



HAL
open science

Unprecedented Sequence Control and Sequence-Driven Properties in a Series of AB-Alternating Copolymers Consisting Solely of Acrylamide Units

Yuki Kametani, François Tournilhac, Mitsuo Sawamoto, Makoto Ouchi

► **To cite this version:**

Yuki Kametani, François Tournilhac, Mitsuo Sawamoto, Makoto Ouchi. Unprecedented Sequence Control and Sequence-Driven Properties in a Series of AB-Alternating Copolymers Consisting Solely of Acrylamide Units. *Angewandte Chemie International Edition*, 2020, 59 (13), pp.5193-5201. 10.1002/anie.201915075 . hal-03003112

HAL Id: hal-03003112

<https://hal.science/hal-03003112>

Submitted on 13 Nov 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Unprecedented Sequence Control and Sequence-Driven Properties in A Series of AB-Alternating Copolymers Consisting Solely of Acrylamide Units

Yuki Kametani,^[a] François Tournilhac,^[b] Mitsuo Sawamoto,^[c] and Makoto Ouchi^{*[a]}

[a] Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan.

[b] Molecular, Macromolecular Chemistry, and Materials, CNRS, ESPCI-Paris, PSL Research University, 10 rue Vauquelin, 75005 Paris, France.

[c] Institute of Science and Technology Research, Chubu University, 1200 Matsumoto-cho, Kasugai, Aichi 487-8501, Japan.

* E-mail: ouchi@living.polym.kyoto-u.ac.jp

Abstract: In this article, we report a method to synthesize a series of alternating copolymers that consist exclusively of acrylamide units. Crucial to realizing the unprecedented polymer synthesis is the design of a divinyl monomer that contains acrylate and acrylamide moieties connected via two activated ester bonds. This elaborate design, which is based on the reactivity ratio of the embedded vinyl groups, allows a “selective” cyclopolymerization, wherein the intramolecular and intermolecular propagation are repeated alternately under dilute conditions. The addition of an amine to the resulting cyclopolymers afforded two different acrylamide units, i.e., an amine-substituted acrylamide and a 2-hydroxy-ethyl-substituted acrylamide in alternating sequence. Using this method, we were able to furnish ten types of alternating copolymers; some of these exhibit unique properties in solution and in the bulk, which are clearly different from those of the corresponding random copolymers, and we attributed the observed differences to the alternating sequence.

Introduction

The “sequence” in polymer science, which can be defined as the order of the pendant groups that are attached to the repeat units in the polymer backbone or main chain. In e.g. proteins and DNA, it is arguably the most crucial structural factor for natural polymers, as it determines the higher-order structures that lead to smart functions. These natural macromolecules are copolymers that consist of one type of monomer, i.e., amino acids or nucleotides, and various substituents on the side chains are combined to realize cooperative functions due to the well-defined sequence. Although comonomers of the same type usually exhibit similar reactivity, the sequence-programmed propagation is perfectly controlled on account of a template system. Unfortunately, in the context of synthetic macromolecules such a template-based sequence control is currently beyond our reach, even though the synthesis of sequence-defined macromolecules has attracted substantial attention from polymer chemists and physicists.¹⁻⁶ Recent progress in the area of the reversible deactivation radical polymerization (or living/controlled radical polymerization) has allowed regulating the initiation/propagation in the absence of irreversible deactivation, which offers a way to control the molecular weight, the chain-end structure, and the architecture.⁷⁻⁹ One issue that remains to be addressed in this context is the precision of the synthesis of polymers with a well-defined sequence and sequence-oriented properties/functions, which could potentially lead to a ground-breaking paradigm shift for the synthesis of polymer materials.

Copolymerizations have been widely used for the synthesis of polymer materials with practical applications, and especially radical copolymerizations have been particularly useful due to the robustness of the process and the wide variety of applicable comonomers, which include polar and functional derivatives. The composition or sequence of the comonomer units in the resulting chains can be discussed, to a certain extent, in terms of the reactivity ratios. For example, totally random copolymers are synthesized via the so-called ideal copolymerization of two comonomers with the same reactivity (Figure 1, right, $r_1 = r_2 = 1$). This is mostly the case using the same type of monomer, whereby derivatives differ only with respect to the pendant groups as in e.g. styrenes, (meth)acrylates, or acrylamides. On the other hand, perfectly alternating copolymerization occurs when two comonomers that show cross-over propagation ($r_1 = r_2 = 0$) are used, e.g. a combination of vinyl ethers and maleic anhydrides.¹⁰⁻¹² Alternating propagation is caused by a large difference in electron density between the two monomers,¹³⁻¹⁹ or by addition of a Lewis acid to an electron-poor comonomer in order to further deplete electron density.^{20,21} It is thus easy to understand that achieving genuine sequence control in the copolymerization of one type of monomer with different pendants is very challenging. Indeed, even control of simple periodic sequences such as AB alternating made of one type of repeating unit remains unprecedented in the long history of polymer science (Figure 1, left).

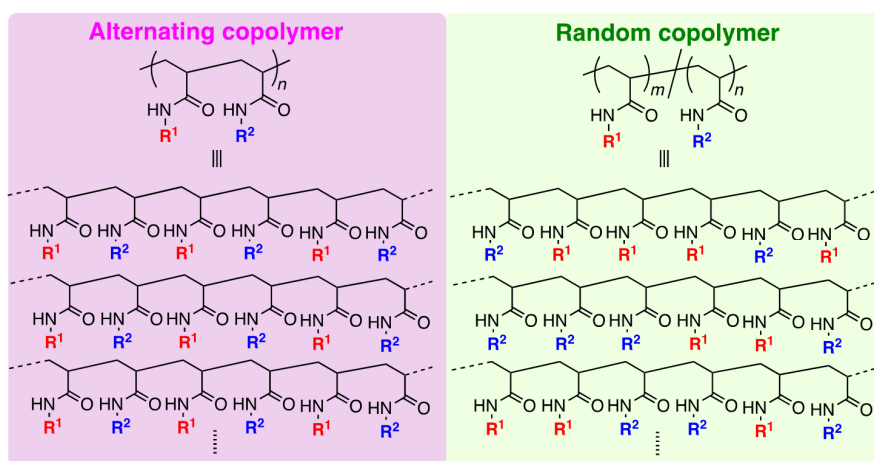


Figure 1. An alternating copolymer(left) that consists only of one type of repeating unit (acryl amide) with different substituents in comparison with the corresponding random copolymer (right).

We have recently developed a method to control the alternating sequence in copolymers via selective radical cyclopolymerization and the cleavage of the cyclo-spacer in the resulting repeat units.²²⁻²⁶ The spacer of the divinyl monomer can either be cleaved or transformed, and the design determines the pendant groups in the resulting alternating sequence. For instance, one design is based on two types of cleavable bonds, tertiary ester and activated ester bonds, which have been embedded in the spacer between methacrylate and acrylate vinyl groups. We obtained alternating copolymer of methacrylic acid and *N*-isopropyl acrylamide via selective cyclopolymerization and side-chain cleavage of the designed divinyl monomer. The alternating copolymer showed sequence-specific properties: the thermal and pH responses in aqueous solution were different from those of the corresponding random copolymers.²⁶

Even though these studies on the cyclopolymerization approach for sequence control are very promising, the applicable types of repeat units in the resulting copolymers remain limited. Moreover, since this method partially depends on the reactivity ratio of the embedded monomers, controlling the sequence of copolymers that consist of identical repeat units remains challenging. Against this background, we designed a new divinyl monomer that could provide an AB-alternating sequence while consisting of only acrylamide repeat units. The resulting alternating copolymers showed sequence-specific features that are different from those of the corresponding 1:1 random copolymers. Examples on such sequence control of pendant groups for identical repeat units have not yet been reported, and this research provides a step toward synthetic polymers that show sequence-oriented functions similar to natural polymers.

Results and Discussion

We designed a new divinyl monomer and scheme that was expected to furnish AB-alternating copolymers that consist of the same type of repeat unit after the spacer transformation (Figure 2A). This divinyl monomer (**1**) consists of an electron-deficient acrylate and an acrylamide, and the two vinyl monomers are connected by two ester bonds that can be cleaved by a reaction with amines. The different reactivity of two monomers allows selective cyclopolymerization consisting of intramolecular cyclopropagations that rely on the neighboring effect under dilute conditions and selective intermolecular propagations based on the inherent reactivity of the embedded vinyl comonomers (Figure 2B). The obtained polymer is AB alternating sequence embedded cyclopolymer. The vinyl group in the electron-deficient acrylate is an acrylate with a 4-nitrophenyl ester substituent intended for a subsequent transformation into an acrylamide through the reaction with the amine due to the reactivity of the activated ester.^{27,28} Moreover, 2-hydroxyethyl acrylamide (HEAm) was connected to the phenyl ring of the electron-poor acrylate via an ester bond. The ester bond would be also activated thanks to the electron-withdrawing substituent ($-\text{NO}_2$), albeit that the orientation of the ester bond is in opposing direction in order to permit the generation of different types of substituents (Figure 2C). The spacer design should allow incorporating various

substituents on the original acrylate unit via a transformation into the acryl amide analogue by a reaction with the amine under concomitant cleavage of the spacer and liberation of another HEAm unit.

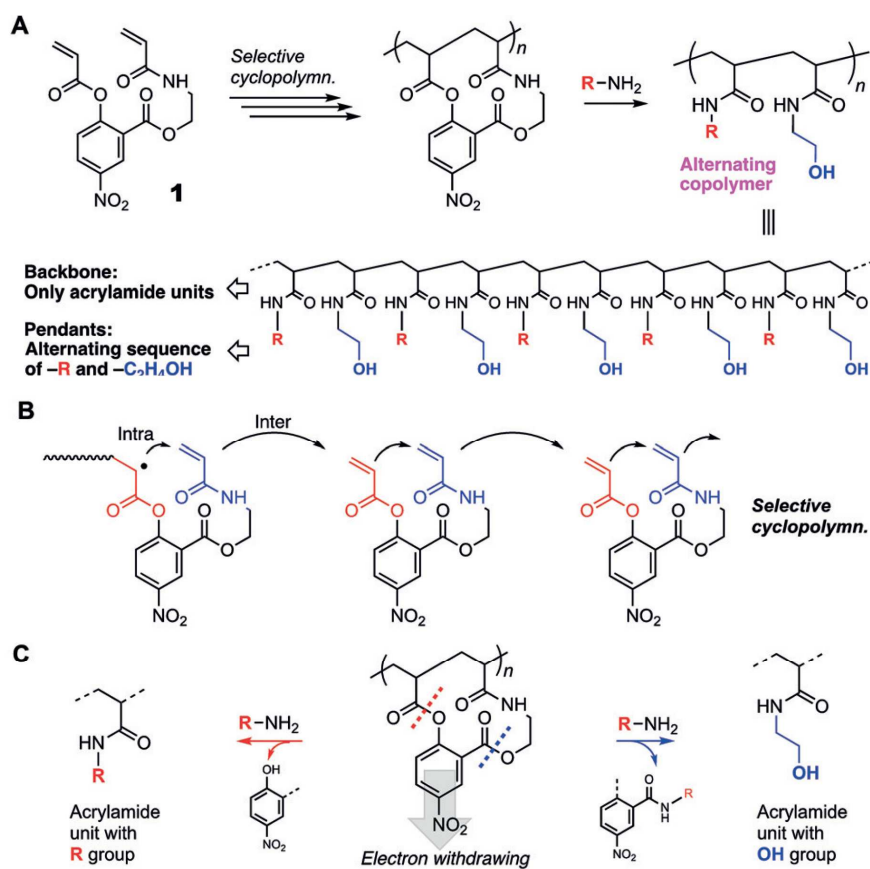


Figure 2. (A) selective cyclopolymerization of **1** and transformation by addition of an amine; (B) selective cyclopolymerization; (C) cleavage of the activated esters in side-chain of the cyclo-units.

A preliminary study of the radical cyclopolymerization of **1** revealed that the resulting polymer was insoluble in most common solvents, but soluble in DMF; a small portion of the spacer in cyclopolymer derived from **1** was damaged during the polymerization in DMF, probably due to the very high polarity of the solvent. Therefore, we tuned the polarity of the solvent for the polymerization by mixing DMF with dioxane (dioxane/DMF = 8/2; v/v) to balance the solubility of the obtained polymer and the stability of the spacer. First, the cyclopolymerization proceeded readily to afford a soluble polymer via a free radical polymerization similar to the RAFT system ($[1]_0 = 100$ mM; $[AIBN]_0 = 2$ mM). Both conversions of the vinyl groups were identical (Table S1, Entry 1). Thus, we tried to control the polymerization with various conditions of reversible deactivation radical polymerization. First, ATRP conditions were applied to the cyclopolymerization of **1** under dilute conditions ($[1]_0 = 100$ mM; $[initiator]_0 = 2.0$ mM), which are similar to those of the cyclopolymerization of the methacrylate-acrylate divinyl monomer in our previous study.^{24,26} However, the conversion of the vinyl groups in **1** reached a plateau less than 50% during the early stages of the reaction, affording low molecular weight polymers with any ligands and additives, even if iron and copper catalysts were used (Table S1, entry 2-9). This could be reasonably interpreted in terms of catalyst poison by the nitro group.²⁹

Then, we used a RAFT polymerization technique³⁰ to control the cyclopolymerization (Table 1, entry 10-13, Figure 3A). RAFT polymerization with CPDTC gave high conversion and narrow molecular weight distribution. The two vinyl groups were consumed at an almost identical rate, i.e., the difference was less than 1%. The SEC curves of the obtained polymer shifted to higher molecular weight, while retaining their unimodal shape, albeit that the molecular weight distribution was slightly broad ($M_w/M_n \sim 1.7$, Figure 3B). When the concentration was increased ($[1]_0/[chain\ transfer\ agent]_0 = 200/4$ or $500/10$ mM), the difference between the conversions of the two vinyl groups increased, and a small shoulder peak at higher molecular weight was observed and molecular weight distribution becomes larger at longer reaction time, indicating an uncontrolled cyclopropagation and thereby cross-linking reaction (Table 1, entry

12,13 and Figure S2). These results suggest that dilute conditions (e.g. 100 mM of the divinyl monomer) are required to control the cyclopolymerization. Figure 3C shows the ^1H NMR spectrum of the product of the polymerization of **1**. The spectrum is very broad, most likely due to the rigid cyclic structure. Very small peaks from the dangling olefinic protons caused by non-cyclopropagation were observed at 5.4-7.3 ppm, and the integral ratio indicates the error was about 3% relative to the whole number of repeat units (Figure S19). These results suggest the intramolecular reaction was well controlled under such a dilute condition.

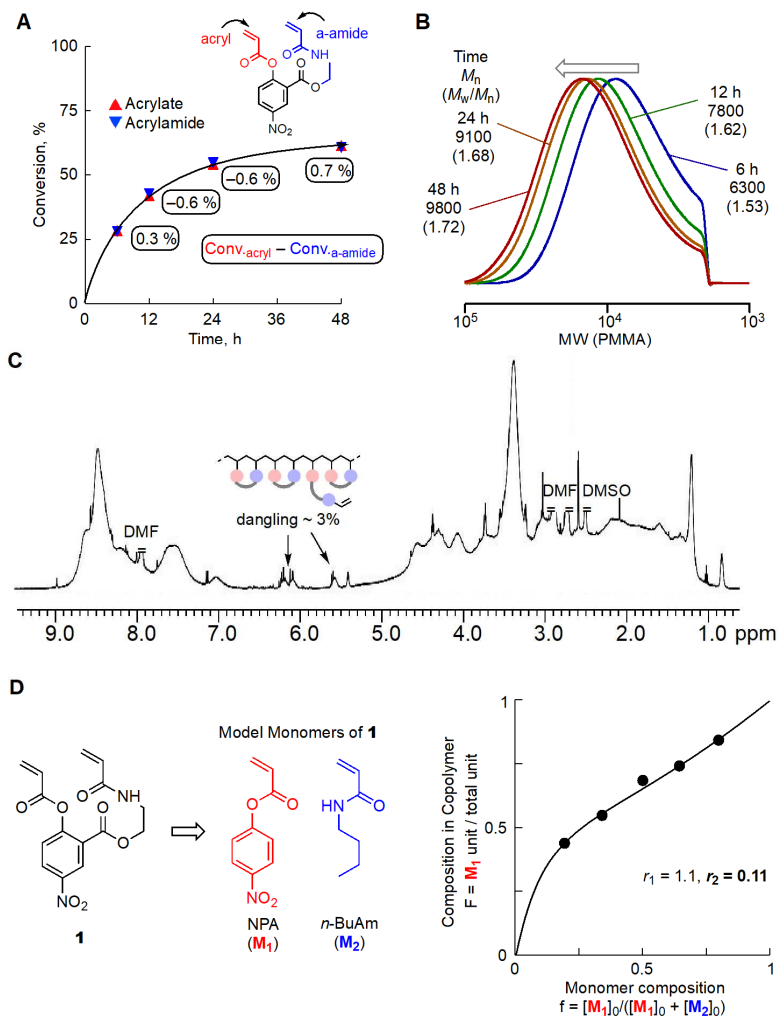


Figure 3. Cyclopolymerization of **1** using a RAFT system: $[1]_0/[CPDTC]_0/[AIBN]_0 = 100/2/2$ mM in dioxane/DMF (8/2; v/v) at 60 °C. (A) Plots of conversions of the two vinyl groups against polymerization time; (B) SEC curves of the cyclopolymer; (C) ^1H NMR spectrum of obtained cyclopolymer obtained in 48 hours; (D) monomer reactivity ratio of the model monomers. CPDTC: 2-Cyano-2-propyl dodecyl trithiocarbonate.

In order to realize the alternating sequence, it is also crucial to exercise control over the selectivity of the intermolecular propagation process, which depends on the reactivity ratio of the two vinyl monomers²⁶. The reactivity ratios were estimated by the Fineman-Ross method³¹ via the free radical copolymerizations of *p*-nitrophenoxy acrylate (NPA) and *n*-butyl acrylamide (BuAm) as the model comonomers, which afforded the following values: $r_1 = 1.1$, $r_2 = 0.11$ (M_1 : NPA; M_2 : BuAm) (Figure 3D). In general, a combination of common acrylate (M_1) and acrylamide (M_2) gives higher r_2 value [e.g., $r_1 = 1.2$, $r_2 = 0.26$ for methyl acrylate (M_1) and *n*-propyl acrylamide (M_2)³²]. Thus, the lower r_2 value is most likely due to the electron-withdrawing substituent of NPA and helpful in enhancing the selectivity of the intermolecular propagation that leads to a highly alternating sequence.

To permit a transformation of the resulting cyclopolymer into an alternating copolymer, the quantitative cleavage of the two activated ester bonds in the cyclic units is required. Thus, the cleavage characteristics of the spacer in divinyl monomer **1** were evaluated using model compound **2**, which exhibits a similar chemical structure without the vinyl groups, as the vinyl groups engage in Michael addition reactions with the primary amines. For that purpose, an excess of *n*-butylamine was added to a DMSO- d_6 solution of **2** and

the reaction was monitored by ^1H NMR spectroscopy (Figure 4). Soon after the addition, the phenoxy ester bond was cleaved to form phenol and amide moieties, which was supported by the up-field shift of the aromatic protons ($b, c, d \rightarrow b', c', d'$) and the emergence of peaks derived from the amide compound (a', f). After several days, another ester bond in the phenol compound was cleaved to afford ethanol and amide moieties, which was supported by the emergence of peaks attributed to the methylene moiety of ethanol (e') and another type of methylene moiety adjacent to the amide (f''). Importantly, all these peaks were detected with reasonable integration ratios, which supports the notion of a quantitative transformation.

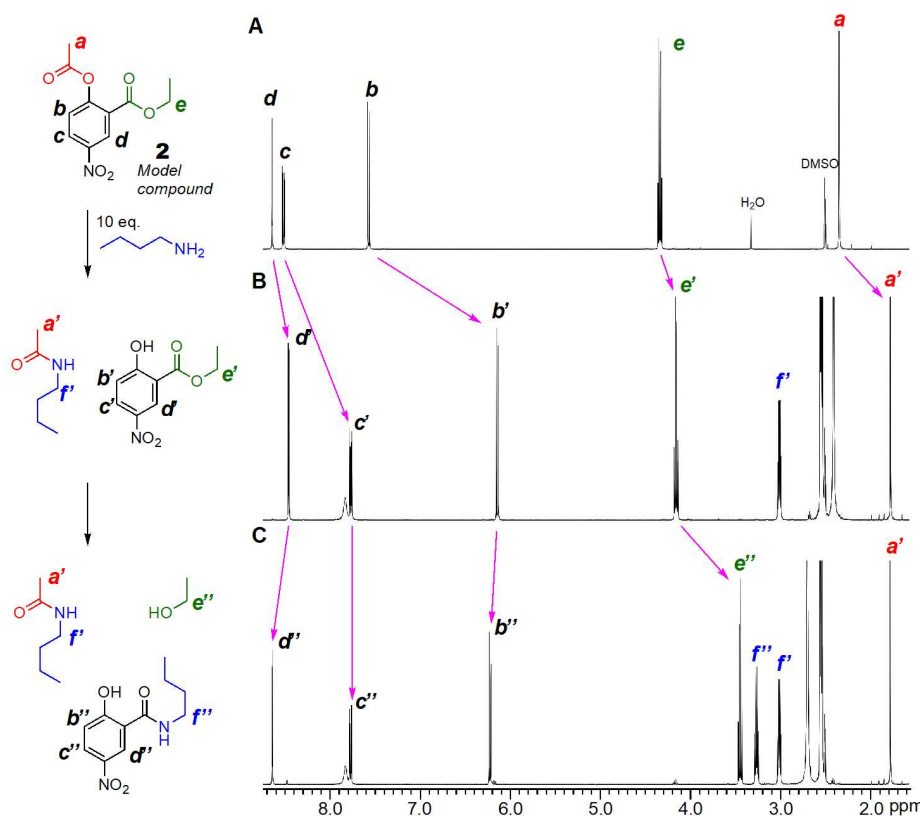


Figure 4. ^1H NMR study on the quantitative transformation of the two ester bonds in model compound **2** upon addition of $n\text{-BuNH}_2$: $[\mathbf{2}]_0/[n\text{-BuNH}_2]_0 = 100/1000$ mM in $\text{DMSO-}d_6$ at room temperature.

Thus, we studied conversion of the cyclopolymer into alternating copolymer. At first, we used n -butylamine to synthesize BuAm-HEAm alternating copolymer. an excess amine (~ 20 eq.) was directly added to the polymerization solution and the solution was stirred at room temperature for 2 days in order to ensure a quantitative cleavage of the two ester bonds. As the expected product was an alternating copolymer of BuAm and HEAm, the corresponding 1:1 random copolymer was also synthesized via RAFT copolymerization of the two acrylamide monomers (Figure 6A). Figure 6B shows the ^1H NMR spectrum of the product after the treatment with $n\text{-BuNH}_2$ and corresponding random copolymer. The spectrum is quite similar to that of the 1:1 random copolymer, and an analysis of the peak integration ratios indicated a 1:1 ratio of the two units. In addition, Figure 5C shows ^{13}C NMR of the obtained copolymer in comparison with the random copolymer, and the spectra exhibit almost identical shapes and peak-splitting patterns. Peculiar peaks specifically due to the alternating sequence were not observed though ^{13}C NMR of alternating copolymer was different from random ones, and it clarified the sequence in previous works of sequence control.^{23,24,26,33}

On the other hand, we recorded quite different MALDI-TOF mass spectra³⁴ from the product after cleavage with n -butylamine to the random copolymer (Figure 5D). The random copolymer of BuAm and HEAm showed a series of distributed peaks similar to those of typical random copolymers.³⁵ In sharp contrast, the copolymer obtained after cyclopolymerization and cleavage showed a different peak series, consisting of alternating molecular-weight intervals that correspond to the BuAm and HEAm units. The molecular weight was corresponding to alternating copolymer or a polymer with only one sequence error. This result also shows the terminal group was well controlled like Scheme S7. RAFT end group was eliminated via aminolysis and the thiol reacts with residue monomer (thiol-

ene reaction) during the side chain transformation. Given the results of the reactivity ratios of the model comonomers, the cyclopolymerization without cross-linking, the 1:1 composition established by the ^1H NMR analysis, and MALDI-TOF-MS analysis, it is feasible to attribute an alternating sequence to the obtained copolymer.

As the cyclopolymerization proceeds via an iterative intra- and intermolecular propagation, the tacticity of the resulting polymer after the cleavage could be different from that obtained via a conventional propagation process.^{36,37} As the tacticity could affect the physical properties, its characterization is important in order to study the sequence-dependent properties. Therefore, we examined the tacticity of the resulting polymer via the conversion into HEAm homopolymers using 2-amino ethanol for the cleavage reaction, considering that it is difficult to characterize the tacticity of copolymers. Figure S4 shows the ^{13}C NMR spectra of the product (top) in comparison with poly(HEAm) synthesized via the radical polymerization of HEAm (bottom). Although some slight differences were observed, the peak shapes were almost identical, indicating similar tacticity to the polymer obtained via general propagation. The little change in tacticity is likely due to that the spacer is not so rigid as our previous design with naphthalene leading to heterotactic-rich tacticity. Thus, it is feasible to conclude that influence of the tacticity is negligible.

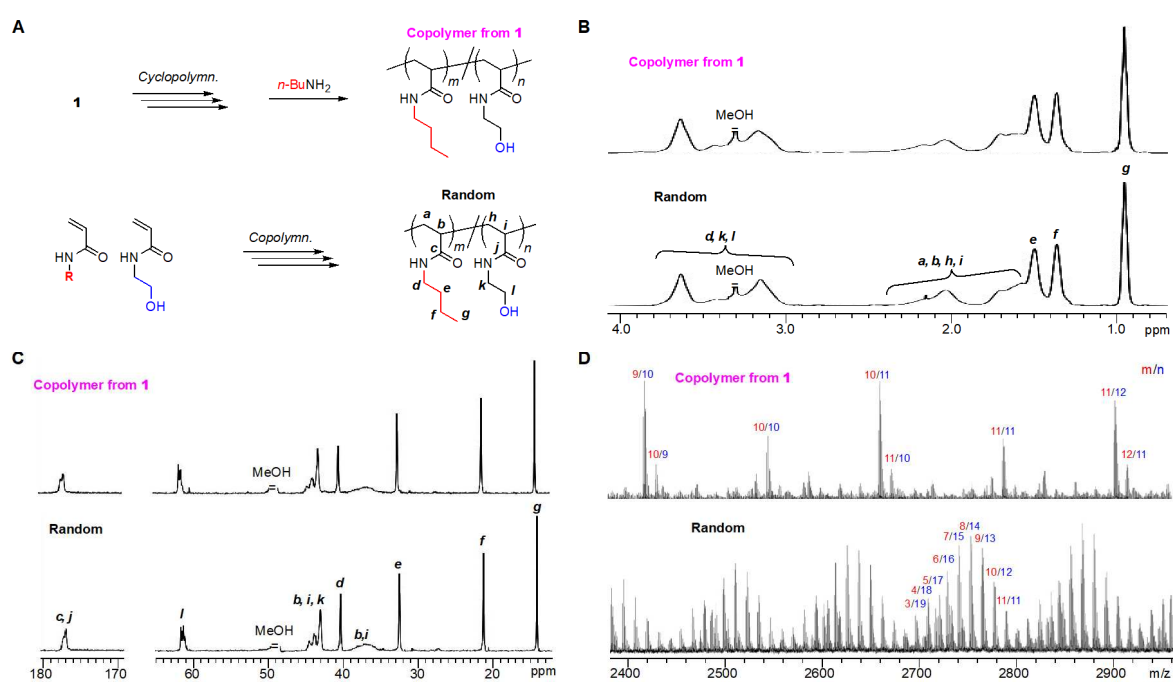


Figure 5. Comparison of the alternating copolymer and random copolymer of BuAm and HEAm (A) Scheme for the synthesis of the alternating and the corresponding random copolymers; (B) ^1H NMR spectra of the copolymers; (C) ^{13}C NMR spectra of the copolymers; (D) MALDI-TOF MS spectra of the copolymers. The m/z peaks were detected as Na^+ adduct of copolymer.

Once the cyclopolymer is synthesized, various alternating copolymers can be generated by selecting different amines for the cleavage, which is a particular advantage of this method. Thus, a variety of amine derivatives was directly added after the cyclopolymerization to incorporate the corresponding substituents on one of acrylamide units in the alternating sequence. For all the amine compounds studied in this work, the addition led to a quick and quantitative cleavage of the 4-nitrophenyl ester bonds. As already confirmed by the model reaction (*vide supra*), the 3-nitrobenzoate esters undergo cleavage after the transformation of the nitrophenyl ester bonds (Figure 6, path A). However, some amines, such as isopropyl amine, stearylamine, benzylamine, picorylamine, morpholine, and histamine, were not capable of effectively cleaving the 3-nitrobenzoate ester bonds. In these cases, a post addition of *n*-butyl amine quantitatively cleaved the nitrobenzoate ester bonds (Figure 6, path B). In the case of stearylamine, higher temperature was needed due to the solubility. Secondary amine, morpholin also needs higher temperature to complete the conversion of 4-nitrophenyl ester. The structures of the series of alternating copolymers were confirmed by ^1H NMR analysis after purification (dialysis or reprecipitation) in order to remove any low-molecular-weight compounds (Figure S20-S31). Some peaks characteristic for the substituents of the added amines were unequivocally observed with reasonable chemical shifts and integration ratios.

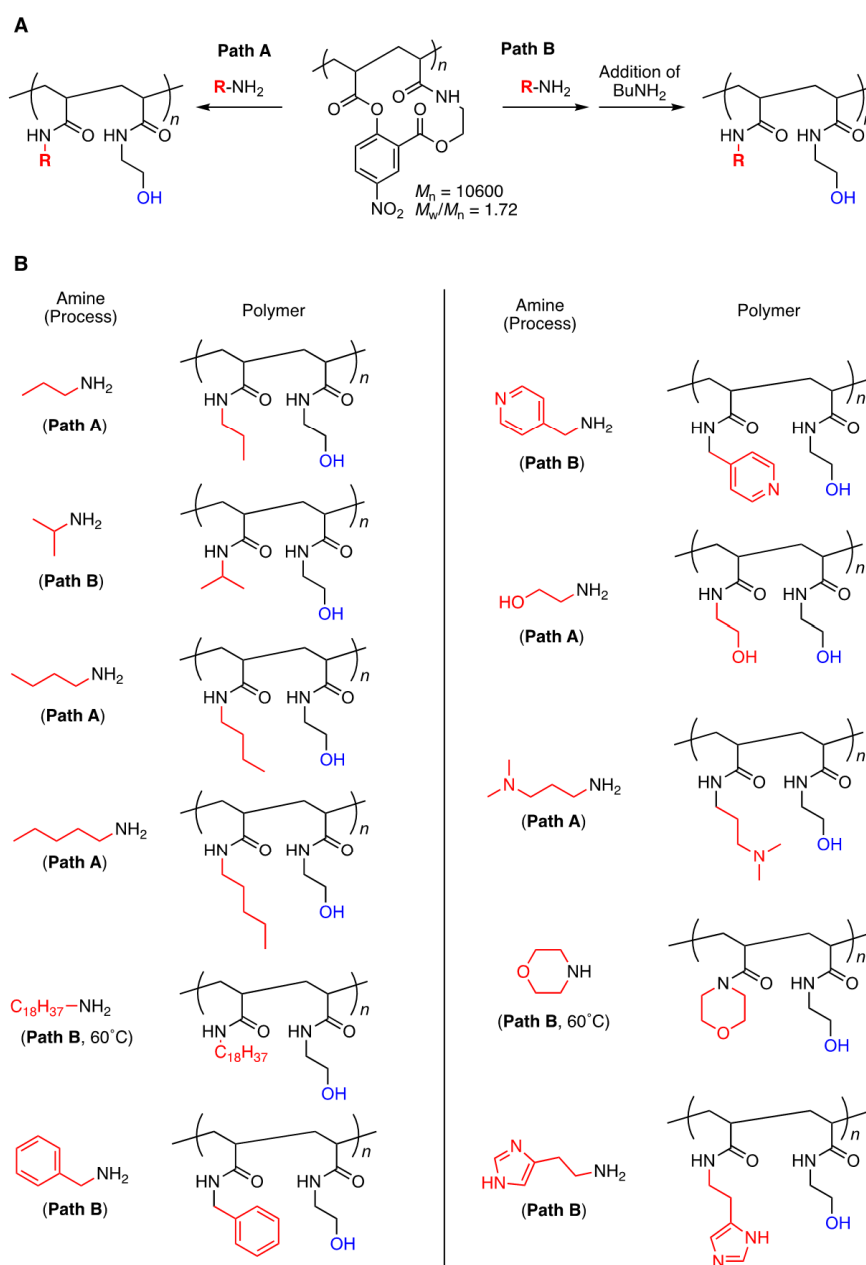


Figure 6. Side chain cleavage into a series of alternating copolymers. (A) Scheme for alternating copolymers; (B) List of alternating copolymers

Subsequently, we studied the solubility of the series of acryl-amide-based alternating copolymers in H_2O and $CHCl_3$ (Figure 7A). The propyl-based copolymers showed similar solubility, regardless of the branch structure (normal vs. iso), i.e., they were soluble in H_2O but not in $CHCl_3$. The latter, obtained from *N*-isopropyl acrylamide (NIPAM), showed no thermal response, unlike the corresponding homopolymer.³⁸ This behavior is most likely due to the hydrophilicity of the HEAm units. However, when the pendant was increased by one carbon atom to butyl, the copolymer showed thermal response in H_2O , i.e., the copolymer was soluble in H_2O at ambient temperature but insoluble at higher temperature. The thermal response was further investigated by variable-temperature UV-vis transmittance measurements in comparison with the copolymers obtained 1:1 radical copolymerization of the corresponding comonomers, i.e., *n*-butyl acrylamide and HEAm (Figure 7B; 10 mg/mL; 1 °C/min; $\lambda = 670$ nm). Sequence of the copolymer for comparison should be random, as both comonomers exhibit almost identical reactivity.

The alternating copolymer showed a sharp response, i.e., the width of the transmittance decreased from 90% to 10% within 2 °C. On the other hand, the solution of the random copolymer became gradually cloudy and the response was less sharp (90% to 10% within 5 °C). The average composition of the random copolymer is 1:1, i.e., identical to the alternating copolymer, but vital differences were

observed between the two copolymers. The same trend was also observed during the cooling process, albeit that some hysteresis processes were observed (Figure S5). This difference should be attributed to the presence of mixtures of polymer chains with various compositions that afford on average a 1:1 ratio. In the distributed mixture, the BuAm-rich copolymers would be expected to show poorer solubility at lower temperature to afford aggregates that partially scatter light. On the other hand, the HEAm-rich copolymer, which is more hydrophilic, forms aggregates at higher temperature. The sharp thermal response of the alternating copolymer truly indicates that the copolymer exhibits a uniform sequence. Dynamic light scattering (DLS) measurements corroborated these results by revealing that for the random copolymers, the size of the aggregates increased gradually, while the size of the alternating copolymer increased more sharply (Figure S6).

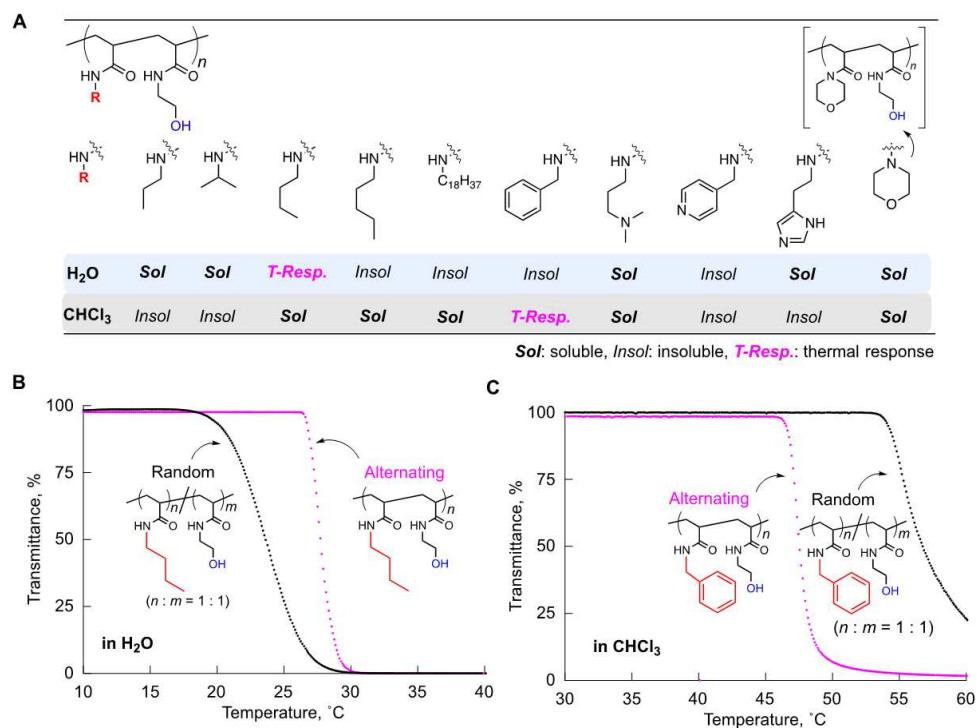


Figure 7. Solution properties of the alternating copolymers. Variable-temperature transmittance measurements with butyl- and benzyl-based alternating copolymers in H₂O and CHCl₃ (10 mg/mL; heating; 1 °C/min).

When the number of the carbon atoms in the alkyl chain was further increased to pentyl and octadecyl, the copolymers became hydrophobic. Interestingly, the copolymer containing benzyl acryl amide units showed thermal response in CHCl₃. The CHCl₃ solvent in this study contains EtOH as stabilizer (0.3 – 1.0%), which might affect the thermal response.³⁹ Anyway, the thermal response was different from the corresponding random copolymer, similar to the case with the butyl group in H₂O, i.e., the response was sharper than for the random copolymer, and similar trends were observed during the cooling process (Figure S7). The difference is also likely due to an absence of any composition distribution among the chains. The dimethyl-amine-embedded alternating copolymer is amphiphilic, whereas the pyridine-based alternating copolymer is insoluble in both solvents. The alternating copolymer that carries imidazole pendants is hydrophilic. These amine-containing alternating copolymers might find applications in catalysis and bio-related materials, which is currently under investigation in our laboratory.

Finally, the crystalline behaviour of the alternating copolymer that contains octadecyl acryl amide⁴⁰ was evaluated by DSC measurements. A sharp endothermic peak derived from melting was observed at 31.2 °C (T_m), which is similar to the homopolymer of octadecyl acryl amide. In such virtually atactic copolymers, the crystallization is solely due to the presence of crystallizable C18 side chains. The melting enthalpy ($H_m = 35$ J/g) relative to the weight fraction of the octadecyl substituent (74%) is comparable to that of the homopolymer (53 J/g). Moreover, the peak was sharper, as evident from the half-width values (alternating copolymer: 10 °C; homopolymer: 15 °C). On the other hand, the corresponding random copolymer exhibited lower enthalpy and a much broader melting peak at lower temperature ($T_m = 19.7$ °C; half-width= 21 °C; $H_m = 29$ J/g). A shift of the base line derived from the glass transition was observed, albeit that the glass transition temperature (T_g) was identical to that of the random copolymer, and that the value was

almost equal to the average of the two homopolymers. Interestingly, another endothermic peak was observed at higher temperature (181.3 °C), which was not observed for the random copolymer and the homopolymers. Similar trends were observed during the cooling process (Figure S8). These results suggest that the alternating copolymer chains crystallize faster and more tightly than their random analogues or the corresponding homopolymers, and that some specific phase transition occurs at high temperature

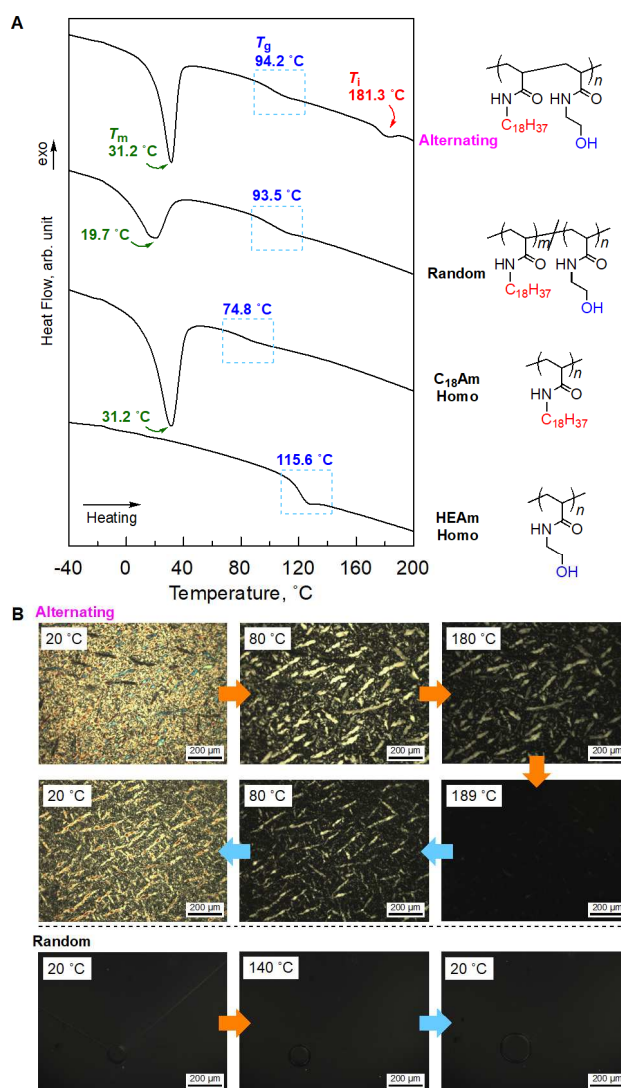


Fig 8. Solid phase transitions of the alternating copolymer of C₁₈Am and HEAm: (A) DSC profiles of the alternating copolymer of C₁₈Am and HEAm in comparison with the random copolymer and the polyC₁₈Am and polyHEAm homopolymers. Samples were heated from -50 °C to 210 °C at 10 °C/min (2nd heating); (B) POM image of the alternating copolymer of C₁₈Am and HEAm. Samples were pressed at 140°C between glass slides and cooled to RT. Textures are recorded on second heating/cooling cycle. For further information on the details of the measurements, see the Supporting Information.

To clarify the event, the phase transition was observed by polarizing optical microscopy (POM). Below 130°C, both copolymers behaved as solid powders (Figure S9). When heated to 140°C, i.e., well above the glass transition revealed by DSC, the random copolymer became a fluid that easily filled the gap between the glass slide and the coverslip driven by capillary forces. Viewed between crossed polarizers, the sample appeared black, i.e., this fluid is an optically isotropic liquid, and the black texture remained down to room temperature and during the next heating/cooling cycle (Figure 8B). The alternating counterpart also liquified at 140°C, but showed birefringence colors between crossed polarizers, and birefringence disappeared only above 180°C (clearing point) (Figure S9). The clearing point was well corresponding to that of the specific endothermic peak on the DSC measurement and thus, the peak can be assigned to the phase transition from anisotropic liquid to isotropic liquid (T_i). It was concluded that the alternating copolymer shows a mesomorphic state between melting and clearing points, whereas the random copolymer merely shows an

ordinary liquid phase as soon as the sample is liquefied. The nature of the mesophase exhibited by the alternating copolymer was identified from its optical textures: when the sample was carefully cooled across the clearing point, birefringence appeared in the form of "bâtonnets"⁴¹ that gradually extend within the whole sample to form the classical "focal conics" texture. After cooling, the focal conics texture survived until room temperature, but an increase of birefringence was observed when passing the crystallization point. During the next heating cycle, illustrated in figure 8B, the same sequence of images was observed and the resulting texture between T_m and T_{iso} was the same as before.

X-ray diffraction data were recorded to clarify the structure. The X-ray pattern of the random copolymer sample evaporated from dichloromethane solution at 25°C is plotted in Figure 9C. At low q , a series of broad reflexions with maxima at about $q = 0.2, 0.4, 0.6 \text{ \AA}^{-1}$ is detected. At large q , another broad complex signal is detected around $q = 1.5 \text{ \AA}^{-1}$. The temperature evolution reveals that this latter is the overlap of a single Bragg peak at 1.54 \AA^{-1} and a halo with maximum at $q = 1.39 \text{ \AA}^{-1}$. These features indicate a semicrystalline morphology and the lack of any long-range order of this polymer at room temperature. The pattern is similar to the one recorded for the homo-C18 homopolymer in the same conditions but with lower crystallinity and smaller size of crystallites in the random copolymer. The characteristic feature of the random copolymer is precisely that it contains more or less important fragments of homopolymer. Thus, the pristine sample contains areas of microphase separated short homo-C18 fragments that reproduce crystalline features of the homopolymer. At 80°C small Bragg peaks are detected at $q = 0.146 \text{ \AA}^{-1}$ and $q = 0.294 \text{ \AA}^{-1}$ but thus disappear and 120°C and then do not reappear anymore. The cooling cycle is shown in figure 9D, where the random copolymer appears essentially amorphous at any temperature.

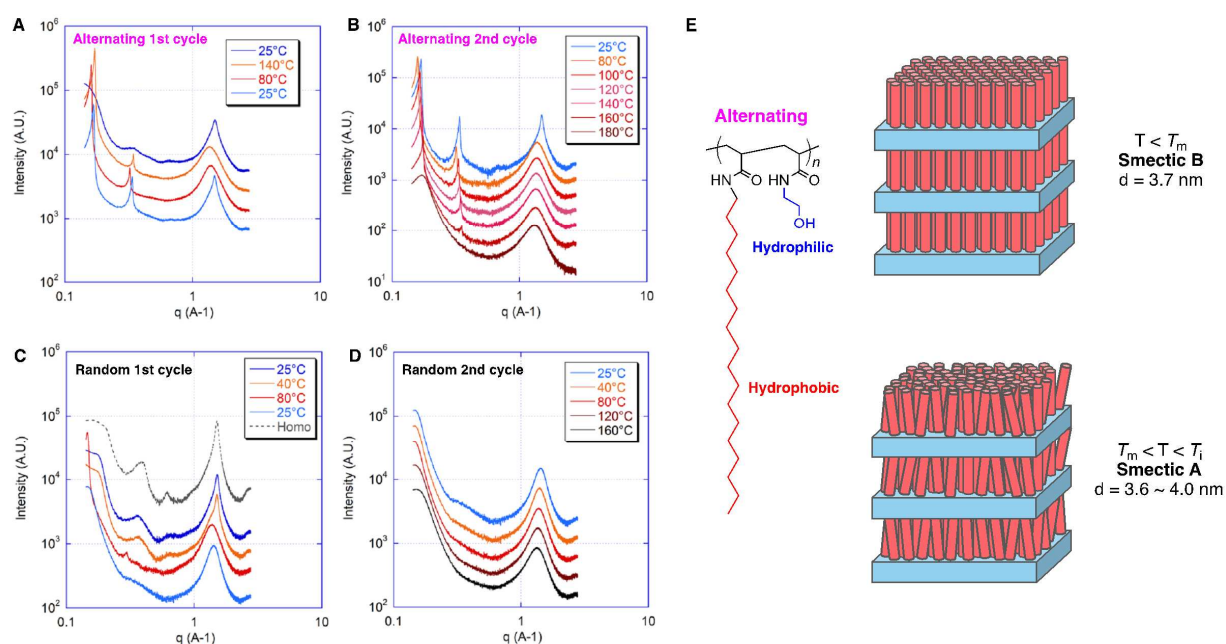


Figure 9. X-ray diffraction of alternating copolymer of $C_{18}Am$ and $HEAm$ alternating (A, B) and random copolymers (C, D); (E) predicted structure of the alternating copolymer. For further information on the details of the measurements, see the Supporting Information.

In the case of alternating copolymer, it showed quite different result. The first heating cycle is illustrated in Figure 9A. Contrarily to its random counterpart, the alternating copolymer becomes more ordered upon thermal annealing. Thus in the low- q region, whereas broad features are scarcely detected in the pristine sample, heating reveals the presence of Bragg peaks which are then constantly observed during further cycles up to about 180°C where the pattern becomes essentially amorphous. The temperature variations of crystalline parameters are reported in table S2. At room temperature, low q signals are indexed as 001 and 002 reflections of a layered structure with a layer spacing of about 37.2 \AA . These reflections are sharp thus indicating that once annealed, this layer structure has a long-range ordering. At large q the presence of a single Bragg peak indicates a 2D hexagonal ordering with a spacing of 4.2 \AA (hexagonal parameter $4.2 \times 2/\sqrt{3} = 4.8 \text{ \AA}$). This value is typical of alkyl chains in a hexagonal arrangement (e.g. structure of soaps). This phase is recognized as smectic B. Between 25°C and 80°C, a phase transition is detected: both low q signals and the

large q signal show a discontinuity. Furthermore, the ratio of intensities I_{002}/I_{001} drops from about 0.07 to 0.01, indicating much larger thermal fluctuations in the higher temperature phase. Nevertheless both 001 and 002 signals remain sharp, indicating that long range layer order is still present. At large q , the Bragg peak is no longer detected but a halo with maximum at about 4.6 Å is observed indicating a ²D liquid-like order inside the layers. At 80°C, the layer spacing is of about 39.5 Å i.e. larger than at 25°C but upon further heating, the interlayer spacing gradually decreases whereas the intralayer spacing gradually increases thus accounting for the shortening of the end-to-end distance of the alkyl chains. Such features are typical of the smectic A phase where elongated molecules are packed perpendicular to the layer planes. This second mesophase is stable up to about 180°C, whereupon transition to the isotropic liquid is observed. Appearance of reversible smectic B and smectic A phases, with long range positional ordering in a large range of temperature is the specific feature of the alternating copolymer. The formation of such mesophases is due to the controlled sequence of hydrophobic and hydrophilic groups, conducive to a layered arrangement with regular alternation of well-defined octadecyl and hydroxyethyl sublayers. Self-assembly in the bulk through segregation of short incompatible fragments is well known for small mesogenic molecules,⁴³ but was also observed in random⁴⁴ and alternating⁴⁵ copolymers. The interesting fact in this work is that the formation of layers is inhibited in the random copolymer and specific to the alternating sequence.

Conclusion

We have presented a method that allows controlling the alternating sequence for two kinds of repeat units that differ only with respect to the pendant groups (in this case: acryl amides). This method is based on the design and synthesis of a special divinyl monomer (1), in which two cleavable bonds were embedded in the linker. The selectivity of the cyclopolymerization of 1 was experimentally examined and the quantitative transformation from the cyclopolymer into the targeted alternating copolymers was achieved using ten different amines for the cleavage reactions. Thus, we generated a series of alternating copoly(acrylamide)s that contain a 2-hydroxy- and another substituent that depends on the nature of the amine. Importantly, the alternating copolymers showed different thermal responses in solution as well as different phase transitions in the bulk relative to the corresponding random copolymers. In particular, the regular alternation of incompatible side groups induced the formation of layered structures over a very large temperature range whereas the random distribution of the same monomers did not. This unprecedented method to control the sequence in copolymers could open new routes to advanced hitherto inaccessible copolymeric materials with attractive properties/functions.

Experimental Section

In a round bottom flask was placed divinylmonomer **1** (3.63 g, 10.8 mmol) and AIBN (35.7 mg, 0.216 mmol) under argon. Then, degassed anhydride dioxane (83.1 mL), DMF (20.8 mL), and CTA (0.89 mL of 244 mM stock solution in toluene, 0.216 mmol) were added sequentially in this order at room temperature under dry argon; the total volume was 109 mL. For immediately after mixing, the flask was placed in an oil bath kept at 60 °C for 48 h. The reaction was terminated by cooling the solution to -78 °C. To 5 mL polymerization solution (monomer unit 0.5 mmol) was directly added butylamine (0.988 mL, 10 mmol). The reaction mixture was stirred at ambient temperature for 48 hours. Then, the reaction mixture was purified by dialysis with MeOH (about 12 hours stirring; 4 times replacement of the solvent). M_n and M_w/M_n were measured by GPC ($M_n = 7600$ $M_w/M_n = 1.37$).

Acknowledgements

The authors would like to thank Dr. Takaya Terashima (Kyoto University) for fruitful discussions, Karin Nishimura (Kyoto University) for MALDI-TOF-MS measurements and Dr. Antoine Tissot (ENS, Paris) for help in X-ray measurements. This work was partially supported by the Strategic International Collaborative Research Program (SICORP) from The French National Research Agency (ANR) and the Japanese Science and Technology Agency (JST), the ANR-15-JTIC-0004 grant, as well as by JSPS KAKENHI grants 17H06453 and 19H00911.

References

- [1] J. F. Lutz, M. Ouchi, D. R. Liu, M. Sawamoto, *Science* **2013**, *341*, 1238149.
- [2] J. F. Lutz, *Sequence-Controlled Polymers*, Wiley-VCH, Weinheim, **2018**.
- [3] J. F. Lutz, *Polym. Chem.* **2010**, *1*, 55–62.
- [4] M. Ouchi, N. Badi, J. F. Lutz, M. Sawamoto, *Nat. Chem.* **2011**, *3*, 917–924.
- [5] J. F. Lutz, *Macromol. Rapid Commun.* **2017**, *38*, 1–12.
- [6] M. Ouchi, M. Sawamoto, *Polym. J.*, **2018**, *50*, 83–94.
- [7] W. A. Braunecker, K. Matyjaszewski, *Prog. Polym. Sci.* **2007**, *32*, 93–146.
- [8] K. Matyjaszewski, N. V. Tsarevsky, *J. Am. Chem. Soc.* **2014**, *136*, 6513–6533.
- [9] J. F. Lutz, J. M. Lehn, E. W. Meijer, K. Matyjaszewski, *Nat. Rev. Mater.* **2016**, *1*, 1–14.
- [10] G. Moad, D. H. Solomon, *The Chemistry of Radical Polymerization*, ELSEVIER, Amsterdam, **2006**.
- [11] G. W. Coates, M. Sawamoto, *Polymer Science: A Comprehensive Reference, volume 3, Chain Polymerization of Vinyl Monomers*, ELSEVIER, Amsterdam, **2012**.
- [12] D. T. G. Hill, J. J. O'Donnel, P. W. M. O'Sullivan, *Prog. Polym. Sci.* **1982**, *8*, 215–276.
- [13] J. Huang, S. R. Turner, *Polymer* **2017**, *116*, 572–586.
- [14] S. Banerjee, I. Domenichelli, B. Ameduri, *ACS Macro Lett.* **2016**, *5*, 1232–1236.
- [15] Z. Huang, B. B. Noble, N. Corrigan, Y. Chu, K. Satoh, D. S. Thomas, C. J. Hawker, G. Moad, M. Kamigaito, M. L. Coote, C. Boyer, J. Xu, *J. Am. Chem. Soc.* **2018**, *140*, 13392–13406.
- [16] M. Tesch, J. A. M. Hepperle, H. Klaasen, M. Letzel, A. Studer, *Angew. Chem., Int. Ed.* **2015**, *54*, 5054–5059.
- [17] E. Mishima, S. Yamago, *Macromol. Rapid Commun.* **2011**, *32*, 893–898.
- [18] D. Valade, F. Boschet, B. Améduri, *Macromolecules* **2009**, *42*, 7689–7700.
- [19] K. Satoh, M. Matsuda, K. Nagai, M. Kamigaito, *J. Am. Chem. Soc.* **2010**, *132*, 10003–10005.
- [20] B. Kirci, J. F. Lutz, K. Matyjaszewski, *Macromolecules* **2002**, *35*, 2448–2451.
- [21] K. Satoh, H. Hashimoto, S. Kumagai, H. Aoshima, M. Uchiyama, R. Ishibashi, Y. Fujiki, M. Kamigaito, *Polym. Chem.* **2017**, *8*, 5002–5011.
- [22] Y. Hibi, S. Tokuoka, T. Terashima, M. Ouchi, M. Sawamoto, *Polym. Chem.* **2011**, *2*, 341–347.
- [23] Y. Hibi, M. Ouchi, M. Sawamoto, *Angew. Chem., Int. Ed.* **2011**, *50*, 7434–7437.
- [24] M. Ouchi, M. Nakano, T. Nakanishi, M. Sawamoto, *Angew. Chem., Int. Ed.* **2016**, *55*, 14584–14589.
- [25] Y. Kametani, M. Nakano, T. Yamamoto, M. Ouchi, M. Sawamoto, *ACS Macro Lett.* **2017**, *6*, 754–757.
- [26] Y. Kametani, M. Sawamoto, M. Ouchi, *Angew. Chem., Int. Ed.* **2018**, *57*, 10905–10909.
- [27] A. Das, P. Theato, *Chem. Rev.* **2016**, *116*, 1434–1495.
- [28] M. Bodanszky, *Nature.* **1955**, *175*, 685–685.
- [29] Y. Liu, L. Wang, C. Pan, *Macromolecules* **2002**, *32*, 8301–8305.
- [30] G. Moad, E. Rizzardo, S. H. Thang, *Polymer* **2008**, *49*, 1079–1131.
- [31] M. Fineman, S. D. Ross, *J. Polym. Sci.* **1950**, *5*, 259–265.
- [32] J. Brandrup, E. H. Immergut, E. A. Grulke, *Polymer handbook fourth edition* Wiley-Interscience, USA, 1999.
- [33] S. Mochizuki, N. Ogiwara, M. Takayanagi, M. Nagaoka, S. Kitagawa, T. Uemura, *Nat. Commun.* **2018**, *9*, 329.
- [34] K. Nishimori, M. Ouchi, M. Sawamoto, *Macromol. Rapid Commun.* **2016**, *37*, 1414–1420.
- [35] M. W. F. Nielen, *Mass Spectrom. Rev.* **1999**, *18*, 309–344.
- [36] D. Pasini, D. Takeuchi, *Chem. Rev.* **2018**, *118*, 8983–9057.
- [37] T. Kakuchi, M. Obata, *Macromol. Rapid Commun.* **2002**, *23*, 395–406.
- [38] A. Halperin, M. Kröger, F. M. Winnik, *Angew. Chem., Int. Ed.* **2015**, *54*, 15342–15367.
- [39] S. Amemori, K. Kokado, K. Sada, *J. Am. Chem. Soc.* **2012**, *134*, 8344–8347.
- [40] H. W. S. Hsieh, B. Post, H. Morawetz, *J. Polym. Sci. Polym. Phys. Ed.* **2003**, *14*, 1241–1255.
- [41] G. Friedel, Les états mésomorphes de la matière. *Ann. Phys. (Paris, Fr.)* **1918**, *273–474* **1922**.
- [42] G. W. Gray, J. W. G. Goodby *Smectic liquid crystals: textures and structures* Leonard Hill, Glasgow, Scotland, **1984**.
- [43] D. Guillon, G. Poeti, A. Skoulios, E. Fanelli, *J. Phys., Lett.* **1983**, *44* (12), 491–494.
- [44] G. Hattori, M. Takenaka, M. Sawamoto, T. Terashima, *J. Am. Chem. Soc.* **2018**, *140*, 8376–8379.
- [45] K. Nishimori, E. Cazares-Cortes, J. -M. Guigner, F. Tournilhac, M. Ouchi, *Polym. Chem.* **2019**, *10*, 2327–2336.