the thermal properties, such as LCST and T_g . However, in comparison with **4**, **5** and **6** or **10**, **11** and **12**, the weight of THF hydrate had a tendency to decrease with low temperature LCST. For example, when the LCST was 48°C (Table 2, entry 6) which was a lower temperature than those of **4** (Table 2, entry 4: 59°C) and **5** (Table 2, entry 5: 69°C), the weight of the THF hydrate of **6** was 2.03 g (Table 3, entry 6) which was lighter than that of **4** (Table 3, entry 4: 3.45 g). Furthermore, EOE and 2EOE unit polymers shared the same tendency with respect to the relationship between LCST and weight of THF hydrate. When the LCST of **12** was 77°C (Table 2, entry 12) which was a lower temperature than those of **10** (Table 2, entry 10: 87°C) and **11** (Table 2, entry 11: 89°C), the weight of the THF hydrate of **12** was 4.15 g (Table 3, entry 12) which was lighter than those of **10** (Table 3, entry 10: 4.74 g) and **11** (Table 3, entry 11: 5.56 g).

It was surprising that homopolymers in each series possessed good prevention abilities for THF hydrate crystal growth in Figure 5, although the difference was not so large. When the results were compared among MOE unit polymers (**1**, **2** and **3**), the prevention

ability seemed to decrease by copolymerizing with NVF and MNVA. We would speculate that the conformation of the polymer is affected in different ways, resulting in the influence on the polymer adsorption onto the THF hydrate surface. At last, polymer solutions of poly(*N*-vinylamide) derivatives bearing an OEG chain at the *N*-position inhibited the growth of the THF hydrate crystal and that inhibition behaviors were slightly influenced by monomer structure, specifically those without OEG chain monomers.

Conclusions

In conclusion, thermosensitive poly(*N*-vinylamide) derivatives bearing OEG at the *N*-position were synthesized for the development of KHI and their thermosensitive behaviors were investigated. KHI values of these polymers were also evaluated by the THF hydrate crystal growth method. Polymer compositions of the synthesized polymers were almost same for initially monomer ratio without **10** and **11**, in which the polymer composition was influenced by the effect of steric bulkiness due to a long ethylene glycol chain. Poly(*N*-vinylamide) derivatives including MOENVF units or 2MOENVF units (**1**, **2**, **3**, **7**, **8** and **9**) did not exhibit thermosensitive behavior and dissolved in water at every

temperature because the methoxy group is hydrophilic. On the other hand, the other poly(*N*-vinylamide) derivatives including EOENVF units or 2EOENVF units (**4**, **5**, **6**, **10**, **11** and **12**) showed thermosensitive behaviors (LCST: 55°C ~ 90°C) which were observed by light transmittance and DSC measurement. The results of DSC measurement indicated that phase transitions of poly(*N*-vinylamide) derivatives including EOENVF units or 2EOENVF units were coil-globule transitions because the heat quantities were low values. Finally, the KHI value of poly(*N*-vinylamide) derivatives were evaluated by the THF hydrate crystal growth method. These results indicated that nearly all synthesized poly(*N*-vinylamide) derivatives bearing OEG at the *N*-position inhibited the growth of the THF crystal by more than 60% and the weight of the THF crystal in the lowest LCST polymer of **6** was decreased by about 85%. Substituents of monomers with methoxy and ethoxy groups did not influence on THF crystallization very much. Homopolymers (**3**, **6**, **9** and **12**) have better prevention abilities of THF hydrate crystal growth than those of copolymers, possibly due to the conformation of the copolymers, which would be associated with the polymer adsorption onto THF hydrate surface. Generally, the inhibition behaviors were influenced by monomer structure, specifically those without OEG chain monomers.

References

- [1] Rodrigues, V. F.; Frota, H. M.; Loures, L. G. L.; Siqueira, F. D. *Proceedings of the 8th European Formation Damage Conference*; Scheveningen, Netherlands, May 27–29, 2009.

- [2] Sloan, E. D.; Koh, C. A. *Clathrate Hydrates of Natural Gases*, 3rd ed.; CRC Press: Boca Raton, FL, 2008; Vol. 119.

- [3] Kelland, M. A. History of the Development of Low Dosage Hydrate Inhibitors. *Energy Fuels* **2006**, *20*, 825.

- [4] Yang, J.; Tohidi, B. Characterization of inhibition mechanisms of kinetic hydrate inhibitors using ultrasonic test technique. *Chem. Eng. Sci.* **2011**, *66*, 278.

- [5] Arjmandi, M.; Tohidi, B.; Danesh, A.; Todd, A. C. Is subcooling the right driving force for testing low-dosage hydrate inhibitors? *Chem. Eng. Sci.* **2005**, *60*, 1313.

- [6] Koh, C. A. Towards a fundamental understanding of natural gas hydrates. *Chem. Soc. Rev.* **2002**, *31*, 157.
- [7] Moon, C.; Taylor, P. C.; Rodger, P. M. Clathrate nucleation and inhibition from a molecular perspective. *Can. J. Phys.* **2003**, *81*, 451.
- [8] J-H. Sa, G-H. Kwak, B. R. Lee, D-H. Park, K. Han, K-H. Lee, Hydrophobic amino acids as a new class of kinetic inhibitors for gas hydrate formation. *Sci. Rep.* **2013**, *3*, 2428.
- [9] H. Ji, D. Chen, G. Wu, Molecular Mechanisms for Cyclodextrin-Promoted Methane Hydrate Formation in Water. *J. Phys. Chem. C* **2017**, *121*, 20967.
- [10] Colle, K. S.; Costello, C. A.; Oelfke, R. H.; Talley, L. D.; Longo, J. M.; Berluche, E. U.S. Patent 5,600,044, 1997.
- [11] Kelland, M. A.; Svartaas, T. M.; Øvsthus, J.; Namba, T. A New Class of Kinetic Hydrate Inhibitor. *Ann. N. Y. Acad. Sci.* **2000**, *912*, 281.
- [12] Leinweber, D.; Feustel, M. World Patent Application WO/2006/084613, 2006.

- [13] Leinweber, D.; Feustel, M. World Patent Application WO/2007/054226, 2007.
- [14] Arjmandi, M.; Leinweber, D.; Allan, K. 19th International Oilfield Chemical Symposium, Geilo, Norway, March 2008.
- [15] Gil, E. S.; Hudson, S. M. Stimuli-responsive polymers and their bioconjugates. *Prog. Polym. Sci.* **2004**, *29*, 1173.
- [16] Wei, H.; Cheng, S.; Zhang, X.; Zhuo, R. Thermo-sensitive polymeric micelles based on poly(N-isopropylacrylamide) as drug carriers. *Prog. Polym. Sci.* **2009**, *34*, 893.
- [17] Hocine, S.; Li, M. Thermoresponsive self-assembled polymer colloids in water. *Soft Matter*, **2013**, *9*, 5839.
- [18] Kubota, K.; Fujishige, S.; Ando, I. Single-chain transition of poly (N-isopropylacrylamide) in water. *J. Phys. Chem.* **1990**, *94*, 5154.
- [19] Otake, K.; Inomata, H.; Konno, M.; Saito, S. Thermal analysis of the volume phase transition with N-isopropylacrylamide gels. *Macromolecules* **1990**, *23*, 283.

- [20] Ringsdorf, H.; Venzmer, J.; Winnik, F. M. Fluorescence studies of hydrophobically modified poly (N-isopropylacrylamides). *Macromolecules* **1991**, *24*, 1678.
- [21] Wiu, J.; Suo, X.; Zhang, R.; Yuan, S.; Wu, Z.; Lu, Q.; Yu, Y. RAFT preparation and self-assembly behavior of thermosensitive triblock PNIPAAm-b-PODA-b-PNIPAAm copolymers. *Colloid Polym. Sci.* **2016**, *294*, 1989.
- [22] Sun, W.; An, Z.; Wu, P. UCST or LCST? Composition-Dependent Thermoresponsive Behavior of Poly(N-acryloylglycinamide-co-diacetone acrylamide). *Macromolecules* **2017**, *50*, 2175.
- [23] Li, X.; Liu, W.; Ye, G.; Zhang, B.; Zhu, D.; Yao, K.; Liu, Z.; Sheng, X. Thermosensitive N-isopropylacrylamide–N-propylacrylamide-vinyl pyrrolidone terpolymers: Synthesis, characterization and preliminary application as embolic agents. *Biomaterials* **2005**, *26*, 7002.
- [24] Fang, Y.; Yu, H.; Chen, L.; Chen, S. Facile Glycerol-Assisted Synthesis of N-Vinyl Pyrrolidinone-Based Thermosensitive Hydrogels via Frontal Polymerization. *Chem. Mater.* **2009**, *21*, 4711.

- [25] Salehi, R.; Arsalani, N.; Davaran, S.; Entezami, A. A. Synthesis and characterization of thermosensitive and pH-sensitive poly (N-isopropylacrylamide-acrylamidevinylpyrrolidone) for use in controlled release of naltrexone. *J. Biomed. Mater. Res., Part A* **2009**, *89*, 919.
- [26] Liang, X.; Kozlovskaya, V.; Cox, C. P.; Wang, Y.; Saeed, M.; Kharlampieva, E. Synthesis and Self-Assembly of Thermosensitive Double-Hydrophilic Poly(N-vinylcaprolactam)-b-poly(N-vinyl-2-pyrrolidone) Diblock Copolymers. *J. Polym. Sci., Part A: Polym. Chem.* **2014**, *52*, 2725.
- [27] Vihola, H.; Laukkanen, A.; Valtola, L.; Tenhu, J.; Hirvonen, J. Cytotoxicity of thermosensitive polymers poly(N-isopropylacrylamide), poly(N-vinylcaprolactam) and amphiphilically modified poly(N-vinylcaprolactam). *Biomaterials* **2005**, *26*, 3055.
- [28] Vihola, H.; Laukkanen, A.; Hirvonen, J.; Tenhu, H. Binding and release of drugs into and from thermosensitive poly(N-vinyl caprolactam) nanoparticles. *Eur. J. Pharm. Sci.* **2002**, *16*, 69.

- [29] Sudhakar, K.; Rao, K. M.; Subha, M. C. S.; Rao, K. C.; Sadiku, E. R. Temperature-responsive poly(N-vinylcaprolactam-co-hydroxyethyl methacrylate) nanogels for controlled release studies of curcumin. *Des. Monomers Polym.* **2015**, *18*, 705.
- [30] Okhapkin, I. M.; Nasimova, I. R.; Makhaeva, E. E.; Khokhlov, A. R. Effect of Complexation of Monomer Units on pH- and Temperature-Sensitive Properties of Poly(N-vinylcaprolactam-co-methacrylic acid). *Macromolecules* **2003**, *36*, 8130.
- [31] Boyko, V.; Pich, A.; Lu, Y.; Richter, S.; Arndt, K. F.; Adler, H. J. P Thermo-sensitive poly(N-vinylcaprolactam-co-acetoacetoxyethyl methacrylate) microgels: 1— synthesis and characterization. *Polymer* **2003**, *44*, 7821.
- [32] Prabakaran, M.; Grailer, J. J.; Steeber, D. A.; Gong, S. Thermosensitive Micelles Based on Folate-Conjugated Poly(N-vinylcaprolactam)-block-Poly(ethylene glycol) for Tumor-Targeted Drug Delivery. *Macromol. Biosci.* **2009**, *9*, 744.
- [33] Liang, X.; Kozlovskaya, V.; Chen, Y.; Zavgorodnya, O.; Kharlampieva, E. Thermosensitive Multilayer Hydrogels of Poly(N-vinylcaprolactam) as Nanothin Films and Shaped Capsules. *Chem. Mater.* **2012**, *24*, 3707.

- [34] Suwa, K.; Morishita, K.; Kishida, M.; Akashi, A. Synthesis and Functionalities of Poly(N-Vinylalkylamide) . V. Control of a Lower Critical Solution Temperature of Poly (N-Vinylalkylamide). *J. Polym. Sci. Part A: Polym. Chem.*, **1997**, *35*, 3087.
- [35] Suwa, K.; Yamamoto, K.; Akashi, M.; Takano, K.; Tanaka, N.; Kunugi, S. Effects of salt on the temperature and pressure responsive properties of poly(N-vinylisobutyramide) aqueous solutions. *Colloid Polym. Sci.* **1998**, *276*, 529.
- [36] Kunugi, S.; Tada, T.; Tanaka, N.; Yamamoto, K.; Akashi, M. Microcalorimetric Study of Aqueous Solution of a Thermoresponsive Polymer, poly(N-vinylisobutyramide) (PNVIBA) *Polym. J.* **2002**, *34*, 383.
- [37] Serizawa, T.; Nanameki, K.; Yamamoto, K.; Akashi, M. Thermoresponsive Ultrathin Hydrogels Prepared by Sequential Chemical Reactions. *Macromolecules* **2002**, *35*, 2184.
- [38] Yamamoto, K.; Serizawa, T.; Akashi, M. Synthesis and Thermosensitive Properties of Poly[(N-vinylamide)-co-(vinyl acetate)]s and Their Hydrogels. *Macromol. Chem. Phys.* **2003**, *204*, 1027.

- [39] Mori, T.; Fukuda, Y.; Okamura, H.; Minagawa, K.; Masuda S.; Tanaka, M. Thermosensitive Copolymers Having Soluble and Insoluble Monomer Units, Poly(N-vinylacetamide-co-methyl acrylate)s: Effect of Additives on Their Lower Critical Solution Temperatures. *J. Polym. Sci. Part A: Polym. Chem.* **2004**, *42*, 2651.
- [40] Suwa, K.; Wada, Y.; Kikunaga, Y.; Morishita, K.; Kishida, A.; Akashi, M. Synthesis and Functionalities of Poly(N-vinylalkylamide) . IV.* Synthesis and Free Radical Polymerization of N-vinylisobutyramide and hermosensitive Properties of the Polymer. *J. Polym. Sci. Part A: Polym. Chem.*, **1997**, *35*, 1763.
- [41] Yamamoto, K.; Serizawa, T.; Muraoka Y.; Akashi, M. Synthesis and Functionalities of Poly(N-vinylalkylamide). XII. Synthesis and Thermosensitive Property of Poly(vinylamine) Copolymer Prepared from Poly(N-vinylformamide-co-N-vinylisobutyramide). *J. Polym. Sci. Part A: Polym. Chem.*, **2000**, *38*, 3674.
- [42] Kawatani, R.; Kan, K.; Kelland, M. A.; Akashi, M.; Ajiro, H. Remarkable Effect on Thermosensitive Behavior Regarding Alkylation at the Amide Position of Poly(N-vinylamide)s. *Chem. Lett.* **2016**, *45*, 589.

- [43] Akashi, M.; Yashima, E.; Yamashita, T.; Miyauchi, N.; Sugita, S.; Marumo, K. A novel synthetic procedure of vinylacetamide and its free radical polymerization. *J. Polym. Sci., Part A: Polym. Chem.* **1990**, *28*, 3487.
- [44] Yamamoto, K.; Serizawa, T.; Muraoka, Y.; Akashi, M. Synthesis and Functionalities of Poly(N-vinylalkylamide). 13. Synthesis and Properties of Thermal and pH Stimuli-Responsive Poly(vinylamine) Copolymers. *Macromolecules* **2001**, *34*, 8014.
- [45] Ajiro, H.; Takemoto, Y.; Asoh, T.; Akashi, M. Novel polyion complex with interpenetrating polymer network of poly(acrylic acid) and partially protected poly(vinylamine) using N-vinylacetamide and N-vinylformamide. *Polymer* **2009**, *50*, 3503.
- [46] Takemoto, Y.; Ajiro, H.; Asoh, T.; Akashi, M. Fabrication of Surface-Modified Hydrogels with Polyion Complex for Controlled Release. *Chem. Mater.* **2010**, *22*, 2923.

- [47] Kelland, M. A.; Svartås, T. M.; Andersen, L. D. Gas hydrate anti-agglomerant properties of polypropoxylates and some other demulsifiers. *J. Petr. Sci. Eng.* **2009**, *64*, 1.
- [48] Lee, J. D.; Englezos, P. Enhancement of the performance of gas hydrate kinetic inhibitors with polyethylene oxide. *Chem. Eng. Sci.* **2005**, *60*, 5323.
- [49] Kelland, M. A. A review of kinetic hydrate inhibitors - Tailormade water-soluble polymers for oil and gas industry applications. In *Advances in Materials Science Research*; Wytherst, M. C., Ed.; Nova Science Publishers, Inc.: New York, 2011; Vol. 8, Chapter 5
- [50] Wytherst, M. C., Ed.; Nova Science Publishers, Inc.: New York, 2011; Vol. 8, Chapter 5.
- [51] Talaghat, M.R. Intensification of the performance of kinetic inhibitors in the presence of polyethylene oxide and polypropylene oxide for simple gas hydrate formation in a flow mini-loop apparatus. *Fluid Phase Eq.* **2010**, *289*, 129.
- [52] Klomp, U. C. U.S. Patent Application, 20150024977.

- [53] Ajiro, H.; Takemoto, Y.; Akashi, M.; Chua, P. C.; Kelland, M. A. Study of the Kinetic Hydrate Inhibitor Performance of a Series of Poly(N-alkyl-N-vinylacetamide)s. *Energy Fuels* **2010**, *24*, 6400.
- [54] Chua, P. C.; Kelland, M. A.; Ajiro, H.; Sugihara, F.; Akashi, M. Poly(vinylalkanamide)s as Kinetic Hydrate Inhibitors: Comparison of Poly(N-vinylisobutyramide) with Poly(N-isopropylacrylamide). *Energy Fuels* **2013**, *27*, 183.
- [55] Kelland, M. A.; Abrahamsen, E.; Ajiro, H.; Akashi, M. Kinetic Hydrate Inhibition with N-Alkyl-N-vinylformamide Polymers: Comparison of Polymers to n-Propyl and Isopropyl Groups. *Energy Fuels* **2015**, *29*, 4941.
- [56] Q. Zhang, R. Kawatani, H. Ajiro, M. A. Kelland, Optimizing the Kinetic Hydrate Inhibition Performance of N-Alkyl-N-vinylamide Copolymers. *Energy Fuels* **2018**, *32*, 4925-4931.

- [57] W. Ke, M. A. Kelland. Kinetic Hydrate Inhibitor Studies for Gas Hydrate Systems: A Review of Experimental Equipment and Test Methods. *Energy Fuels* 2016, 30, 10015.
- [58] Makogon, T. Y.; Larsen, R.; Knight, C. A.; Sloan, E. D. J. Melt growth of tetrahydrofuran clathrate hydrate and its inhibition: method and first results. *Cryst. Growth* **1997**, 179, 258.
- [59] Larsen, R.; Knight, C. A.; Sloan, E. D. Clathrate hydrate growth and inhibition. *Fluid Phase Equilib.* **1998**, 150, 353.
- [60] Del Villano, L.; Kommedal, R.; Hoogenboom, R.; Fijten, M. W. M.; Kelland, M. A. A Study of the Kinetic Hydrate Inhibitor Performance and Seawater Biodegradability of a Series of Poly(2-alkyl-2-oxazoline)s. *Energy Fuels*. **2009**, 23, 3665.
- [61] Kelland, M. A.; Del Villano, L. Tetrahydrofuran hydrate crystal growth inhibition by hyperbranched poly(ester amide)s. *Chem. Eng. Sci.* **2009**, 64, 3197.

[62] Chua, P. C.; Kelland, M. A. Tetra(iso-hexyl)ammonium Bromide—The Most Powerful Quaternary Ammonium-Based Tetrahydrofuran Crystal Growth Inhibitor and Synergist with Polyvinylcaprolactam Kinetic Gas Hydrate Inhibitor. *Energy Fuels* **2012**, *26*, 1160.