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Synthetic Polymeric Variant of *S*-Adenosyl Methionine Synthetase

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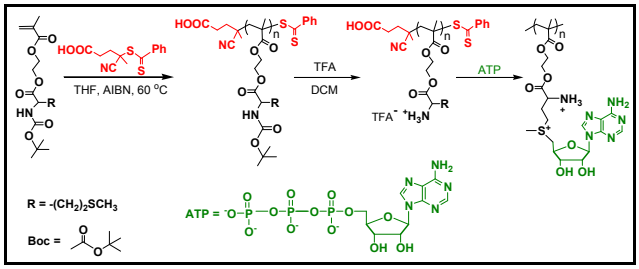
S-Adenosyl methionine (SAM) is a conjugate of methionine and the adenosine moiety of adenosine 5′-triphosphate (ATP), generally formed in a reaction catalysed by methionine adenosyltransferase enzyme (also known as SAM synthetase). SAM serves mainly as a methyl donor in various biological processes in the presence of methyltransferase enzyme. To obtain the SAM moiety in the synthetic polymer, methionine containing polymers are synthesized using the *tert*-butyloxycarbonyl (Boc)-L-methionine methacryloyloxyethyl ester (METMA) monomer *via* reversible addition-fragmentation chain transfer (RAFT) polymerization. These polymers were reacted with ATP to install SAM moiety in the polymer side-chains in the absence of SAM synthetase, therefore polymers mimic the activity of SAM synthetase. The ability to donate methyl group by the SAM containing moiety in the polymer is confirmed in the absence of methyltransferase enzyme, thus, confirms the enzyme-like activity of methionine based polymers.

Introduction

Recently there has been great interest in the design and synthesis of enzyme-like polymers.[1,2] The field of artificial enzymes has been greatly concerned with mimicking hydrolytic enzymes namely; chimotripsin, lipase, phosphatase, etc., where synthetic polymers are used as backbones of enzyme models.[3] For obtaining polymeric catalysts as enzyme mimics, catalytically active side chain moieties containing the desired arrangement of functional groups are introduced within the polymer chain. For example, Han et al. have proposed the mechanism for the catalytic activity of the ribose containing polymers for the cleavage of DNA.[4] They also reported polymers containing ribose rings as enzyme mimics, which catalyzed the hydrolysis of phosphodiester and phosphomonoester substrates.[5]

Biological processes make use of ATP as energy currency and SAM as a cofactor which primarily serves as a methyl donor. Although ATP directed enzyme responsive polymeric architectures have been developed,[6,7] synthesis of methionine based polymer triggered enzyme catalytic centre have not been yet reported. It has previously been shown that at acidic pH the alkylation of methionine proceeds readily, whereas other nucleophiles in proteins become protonated and their alkylation is suppressed.[8,9] Alkylation creates positively charged sulfonium,[10] which has reasonable stability.[11] Realizing that the alkylation of methionine residues has potential to be much broader in scope, we sought to develop the synthesis of well-defined methionine containing polymeric architectures, which mimics enzymes when serving as catalysts for specific nucleophilic reactions.

Naturally occurring amino acid containing functional monomers and polymers have been comprehensively investigated in recent years for the preparation of synthetic non-biological macromolecules with biomimetic structures and properties for various biomedical applications.[12,13] Methionine, one of the two sulphur-containing proteinogenic amino acids, has been studied very little in the area of polymer chemistry although methionine plays major roles in biosynthesis of proteins, DNA methylation activity, etc.[14] Poly-L-methionine was prepared by ring-opening polymerization (ROP) of L-methionine *N*-carboxyanhydride (Met NCA).[15] The influence of counterions on the polyelectrolyte behaviour and the conformation of poly-L-methionine *S*-methylsulfonium salts in aqueous medium were investigated.[16,17]



Scheme 1 RAFT Polymerization of METMA, reaction of side-chain methionine moiety with ATP in the Boc deprotected homopolymer, protected and deprotected block copolymers in aqueous medium at room temperature.

The main reason for the limited research with methionine moiety may be due to the difficulty to synthesize pure Met NCA for ROP. Recently, Kramer and Deming described the application of flash column chromatography on silica gel as a

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rapid and general method to obtain several pure α-amino acid-*N*-carboxyanhydride (NCA) monomers including methionine to form high molecular weight polypeptides.[18] Later, they extended their study to alkylate the methionine residues in polypeptides *via* "click" type reactions.[19] Although in these few reports methionine based polymers were achieved by ROP of Met NCA, much attention has been recently devoted to the controlled/living radical polymerization (CRP) of amino acid based vinyl monomers,[20] due to its high tolerance for various functional groups, precise control over polymer chain ends, controllable molecular weights and narrow dispersity (*Đ*).[21] Therefore, our work is specifically based on design, synthesis and evolution of side-chain methionine based polymers.

With these features in mind we prepared *tert*-butyloxycarbonyl (Boc)-methionine methacryloyloxyethyl ester (METMA) and polymerized by RAFT polymerization to prepare homopolymer (PMETMA) and block copolymer with poly(ethylene glycol) methyl ether methacrylate (PEGMA). Upon addition of ATP to the Boc deprotected homopolymer and Boc protected or deprotected block copolymer solutions in aqueous medium, the methionine pendants in the side chains react with ATP to produce adenosyl conjugated sulfonium moiety of methionine. Finally, methyl group donation capability by the SAM containing moiety in the polymer is demonstrated. Methionine and SAM containing polymers are expected to be biocompatible as reported by our group for various side-chain amino acid based polymers.[20]

To prepare side-chain methionine containing methacrylate monomer, firstly Boc-L-methionine (Boc-L-Met-OH) was reacted with 2-hydroxyethyl methacrylate (HEMA) in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) *via* esterification reaction.[22] The structure of METMA was characterized by ^{1}H NMR spectroscopy (Fig. S1) and electrospray ionization mass spectrometry (ESI-MS) (Fig. S2). Then, METMA was polymerized *via* RAFT technique to obtain polymers with controlled molecular weight, narrow *Đ* and defined chain ends. In a previous publication,[23] we demonstrated effectiveness of 4-cyanopentanoic acid dithiobenzoate (CTP) for the controlled RAFT polymerization of methacrylate derivatives containing L/D-tryptophan in tetrahydrofuran (THF) in the presence of 2,2′-azobisisobutyronitrile (AIBN). Therefore, polymerization reactions of METMA were carried out in THF at 60 ^{o}C using AIBN as radical initiator and CTP as chain transfer agent (CTA) (Scheme 1) at different [METMA]/[CTP] ratios between 15 to 50, keeping CTP to AIBN ratio at a constant value of [CTP]/[AIBN] = 1:0.2. Fig. 1A shows the gel permeation chromatography (GPC) chromatograms of purified polymers, where unimodal refractive index (RI) traces shifted toward lower elution volume with increasing [METMA]/[CTP] ratios with no evidence of high molecular weight species from bimolecular termination and low molecular weight shoulders. Number average molecular weights ($M_{n,GPC}$) and *Đ* values were determined from GPC analysis (see Instrumentation section in the supporting information) and results are shown in Table S1, which clearly shows increase in the $M_{n,GPC}$ with the [METMA]/[CTP] ratio, and the *Đ* remains narrow (1.13–1.29).

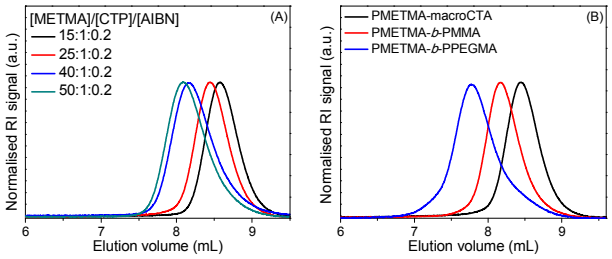

Fig. 1 GPC RI traces of (A) PMETMA synthesized at different [METMA]/[CTP] ratios and (B) PMETMA-macroCTA and corresponding block copolymers with MMA (Expt. 5 in Table S1) and PEGMA (Expt. 8 in Table S1).

We also calculated theoretical number average molecular weight ($M_{n,theo}$) from the gravimetric conversion data using the following equation: $M_{n,theo}$ = (([METMA]/[CTP] × molecular weight (MW) of METMA × conversion) + (MW of CTP)). Table S1 shows excellent matching between $M_{n,GPC}$ and $M_{n,theo}$ values, indicating feasibility to control the molecular weight based on the [METMA]/[CTP] ratio for the RAFT polymerization of METMA under the described synthetic protocol.

The resulting homopolymer, PMETMA, was soluble in most of the tested solvents, except in water, hexanes, pet ether and diethyl ether (Table S2). PMETMA was characterized by ^{1}H NMR spectroscopy in $CDCl_3$ (Fig. S3A), where typical resonance signals for the different protons in the repeating unit of the polymer are observed. Incorporation of CTP at the chain ends of PMETMA is also noticed by the characteristic resonance signals in the aromatic region, where terminal phenyl moiety appeared at 7.3-7.9 ppm. Comparison of the integration areas from the terminal phenyl group at 7.3-7.4 ppm (2H) and repeating unit protons at 4.1-4.5 ppm (5H) allowed determination of the number-average molecular weight ($M_{n,NMR}$) from the NMR study. The $M_{n,NMR}$ values are presented in Table S1, which again match nicely with the corresponding $M_{n,GPC}$ and $M_{n,theo}$ values.

Next, possibility of block copolymer synthesis (Scheme S1) is examined by polymerizing methyl methacrylate (MMA) and PEGMA using PMETMA-macroCTA at different feed ratios of [MMA or PEGMA]/[PMETMA-macroCTA] in THF at 60 ^{o}C, keeping PMETMA-macroCTA to AIBN ratio at a constant value of 1:0.2 (Table S1). Fig. 1B shows unimodal RI traces of block copolymers (PMETMA-*b*-PMMA and PMETMA-*b*-PPEGMA) moved towards the higher molecular weight region with respect to the RI trace of PMETMA-macroCTA. Here too, we did not observe high molecular weight species from bimolecular termination reactions and *Đ* remains narrow (1.13-1.33). The $M_{n,GPC}$ values of the block copolymers are in reasonable agreement with the $M_{n,theo}$ values determined from conversion data (Table S1). The NMR spectra of the block copolymers confirmed the presence of the signals associated with each block (Fig. S4 for PMETMA-*b*-PMMA and Fig. S5A for PMETMA-*b*-PPEGMA). From the integration ratio of aromatic protons at 7.3-7.9 ppm from the chain end phenyl group to ester methyl protons at 3.59 ppm in PMMA segment and side-chain $-OCH_3$ protons in PPEGMA block at 3.39 ppm, the

numbers of MMA and PEGMA units in the corresponding block copolymers were calculated, respectively. Then, $M_{n,NMR}$ values were determined by using the following formula: molecular weight (MW) of PMETMA macro-CTA + degree of polymerization of MMA (or PEGMA) × MW of MMA (or PEGMA). Results are shown in Table S1, where the $M_{n,NMR}$ values match well with the $M_{n,GPC}$ values for PMETMA-*b*-PMMA and PMETMA-*b*-PPEGMA block copolymers. Therefore, the PMETMA macro-CTA can be successfully employed for the synthesis of the methionine-based block copolymers with a relatively narrow *Đ*, controlled molecular weights, and precise chain ends. Note that the PMETMA-*b*-PMMA (Expt. 5 in Table S1) and PMETMA-*b*-PPEGMA (Expt. 6 in Table S1) block copolymers were not soluble in water due to the double hydrophobic blocks in PMETMA-*b*-PMMA and higher hydrophobicity of PMETMA block than the PPEGMA segment in the PMETMA-*b*-PPEGMA, respectively. However, the $PMETMA_{14}$-*b*-$PPEGMA_{42}$ (Expt. 7 in Table S1) and $PMETMA_{14}$-*b*-$PPEGMA_{51}$ (Expt. 8 in Table S1) were nicely soluble in aqueous medium, although they self-assembled to micellar structure (*vide infra*).

Deprotection of side-chain Boc groups in the homopolymer and block copolymers was accomplished under acidic condition using trifluoroacetic acid (TFA)/dichloromethane at room temperature. After Boc deprotection, homopolymer (DPMETMA) was soluble in aqueous medium (Table S2). Successful removal of Boc protecting groups was confirmed by the complete disappearance of the *tert*-butyl signal at 1.43 ppm in the ^{1}H NMR spectra of the DPMETMA (Fig. S3B) and block copolymer (DPMETMA-*b*-PPEGMA) (Fig. S5B) after TFA treatment yielding polymers with ammonium (-NH^+) groups in the side chains. In the FT-IR analysis, the absorption peak at 1518 cm^{-1} in PMETMA due to the N-H deformation (amide II band) disappeared in DPMETMA (Fig. S6). Additionally, a broad band at 1536 cm^{-1} appears in DPMETMA due to the transformation of Boc protected amino group into $–NH_3^+$ functionality.

Inspired by the efficient *in vivo* biosynthesis of SAM we envisioned a polymer triggered chemical synthesis of SAM analogue from the reaction of water soluble homopolymer DPMETMA, and $PMETMA_{14}$-*b*-$PPEGMA_{42/51}$ block copolymers with ATP. ATP and the polymers were mixed in buffer solution, kept at room temperature for 48 h, dialyzed and lyophilized (see Supporting Information). In case of ATP, the ^{1}H NMR signals for the protons present in the adenine moiety appeared at 8.57 and 8.39 ppm (Fig. 2). After reaction between PMETMA-*b*-PPEGMA block copolymer and ATP, we observed adenine moiety protons at 8.53 and 8.27ppm (inset in Fig. 2). Similar observations were noted for the deprotected homopolymer DPMETMA-ATP (Fig. S7) and DPMETMA-*b*-PPEGMA-ATP block copolymer (Fig. S8) complexes. Since in D_2O we did not find CTP resonance signals in the aromatic region at 7.3-7.9 ppm, we could not determine % SAM functionalization in the homo and block copolymers. Nevertheless, high intensity (particularly in the case of DPMETMA-ATP (Fig. S7) and DPMETMA-*b*-PPEGMA-ATP block copolymer (Fig. S8)) of the peaks at 8.53 and 8.27 ppm indicates high percentage of functionalization.

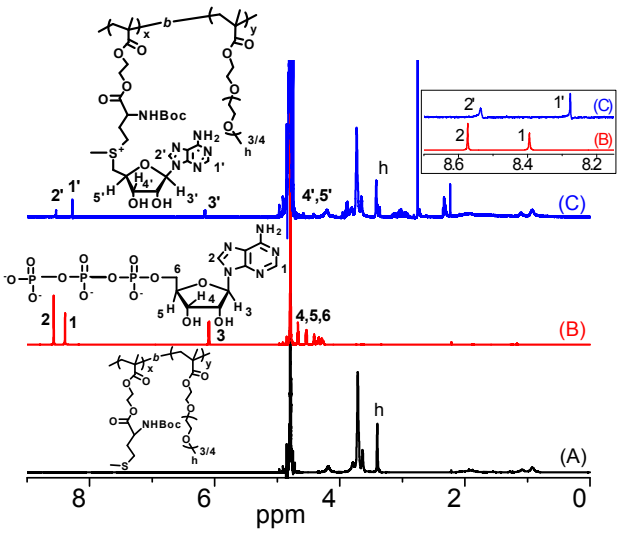

Fig. 2 ^{1}H NMR spectra of (A) $PMETMA_{14}$-b-$PPEGMA_{42}$, (B) ATP and (C) $PMETMA_{14}$-b-$PPEGMA_{42}$-ATP complex in D_2O.

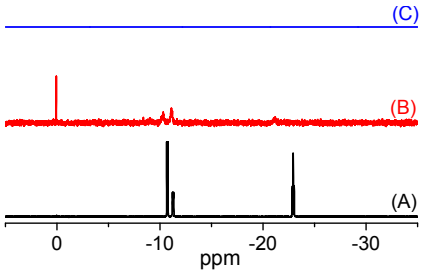

Fig. 3 ^{31}P NMR spectra in D_2O of ATP (A), and $PMETMA_{14}$-*b*-$PPEGMA_{42}$-ATP complex before (B) and after (C) dialysis.

To monitor the reaction pathway, ^{31}P NMR spectra were recorded for the $PMETMA_{14}$-*b*-$PPEGMA_{42}$-ATP complex before and after dialysis. In Fig. 3, ^{31}P NMR spectrum of ATP showed three peaks for three different kinds of phosphorous present in the triphosphate moiety. As shown in Fig. 3B, in case of the unpurified complex (taken after 6 h of reaction time, before dialysis), signals due to the triphosphate group of ATP is almost vanished and peaks due to the hydrolysed product (phosphoric acid) is started to appear, suggesting the phosphate group removal from ATP by the PMETMA-*b*-PPEGMA block copolymer. Interestingly, after dialysis of PMETMA-*b*-PEGMA-ATP complex, there was no peak due to phosphorous in the ^{31}P NMR spectrum (Fig. 3C). This result confirmed complete removal of triphosphate group and formation of SAM analogue polymer. Note that SAM is a conjugate of methionine and the adenosine moiety of ATP, generally formed in a reaction catalysed by methionine adenosyltransferase enzyme (also known as SAM synthetase).[24] Based on the experimental results described above, side-chain methionine based

polymers installed SAM moiety in the absence of SAM synthetase, thus confirms enzyme like activity of the polymer.[25] The reaction occurs through simple S_N2 cleavage, where the sulphur atom present in the side chain methionine moiety attacks the adjacent carbon of triphosphate group in ATP, resulting in the removal of triphosphate group from ATP moiety, as cleavage of the phosphate group in ATP by the polymer is confirmed by the ^{31}P NMR spectra.

The spectral features associated with the phosphate groups of ATP are generally observed within 800-1300 cm^{-1} region. A signature stretching at 1240 cm^{-1} is appeared due to the overlapping asymmetric stretching vibrations of the α-PO_2^- (closest to the ribose) and β-PO_2^-. The out of phase symmetrical stretching and the P–O stretches of the main chain are appeared namely at 1100 and 900 cm^{-1} that are all absent in case of DPMETMA-ATP (Fig. S9), $PMETMA_{14}$-*b*-$PPEGMA_{42}$-ATP (Fig. S10), $DPMETMA_{14}$-*b*-$PPEGMA_{42}$-ATP (Fig. S11) complexes as only the adenosine part have been transferred towards the polymeric backbone through the cleavage of the phosphate groups.

The ^1H NMR spectrum of $PMETMA_{14}$-*b*-$PPEGMA_{42}$ in $CDCl_3$ (Fig. S5A) shows peaks for all the protons from both the blocks but characteristic resonance signals from the PMETMA segment were completely lost when the NMR was recorded in D_2O (Fig. 2A). This could be due the formation of higher-order structure from the amphiphilic $PMETMA_{14}$-*b*-$PPEGMA_{42}$ block copolymer through arrangement of micelle-like structure with the PPEGMA units on the shells and PMETMA segments in the core. Therefore, the protons in the core of the micelle such as Boc group protons at 1.43 ppm did not appear in the NMR spectrum in D_2O. Hence, self-assembly of the $PMETMA_{14}$-*b*-$PPEGMA_{42}$, $DPMETMA_{14}$-*b*-$PPEGMA_{42}$ and $DPMETMA_{14}$-*b*-$PPEGMA_{42}$-ATP complex was studied by dynamic light scattering (DLS) in aqueous medium at 25 °C. The average hydrodynamic diameter (D_h) of $PMETMA_{14}$-*b*-$PPEGMA_{42}$ was obtained as 30 nm, while Boc- deprotected double hydrophilic block copolymers and its ATP complex show D_h values of 7 and 6 nm, respectively (Fig. S12). Additionally, D_h's for $PMETMA_{14}$-*b*-$PPEGMA_{51}$ and $PMETMA_{14}$-*b*-$PPEGMA_{51}$-ATP in aqueous medium were found to be 43 and 52 nm, respectively (Fig. S13A). $PMETMA_{14}$-*b*-$PPEGMA_{51}$ showed comparatively higher size than the $PMETMA_{14}$-*b*-$PPEGMA_{42}$, because of increasing hydrophilic PPEGMA segment. But $PMETMA_{14}$-*b*-$PPEGMA_{51}$ showed D_h = 9 nm in methanol (size corresponds to unimers), which was a good solvent for both the block (Fig. S13A). These results indicate that Boc-protected block copolymers undergo self-assembly in water at room temperature. More information on the size and structure of these self-assembled species was obtained from field emission scanning electron microscopy (FE-SEM) analysis, where the $PMETMA_{14}$-*b*-$PPEGMA_{51}$ and $PMETMA_{14}$-*b*-$PPEGMA_{51}$-ATP complex clearly revealed formation of spherical micelles in aqueous solution with size around 52 and 76 nm, respectively (Fig. S13B). SEM data agrees with the DLS observations considering the different measurement conditions. Note that, although PMETMA-*b*-PPEGMA formed micellar structure with PMETMA segments in the core, it reacted with ATP because methionine moiety on the surface of the core slowly cleaved ATP to install adenosine groups in the side chain of polymers. As a result intensity of protons from adenine moiety was much less in $PMETMA_{14}$-*b*-$PPEGMA_{42}$-ATP complex (Fig. 2C) compared to the DPMETMA-ATP (Fig. S7C) and DPMETMA-*b*-PPEGMA-ATP complexes (Fig. S8C), where polymer chains remained as unimers in aqueous solution while reaction with the ATP (both DPMETMA and PPEGMA blocks are nicely soluble in water).

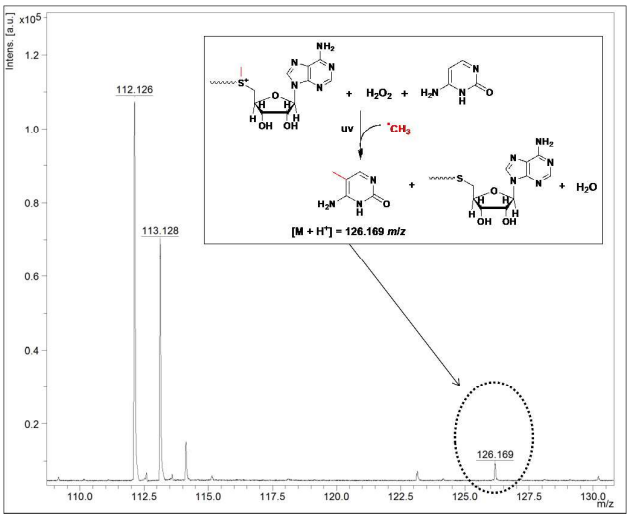

Fig. 4 MALDI-TOF spectrum of the reaction mixture after the methyl transfer reaction to cytosine in the presence of H_2O_2 and $DPMETMA_{14}$-*b*-$PPEGMA_{42}$-ATP complex.

To highlight the potential of our SAM modified polymers for the methyl group donation, we reacted cytosine in the presence of H_2O_2 and our SAM modified polymers. Cytosine is one of the nucleobases of DNA. Methylation of DNA at 5 position of cytosine is the most significant post synthetic modification that has the specific effect on gene expression of higher eukaryotes. The covalent addition of a methyl group to cytosine bases holds particular analytical advantages towards dealkylation property of the SAM analogue polymer. As it is previously reported that direct photolysis of H_2O_2 produces hydroxyl radicals,[26] the photochemical approach to generating free radicals in aqueous H_2O_2 solutions was selected instead of following the Fenton reaction[27,28] pathway in order to avoid artifacts that arise from the initial stages of mixing reagents that results in a local rising of concentrations. Therefore, the method presented here is based on radical induced cleavage of the thio-ether bond from the tertiary sulfonium cationic polymer, resulting formation of methyl radical and in situ methylation of cytosine *via* the methyl radical. After 3 h reaction, the matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) spectrum of the reaction mixture is shown in Fig. 4, where we observed a peak at *m/z* = 126.169 due to the 5-methyl cytosine. 5-Methyl cytosine is generated from radical induced methylation *via* transfer of the methyl group from the SAM analogue polymer ($DPMETMA_{14}$-*b*-$PPEGMA_{42}$-ATP complex) to the C-5 position of cytosine. At first, the $^{\bullet}OH$ radicals interact with the polymer to form $^{\bullet}CH_3$

radicals. As soon as the $^{\bullet}CH_3$ radicals are appeared within the reaction environment, cytosine residues in the vicinity undergo C-5 methylation. The 5-methyl cytosine peak was also observed in MALDI-TOF analysis of the reaction mixtures after the methyl transfer reaction to cytosine in the presence of H_2O_2 and $PMETMA_{14}$-*b*-$PPEGMA_{51}$-ATP (Fig. S14) or DPMETMA-ATP (Fig. S15) complexes. Control reaction was also carried out under similar conditions, where no polymer-ATP complex was used during the photo-reaction between cytosine and H_2O_2. Figure S16 indicate absence of the peak corresponding to the 5-methyl cytosine, thus demonstrate effectiveness of our SAM modified polymers for the methyl group donation in the absence of methyltransferase enzyme. The mechanism of methyl transfer reaction to cytosine in the presence of SAM modified polymer is shown in Fig. 4 inset.

In summary, we have successfully established the RAFT polymerization of a methacrylate having the L-methionine moiety to synthesize enzyme like polymers with pre-determined molecular weights, a narrow *Đ*, and defined chain end structures. The ability of side-chain methionine moiety to react with ATP was studied to install SAM component in the polymer. The major advantage of our SAM modified polymers is the possibility of methyl group donation in the absence of methyltransferase enzyme. This technique is effective, practical and most importantly does not require a biological enzyme. Further work will explore the extension of these side-chain methionine pendant systems for methyl group donations in biological systems, and pH/temperature induced recovery of the polymer catalyst.

Acknowledgements

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Synthetic Polymeric Variant of *S*-Adenosyl Methionine Synthetase

Lakshmi Priya Datta, Binoy Maiti and Priyadarsi De

Side-chain L-methionine containing polymers showed ability to donate methyl group in the absence of methyltransferase enzyme, which confirms their enzyme-like activity.