Polymer Chemistry

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Polym. Chem.*, 2022, **13**, 5798

Nucleobase-containing polymer architectures controlled by supramolecular interactions: the key to achieve biomimetic platforms with various morphologies

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Received 14th July 2022,
Accepted 26th September 2022

DOI: 10.1039/d2py00920j

rsc.li/polymers

In biological systems, DNA formation occurs due to complementary H-bond interactions between nucleobases, as well as hydrophobic supramolecular interactions. It inspired polymer chemists in the development of supramolecular artificial platforms based on nucleobase-containing polymers. Despite their biomimetic nature and their huge potential to develop bioinspired supramolecular assemblies, nucleobase-containing polymers are in their infancy. The first part of this review aims to highlight the synthetic challenges related to the synthesis of nucleobase-containing monomers and polymers. The second part illustrates how to guide supramolecular interactions of nucleobase-containing copolymer architectures in order to obtain particular morphologies of the resulting supramolecular systems.

I. Introduction

Self-assembly describes a process in which a disordered system becomes ordered as a result of interactions within itself.[1] In other words, this phenomenon involves the spontaneous organization of molecular entities into well-defined organized architectures. The interactions involved in self-assembly are weak non-covalent bonds (*e.g.*, van der Waals forces, solvophobic interactions, H-bonds, crystallization, *etc.*).

Historically, the first self-assemblies in solution were obtained from small amphiphilic molecules such as surfactants.[2] These self-assemblies originated from solvophobic interactions between the aliphatic moieties of the surfactant-active chains and led to the formation of various morphologies including spheres or vesicles.[3] Later, amphiphilic block copolymers were used to perform self-assembly as they present a lower critical micellar concentration (CMC) and were also shown to be able to self-assemble into various morphologies. As for small surfactant molecules, the main interactions controlling the self-assembly of block copolymers were the solvophobic interactions. Similarly to surfactants, these polymers include a solvophilic and a solvophobic block which self-assemble in a selective solvent. By adjusting the volume fraction of the blocks, not only spherical structures, but also cylindrical and lamellar ones become accessible.[4–6]

Other non-covalent interactions such as H-bonds can also be used when performing the self-assembly of amphiphilic block copolymers. Most processes taking place in nature involve H-bonds. For example, genetic replication requires H-bond recognition between complementary nucleobases (Fig. 1).[7] Nucleobases were key motifs used to develop various biomimetic self-assembled systems.[8–10] However, most of these self-assembled architectures were constructed by using small organic molecules containing nucleobases, oligonucleotides or DNA-containing polymers.[8–10] In the field of self-assembled polymers containing nucleobase motifs, DNA-copolymer hybrids (where fragments of DNA are covalently linked to the copolymers) are the first examples of DNA-inspired polymer systems. Their DNA fragment can induce self-assembly by base pairing.[11–13] Some interesting examples of DNA-

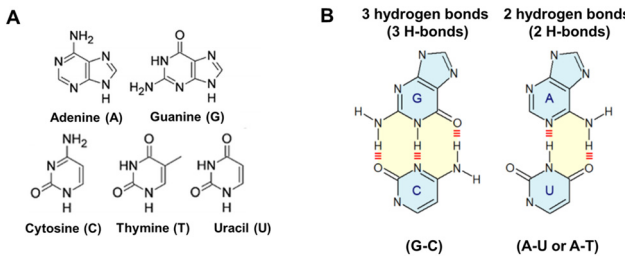

Fig. 1 (A) Structures of nucleobases; (B) pairing of complementary nucleobases: pairing of G and C involves three H-bonds, while pairing of A and U or A and T involves two H-bonds.

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containing triblock copolymer conjugates were reported to illustrate the influence of H-bond recognition between nucleobases on the morphological transition from spheres to cylinders when increasing the length of the DNA (Fig. 2).[13,14]

Although these systems present a huge potential for the control of self-assemblies in solution state, an important drawback of amphiphilic DNA-containing copolymers lies in the difficulty of DNA synthesis and of the complete coupling with polymer. Therefore, in order to mimic DNA, chemists have developed nucleoside-containing polymers.[15] First significant attempts were reported by Haddleton *et al.*[16] to prepare nucleoside-containing polymers (*i.e.*, with adenosine or uridine) by using Atom Transfer Radical Polymerization (ATRP). Moreover, Ring Opening Polymerization (ROP) was applied to develop a range of thymidine-containing polymers.[17] Furthermore, using nucleobase motifs instead of nucleosides in the development of polymers was reported to be more advantageous in terms of difficulties associated to the organic synthesis.[15] For example, the group of Van Hest *et al.*[18] prepared polymethacrylates containing adenine, thymine or cytosine by ATRP. Moreover, monomers of styrene funcionalized by adenine and thymine were used in the NMP polymerization, as stated by Long and collaborators.[19] Other significant contributions were made by Rowan *et al.*,[20] Leibler *et al.*[21] as well as Binder *et al.*[22] in the field of adenine and thymine-containing telechelic polymers.

These supramolecular systems using nucleobases have been the subject of some recently published comprehensive reviews.[23,24] The nucleobase-containing polymer structures reported so far for self-assembly applications in solution are based on either commercial polymers modified with nucleobases, or more often on nucleobase-containing block copolymers prepared particularly by RAFT polymerization of nucleobase-containing monomers.[17,25] Professor O'Reilly performed pioneer works in the field of self-assembly in solution state of nucleobase-containing polymers prepared by RAFT.[26] In this context, a block topology was generally chosen in order to access an amphiphilic behavior. In this case the nucleobase-containing block was hydrophobic and was combined with a hydrophilic block mainly of poly(*N*-acryloylmorpholine). These block copolymers led to architectures able to self-assemble mainly *via* H-bond recognition between the nucleobases. Nevertheless, a disadvantage of nucleobase-containing copolymers is the impossibility to achieve the perfect sequence control of nucleobases that nature possesses in the case of DNA, because these structures are prepared by chain polymerization.

Few studies indicated that, by modifying the nucleobase-containing block (*i.e.* the number and the ratio of nucleobases, the addition of hydrophilic or hydrophobic co-monomers *etc.*), different self-assembled morphologies can be obtained.[26] These studies also showed that the obtained type of morphology can vary when some parameters including the pH or solvent type are changed.[26] Indeed, these parameters affected the H-bonds between nucleobases responsible for the self-assembly and in consequence the self-assembled morphology.

The correlation between complementary H-bonds in nucleobase-containing copolymers and their morphology is still under investigation. So far, few papers (~25) studied different ways to modulate the morphology of self-assembled nucleobase-containing copolymers by changing a range of parameters. This review will highlight how to guide supramolecular interactions of nucleobase-containing copolymer architectures towards a particular morphology, by summarizing the main observations reported so far. First, synthetic challenges associated with nucleobase-containing monomers will be presented, and a brief update of the synthesis methods of nucleobase-containing copolymer structures will be presented. Then, the second part of this review will explain how changes in the supramolecular interactions in nucleobase-containing polymers enable the resulting self-assembled architectures obtained in solution state to adopt a particular morphology.

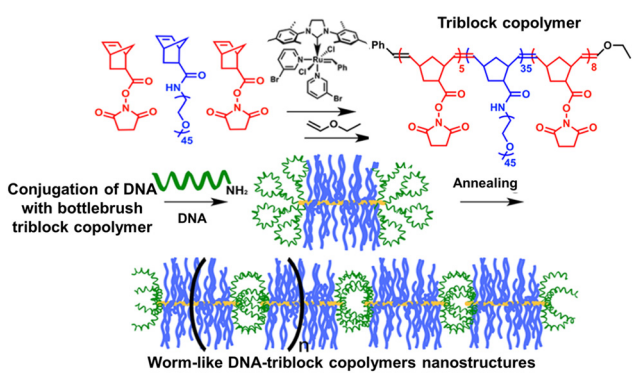

Fig. 2 The design of worm-like nanostructures *via* the conjugation of triblock bottlebrush copolymers with DNA. Reprinted with permission from ref. 14 Copyright (2014) American Chemical Society.[14]

II. Nucleobase-containing monomers and polymers

A. Nucleobase-containing monomers

This section focused on the synthesis of nucleobase-containing monomers polymerizable by radical polymerization. Radical polymerization is a versatile and compatible polymerization technique with the functional groups contained in the nucleobases. The synthesis of nucleobase-containing vinyl monomers has been seldomly described so far. The most common and cited method to synthesize nucleobase-containing vinyl monomers is nucleophilic substitution (SN) reactions.[24] This method was mainly used to prepare adenine and thymine (or uracil)-containing monomers. Previous reports mentioned that in the case of cytosine- and guanine-containing vinylic monomers this method is challenging due to side reaction products and low reaction yields (below 48%).[18] Similar to the vinylic monomers, the synthesis of cytosine and guanine-containing nucleobase copolymers is very complex, and the number of examples of self-assembled architectures made from these polymers are in consequence very limited.[15,26,27] Since most of the examples of self-assembled nucleobase-containing copolymers concern adenine and/or

thymine (uracil) derivatives,[26,28] the discussion of this section will focus on monomers containing these nucleobases prepared by SN reactions.

A.1. Reactivity of nucleobases in nucleophilic substitution (SN) reactions. The synthesis of nucleobase-containing vinylic monomers reported in the literature takes place in anhydrous polar aprotic solvents. The main strategy used to synthesize these monomers comprises two steps: deprotonation of the nucleobase (Step 1) and bimolecular nucleophilic substitution (SN_2) of the deprotonated nucleobase with a primary alkyl halide (Step 2).

The nucleobases are nucleophilic agents in nucleophilic substitution reactions since they contain electron donor amino groups. To increase the nucleophilicity of nucleobases in SN_2 type reaction, the treatment of nucleobases with inorganic bases (*i.e.*, NaH, or K_2CO_3) is preferentially performed. The inorganic bases deprotonate the amino functions of nucleobases, which results in strong nucleophilic anions, appropriate for SN_2 reaction.[29]

A.2. Synthesis of nucleobase-containing monomers

Adenine-containing monomers. The adenine presents a primary amino group which is involved in the H-bonds with thymine (or uracil). Therefore in order to perform a nucleophilic substitution with adenine, the primary amino group should be preserved, while substituting the NH group in the imidazole ring. Thus, the NH group of the imidazole ring should be deprotonated by inorganic bases to form a strong nucleophilic agent (Fig. 3A). Strong inorganic bases such as NaH are used to deprotonate the secondary cyclic amine structure of the adenine. The secondary amine proton of the imidazole ring present a $pK_a \sim 9.8$ (of the non-protonated form),[29] so it can be deprotonated by strong bases. Then, the deprotonated adenine reacts with primary alkyl bromo halides containing polymerizable synthons (acrylamide-, acrylate- or methacrylate-), leading to the final monomer (Fig. 3B).

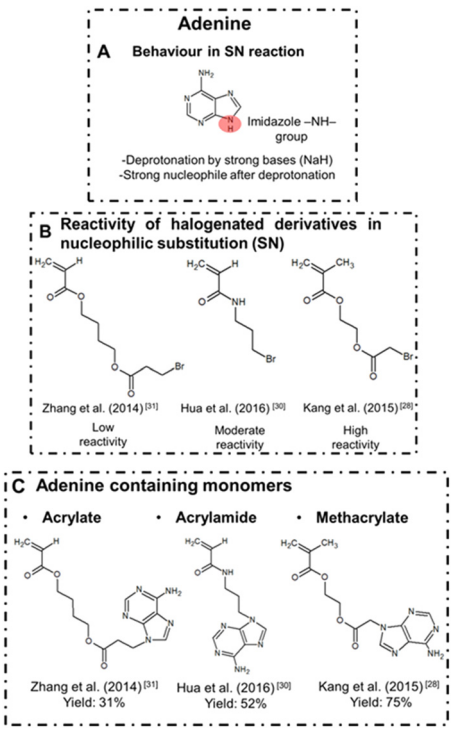

Fig. 3 (A) Acid–base properties of adenine and behavior in SN reaction; (B) reactivity of alkyl halides in the nucleophilic substitution; (C) structures of adenine-containing monomers.

Acrylamide-, acrylate- and methacrylate- derived adenine-containing monomers were reported in the literature with low or moderate reaction yields (Fig. 3C). For example, acrylamide-alkyl monomers containing adenine were previously obtained by Hua *et al.*[30] with low yield and small scale (52%, 1 g) due to an undesired attack of NaH on the amide of acrylamide region of the bromo alkyl halide, which led to secondary substitution products. Then, Zhang *et al.*[31] synthesized an adenine-containing acrylate as polymerizable synthon. However, the authors reported a global yield of the reaction of 31%. Compared to the example of the acrylamide adenine-containing monomers,[30] the low reaction yield was a consequence of the structure of the bromoderivative used in the SN reaction (*i.e.* where the halogen group was placed at the β position of an ester), as illustrated by Zhang *et al.*[31] Moreover, Kang *et al.*[28] reported the successful synthesis of adenine-containing methacrylates, in moderate yield and small scale (75%, 3.5 g). The higher yield (compared to that of acrylate or acrylamide type monomers) was explained by the activation of the halogen group which was situated at the α position of an ester.[28]

Thymine-containing monomers. The deprotonation of thymine molecules to be further used in nucleophilic substitution reactions is different due to the presence of two –NH– groups with different reactivities: one imide group (1) and a secondary cyclic amide (2) (Fig. 4A). In order to achieve the complementary H-bonds with adenine synthon as in the biological systems, the imide group should be free. Thus, the secondary cyclic amide proton (2) should be selectively targeted to perform the substitution reactions.

The approach used by Hua *et al.*[30] to prepare thymine-containing acrylamide monomers was to protect the imide group (1) of thymine with benzoyl chloride in the presence of K_2CO_3. By this way, the cyclic amide group (2) of thymine was deprotonated by NaH and then involved in the SN reaction with the bromo alkyl acrylamide derivative (Fig. 4B and C).[30] The protection of the imide group was required since its pK_a (*i.e.*, 9.5) makes it sensitive to NaH attack. Then, deprotection of the benzoylated imide group was performed using TFA. The global yield of the three-steps synthesis of acrylamide-alkyl thymine was 35%. As stated by the authors, the decreased yield compared to the adenine derivative was mainly due to the protection/deprotection steps of thymine.

Thymine-containing methacrylate were synthesized by Kang *et al.*[28] using an iodide derivative to perform the SN with deprotonated thymine (deprotonation realized with K_2CO_3). In this case, the use of a softer base for the deprotonation of the thymine prevents the protection/deprotection steps.

A 60% reaction yield was reported by the authors. Compared to the yield of thymine-containing acrylamide and

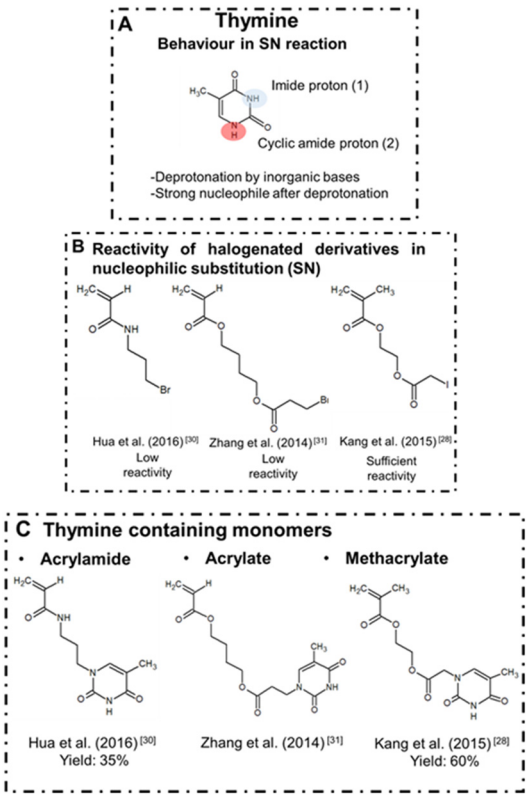

Fig. 4 (A) Acid–base properties of thymine and behavior in SN reaction; (B) reactivity of halogeno intermediary products in the nucleophilic substitution; (C) structures of thymine-containing monomers.

acrylate, the increased yield was a consequence of the increased reactivity of iodide group compared to the bromo group in the SN, as well as due to the absence of protection/deprotection steps during synthesis (Fig. 4B and C).

To summarize, the low reaction yields (31–75%) and the difficulty to scale up the synthesis protocols (a few grams) are the main challenges of nucleobase-containing monomers reported until now in the literature.

B. Nucleobase-containing polymers

A first approach to obtain nucleobase-containing polymers consists in the polymerization of nucleobase-containing monomers. While the synthesis of nucleobase-containing monomers can be difficult as shown in the previous section, the synthesis of the corresponding nucleobase-containing (co) polymers is easy in high yields. The polymer synthesis can be performed using radical controlled polymerization techniques which allow the synthesis of well-defined statistical copolymers or block copolymers containing predetermined numbers of nucleobases. Controlling the position, proportion and the number of nucleobase units in each polymer chain is key to obtain desired H-bond recognition during self-assembly. Among the well-known radical controlled polymerization techniques, RAFT is the most often reported technique to prepare nucleobase-containing copolymers (and in particular nucleobase-containing block copolymers). The pioneering works of the O'Reilly group described the synthesis of amphiphilic block copolymers by RAFT polymerization of adenine-acrylamide (AM-A), thymine-acrylamide (AM-T), *N*-isopropylacrylamide (NIPAM) and *N*-acryloylmorpholine (NAM) (Fig. 5A).

The strategy consisted in the synthesis of a thermoresponsive poly(NIPAM-*co*-NAM) macro-CTA followed by chain extension using the nucleobase-containing AM-A monomers.[32] The same strategy was employed by Kang *et al.*[28] to synthesize poly(methyl methacrylate)-*b*-poly(adenine methacrylate) (PMMA-*b*-PAMA) and poly(methyl methacrylate)-*b*-poly(thymine methacrylate) (PMMA-*b*-PTMA) block copolymers containing from 20 to 200 nucleobase units per polymer chain (Fig. 5B). Longer chains (Fig. 5C)[32] were reported for poly(*N*-acryloyl morpholine)-*b*-poly (thymine acrylamide) (PNAM-*b*-PTAm) block copolymers containing up to 300 thymine units. Wang *et al.*[33] and Kim *et al.*[34] reported the RAFT polymerization of nucleobase-containing monomers providing rigid backbones, such as poly(vinyl benzyl-adenine) (PA) and poly(vinyl benzyl-thymine) (PT)

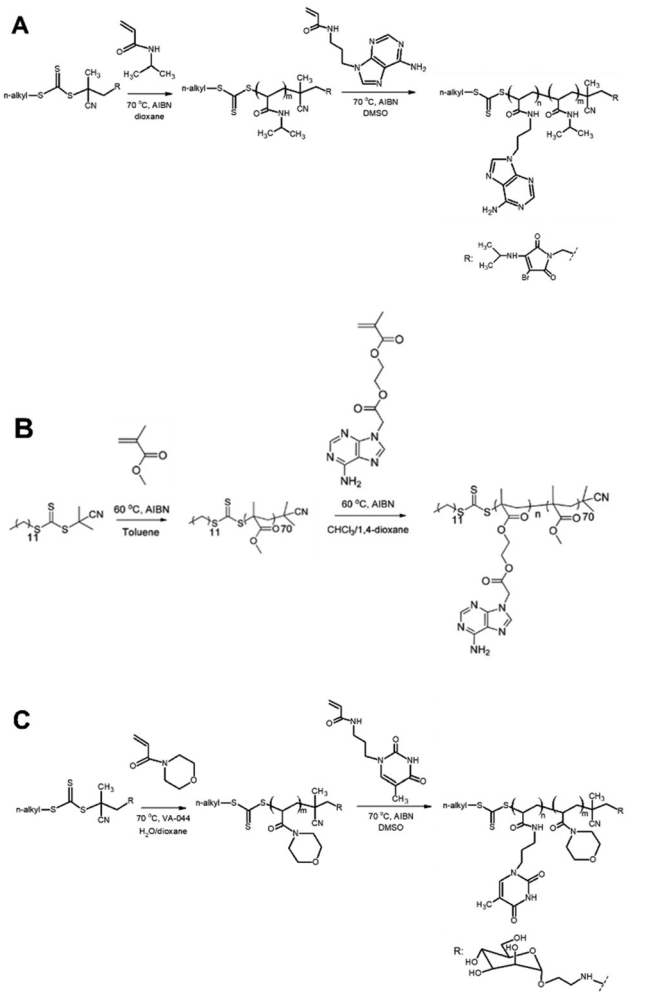

Fig. 5 (A) Synthesis of adenine-containing copolymers based on acrylamide type backbone[32] and (B) methacrylate type backbone;[28] (C) synthesis of thymine-containing copolymers based on acrylamide type backbone.[32]

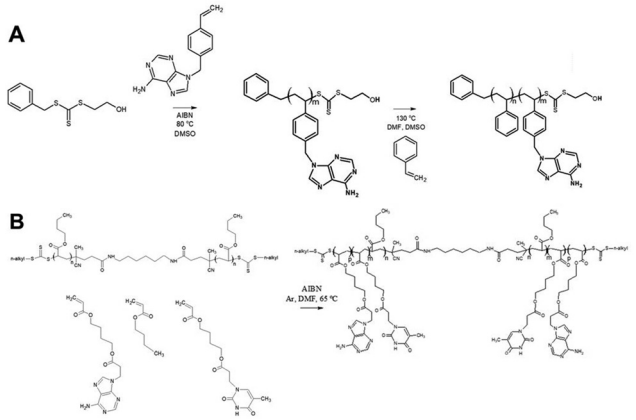

Fig. 6 (A) Synthesis of poly(adenine-styrene)-*b*-poly(styrene) copolymers[34] and of (B) poly(butylacrylate)-*b*-poly(thymine-methacrylate-co-adenine-methacrylate) copolymers.[35]

(Fig. 6A).[33,34] Furthermore, multiblock amphiphilic copolymers were designed by the sequential RAFT polymerization of thymine acrylate, *n*-butyl acrylate, and adenine acrylate using a bifunctional macro-CTA agent (Fig. 6B).[35]

Overall, the previous examples consisted in the RAFT polymerization of nucleobase-containing monomers. In addition, the RAFT agent used in the polymerization can be modified with nucleobases prior to perform the RAFT polymerization. For example, in the study reported by Wang *et al.*,[36] a RAFT chain transfer agent (CTA) possessing a carboxylic acid end-group was esterified with adenine or thymine bearing 2-hydroxyethyl groups (with yield up to 85%). Then, the resulting modified RAFT agent was used to copolymerize oligo(ethylene glycol) methacrylate and *n*-butyl methacrylate, in order to obtain poly(oligo(ethylene glycol) methacrylate)-block-poly(*n*-butyl methacrylate) (POEGMA-*b*-PMBA) block copolymers with adenine (A) or thymine (T) end-groups (Fig. 7).

The second approach to obtain nucleobase-containing polymers consists in the post-functionalization of commercial polymers with nucleobases. In order to post-functionalize macromolecular architectures, click-chemistry is an efficient option owing to the simplicity in experimental setup, the versatility of this class of reaction both in terms of reaction conditions and in variety of substrates.[37–39]

Copper(I)-catalyzed alkyne–azide cycloaddition (CuAAC) was used by Huang *et al.*[40] to produce thymine-containing poly(carbazole) (PC-T) and thymine-functionalized carbazole-triphenylaniline copolymers (PTC-T) in high yields (up to 95%) (Fig. 8A). The same strategy was applied to graft uracyl-bearing propargyl moieties on azide-functionalized poly(caprolactone) (PCL) with 71% yield (Fig. 8B).[41,42] This relatively low yield for a click-chemistry reaction was ascribed to the hindered azide-PCL structure. Another example of click chemistry is the aza-Michael addition (Fig. 9), successfully used for the synthesis of telechelic uracyl-functionalized poly(propylene glycol) (BU-PPG)[43] (Fig. 9A) and telechelic adenine-functionalized poly(ethylene glycol) (BA-PEG) (Fig. 9B) in high yields (96%).[42]

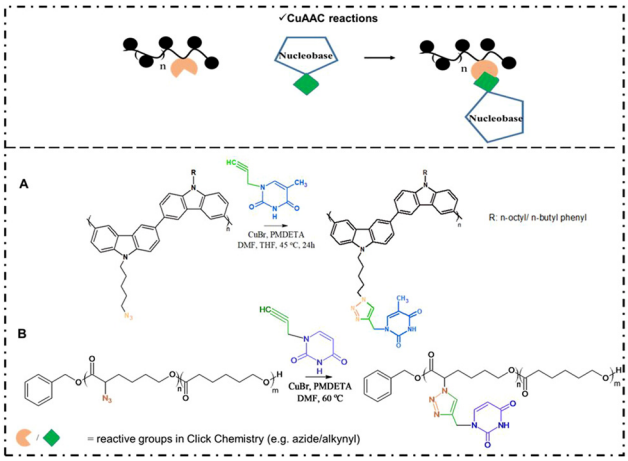

Fig. 8 CuAAC reactions for the nucleobase-functionalization of polymers.[40,42]

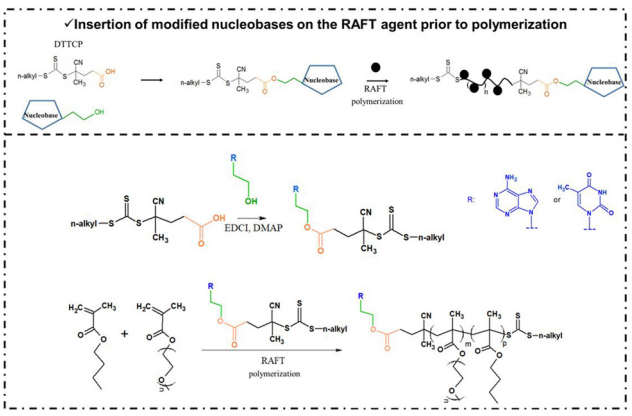

Fig. 7 Synthesis of nucleobase-containing copolymers by the functionalization of the RAFT agent with nucleobases prior to polymerization.[36]

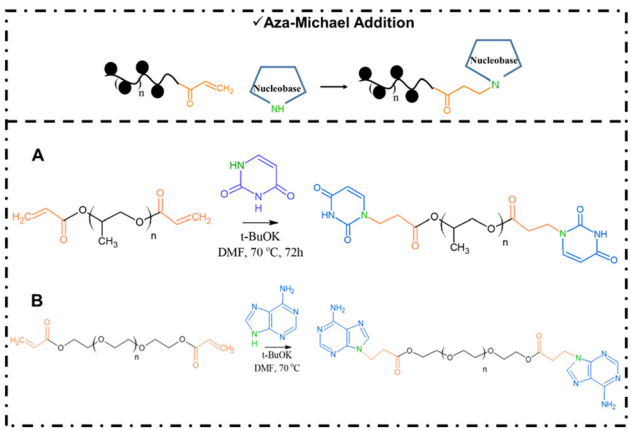

Fig. 9 Aza-Michael Addition for the nucleobase-functionalization of polymers.[42,43]

Another type of reaction used to functionalize commercial polymers with nucleobases is the esterification. Zhao *et al.*[44] applied a similar concept (*i.e.* esterification as linkage reaction), to functionalize a poly(2-hydroxyethyl acrylate)-*b*-poly (caprolactone) with an adenine bearing a 2-carboxyethyl group. This way, adenine-containing PCL amphiphilic block copolymers were obtained with 75% yield (Fig. 10).[44]

In conclusion, two different methods were used to prepare nucleobase-containing copolymers.

The first one consists in the controlled radical polymerization of nucleobase-monomers (Fig. 11). This method affords nucleobase-containing polymers with controlled architecture, degrees of polymerization and co-monomers ratios. Nevertheless, this method requires to synthesize the nucleobase-containing monomers, which involve challenging organic synthesis, as described in the previous section.

Alternatively, nucleobase-ended polymers can be obtained by using a nucleobase-functionalized RAFT chain transfer agent, but only a single nucleobase is inserted in the polymer chain.

The second method consists in the post-functionalization of polymers, using click-chemistry reactions (CuAAC, aza-Michael Addition) or esterification for examples (Fig. 12). This method is advantageous since it allows to prepare librairies of polymers only different in their degree of functionalisation.

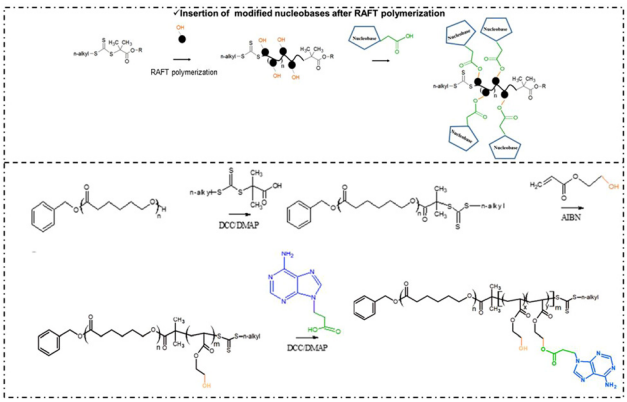

Fig. 10 Functionalization with nucleobases by insertion of modified nucleobases after RAFT polymerization.[44]

III. Self-assembly of nucleobase-containing polymers

Few examples of self-assembled structures formed in solution state based on synthetic nucleobase-containing polymers have been reported so far, probably because the synthesis of these polymers is very labor-intensive, as presented in the previous section. Until now, the reported self-assembled nucleobase-containing polymer architectures were formed from synthetic nucleobase-containing block copolymers or commercial polymers functionalized with nucleobases. Various parameters (internal: chain length, density and position of nucleobases on the macromolecular backbone, incompatibility of the blocks;

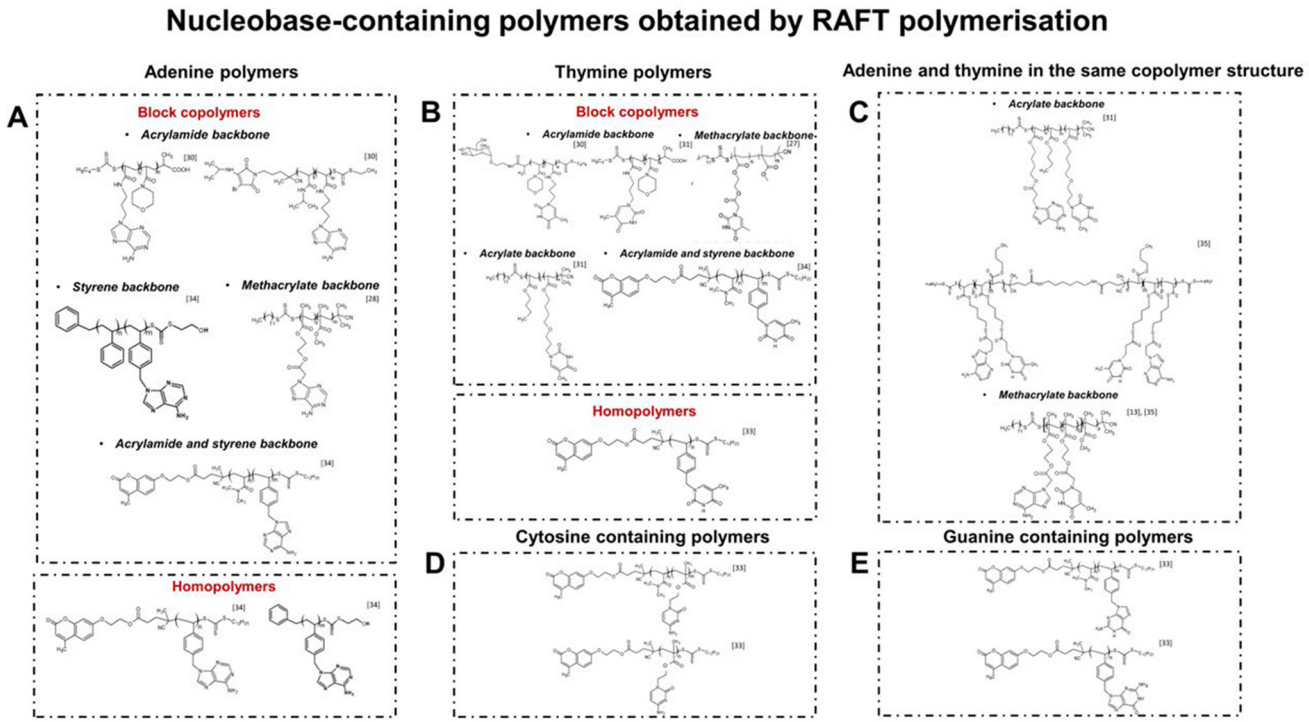

Fig. 11 Nucleobase-containing polymers obtained by RAFT polymerization: (A) Adenine-containing polymers; (B) thymine-containing polymers; (C) adenine- and thymine-containing polymers; (D) cytosine-containing polymers and (E) guanine-containing polymers.

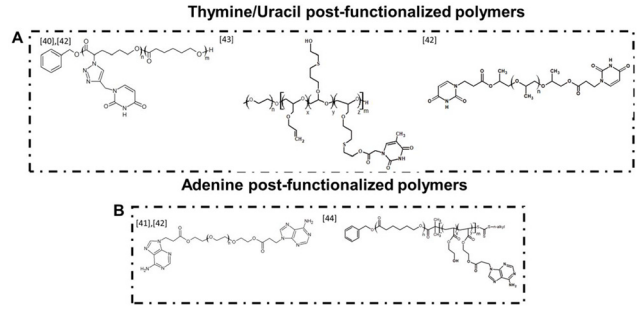

Fig. 12 Nucleobase-containing polymers obtained by post-functionalisation reactions.

or external: pH, temperature, solvent *etc.*) are known to influence the self-assembly of nucleobase-containing polymers. While these parameters were many times reported to change the morphology (in terms of shape or size) of the self-assemblies, a clear correlation between the varied parameter and the obtained morphology has never been explained, to our knowledge.

Most of the self-assembled nucleobase-containing polymers mentioned in the literature were prepared in organic solvents. The nucleobase-containing homopolymers reported so far were not water soluble. Indeed, in DNA or RNA, water-solubility comes from the charged backbone. To mimic DNA, water solubility is an important parameter. Only few water-soluble self-assemblies made of nucleobase-containing copolymers have been reported.

In this section, the main properties of self-assembled nucleobase-containing polymers are classified according to the type of solvent used (organic solvent, mixture of organic solvent/water or water).

A. Self-assembled nucleobase-containing polymers prepared in organic solvents

According to Kang *et al.*, distinct morphologies (Fig. 13A) could be obtained by changing the organic solvent used for the self-assembly of poly(2-(2-(thymine-1-yl)acetoxyl)ethyl methacrylate)-*b*-poly(methyl methacrylate) diblock copolymers (DP of thymine containing block = 100).[45] In non-polar solvents such as chloroform, well-defined spherical micelles were formed. This morphology was confirmed by Small Angle Neutron Scattering (SANS) indicating a total radius of 108.3 nm and a shell thickness of 38.3 nm. In a chloroform/1,4 -dioxane (75 vol% $CHCl_3$) binary mixture, the block copolymer self-assembled into complex morphologies of lamellae with tentacles presenting a hydrodynamic diameter of 300 nm confirmed by dynamic light scattering (DLS). The composition of the solvent had an influence on the observed morphologies. At 50 vol% of $CHCl_3$, long flexible cylinders (5 μm) were observed whereas short worm-like structures of 75 nm long were obtained at 12.5 vol% $CHCl_3$. In pure 1,4-dioxane, core–shell spherical morphologies with a mean diameter of 100 nm were obtained.

Changing the length of the thymine-containing block (Fig. 13B) led to unexpected results in 1,4-dioxane. Indeed, at

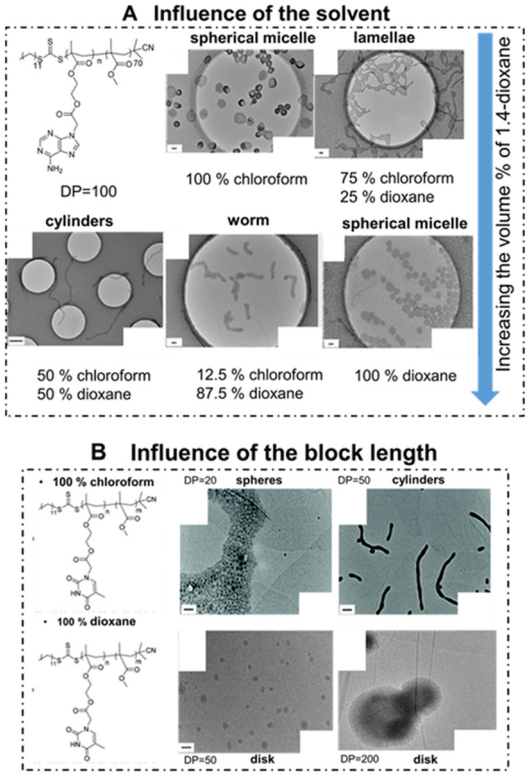

Fig. 13 (A) Morphologies of Poly(2-(2-(thymine-1-yl) acetoxyl) ethyl methacrylate)-*b*-Poly(methyl methacrylate) micelles at different compositions of solvents; morphologies of the micelles in chloroform (B) and in dioxane for different thymine-containing block length. Scale bar: 100 nm. Adapted from ref. 45 with permission from the Royal Society of Chemistry Copyright 2015.[45]

DP = 50, disk like morphologies were observed, whereas at DP = 100 spherical core shell morphologies were noted and at DP = 200 disk like morphologies appeared again (Fig. 13B). In chloroform, an increase of the degree of polymerization of the thymine-containing block from 20 to 50 led to spherical micelles and cylinders respectively (Fig. 13B). According to the authors, the morphological transitions in the presence of a non-polar solvent occurred due to the poor solubility of the polymers in chloroform which increased the intra- and intermolecular chain interactions. In 1,4-dioxane, the nucleobase-containing blocks of the polymers were more soluble than in chloroform and thus, the non-covalent chain interactions were limited and the morphology was kept constant.

B. Self-assembled nucleobase-containing polymers prepared in organic solvent/water mixtures

B.1. The influence of the amount of complementary nucleobase-containing polymers. In 2016, Cheng *et al.*[42] showed that the co-assembly in a THF/water mixture of uracil functionalized poly(caprolactone) (U-PCL, M_n = 37 600 g mol^{-1}) with adenine-difunctionalized telechelic poly(ethylene glycol) (BA-PEG, M_n = 2000 g mol^{-1}) led to micelles with a pore-like morphology. The micelles were prepared by slow addition of the polymer solutions (prepared in THF) in water, under con-

tinuous stirring. The cores were composed of U-PCL units attached to the BA-PEG corona (Fig. 14A). An increase in the BA-PEG amount from 50 to 91 wt% led to a decrease of the micelle diameter from 176 to 97 nm due to a change in hydrophobic/hydrophilic balance (Fig. 14B). According to the authors, since the amount in BA-PEG increased, more U-PCL units were bound by H-bonds and the micelle became more compact. Changes in the amount of complementary nucleobase-containing polymer chain enabled modifications of the size of self-assembled spherical micelles obtained after self-assembly without shape modifications.

B.2. Influence of chain length of nucleobase-containing block. In the study described by Hua *et al.*,[30] an increase in the nucleobase-containing block l6ngth was key to obtain various morphologies. In their work, Hua *et al.* studied block copolymers consisting of a hydrophilic poly(4-acryloyl morpholine) (PNAM) block and a hydrophobic poly(thymine propyl acrylamide) (PTAm) block, as presented in Fig. 15.

These block copolymers self-assembled in DMF/water mixture into spherical micelles with thymine-containing cores and hydrophilic PNAM shell. The authors stated that for short PTAm blocks (17 T to 34 T motifs), small micelles (N_{agg} ~ 13) were formed due to a low density of non-covalent interactions. Longer PTAm blocks (114 T to 301 T units) led to changes from spheres (114 T) to cylinders (160 T) and to smaller spheres (301 T). According to the authors, long chain thymine block enabled more non-covalent interactions inside the hydrophobic blocks that forced the structural packing in smaller micellar objects (Fig. 15).

B.3. Influence of the flexibility/rigidity of nucleobase-containing block. Another way to modify hydrophobic/hydrophilic balance and hence the ability of nucleobase-containing copolymers to self-assemble in different morphologies is to use more flexible or more rigid polymer backbones. Wang *et al.*[33] reported the synthesis of different diblock copolymers with PNIPAM as the hydrophilic block. The hydrophobic block was either made of poly(styrene-adenine/thymine/guanine) ($P_sA/P_sT/P_sG$) as rigid block backbones (due to the presence of aromatic regions which create stacking effects), and hydrophobic poly(methacrylate-cytosine) (P_mC) as flexible block backbones (as a consequence of alkyl chains) (Fig. 16A).[33] All block copolymers (*i.e.* P_sA-*b*-PNIPAM, P_sT-*b*-PNIPAM, P_mC-*b*-PNIPAM, P_sG-*b*-PNIPAM) presented the same molar mass, around 9 kDa, while the DP of PNIPAM was ~30 and the DP of

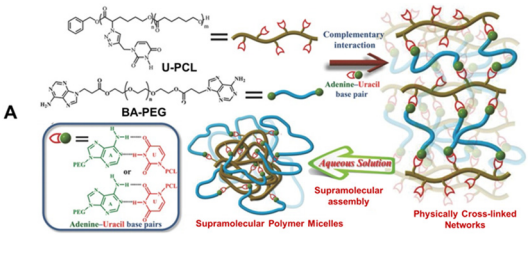

Fig. 14 (A) Formation of micelles *via* the self-assembly of Uracyl-poly (caprolactone) (U-PCL) and biadenine-poly(ethylene glycol) (BA-PEG); (B) The size diameters of U-PCL/BA-PEG micelles depending on the weight ratios of the mixture. Adapted with permission from ref. 42 Copyright (2016) Wiley.[42]

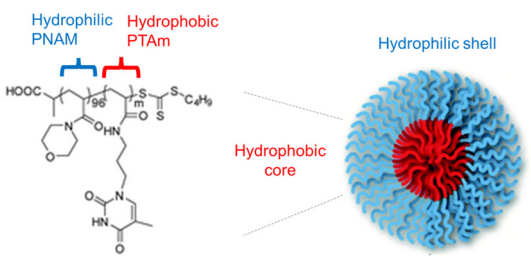

Fig. 15 Representation of Poly(4-acryloylmorpholine-*b*-poly(3-(thymine-9-yl)propyl acrylamide) diblock copolymer micelles. Adapted from ref. 30 with permission from the Royal Society of Chemistry Copyright 2015.[30]

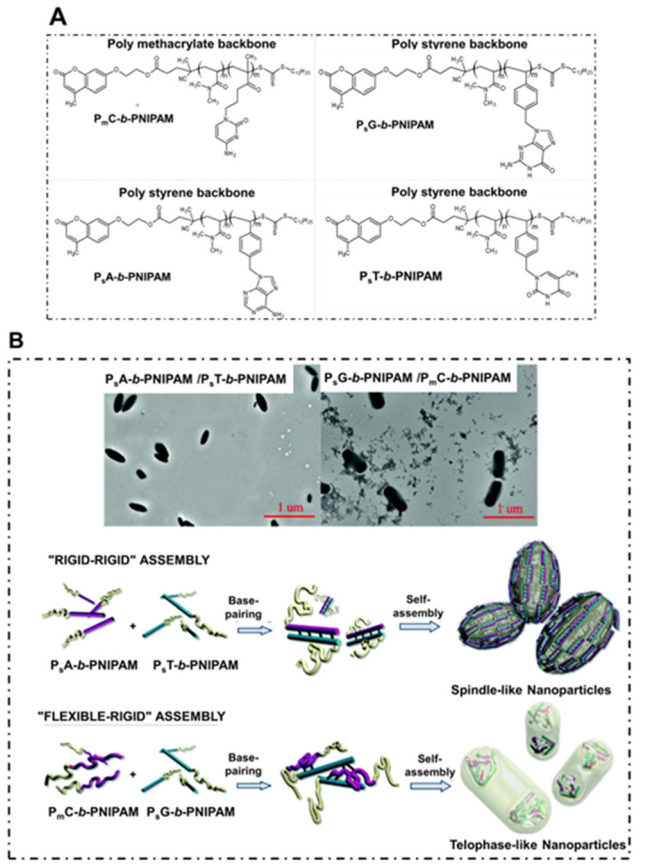

Fig. 16 (A) Structures of polymers containing nucleobases; (B) Morphologies obtained *via* the H-bond co-assembly of polymers containing nucleobases. Adapted from ref. 33 with permission from the Royal Society of Chemistry Copyright 2019.[33]

nucleobase-containing block was ~20. The co-assembly in DMSO/water of the rigid-rigid P_sA-*b*-PNIPAM and P_sT-*b*-PNIPAM (in 1 : 1 molar ratio) mixture resulted in spindle-like aggregates. In contrast, the co-assembly of the flexible P_mC-*b*-PNIPAM with the rigid P_sG-*b*-PNIPAM led to a telophase-like structures (Fig. 16B).

According to the authors, these morphological differences were direct consequences of the steric confinement induced by the structure of the nucleobase-containing block. In the co-assembly formed by mixing P_sA-*b*-PNIPAM and P_sT-*b*-PNIPAM diblock copolymers, the hydrophobicity of poly(styrene) enabled the polymer chains to stack with each other, while the hydrophilic PNIPAM chains were displayed on both sides to reduce steric hindrance. According to the authors, these steric confinement effects explained the spindle-like morphology. The use of flexible P_mC, in copolymerization with PNIPAM, resulted in flexible P_mC-*b*-PNIPAM block copolymers (Fig. 16B). During H-bond recognition with complementary rigid P_sG-*b*-PNIPAM block, this flexibility allowed the polymer chains to aggregate which explained the dark points observed by TEM of the telophase structures. Overall, the rigidity of nucleobase-containing block is a crucial parameter that guide the H-bond based self-assembly to adopt a hindered morphology. Oppositely, a flexible nucleobase-containing block favors a facile co-assembly and thus access to a different morphology.

Otherwise, the non-covalent interactions established during the co-assembly of complementary nucleobase-containing copolymers are correlated to the flexibility of the polymer backbones. For example, Huang *et al.*[40] reported the formation of spherical micelles with a dot-type morphology (diameter lower than 200 nm) when mixing poly(carbazole-thymine) (PC-T) with adenine monofunctionalized poly(ethylene glycol) (PEG-A) in THF/water (Fig. 17A and B). The micelles had a hydrophobic core composed of PC-T covered by a PEG shell. In order to investigate the influence of hydrophobic PC-T and hydrophilic PEG in the formation of supramolecular complex, DSC experiments were performed. As the authors stated, the association of complementary H-bonds between T and A led to a decrease in the T_g from 145 °C (for pure PC-T) to 119 °C (for the supramolecular complex), while the T_g of PEG-A disappeared. The decrease in T_g was caused by changes in the system packing towards an increased flexibility induced by PEG-A chains. This work illustrated, as stated by the authors, that the hydrophilic behavior of co-assembled nucleobase-containing polymers can be improved by using flexible chain water-soluble polymers containing nucleobases.

B.4. Influence of the nucleobase position. The position of the H-bond-promoting nucleobase at the extremity of the hydrophobic block or at the extremity of the hydrophilic block in the nucleobase-containing di-block copolymer structure significantly influenced the pairing ability with a complementary nucleobase, as shown by Wang *et al.*[36] In their work, the authors reported thymine-containing poly(*n*-butyl methacrylate) polymers T-PMBA, as well as poly(oligo(ethylene glycol) methacrylate)-*b*-poly (*n*-butyl methacrylate) (POEGMA-*b*-PMBA) block copolymers end-conjugated with adenine. In the case of adenine-containing copolymers, the adenine was attached either at the end of the hydrophilic block (P1, noted as A-POEGMA-*b*-PMBA, Fig. 18A) or at the end of the hydrophobic block (P2, noted as A-PMBA-*b*-POEGMA, Fig. 18A).

To obtain the co-assemblies, adenine-containing copolymers were dissolved in DMSO, the solution being slowly dropped to phosphate buffer solution (PBS). Then, a solution of thymine-containing polymer (prepared in PBS) was added to the adenine-containing solution. In order to investigate the role of the adenine position in the copolymer and the ability of H-bond co-assembly with thymine-containing polymer, the authors performed NMR experiments (in DMSO-d6/PBS solvent mixture), where the solution of thymine-containing polymer T-PMBA (40 mM) was mixed with solutions of adenine-containing polymer (P1, Fig. 18, B-1

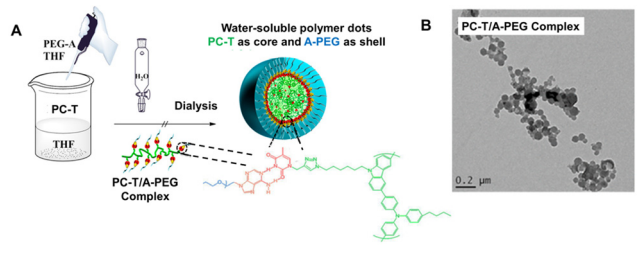

Fig. 17 (A) Pol(yethylene glycol)-Adenine (PEG-A) and poly(carbazoles-thymine) (PC-T) Micelles; (B) Morphology of PC-T/A-PEG complex micelles. Adapted with permission from ref. 40 Copyright (2017) American Chemical Society.[40]

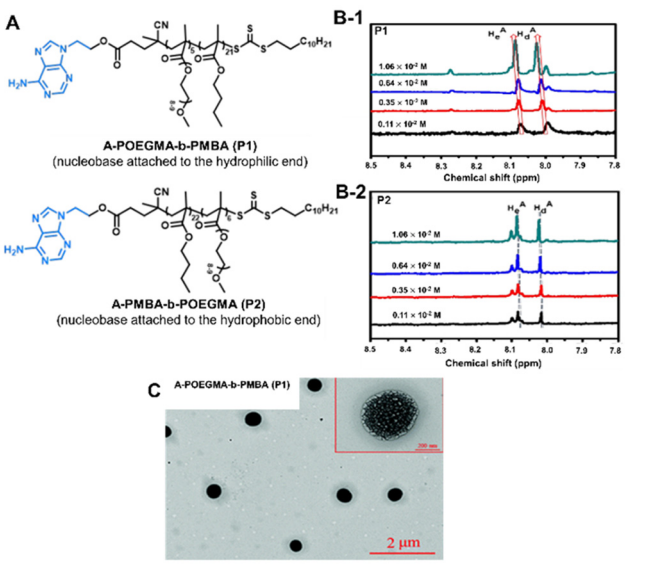

Fig. 18 (A) Representation of Adenine-poly(oligo(ethylene glycol) methacrylate)-poly(*n*-butyl methacrylate) (A-POEGMA–PMBA) systems; (B) NMR experiments (in DMSO-d6/PBS solvent mixture), where the solution of thymine-containing polymer T-PMBA (40 mM) was mixed with solutions of adenine-containing polymer (P1, Fig. B-1. and P2, in B-2.) in different concentrations (1.1 mM, 3.5 mM, 6.4 mM and 10.6 mM). (C) Morphology of the co-assemblies of P1 with T-PMBA. Adapted from ref. 36 with permission from the Royal Society of Chemistry Copyright 2018.[36]

and P2, in Fig. 18, B-2) in different concentrations (1.1 mM, 3.5 mM, 6.4 mM and 10.6 mM). These NMR experiments showed, as stated by the authors, a shift of the protons of adenine in P1 upon interaction with the thymine polymer (Fig. 18, B-1), whereas in P2 this interaction was not detected (Fig. 18, B-2). As stated by the authors, the molecular recognition between complementary nucleobases was influenced by their availability to be involved in H-bonding, which depended on the nucleobase position on the polymer backbone. In P2 the adenine at the hydrophobic end of the block copolymer located in the core of the micelles was inaccessible to thymine which cannot diffuse inside the micelle to bind adenine. In contrast, in P1 the adenine was on the hydrophilic block which form the shell of the micelle and thus is easily accessible for complementary recognition with thymine (Fig. 18C). However, these results were surprising, since a single adenine–thymine interaction is rather weak in DMSO/water medium. Nevertheless, the main conclusion according to Wang *et al.*[36] was that adenine–thymine binding was possible because the complementary nucleobases were accessible on the exterior of the micelles.[36]

B.5. Influence of the pH. The pH is another parameter which can influence the formation of different morphologies of self-assembled nucleobase-containing polymers. Nucleobases are sensitive to pH changes, especially to low pH. Indeed, in acidic conditions, the nitrogen atoms of the nucleobases which are involved in the H-bond recognition are protonated. As a consequence, the H-bond ability of the nucleobases is affected and the co-assembling properties (and morphologies) are modified.

In 2016, Zhao *et al.*[44] developed amphiphilic conjugates able to co-assemble forming small-size (below 100 nm) nanoparticles (NPs), by mixing poly(ε-caprolactone)-*graft*-poly(2-hydroxyethyl-acrylate-adenine) (abbreviated as A-PCL) with poly(ethylene glycol)-*block*-poly(allyl glycidyl ether-β-mercaptoethanol-thymine) (abbreviated as T-PEG), in DMSO/water. A-PCL and T-PEG functionalized polymers co-assembled *via* molecular recognition between complementary nucleobases (A and T) (Fig. 19A). As stated by the authors, in neutral conditions (pH 7.4), the resulting NPs with a diameter of 45 nm were stable due to strong H-bonds linking the A and T moieties. Upon decrease of the pH to 6, the NPs diameter decreased to 25 nm due to the protonation of the nucleobases that partially disrupted the A-T H-bonds, provoking the shedding of the T-PEG corona (Fig. 19B).

Interestingly, the variation of H-bond strength between nucleobases as a result of pH modification, was shown to have a high impact on the use of nucleobase-containing polymers co-assemblies in the field of drug delivery. Cheng *et al.* showed that the H-bonds stability of co-assembled nucleobase polymers used for doxorubicin (DOX, a drug used in anticancer therapy) release is influenced by the pH. They prepared micelles *via* the co-assembly of uracil-containing poly(caprolactone) (U-PCL) and telechelic poly(ethylene glycol) functionalized with two adenine groups (BA-PEG) (Fig. 20).[42] This system was tested for DOX release at acidic (pH 5) and neutral pH (pH 7.4). The micelles showed a faster release of DOX at pH 5 than at pH 7.4. According to the authors, these results were explained by the disassembly of the supramolecular U-A interactions in the micelles upon acidification. However, no information was given concerning the evolution of shape or dimension of the prepared micelles when pH was changed.

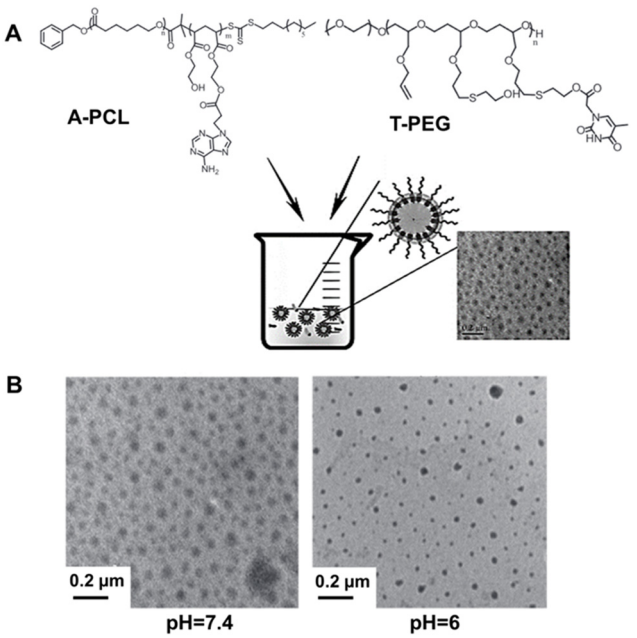

Fig. 19 (A) Poly(adenine)-poly(caprolactone) (A-PCL) and poly (thymine)– poly(ethylene glycol) (T-PEG) micelles; (B) TEM images of A-PCL/T-PEG micelles at different pH. Note: a carbon in the structure of the repeating unit of A-PCL and the parenthesis of the repeating units of T-PEG are missing in the figure published. Reprinted with permission from ref. 44 Copyright (2016) Wiley.[44]

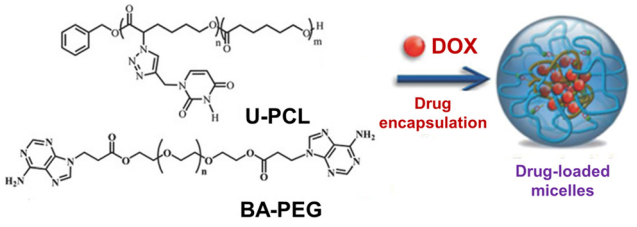

Fig. 20 Uracil-poly(caprolactone) (U-PCL) and biadenine-poly(ethylene glycol) (BA-PEG) micelles entrapping DOX. Adapted with permission from ref. 42 Copyright (2016) Wiley.[42]

C. Self-assembled nucleobase-containing polymers prepared in water

C.1. Influence of the temperature. Gebeyehu *et al.*[43] reported that self-assembled biuracil-poly(propylene glycol)-based micelles can change in size when the temperature is modulated. The nucleobase-containing polymer involved in the self-assembly was designed as follows: a bifunctional telechelic poly(propylene glycol) was end-capped with two uracil units (BU-PPG). BU-PPG polymers were able to self-assemble in water *via* H-bonds formed between uracil units into micelles with size between 148–370 nm and endowed with thermosensitive morphologies.

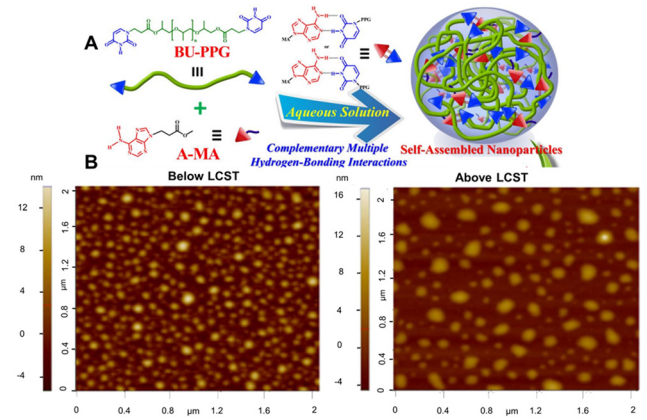

Fig. 21 (A) Development of micelles composed *via* co-assembly of biuracil-poly(propylene glycol) (BU-PPG) and adenine-methyl acrylate (A-MA); (B) AFM images of micelles below and above LCST. Adapted with permission from ref. 46 Copyright (2016) Elsevier.[46]

In the systems described by Gebeyehu *et al.*[43] the self-assembly took place as a result of H-bonds between the same nucleobase (uracil). Cheng *et al.*[46] investigated if the presence of a complementary nucleobase (*i.e.* adenine) influences the strength of H-bonds and in consequence the behavior of co-assembled systems at various temperature, as well as the morphology. In this regard, they used adenine-methyl acrylate (A-MA) that co-assembled through complementary H-bonds with uracil fragments from BU-PPG (bi-uracil end-capped poly (propylene glycol)). As previously presented by the work of Gebeyehu *et al.*,[43] BU-PPG is a thermo-responsive polymer. Below the LCST (25 °C) the association of BU-PPG with A-MA (1 : 2 molar ratio) led to spherical micelles with diameters around 85 nm. For temperatures above LCST (45 °C), larger aggregates of about 240 nm were formed (Fig. 21). As stated by the authors, the complementary H-bonds between A and U promoted the formation of low-dimensional particles (for temperatures below LCST). For temperatures above the LCST, the increase of the particle size was explained by the presence of hydrophobic effects induced by PPG chains that destroy the H-bonds and led to large aggregates.

IV. Conclusions

This review aimed to emphasize the importance of different parameters such as polymer structure, pH, solvents and temperature in the formation of various morphologies of self-assembled nucleobase-containing copolymers.

First, this review summed up the main examples of nucleobase-derived monomers and the corresponding polymers resulting from these monomers. Few examples of monomers- and polymers-containing nucleobases were reported so far. The low number of synthetic macromolecules containing nucleobases reported until now might be a consequence of significant issues related to the synthesis of the starting monomers, especially during the purification steps.

However, nucleobase-containing copolymers have attracted a high interest in the field of bioinspired supramolecular self-assembly, since the nucleobases are functional moieties found in the genetic material. The reported self-assemblies made from nucleobase-containing copolymers are formed *via* hydrophobic interactions, and *via* H-bonds established between complementary nucleobases. These interactions (and particularly the H-bonds) are sensitive to changes related to the polymer structure, pH, solvents or temperature.

These observations have already been stated by different research groups. However, not many papers illustrated how the morphology can be tailored by the above-mentioned parameters. For this reason, the second part of this review dealt with this aspect. Even if the papers presented in this review revealed interesting results in terms of morphology changes under a variety of conditions, the prediction of the obtained morphologies obtained under the influence of different parameters remains a difficult task. This subject is still under investigation and it is highly challenging because it aims to define the "rules" that direct the self-assemblies of nucleobase-containing copolymers into specific morphologies.

A preliminary step to get closer to this aim was to analyze how these parameters affected the self-assembled polymers and the obtained morphologies.

First, it was observed that the structural features (length of nucleobase-containing blocks, the number of nucleobase units, the position of nucleobases on the hydrophilic or hydrophobic block, or the flexibility of blocks) of nucleobase-containing polymers involved in the self-assembly can be largely modulated to achieve different morphologies. The most common morphology formed by self-assembly of nucleobase-containing polymer was, without surprise, spherical micelle. However, important changes were observed concerning the size of the spherical micelles when the number of nucleobase units was varied, and were explained due to supplementary effects of hydrophobic interactions between nucleobases. In terms of shape, interesting elongated morphologies were developed when using flexible (alkyl chain containing-) or rigid (aromatic segments containing-) polymer architectures.

Secondly, pH variations induced important modifications to the nucleobase-containing copolymer self-assemblies. Most of the observed modifications concerned the size of the obtained spherical micelles that diminished when the pH decreased. However, the shape of the objects was not changed under pH variations. A possible explanation was that the presence of charges is *a priori* unfavorable to develop self-assembled architectures and in consequence the transition of the morphology.

The H-bonds are sensitive to temperature changes. Especially, the H-bonds between water molecules are completely disrupted at 100 °C. However, the reported self-assembled nucleobase-containing polymers did not show significant sensitivity to temperature. In addition, no morphological changes were reported as a result of temperature variations. Actually, the reported variations in size were mainly a result of LCST behavior of self-assembly induced by the presence of a tempera-

ture-sensitive polymer, without a clear impact of H-bonds between complementary nucleobases.

Lastly, the morphology (in terms of shapes and size) was highly adjusted by exploring different solvents. A possible explanation according to the reviewed papers was that the solvent could interfere with the hydrophilic or hydrophobic blocks and enable the blocks to self-assemble *via* the H-bonds in different shaped objects.

The overall conclusion stated by this review is that the morphology is highly dependent on the architecture of the nucleobase-containing copolymers which can perform self-assemblies with different shapes and sizes. Chemists are able to play with different parameters in order to tailor a variety of self-assembling morphologies, which could be further explored to obtain anisotropic shapes that started to receive a special interest in the field of drug delivery. The interest of an anisotropic shape of the self-assembly advocate for continuing the work to tune the architecture of the nucleobase-containing copolymers. In this context, the work of O'Reilly's group who developed an elegant architecture of nucleobase-containing copolymers, which is forming elongated morphologies, opens new perspectives.[47]

Author contributions

Conceptualization, L. Arsenie, S. Catrouillet and V. Ladmiral; writing—original draft preparation, L. Arsenie; writing—review and editing, L. Arsenie, P. Lacroix-Desmazes, V. Ladmiral, S. Catrouillet. All authors have read and agreed to the published version of the manuscript.

Abbreviations

PNIPAM	Poly(*N*-isopropylacrylamide)
PMA	Poly(methyl acrylate)
PS	Poly(styrene)
PEG	Poly(ethylene glycol)
PPMA	Poly(propargyl methacrylate)
PCL	Poly(caprolactone)
PC	Poly(carbazole)
PC-T	Poly(carbazole-thymine)
PPG	Poly(propylene glycol)
BU-PPG	Telechelic uracyl-functionalized poly(propylene glycol)
BA-PEG	Adenine difunctionalized poly(ethylene glycol)
A-PEG	Adenine monofunctionalized poly(ethylene glycol)
T-PEG	Ahymine functionalized poly(ethylene glycol)
POEGMA	Aoly(oligoethylene glycol methacrylate)
PMBA	Aoly(*n*-butyl methacrylate)
POEGMA-*b*-PMBA	Aoly(oligoethylene glycol methacrylate-*b*-*n*-butyl methacrylate)
A-PCL	poly(2-hydroxyethyl acrylate)-adenine-bpoly(caprolactone)
U-PCL	Uracil functionalized poly(caprolactone)
PA	Poly(vinyl benzyl-adenine)
PNAM	Poly(4-acryloylmorpholine)
PMMA-*b*-PTMA	Poly(methyl methacrylate)-*b*-poly(thymine methacrylate)
PMMA-*b*-PAMA	Poly(methyl methacrylate)-*b*-poly(adenine methacrylate)
PT	poly(vinyl benzyl-thymine)
PNAM-*b*-PTAm	Poly(4-acryloylmorpholine)-b-poly(3-(thymine-9-yl)propyl acrylamide)
PNAM-*b*-PAAm	Poly(4-acryloylmorpholine)-b-poly(3-(thymine-1-yl)propyl acrylamide)
T	Thymine
A	Adenine
U	Uracyl
G	Guanine
C	Cytosine
BU	Bi-uracyl
AM-T	Acrylamide-thymine
AM-A	Acrylamide-adenine
NIPAM	*N*-Isopropylacrylamide
NAM	*N*-Acryloylmorpholine
BA	Bi-adenine
UPy	2-Ureido-4-pyrimidinone
H-bonds	Hydrogen bonds
DNA	Deoxyribonucleic acid
CMC	Critical micellar concentration
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
DOX	Doxorubicin
PBS	Phosphate buffer solution
NPs	Nanoparticles
CuAAC	Copper(I)-catalyzed alkyne–azide cycloaddition
RAFT	Reversible addition fragmentation chain transfer polymerization
CTA	Chain transfer agent
LCST	Lower critical solution temperature
SN	Nucleophilic substitution
T_g	Glass transition temperature
NMR	Nuclear magnetic resonance
DLS	Dynamic light scattering
SLS	Static light scattering
TEM	Transmission electron microscopy

Conflicts of interest

The authors declare no conflict of interest.

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