Synthesis and Characterization of Poly(*N*-(3-(hexylamino)-*N*-(3-(isopropylamino)-3-oxopropyl)acrylamide) Homopolymer

ARCHANA KUMARI, KHEYANATH MITRA,SAMBHAV VISHWAKARMA, SOUROV MONDAL, SHIKHA SINGH, RAJSHREE SINGH, JAYDEEP SINGH, BISWAJIT MAITI, SUSANTA KUMAR SEN GUPTA AND BISWAJIT RAY*

Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi- 221005, India

ABSTRACT

A new acrylamide monomer N-*(3-(hexylamino)*-N-*(3-(isopropylamino)-3-oxopropyl) acrylamide (HA-NIPAM-AM) and a new RAFT agent* O-*propionyl-2-(*N,N-*diphenylcarbamothioylthio) propanoate have successfully been synthesized and used for the synthesis of poly(HA-NIPAM-AM) homopolymers* via *RAFT polymerization. The formed homopolymers have been characterized by GPC, ^{1}H NMR, FTIR, contact angle measurement, TG-DTA, DSC, and PXRD. Number-averagemolar masses of the prepared polymers are in the range of 2,500 – 11,500 g/mol. Self-assembly of homopolymer has been studied* viacmc *determination in water using pyrene as fluorescence probe, HRTEM and DLS. Polymeris thermally stable up to 300 °C and has a glass transition temperature at 85.3 °C. XRD study reveals the presence of nanophases in the polymer matrix. DFT calculation has revealed a helical backbone structure with the pendant groups exposed to inwards and outwards, respectively.*

KEYWORDS: N-*(3-(hexylamino)-N-(3-isopropylamino)-3-oxopropyl) acrylamide, O-propionyl-2-(N,N-diphenylcarbamothioylthio) propanoate, RAFT polymerization, Characterization.*

1. INTRODUCTION

Amphiphilic polymers are made of hydrophilic and hydrophobic chains. In this regard, amphiphilic block copolymers are widely studied.These copolymers undergo self-assembly in complex structures.Such structures have been exploited in drug and gene delivery, catalytic study, sensing etc[1-18].

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Correspondence author e-mail: biswajitray2003@yahoo.co.in
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Amphiphilic homopolymers are also studied to some extent by Thayumanavan et al.[19-24], Wang et al.[25], Cha et al.[26], Hua et al.[27] etc. and utilized those polymers in protein sensing, binding, and extraction. Recently, it has been reported that poly(*N*-alkyl acrylamides), poly(*N*-alkyl acrylates), poly(*N*-alkyl methacrylates), poly(di-*N*-alkyl itaconates) etc. comb-shaped polymers undergoes nanosegregation between their hydrophobic alkyl side chains and main chain on one phase and hydrophilic intermediate chain part on the other phase.[28-30] Recently, a facile pathway for the synthesis of many specific functional monomers with ester, ether, amide and amine functionality has been reported using Aza-Michael addition reaction involving reaction between primary amine and alkene part of vinylic monomer followed by amidation with acryloyl chloride.[31,32,33,34,35] Using this route, two acrylamide monomers have been reported using *N*-isopropylacrylamide (NIPAM) as vinylic monomer and *N,N*-diethylethylenediamine,[31] and 2-(methylamino) ethanol [36] as two different amines, respectively. The homopolymers formed from both monomers have shown dual CO_2 and thermo-responsive properties. Using the same path and in order to explore the use of n-alkyl amine on the properties of formed polymer, we have designed here a new *N*-substituted acrylamide monomer, *N*-(3-(hexylamino)-*N*-(3-(isopropylamino)-3-oxopropyl) acrylamide (HA-NIPAM-AM), having two amide groups in its side chains with 3-(isopropylamino)-3-oxopropyl and 3-(hexyl) moieties connected to acrylamide N atom, and synthesized it *via* Aza-Michael addition reaction between *N*-isopropyl acrylamide and n-hexyl amine, followed by a nucleophilic substitution reaction with acryloyl chloride (**Scheme 1**).Purpose of the synthesis of such monomer is to study the effect of the incorporation of NIPAM moiety in N-hexyl acrylamide monomer on its polymerizability and properties of the formed polymer. Successful formation of monomer has been confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. We have also synthesized a new alkyne group containing reversible addition-fragmentation chain-transfer agent *O*-propionyl-2-(*N,N*-diphenylcarbamothioylthio) propanoate (PDPCP) *via* esterification of 2-bromopropionyl bromide with propargyl alcohol followed by reaction with diphenyl amine and carbon disulfide (**Scheme 2**). As some dithiocarbamates are useful for more active monomer (MAM)s, we have chosen to make this dithiocarbamate which may also be useful to conjugate the polymer to another small or macromolecule *via* Azide-Alkyne click chemistry. [37] Poly(HA-NIPAM-AM) has been synthesized *via* RAFT polymerization using PDPCP as RAFT agent. The formed homopolymers have been characterized by GPC, ^{1}H NMR, FTIR, contact angle measurement,TG-DTA, DSC, and PXRD. Self-assembly of homopolymer has been studied *via* determination of its *cmc* in water using pyrene as fluorescence probe, HRTEM and DLS. Spatial orientation of the two pendant groups of each repeating structural units in the formed polymer has also been explored by DFT calculation at B3LYP/6-31G** level using Gaussian 09 suits of program.[38]

EXPERIMENTAL

Materials and methods

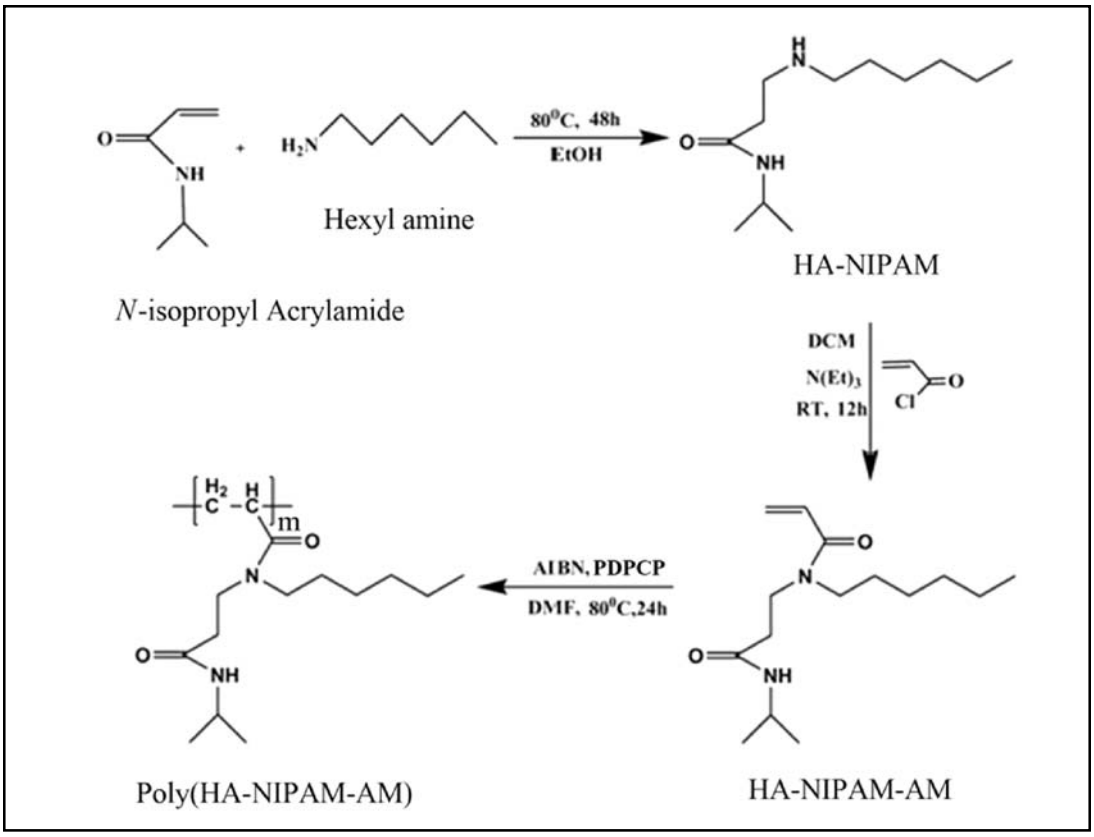
2-bromopropionyl bromide (98%, Aldrich, USA), diphenylamine (99%, SDFCL, India), sodium hydride (60

wt% dispersion in mineral oil; Spectrochem, India), carbon disulfide (95%, Loba Chemie, India), hexane (Laboratory Reagent Grade, S.D. fine, India), ethylacetate (Laboratory Reagent Grade, S.D. fine, India), DCM(Laboratory Reagent Grade, S.D. fine, India),potassium hydroxide (Qualigens, India),hexyl amine (Aldrich, USA), acryloyl chloride (96%, Alfa Aesar, India), and anhydrous magnesium sulfate (Extra Pure, Loba Chemie, India) were used as received. Propargyl alcohol (98%, Loba Chemie, India) was distilled over anhydrous magnesium sulphate. Triethyl amine (Loba Chemie, India) was dried over potassium hydroxide and then distilled. *N*-isopropylacrylamide (NIPAM, Aldrich) waspurified by recrystallization from *n*-hexane. 2, 2′-Azobis(isobutyronitrile) (AIBN) (98%, Spectrochem, India) was re-crystallizedfrom methanol. Ethanol (Saraya Distilliary, India) was left over CaO for overnight and distilled over fresh CaO.*N,N*-dimethyl formamide (DMF) (Spectrochem, India) was dried firstly by azeotropic distillation after mixing with benzene and further dried over magnesium sulfate and distilled under vacuum. Tetrahydrofuran (99%, Loba Chemie, India) was dried over sodium and benzophenone and then distilled freshly. Deionized water was prepared by redistillation of the double distilled water in an all-glass distillation apparatus. Synthesis of *O*-propynyl 2-bromo propionate was madeaccording to our previous report.[39]

JEOL JNM-ECZ500R FTNMR (500 MHz) was used to record the ^{1}H-NMR and ^{13}C-NMR spectraat RT in $CDCl_3$ and DMSO-d_6 as solvents. FT-IR spectra were recorded on Perkin Elmer Spectrum version 10.03.05 Spectrometer in the range of 400-4000 cm^{-1} using KBr pellets. High resolution mass spectrometry (HRMS, TOF-MS) was performed using a X500R QTOF spectrometer. Younglin ACME 9000 GPC, equipped with one guard column [PLgel 5 μm (50 x 7.5 mm) and two PSt gel columns [one PL gel 5 μm 500 Å (300 x 7.5 mm) and one PL gel 5 μm 10E 4 Å column (300 x 7.5 mm)] [Polymer Lab (Agilent)] connected in series to Younglin ACME 9000 Gradient Pump and a Younglin ACME 9000 RI detector, was used to determine the number average molar mass (M_n) and molar mass dispersity (PDI) in THF at 40°C with flow rate 1.0 mL/min, respectively. Calibrations were made against seven polystyrene (PSt) standard samples (Polymer Lab, PSt Calibration Kit, S-M2-10). The M_n(theo) was calculated using the following equation:

$$M_n(theo) = \frac{[\text{Monomer}]_0}{[\text{R}]_0} \cdot X_{\text{Monomer}} \cdot M_{\text{Monomer}} + M_{\text{R}}$$

where, X_{monomer} is the fraction conversion of monomer, M_{monomer} is the molecular weight of monomer and M_{R} is the molecular weight of the RAFT agent (R) used. Monomer conversion was determined by ^{1}H NMR by comparing the integrated peak area of the residual vinylic signals at 5.61ppm (^{1}H) of the monomer with the combined peak area of the methine proton of the isopropyl group in residual monomer and formed polymer at 4.0 ppm. Fluorescence spectra were recorded on a Cary-Eclipse fluorescence spectrophotometer (Agilent Technologies). *cmc* of the polymer was determined using fluorescence spectroscopy.[14,9] For contact angle measurement, films of homopolymer in chloroform was prepared on 18mm x18mm (square size) glass cover slip by drop casting method and dried under high vacuum pump above the glass transition temperature of the homopolymer and measured in duplicate using Kruss tensiometer K-100.TG-DTA was performed under nitrogen atmosphere in PerkinElmer STA 6000 instrument at the heating rate of 10°C/min. DSC was carried out under nitrogen atmosphere using Mettler STAR SW 10.00 instrument. The instrument was calibrated with indium before use and DSC curves were obtained from the second heating run at the rate of 10°C min^{-1}. Powder X-ray diffraction (XRD) pattern was collected on a BRUKER eco D8 ADVANCE diffractometer using a Cu Kα source (λ = 0.1541 nm). Morphology study of poly (HA-NIPAM-AM) was made using HRTEM (Technai G2 20 TWIN, FEI Company of USA) operating at an accelerating voltage of 200 kV. Samples were prepared by drop casting of polymer solution on the carbon coated copper grid. Before measurement solvent was slowly evaporated at room temperature by keeping it overnight. The average particle size (z-average size) of the poly (HA-NIPAM-AM) was measured by using a Horiba nanoparticle analyzer SZ-100 instrument (Horiba Scientific, Japan) at 25°C with fixed angle of 90°.



Scheme 1. Synthesis of monomer and its homopolymer

Synthesis of 3-(hexylamino)-*N*-isopropyl propanamide (HA-NIPAM)

NIPAM (5g, 44.18mmol) was degassed under high vacuum followed by purging with under nitrogen three times and then dissolved in 40 mL of anhydrous de-aerated ethanol. De-aerated hexylamine(7.0 mL, 53.02mmol) was then added to it under vigorous stirring, and finally the reaction mixture was refluxed by dipping in an oil bath of temperature 80°C for 48h. Ethanol was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (230-400 mesh size) eluted with 5% (v/v) ethanol/ethyl acetate along with 0.5% triethylamine ($R_f$value= 0.55) to give pure 8.84g (grav yield = 93.34%) (NMR yield = 99.0%) of the corresponding secondary amine 3-(hexylamino)-*N*-isopropylpropanamide as a light yellow oil.

Synthesis of monomer *N*-hexyl-*N*-(3-(isopropylamino)-3-oxopropyl)acrylamide(HA-NIPAM-AM)

3-(hexylamino)-*N*-isopropylpropanamide(8.84g, 41.24mmol) was degassed under high vacuum followed by purging with nitrogen three times and then dissolved in 120 mL of anhydrous dichloromethane.To it, Et_3N(13.8 mL, 98.91mmol) was added, and then the reaction mixture was cooled to 0°C using an ice bath. Acryloyl chloride (4.00mL, 49.31mmol) was added drop wise to the above reaction mixture over 10 min under stirring. The mixture was slowly warmed up to room temperature under stirring and stirring continued for 12h. Precipitated $N(Et)_3$. HCl salt was removed by filtration and the filtrate was washed with 5% brine solution (3 x500mL) and then with deionized water(2x

200 mL). The organic layer was evaporated using rotoevaporator, and the residue was purified by column chromatography on silica gel (size=230-400mesh size), eluted with 40% ethyl acetate/hexane along with 0.5% (v/v) triethylamine (R_f value = 0.52) to give pure 6.57 g (gravimetric yield = 59.54%) (NMR Yield = 76%) desired product,as a highly viscous colorless oil.

Synthesis of *O*-propionyl 2-(*N,N*-diphenylcarbamothioylthio)propanoate (PDPCP)

A 3-neck500mL RB fitted with a pressure equalizer was degassed under high vacuum followed by nitrogen purging three times. Sodium hydride (1.37 g, 57.42mmol) was taken in the RB and dried and degassed three times under vacuum followed by nitrogen purging. Nitrogen-purged diphenylamine (3.23g, 44.16mmol) was added in the pressure equalizer. Sodium hydride was suspended in 22mL THF and cooled to 0°C and diphenylamine was mixed with degassed solvent mixture containing 40mL DMF and 20mL THF. Diphenylamine solution was added drop wise to the sodium hydride suspension under stirring over 1h and the mixture was stirred for 1h. Subsequently, carbon disulfide (4.41g, 3.5mL,57.42mmol) was added drop wise to the mixture over a 10min period *via* the pressure equalizer and stirred overnight at 0°C. The mixture was then concentrated to remove the unreacted carbon disulfide and re-suspended in 100mL THF taken in a 250mL RB flask. A solution of *O*-propionyl 2-bromopropanoate (5.8g,4.0mL,28.71mmol) in THF (20mL) was then added drop wise to the suspension over a 30min period *via* the pressure equalizer, and the resulting mixture was stirred for 12h. The product was filtered, washed with diethyl ether and purified by column chromatography using 230-400 mesh size silica gel and 5% ethyl acetate/hexane($R_f$value =0.56) as the eluent. The final product was acolorless solidpowder with 50.7% yield (5.17g).

Typical RAFT polymerization of *N*-hexyl-*N*-(3-(isopropylamino)-3-oxopropyl)acrylamide (HA-NIPAM-AM)monomer using RAFT reagent*O*-propionyl 2-(*N,N* diphenylcarbamothioylthio) propanoate (PDPCP) (run 1, Table 1)

Polymer was synthesized *via* RAFT polymerization in DMF solvent using PDPCP as RAFT reagent and AIBN as initiator. For a typical polymerization using [monomer] : [RAFT] : [AIBN] = 100 : 1 : 0.2, monomer HA-NIPAM-AM (1.14 g, 4.25 mmol), RAFT reagent PDPCP (15.1 mg, 4.25 x10^{-2} mmol) and AIBN (1.39 mg, 8.50 x10^{-3} mmol) were taken in a Schlenk tube with a Teflon-coated magnetic bar and dissolved in 1.5 mL dry DMF. The Schlenk tube content was then degassed with N_2 gas at room temperature (RT) for 30 min and then polymerization was performed by dipping the tube into a preheated oil bath maintained at 80°C for 24 h under stirring. After completion, polymerization mixture was quenched by rapid cooling of Schlenk tube *via* immersion in liquid N_2. To get the monomer conversion a small amount of polymerization mixture was taken out for ^{1}H-NMR analysis in $CDCl_3$. Solvent DMF was removed from the remaining polymerization mixture using a high vacuum pump. The obtained residue was then dissolved in THF and precipitated from *n*-hexane at RT and separated by centrifugation. This procedure of dissolution followed precipitation and separation by centrifugation was repeated two moretimes. Finally, the purified separated polymer poly(HA-NIPAM-AM) was dried under vacuum at 50°C for 24h and obtained as white powder. Monomer Conversion = 98.0%.

Kinetic Study

To perform a typical kinetic study, polymerization using [Monomer] : [RAFT] : [AIBN] = 100 : 1 : 0.2, monomer HA-NIPAM-AM (0.6 g, 2.23 mmol), RAFT reagent PDPCP (7.95 mg, 2.23x10^{-2}mmol) and AIBN (0.73 mg, 4.46x10^{-3}mmol) were taken in a Schlenk tube with a Teflon-coated magnetic bar and dissolved in 2.5 mL dry DMF. The Schlenk tube content was then degassed with N_2 gas at room temperature for 30 min.The degassed stock solution was divided into five dry and degassed polymerization glass tubes and sealed under nitrogen atmosphere and then polymerization was performed by dipping the tubes into a preheated oil bath maintained at 80°C for 0.25, 0.5, 1.0, 1.25 and 2 h. Polymerization mixture was quenched at the desired time interval by rapid cooling of polymerization tube in liquid N_2. To get the monomer conversion determination, a small amount of polymerization mixture was taken out for ^{1}H-NMR analysis in $CDCl_3$.

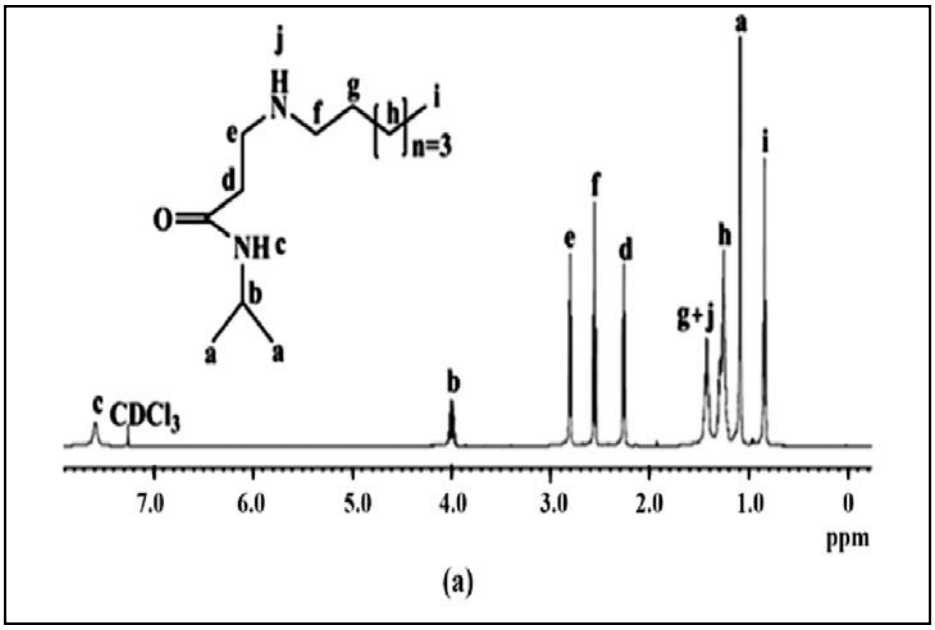
Critical micelle concentration (*cmc*) determination

The critical micelle concentration (*cmc*) of poly (HA-NIPAM-AM) in water was determined using fluorescence spectroscopy A series of aqueous solutions of the polymer with concentrations in the range of $1x10^{-2}$ to $1x10^{-6}$M made *via* the dilution of a stock solution with double distilled water has been used for measurement. For preparation of stock solution of polymer, 1mg polymer was dissolved in 1 mL ethanol, and then its 40μL ethanolic solution was added dropwise to a vial having 1 mL water. Ethanol was evaporated out by keeping open the vial under continuous stirring at room temperature overnight and then further proceeded for dilution of this stock solution having concentration of 0.04 mg/mL in water. A pyrene stock solution in acetone was prepared of which 8μL added to each vial, the acetone was evaporated under nitrogen, and the homopolymer solutions were added to the vials to get a final pyrene concentration of $6 x10^{-7}$ M in each vial. The excitation spectra (300-360 nm) of the solutions were recorded at an emission wavelength of 394 nm using a slit width of 5 nm. The ratio of the peak intensities of the excitation spectra of pyrene at 337.07 nm ($I_{337.07}$) and 333.07 nm ($I_{333.07}$) was plotted as a function of polymer concentration. The *cmc* value was considered as the interception point of the two tangent straight lines at low concentration.[14,9]

3. RESULTS AND DISCUSSIONS

Synthesis of monomer

The monomer *N*-(3-(hexylamino)-*N*-(3-(isopropylamino)-3-oxopropyl)acrylamide (HA-NIPAM-AM) has been synthesized *via* two steps (**Scheme 1**): (i) Secondary amine 3-(hexylamino)-*N*-isopropylpropanamide (HA-NIPAM) has first successfully been synthesized with 99% yield *via* Aza-Michael addition reaction using n-hexyl amine as donor and *N*-isopropyl acrylamide as acceptor. The ^{1}H NMR [**Figure 1(a)**] and ^{13}C NMR [**Figure 1(b)**] spectra in $CDCl_3$ show that vinylic peak of *N*-isopropyl acrylamide is absent and peak of methylene protons near to amino group in hexyl amine at 2.69 ppm has slightly shifted



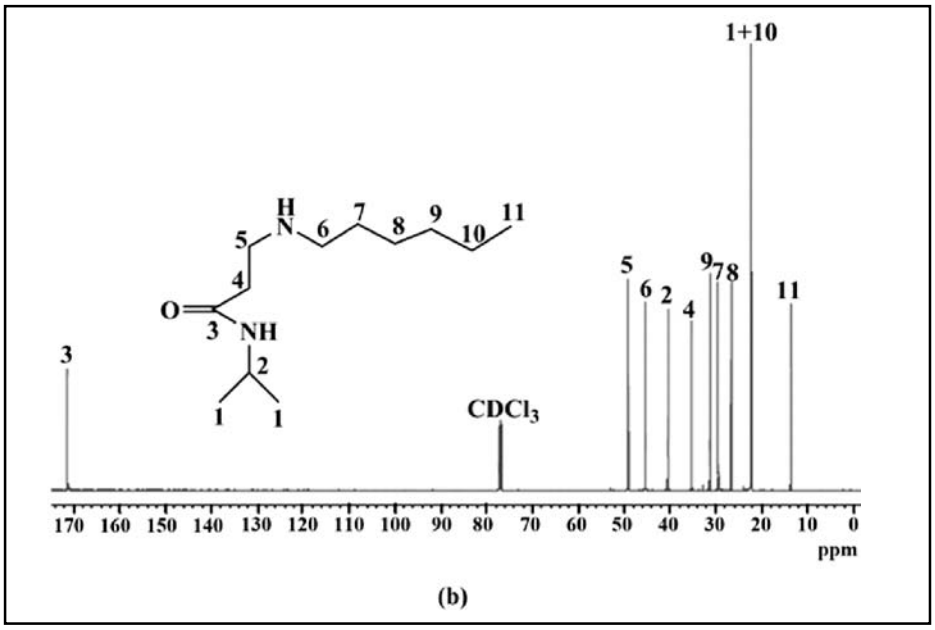


Fig. 1(a) ^{1}H NMR (500 MHz, $CDCl_3$), and (b)^{13}C NMR (125 MHz, $CDCl_3$) spectra of secondary amine 3-(hexylamino)-*N*-isopropylpropanamide (HA-NIPAM).

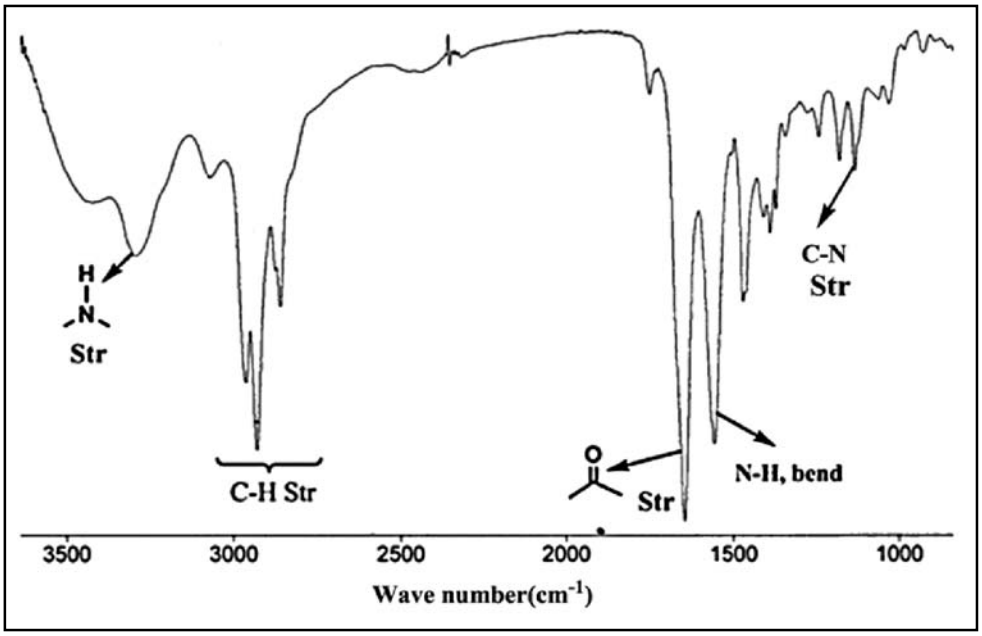


Fig. 2. FT-IR (KBr pellet) spectrum of secondary amine HA-NIPAM.

to upfield "f" at 2.58 ppm and new peaks of methylene carbon "5" and "6" appears at 48.75 and 45.07ppm, respectively. In FT-IR spectrum [**Figure 2**], amide-I band appears at 1644 cm^{-1}, and amide-II bands - mostly N-H bending appears at 1548 cm^{-1} and broad N-H stretching absorption band appears at 3307 cm^{-1}. Thus, ^{1}H, ^{13}C, and FTIR spectroscopic studies have confirmed its formation. (ii) Then this secondary amine HA-NIPAM has been reacted with acryloyl chloride in the presence of triethyl amine in dichloromethane to make the desired monomer *N*-(3-(hexylamino)-*N*-(3-(isopropylamino) -3-oxopropyl) acrylamide (HA-NIPAM-AM). In its ^{1}HNMR spectrumin DMSO-d_6 [**Figure 3(a)**], the peaks "e" and "f" in 3-

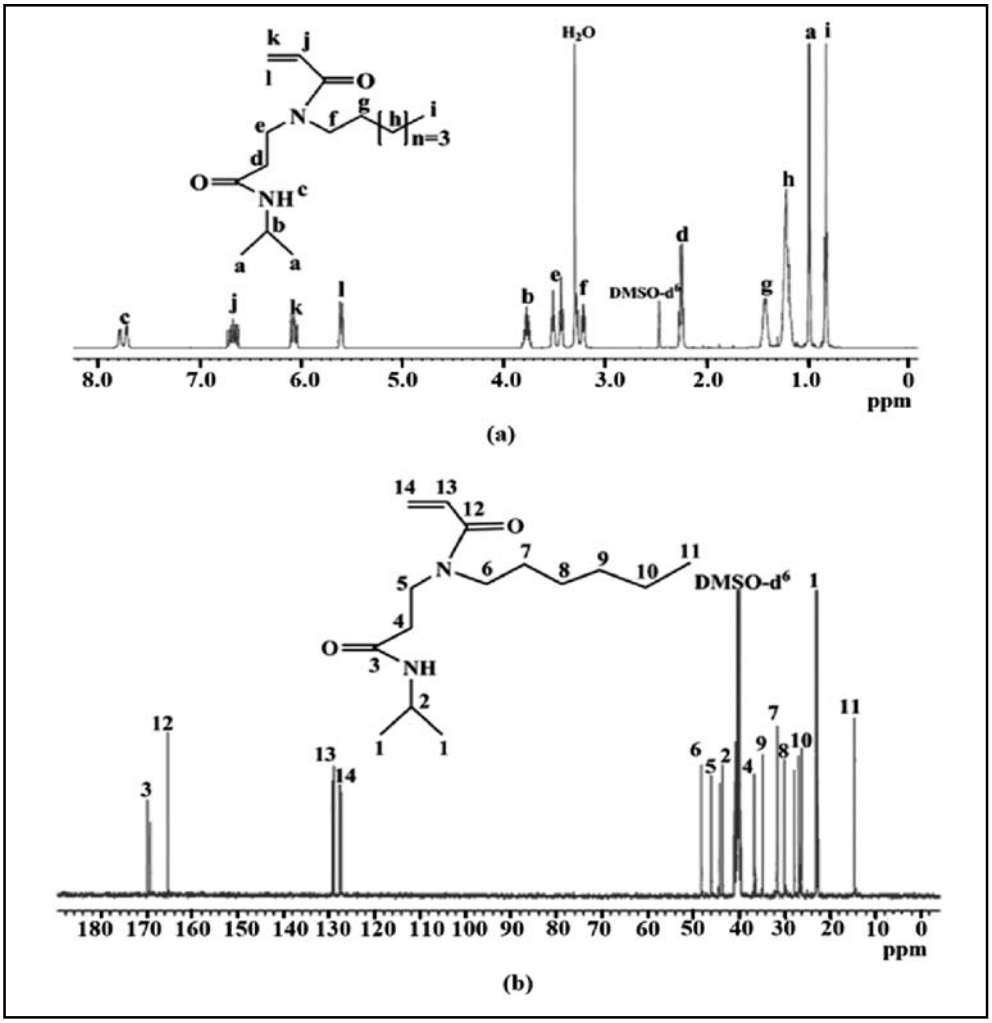


Fig. 3**(a)** ^{1}H NMR (500 MHz, DMSO-d_6), and **(b)** ^{13}C NMR (125 MHz, DMSO-d_6) spectra of monomer *N*-hexyl-*N*-(3-(isopropylamino)-3-oxopropyl)acrylamide (HA-NIPAM-AM).

(hexylamino)-*N*-isopropyl propanamide) shift to downfield at 3.41-3.52 and 3.21-3.29 ppm, respectively. The three vinylic proton peaks appears at 5.61, 6.06 and 6.64ppm, while the remaining all peaks "a", "b", "c", "d", "g","h", and "i" appear at 0.97, 3.76, 7.78, 2.22, 1.4, 1.19, 0.81 of monomer HA-NIPAM-AM, respectively. In addition, from ^{13}C NMR spectrum [**Figure 3(b)**], the resonance signals of vinylic carbon "13" and "14" appear at 127.41 and 128.99 ppm, respectively. The peaks of secondary amide carbon "3" and tertiary amide carbon "12" appear at 165.40 and 169.28-169.84 ppm, respectively.FT-IR spectrum [**Figure 4**] also has revealed that amide-I band appears at 1644 cm^{-1} and amide-II band appears mostly N-H bending band at 1551 cm^{-1} and broad N-H stretching absorption band at 3299 cm^{-1}. The stretching absorption due to C=C appears at 1609 cm^{-1}which clearly confirms the

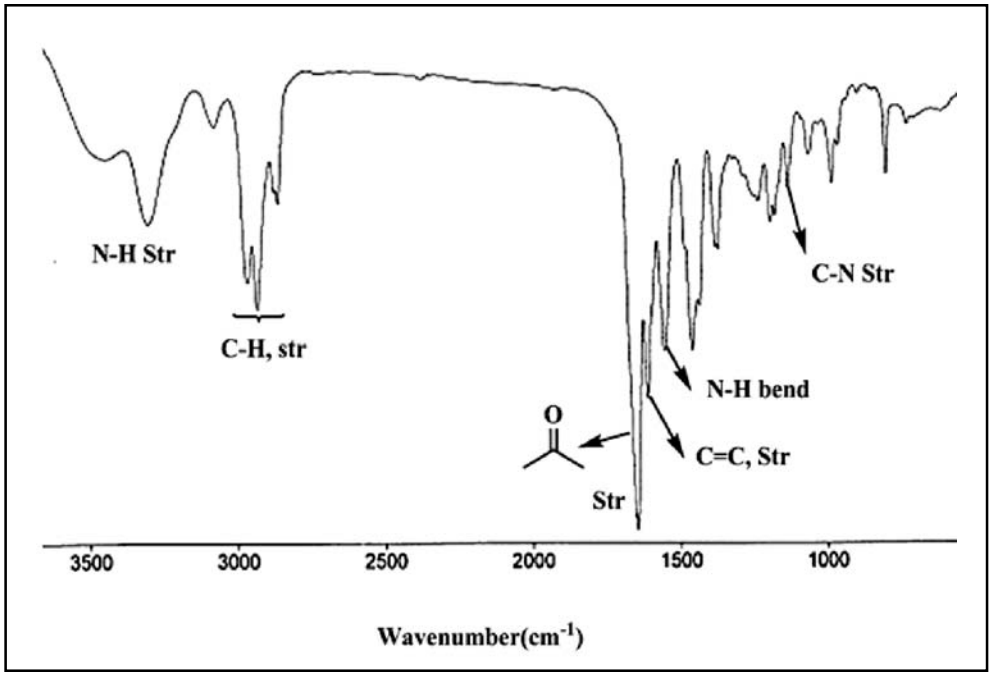
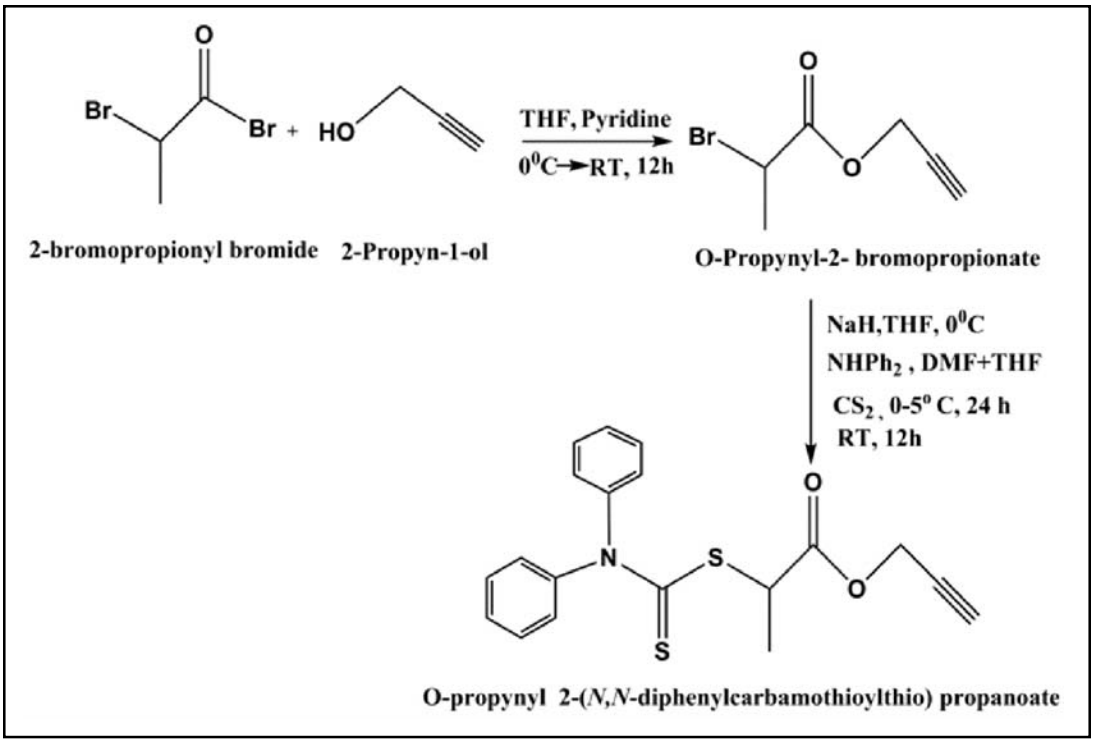


Fig. 4. FT-IR (KBr pellet) spectrum of monomer HA-NIPAM-AM.

incorporation of double bond. High resolution mass spectroscopy (HR-MS) results 269.2202 for molecular formula $C_{15}H_{29}N_2O_2$ consistent with theoretical value of 269.2229. Thus, ^{1}H, ^{13}C, FTIR, and HR-MS spectroscopic studies have confirmed its formation.

Synthesis of RAFT Agent

The alkyne group containing RAFT agent *O*-propionyl-2-(*N,N*-diphenylcarbamothioylthio) propanoate (PDPCP) has been synthesized *via* two steps: (i) synthesis of *O*-propionyl 2-bromopropionate *via* the esterification of



Scheme 2. Synthesis of RAFT agent *O*-propionyl-2-(*N,N*-diphenylcarbamothioylthio) propanoate (PDPCP)

2-bromopropionyl bromide with propargyl alcohol followed by (ii) the reaction of *O*-propionyl 2-bromopropionate with diphenyl amine and carbondisulfide (**Scheme 2**). Synthesis and characterization of *O*-Propynyl-2-bromo propionate were earlier reported by our group.39 ^{1}H [**Figure 5(a)**], ^{13}C [**Figure 5(b)**] and FT-IR [**Figure 6**] spectroscopic studies of PDPCP have confirmed its formation. In ^{1}H NMR spectrum ($CDCl_3$, 500MHz) [**Figure 5(a)**] single and sharp peak due to alkyne proton "a" and aromatic protons "e+f+g" appear at 2.47 and 7.33-7.40 ppm, respectively. The other peaks "b+c" and "d" appear at 4.70 and 1.56ppm, respectively. The ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) [**Figure 5(b)**] supports the expected carbon resonance signals of triple bond "1" and "2" at 75.11 and 77 ppm, respectively and of phenyl group "8", "9" and "10+11" at 145,129.61 and 127.89 ppm, respectively. The resonance signals of carbonyl group "4" and thiocarbonyl group "7" appear at 171.37 and 199.35 ppm, respectively. Remaining signals of carbons "3", "5" and "6" appear at 52.90, 49.56 and 16.70 ppm, respectively. All expected resonance signals of carbon confirm its structure. In its FTIR spectrum [**Figure 6**] prominent sharp stretching peaks at 3243 and 2122 cm-1are observed corresponding to alkyne proton and carbon-carbon triple bond group, respectively. Peaks at 1747 and 1704 cm^{-1} are characteristic peaks assigned for

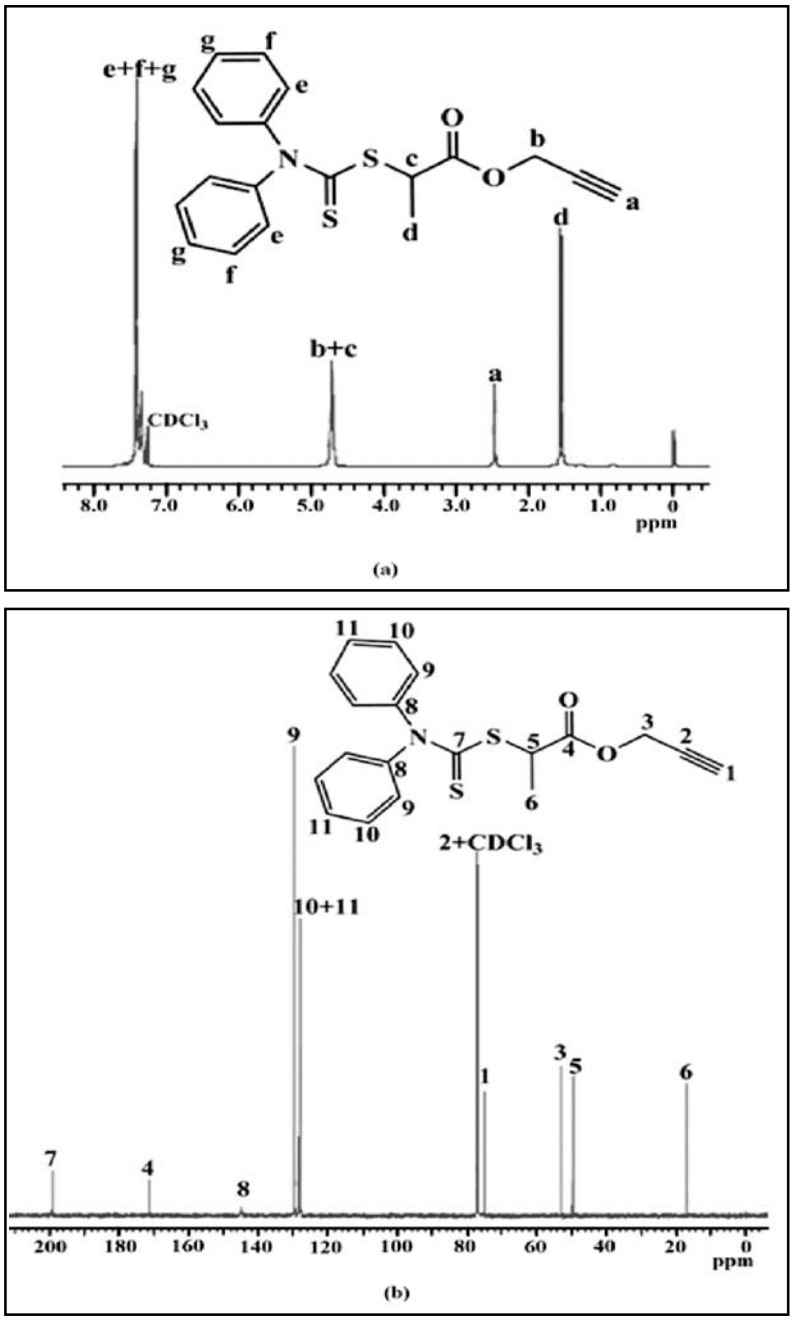


Fig. 5(a) ^{1}H NMR ($CDCl_3$, 500MHz), and (b) ^{13}C NMR ($CDCl_3$, 125 MHz) spectra of the RAFT agent *O*-propionyl 2-(*N, N*-diphenylcarbamothioylthio) propanoate (PDPCP)

stretching mode of C=O and C=S functional groups. The C=C aromatic ring stretching frequencies are appeared at 1588,1560 and 1488 cm^{-1}. The other characteristic peaks at 3060, 2981, 1163 cm^{-1} are attributed to aromatic C-H, aliphatic C-H and C-N stretching, respectively.

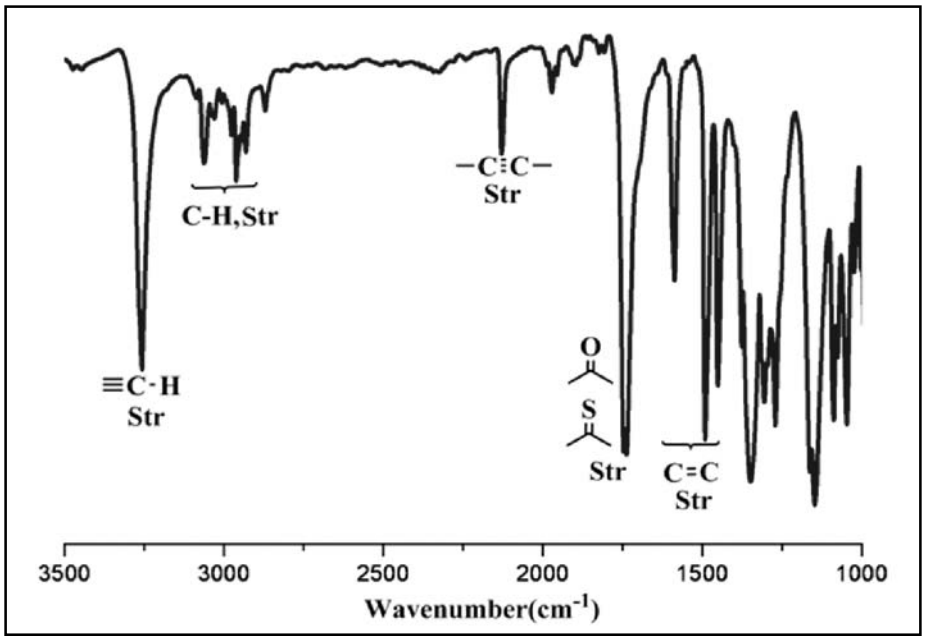


Fig. 6. FTIR (KBr pellet) spectrum of the RAFT agent PDPCP

TABLE 1. RAFT polymerization of HA-NIPAM-AM in DMF using PDPCP[a]

Run	[Monomer] / [RAFT agent]	Conv (%)[b]	M_n(Theo)[c] (g/mol)	M_n(GPC)[d] (g/mol)	PDI[d]
1	100	98.0	26,658	11,500	1.74
2	50	100	13,776	4,500	1.68
3	10	100	3,002	2,500	1.76

a Using [RAFT agent]: [AIBN] = 1:0.2in 1.5 mL DMF at 80°C for 24 h

b Determined by ^{1}H NMR by comparing the integrated peak area of the residual vinylic signals at 5.61ppm (^{1}H) of the monomer with the combined peak area of the methine proton of the isopropyl group in residual monomer and formed polymer at 4.0 ppm.

$$\overline{M}_n(theo) = \frac{[\text{Monomer}]_0}{[\text{R}]_0} \text{x } X_{\text{Monomer}} \cdot M_{\text{Monomer}} + M_{\text{R}}$$

where, x_{Monomer} is the fraction conversion of Monomer, M_{Monomer} is the molecular weight of monomer and $M_{\text{RAFT agent}}$ is the molecular weight of the RAFT agent PDPCP.

d Determined by GPC (THF, 1 mL/min, 40°C) calibrated against Polystyrene standards.

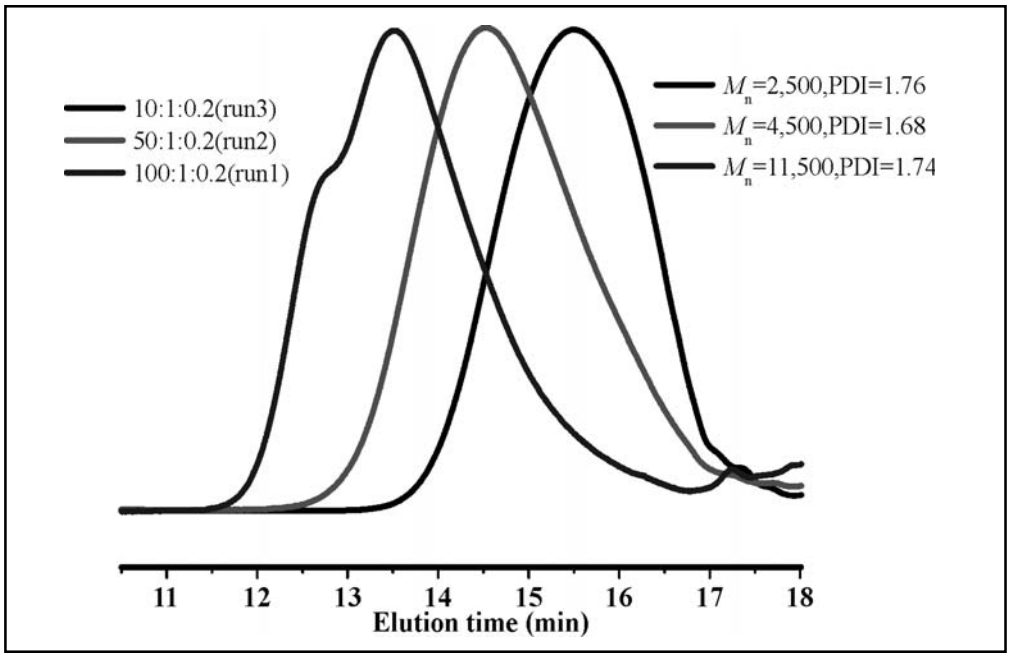


Fig. 7. Typical GPC Chromatograms of poly(HA-NIPAM-AM)s (**runs 1, 2** and **3, Table 1**)

Synthesis of Polymer *via* RAFT Polymerization

We have performed the RAFT polymerization of HA-NIPAM-AM in DMF using PDPCP as RAFT agent and AIBN as initiator at [PDPCP]:[AIBN] = 1:0.2 at 80°C (**Table 1**). Initially, polymerization has been performed using [HA-NIPAM-AM]:[PDPCP]:[AIBN] = 100:1:0.2 (**runs 1**, **Table 1**). It has yielded polymer with molar mass [M_n (GPC) =11,500 g mol^{-1}] with molar mass dispersity of 1.74. Polymerizations with 50 (**run 2**) and 10 (**run 3**) equivalent of monomer (with respect to RAFT agent) keeping other conditions same have resulted in gradual decrease of molar mass.Molor masses of the polymers increase linearly with increase in the monomer loading [**Figure 7 and 8 (a)**]. However, the observed molar masses [M_n(GPC)] [**Figure 5(a)**] are considerably lower than the theoretical values [M_n(theor)]. This may be due to the use of polystyrene as standards. The kinetic study of polymerization using [HA-NIPAM-AM]:[PDPCP]:[AIBN] = 100:1:0.2 in DMF at 80°C has also been carried out. The corresponding plots [**Figure 8(b)**] of the monomer conversion (%) and ln ($[M]_o/[M]$) (where $[M]_o$ = concentration of the monomer at the time, t = 0 min and [M] = concentration of the monomer at the corresponding time of polymerization) *vs.* time reveal that monomer conversion (%) increases slightly exponentially up to almost quantitative conversion, however, the corresponding ln ($[M]_o/[M]$) plot is linear. These results indicate the controlled nature of polymerization.

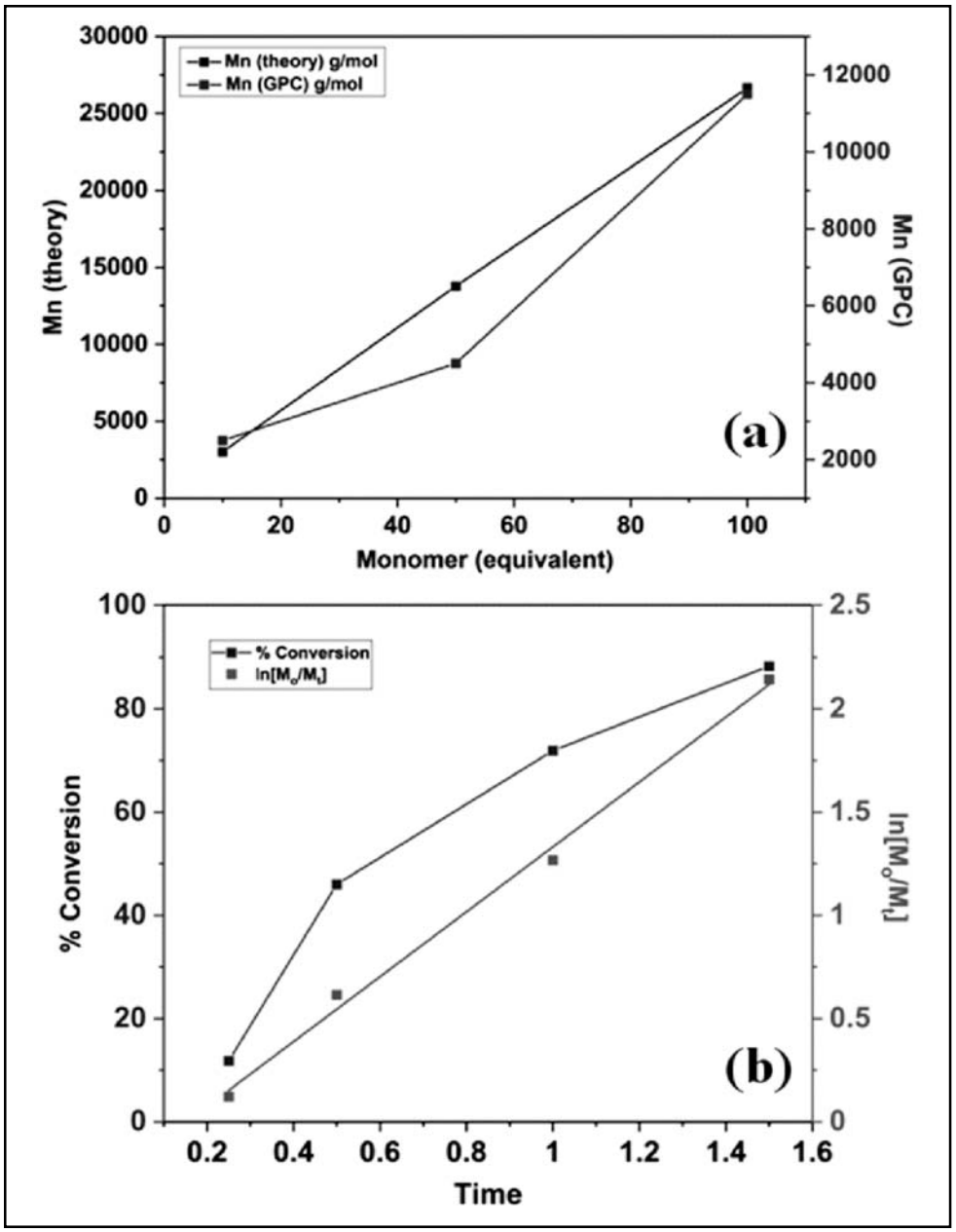


Fig. 8(a). Plots of molar masses of the polymers *vs.* monomer loading (Table 1), and (b) the plots of time *vs.* monomer conversion and ln $[M]_o/[M]$ (where, $[M]_o$ = concentration of the monomer at time t = 0 min and [M] = concentration of the monomer at the corresponding time t) in the polymerization of monomer (HA-NIPAM-AM) in DMF using [HA-NIPAM-AM]:[PDPCP]:[AIBN] =100:1:0.2 at 80°C.

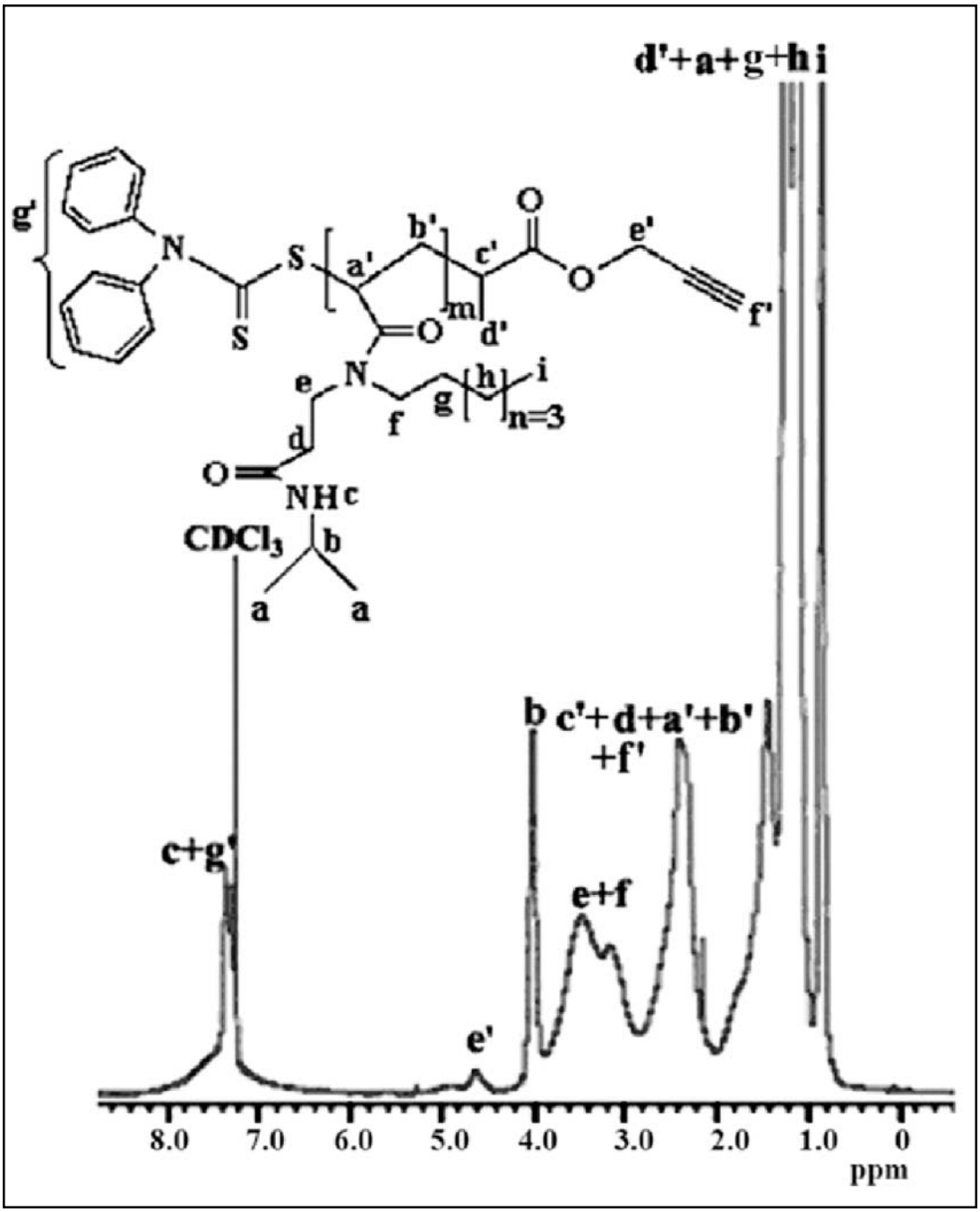


Fig. 9. ^{1}H-NMR (500MHz, $CDCl_3$) spectrum of poly (HA-NIPAM-AM)

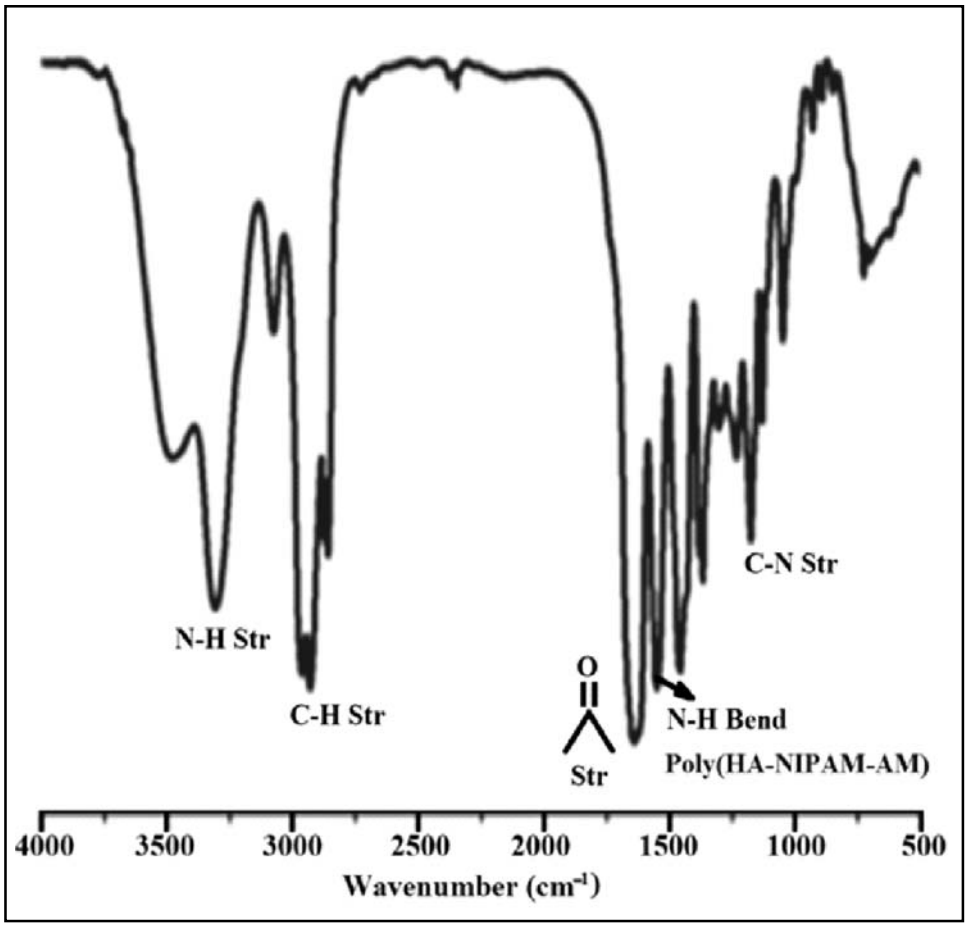


Fig. 10. FTIR (KBr pellet) spectrum of poly (HA-NIPAM-AM)

Chain-end analysis of the homopolymer [M_n (GPC)=2,500 g/mol, PDI=1.76] (**run 3**, **Table 1**), synthesized using [HA-NIPAM-AM]:[PDPCP]:[AIBN] =10:1:0.2 at 80°C,by ^{1}H NMR spectroscopy in $CDCl_3$ (**Figure 9**) confirms RAFT reagent PDPCP mediated polymerization. The characteristic peaks of repeating unit methine proton (**a**′) and methylene proton (**b**′) overlap in the peak centered at 2.45ppm within the range 2.0-2.8 ppm together with that of the methylene proton (**d**) adjacent to keto group in the 3-(isopropylamino)-3-oxopropylpendant chain, methine **c**′ proton and alkyne **f**′ proton of the RAFT agent segment at the w chain-end. The peaks corresponding to methyl **a**, methylene **g** and **h** protons of polymeric side chains overlap in the peak within 1.0 – 2.0 ppm together with the methyl **d**′ protons of the RAFT agent segment at the w chain-end. The peaks at 4.0 and 0.8 ppm correspond the methine **b** proton and the methyl **i** protons of polymeric

side chain, respectively. The broad peak at 7.4 ppm corresponds to the amidic **c** proton of the polymeric side chain together with the aromatic **g**′ proton of the RAFT agent segment at the a-chain-end. The peak corresponding to the methylene **e**′protons of the RAFT reagent at the wchain end of the polymer is observed at 4.6 ppm. The number of repeating unit for this polymer is calculated by dividing the peak area of **b** by one-half of the peak area of **e**′(2H,**e**′/2). Calculated molar mass from ^{1}H NMR [M_n(NMR)] is 3758 g/mol, which is higher than its M_n(GPC) of 2500g/mol and M_n(theor) of 3002 g/mol. In its FTIR spectrum [**Figure10**], strong amide-I band at1644 cm^{-1} and amide-II band at 1548 cm^{-1} attribute to the carbonyl stretching and N-H bending vibration of the poly(HA-NIPAM-AM), respectively. The broad N-H stretching absorption band appears at 3307cm^{-1}.The appearance of amide-I band exclusively at 1644cm^{-1}, not at 1680cm^{-1}, indicates that the carbonyl groups involve in hydrogen bonding, not present in free form. The disappearance of alkene band at 1609 cm^{-1} confirms polyacrylamide formation. The asymmetric (ν_{as}) and symmetric (ν_s) stretching absorption peaksdue to C-H stretching vibration appear at 2962 and 2872cm^{-1}, respectively. The other absorption peaks appear at 1456, 1367, and 1130cm^{-1} due to C-H asymmetric bending vibration of CH_3 and CH_2 group, symmetric bending vibration of isopropyl group, and C-N stretching vibration of amide group, respectively.

Formed polymer (**run 1**, **Table 1**) is insoluble in hexane, DMSO etc., sparingly soluble in water, but highly soluble in ethyl acetate, diethyl ether, dichloromethane, THF, DMF, acetone, ethanol, methanol, chloroformetc. Wettability of the polymer surface by water droplet has been studied by measuring the contact angle of its film in water. The observed advancing and receding contact angles are 140.06 and 137.36°, respectively. Observed such high contact angles between polymer surface and water droplet indicates that the polymer surface is hydrophobic.

Self-assembly of Polymer

For studying the self-assembly capability of these polymers having hydrophilic 3-(isopropylamino)-3-oxopropyl functional group and hydrophobic *n*-hexyl group in each structural repeating unit, we have determined the *cmc* of the polymer in water using pyrene as fluorescence probe [**Figure 11(a)** and **(b)**]. The observed *cmc* value is 7.82 x 10^{-4}mg/mL which is considerably lower than that for amphiphilic homopolymer system reported by Savariar et al.[24] To have an idea about the size of the formed micelle in water, we have tried to get the TEM morphology of polymer in water. However, aggregation of spherical micelles of ~88 (69 – 153.5nm range) nm average size has been observed [**Figure 12(a)**]. The corresponding size of the hydrodynamic volume of these micelles using DLS is found to be of ~143 nm [**Figure 12(b)**]. The observed larger size using the later method is expected due to the inclusion of solvent.

Thermal Studies

Thermal properties of the polymer have been studied using TG-DTA and DSC techniques. TGA study has revealed that polymer undergoes single step degradation from 300°C till 450°C [**Figure 13(a)**]. The corresponding DTA study supports degradation process. DSC study [**Figure 13(b)**] reveals a single

endothermic glass transition temperature involving base line shifting at 85.3°C.This value is higher than the value (80.9°C) reported for the corresponding poly(n-hexyl acrylamide) possibly due to the incorporation of 3-(isopropylamino)-3-oxopropyl moiety as another side chain in the structural repeating unit of the polymer [28]. Another three exothermic peaks without base line shifting have also been observed at 195.1, 211.4 and 233.1°C. Observation of such peaks in its DSC thermogram is presently not clear to us.

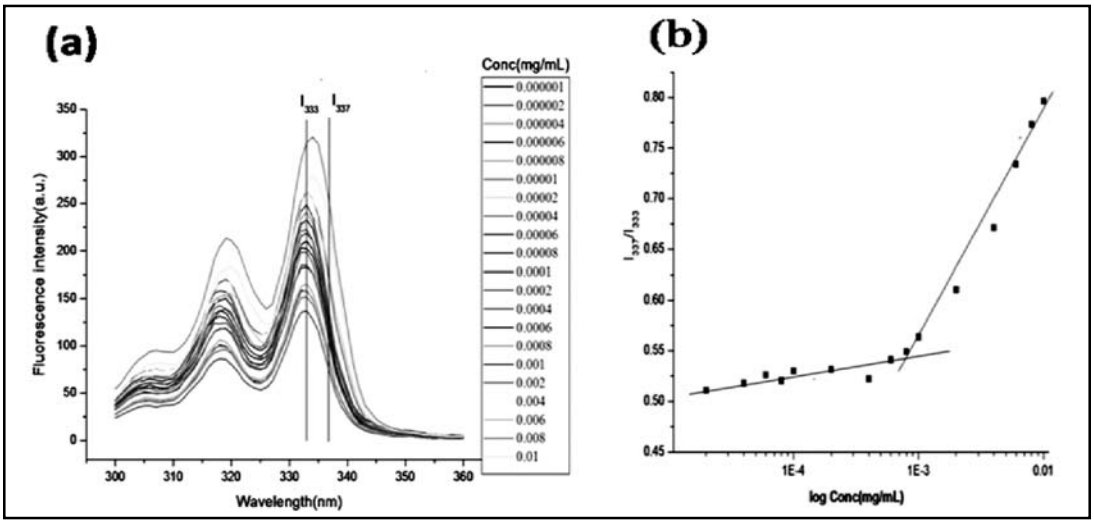


Fig.11(a). Fluorescence excitation spectra (at λ_{em}= 394nm) of pyrene (6 x 10^{-7}M) in the presence of increasing conc.(mg/mL) of poly(HA-NIPAM-AM) in H_2O and (b) the corresponding semi logarithmicplot of the fluorescence excitation intensity ratio (I_{337}/I_{333}) of pyrene *vs.* concentration of poly(HA-NIPAM-AM) in water.

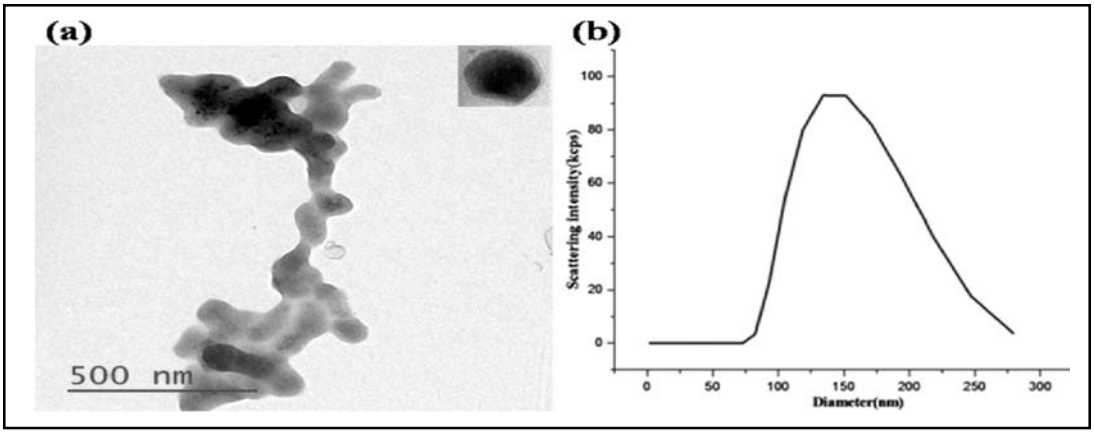


Fig. 12(a). HRTEM morphology of polymer in water (scale bar for inset figure = 112 nm) and (b) Hydrodynamic diameter distributions / plot of scattering intensity vs effective hydrodynamics diameter of poly(HA-NIPAM-AM) in water at 0.3 mg/mL

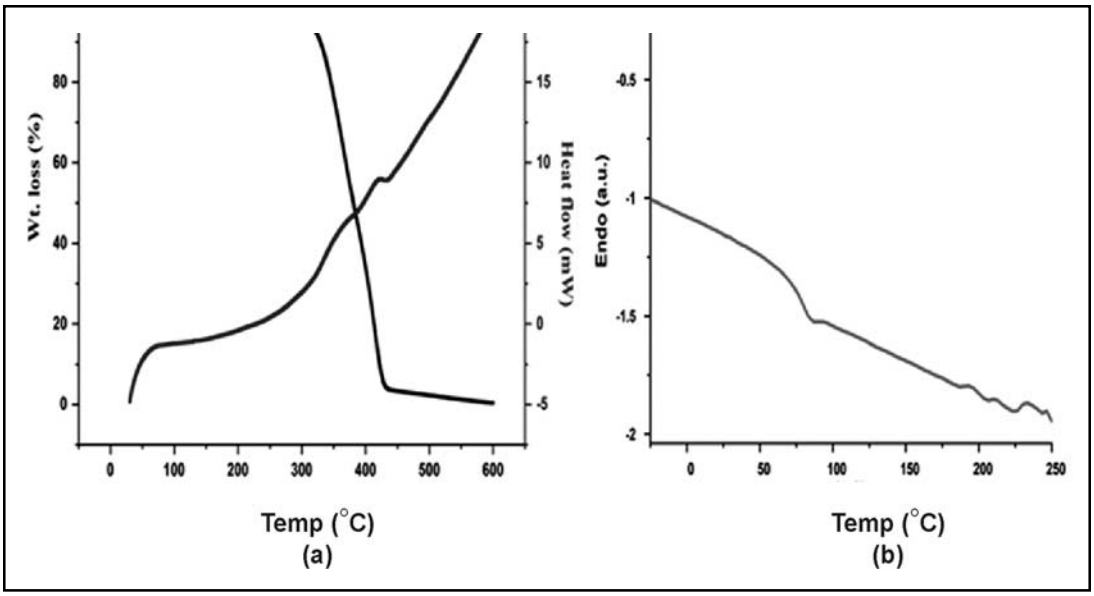


Fig.13(a). TG-DTA and (b) DSC thermograms of poly(HA-PNIPAM-AM)

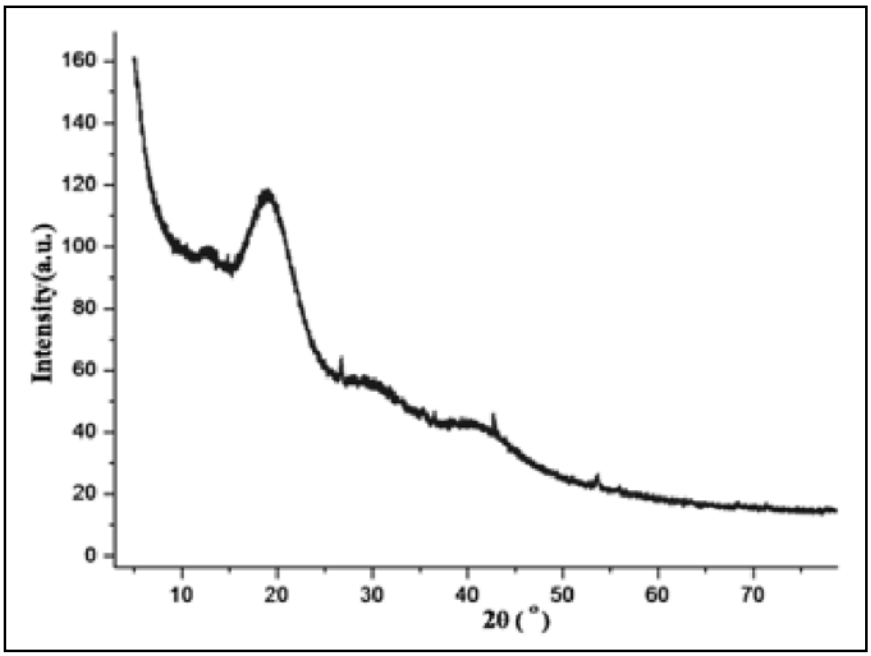
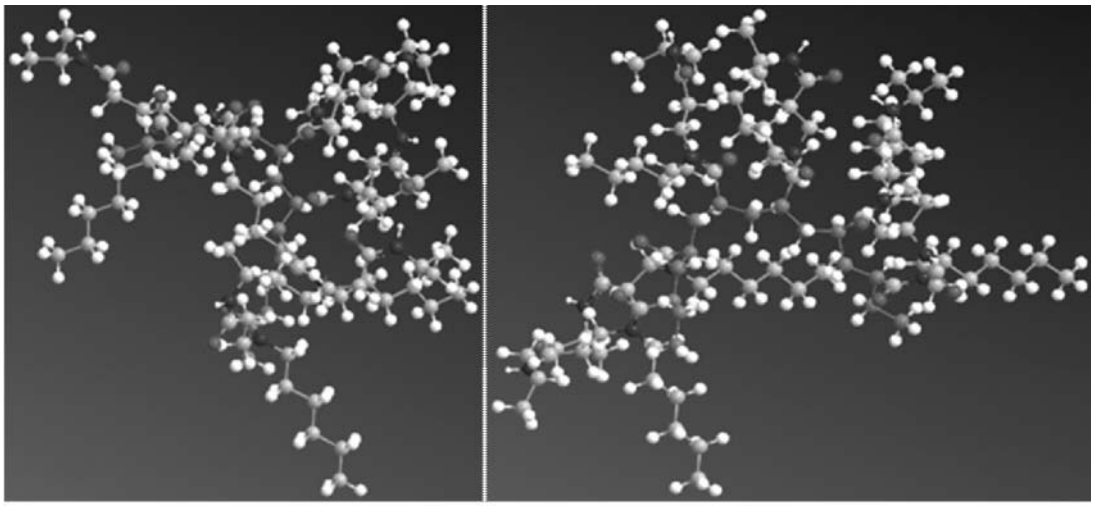


Fig. 14. Powder XRD of poly(HA-NIPAM-AM)

Density Functional Theory Study of Polymer

In order get the idea about the spatial orientation of the two pendant groups of each repeating structural units in the formed polymer, we have performed density functional theory (DFT) study of the polymer assuming degree of polymerization of 6 and chain ends are ended with methyl group. We have used B3LYP density functional theory method in our calculations along with the 6-31G** basis set as implemented in Gaussian 09 suits of program.[38] The DFT calculations were performed in conjunction with the Polarizable Continuum Model (PCM) for solvation (the energy in solution by making the solvent reaction field self-consistent with the solute electrostatic potential) in ethanol.The optimized structure of poly(HA-NIPAM-AM) in two different orientations has been shown in **Figure 15**. Helical backbone structure of the polymer with the pendant group having n-hexyl and 3-(isopropylamino)-3-oxopropyl functional groups at N of vinylic amide group exposed towards inward and outward direction, respectively, has been found. The angle between the n-hexyl and 3-(isopropylamino)-3-oxopropyl functional groups at Nis of the order of 116.6°. We would like to mention here that in poly(HA-NIPAM-AM), there are intramolecular hydrogen bondings between >C=O and H-N< fragments with a hydrogen bond length of the order of 1.98 Å. In addition there are also comparatively weak (but stronger than van der Waals forces) interactions (>C=O……H-C; with hydrogen bond lengths in the range 2.66 to 2.77 Å) between >C=O of oxopropyl fragment and H_2C< unit. This corroborates our FTIR results of the appearance of amide-I band at 1644 cm^{-1} instead of 1680 cm^{-1}, indicating that the carbonyl groups involve in hydrogen bonding, not present in free form.



(a) **(b)**

Fig.15. Optimizedstructure (in two different orientations) of poly(HA-NIPAM-AM) (considering degree of polymerization, n = 6) at B3LYP/6-31G** level of theory using Gaussian 09 suits of program[38]

CONCLUSION

We have successfully synthesized and characterized a new acrylamide monomer *N*-(3-(hexylamino)-*N*-(3-(isopropylamino)-3-oxopropyl)acrylamide (HA-NIPAM-AM) and a new alkyne group containing reversible addition-fragmentation chain-transfer agent *O*-propionyl-2-(*N,N*-diphenylcarbamothioylthio) propanoate (PDPCP). Poly(HA-NIPAM-AM) homopolymers have been synthesized *via* RAFT polymerization using PDPCP as RAFT agent. The formed homopolymers have been characterized by GPC, ^{1}H NMR, FTIR, contact angle measurement, TG-DTA, DSC, and PXRD. Number-average molar masses of the prepared polymers are in the range of 2,500 – 11,500 g/mol with PDI in the range of 1.7 – 1.8. The polymer surface is hydrophobic as revealed by the observation of high advancing and receding contact angles of 140.06 and 137.36°, respectively, in water. Self-assembly study of the polymer in water using pyrene as fluorescence probe has revealed its *cmc* at 7.82 x 10^{-4} mg/mL. TG-DTA study has revealed that polymer undergoes two-step degradation at ~ 300 and 400°C. DSC study has revealed a glass transition temperature involving base line shifting at 85.3°C. Powder XRD study of the polymer has revealed a strong broad peak at $2\theta = 19.12°$ ($d = 0.463$ nm) corresponding to amorphous backbone ethylene segment apart from another three weak broad peaks at $2\theta = 12.72, 30.5, 40.82°$ ($d = 0.695, 0.292,$ and 0.221nm, respectively) corresponding to the formation of nanophases *via* aggregation of side chains through hydrogen bonding of amide groups and hydrophobic interaction of alkyl chains. Quantum chemical calculation of the poly(HA-NIPAM-AM) with degree of polymerization of 6 has revealed a helical backbone structure with the pendant group having n-hexyl and 3-(isopropylamino)-3-oxopropyl functional groups at N of vinylic amide group exposed to inwards and outwards, respectively. The studies of the self-assembly of this polymer in other solvents, conjugation of this polymer to other small molecules or, macromolecules *via* click chemistry using its alkyne functional group at its w-chain-end, and the effect of N-alkyl chain length on the properties of such polymers by synthesizing monomers with different alkyl chain lengths are in progress.

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