Arm-First Approach toward Cross-Linked Polymers with Hydrophobic Domains via Hypervalent Iodine-Mediated Click Chemistry

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ABSTRACT: In this work, synthesis of two cross-linked polymeric systems through isoxazoline ring formation using nitrile oxide–acrylate click chemistry has been described. In the first system, styrenic block copolymer with oxime-functionalized middle block was synthesized using St-bis(α,α′-dimethyl-α′′-acetic acid)trithiocarbonate as chain-transfer agent using reversible addition fragmentation chain-transfer technique. This block copolymer was further utilized to prepare core cross-linked star polymers by reacting with a four-arm acrylic cross-linker by employing environment-friendly, nontoxic PhI(OAc)₂-mediated “click reaction” via the formation of isoxazoline ring. In the second system, two linear styrenic block copolymers, one containing oxime and another containing acrylate group, were reacted to form a cross-linked (CS) polymeric system. Formation of cross-linked polymers and isoxazoline ring was confirmed by Fourier transform infrared spectroscopy, gel permeation chromatography, NMR spectroscopy, and dynamic light scattering studies. Later, we also demonstrated that in aqueous medium these CS polymers produced polymeric nanoparticles (NPs), which can be used as potential carriers of hydrophobic drug molecules. The loading capacity of the hydrophobic domains has been investigated using coumarin dyes with varying hydrophobicity through steady-state and time-resolved spectroscopy studies. The polymeric NPs were also shown to successfully encapsulate a hydrophobic drug doxorubicin.

INTRODUCTION

Cross-linked polymeric systems are a promising field of interest due to their compact architecture, aggregation behavior in selective solvent(s), and unique properties toward the delivery of drugs or dye molecules. For example, core cross-linked star (CCS) polymers, in which the polymer chains emerge from a single core, have found applications in the field of chemical sensing, tissue engineering, cosmetics, catalysis, etc.\(^1\)–\(^4\) Tremendous efforts have been made over the last few years to develop a facile and efficient route to synthesize a new class of cross-linked polymer structures, including core cross-linked star using dynamic covalent chemistry,\(^5\)–\(^7\) alkyne–azide click chemistry,\(^8\)–\(^10\) and thiol–ene click chemistry.\(^11\)–\(^14\) In this context, 1,3-dipolar cycloaddition (1,3-DC) has been successfully utilized as synthetic tool for the formation of complex architectures, owing to its effectiveness in producing functionalized organic compounds. Matyjaszewski\(^10\) and Hvilsted\(^11\) prepared a series of miktoarm star, and on the other hand, cross-linking star via a one-pot synthesis has also been reported.\(^13\)–\(^15\) A highly efficient click reaction was also used for the development of a new class of miktoarm star polymer network. For example, synthesis of star polymers was reported using click chemistry as major pathway, as copper-catalyzed alkyne–azide cycloaddition was carried out, leading to the formation of 1,2,3-triazole systems.\(^16\)–\(^18\) However, complete removal of metals from the residue is often challenging, and considering the cytotoxicity of metals, a significant amount of work based on metal-free procedure for the synthesis of CCS polymers has been carried out in recent years by Sumerlin et al.,\(^19\)–\(^21\) Wiltshire and Qiao,\(^22\)–\(^25\) Fulton et al.,\(^26\)–\(^28\) and Otsuka et al.\(^29\)–\(^31\) In this context, hypervalent iodine(III) reagents,\(^32\)–\(^35\) such as iodobenzonediacetate [PhI(OAc)₂], have drawn considerable attention due to their fairly high activity toward various oxidative organic reactions. We have also reported the synthesis of polystyrene-based CCS polymer assembly with acrylic functionality at the polymer backbone with oxime-functionalized cross-linker via 1,3-dipolar cycloaddition.\(^36\)

During the last decade, to increase the efficiency of drugs with low therapeutic index, different types of drug carriers like liposomes,\(^37\) microparticles,\(^38\) nanoparticles (NPs),\(^39\) nano-associates,\(^40\) drug–polymer conjugates,\(^41\) and polymeric micelles\(^42\) have been formulated. In recent years, polymeric NPs have been the object of growing scientific attention. Polymeric NPs are soft templates with size in the range of 10–1000 nm. This type of nanoparticles is typically composed of a hydrophobic polymeric core, which can effectively solubilize poorly water-soluble drugs with high loading yields.
In this work, we have reported a unique method toward the synthesis of (i) core cross-linked star (CCS) polymers and (ii) cross-linked (CS) polymeric systems having polystyrene backbone via the formation of isoxazoline ring through nitrile oxide−acrylate 1,3-dipolar cycloaddition (1,3-DC) reactions.\textsuperscript{43−45} Reversible addition fragmentation chain transfer (RAFT), one of the most diverse controlled polymerization techniques,\textsuperscript{47−49} has been implemented to synthesize well-defined, controlled block copolymers using styrene-, chlorobenzyl-, and aldehyde-functionalized monomers. This was followed by introduction of appropriate functionality into the polymer molecules, which was subsequently utilized for the formation of targeted CCS/CS polymers via isoxazoline ring formation using nontoxic, environment-friendly reagent iodobenzenediacetate [PhI(OAc)]\textsubscript{2}. Furthermore, we show that the synthesized CS polymers had been utilized in the formation of polymeric NPs in aqueous medium, which can potentially be used as a potent hydrophobic drug carrier.

\textbf{RESULTS AND DISCUSSION}

In this work, our objective was to synthesize polystyrene-based linear block copolymer building blocks displaying the required pendent functional groups for the formation of cross-linked polymers via isoxazoline ring formation. We have synthesized two cross-linked polymeric systems: (i) core cross-linked star...
(CCS) polymers and (ii) cross-linked (CS) polymeric systems. In the first system, a styrene block copolymer with oxime-functionalized middle block was synthesized using RAFT polymerization technique. A four-arm acrylic cross-linker was synthesized via acrylation of pentaerythritol and reacted with the block copolymer to prepare core cross-linked star (CCS) polymers by environment-friendly, nontoxic PhI(OAc)2-mediated click chemistry via the formation of isoxazoline ring. In the second system, two well-defined polystyrene-based linear copolymers containing the reactive functional groups, i.e., oxime and acrylate, were also synthesized separately by RAFT polymerization. The polymer–polymer cross-linked (CS) systems were synthesized from these two linear triblock copolymers. The cross-linked polymeric systems were found to form nanoparticles (NPs) in aqueous media that showed potential as a hydrophobic drug carrier.

**Synthesis of Styrenic Core Cross-Linked Star (CCS) Polymers.** In this approach toward the synthesis of triblock copolymers with reactive oxime functional group in the middle of the polymer (Scheme 1A), the RAFT agent \( S_{S2} \cdot \text{bis(} \alpha, \alpha' \cdot \text{-} \text{di} \text{-} \text{dimethyl} \cdot \alpha' \cdot \text{-} \text{acetic acid}) \text{trithiocarbonate (CTA)} \) was used for the preparation of polystyrene macro-CTA (P1) with controlled molecular weight (MW) and narrow dispersity \( (M_n = 10\,400, D = 1.06, \text{Table 5}) \). Further, P1 was used to mediate the polymerization of 4-vinylbenzaldehyde at \( 80^\circ \text{C} \) and narrow dispersity \( (M_n = 15\,400, D = 1.15) \) with aldehyde-functionalized polystyrene as the middle block flanked by inert polystyrene blocks at the two ends (Scheme 1A). The complete conversion of aldehyde to oxime was confirmed by \(^1\text{H NMR} \) (Figure 1) analysis, where the aldehyde proton, showing chemical shift at 9.87 ppm, completely disappeared and two new peaks due to the formation of oxime appeared at 7.961 and 11.012 ppm. It is noteworthy that postpolymerization modification reactions are usually difficult and not quantitative. However, in the present work, the \(^1\text{H NMR} \) spectra of polymers after postpolymerization functionalization reactions show very high efficiency. Thus, we have successfully designed the triblock copolymers with oxime functional group as a middle block with hydrophobic polystyrene block at the two ends of the polymer.

For comparison purpose, a linear polymer P4 (Scheme 1B) was also prepared, in which styrene and 4-vinylbenzaldehyde were incorporated randomly in the chain in 1:1 ratio using the same chain-transfer agent in 1,4-dioxane at \( 70^\circ \text{C} \) for 24 h, resulting a broad distribution of molecular weight, which may be due to the high reactive nature of 4-vinylbenzaldehyde. P4 was then purified, and the corresponding oxime derivative (P5) was prepared through the reaction with \( \text{NH}_2\text{OH-HCl} \) and NaOAc in tetrahydrofuran (THF)/\( \text{H}_2\text{O} \) (1:1) mixture. On the other hand, an acrylate-based four-arm cross-linker (CL, Scheme 1C) was prepared by acrylation of pentaerythritol by standard organic synthetic method.

These copolymers, block (P2a) and random (P5), were then reacted, as described below, with CL, to prepare the core cross-linked star (CCS) polymers. Core cross-linked polymers were formed through isoxazoline ring formation from oxime functionality dangling from the polymer chain and the acrylic groups present in the cross-linker (CL). The possible architecture of the CCS polymers formed by the reaction between P2a and CL is shown in Figure 2. The aldoxime-functionalized block (P2a) and random copolymer (P5) were reacted with PhI(OAc)2 to produce the nitrile oxide intermediate in situ, which was then reacted with a range of different concentrations of cross-linker, resulting in the formation of various CCS polymers. The CCS polymers were obtained as solid powders after the final purification. Fourier transform infrared (FT-IR) spectral analysis was done, and the results confirmed the reaction between oxime and acrylate, which resulted in the formation of the isoxazoline ring. A nearly complete disappearance of the IR signal at 3450−3480 cm\(^{-1}\) for the free hydroxyl group of oxime and the appearance of a peak at 1420 cm\(^{-1}\) (for \(-\text{C}==\text{N}\)) indicate the formation of isoxazoline from oxime (Figure 3a).

The CCS polymers were further characterized by GPC analysis. Dilute solutions (ca. 1 mg mL\(^{-1}\)) of these polymers in THF were used to analyze the molecular weights and dispersity (D) by GPC. The GPC images of these CCS polymers were
observed at much lower elution volumes compared to the reacting block copolymers (see Figure 3b for an example), indicating a significant increase in the molecular weights of the CCS polymers over the reacting linear triblock copolymers. Moreover, a study of the effect of cross-linker and block copolymer concentration on the molecular weight of the CCS polymers revealed that a decrease in the concentration of the cross-linker as well as the block copolymers resulted in CCS polymers of relatively low molecular weights (Table 1). The molecular weight data show that the concentration of the cross-linker had more effect on the MW of the CCS polymers compared to the concentration of the block copolymers. MW of CCS decreased significantly when CL concentration was halved keeping the polymer concentration same, whereas upon reduction of polymer concentration keeping the concentration of CL same, the MW of the CCS was rather increased. Although the GPC method applied in this work does not provide absolute value of molecular weight, the formation of high-molecular-weight polymers was confirmed from their significantly lower elution volumes relative to their precursor polymer (e.g., P2a).

To conclusively prove the formation of core cross-linked polymer network via the formation of isoxazoline derivatives, the triblock copolymer P2a was reacted with PhI(OAc)₂ and the resulting nitrile oxides intermediate was further trapped by ethyl acrylate. ³¹H NMR analysis (Figure 4) revealed the disappearance of the peak corresponding to oxime at 7.961 and 11.02 ppm and the appearance of new peaks at 5.225 ppm (due to the proton adjacent to oxygen) and 4.153 ppm (due to two diastereotopic protons), suggesting the formation of isoxazoline derivative. This new synthetic strategy may be employed effectively for the development of new polymeric architectures with potential applications in the field of advanced material science and technology. It is to be mentioned here that the random copolymer, P5, produced cross-linked polymeric systems, which were either insoluble or had very low solubility in common organic solvents.

**Synthesis of Styrenic Polymer−Polymer Cross-Linked (CS) Systems.** To extend this synthetic strategy one step further, we have synthesized aldehyde- and benzyl chloride-based random copolymers, in which these reactive functional groups were present in comparatively small amount (5 mol %). The chain length of these two linear polymers was expanded by the addition of polystyrene block in various compositions in search for the enhancement of solubility in different organic solvents. Then, the polymers were transformed into the corresponding oxime (P7a−e)- and acrylate (P9a−e)-functionalyzed polymers via the reactions described in Scheme 2. The formation of oxime-based polymers was confirmed from the proton NMR spectra. Among P7a−e, even the polymer with the lowest oxime concentration showed peaks of oxime at 7.89 and 10.30 ppm [Figure S1, Supporting Information]. On the other hand, the formation of the acrylate group from benzyl

![](image1)

**Figure 2.** Schematic representation of synthesized core cross-linked star (CCS) polymers from P2a and CL via isoxazoline ring formation.

![](image2)

**Figure 3.** (a) IR spectra of polymer P2a (black line) and the corresponding CS of P2a and CL (red line). (b) GPC image of polymer P1 (red line), P2a (blue line), and CS involving P2a and CL (black line).

| exp no. | concentration of block copolymer P2a (mmol) | mol % of cross-linker | Mₙ,a (g mol⁻¹) | dispersity (Đ) |
|--------|------------------------------------------|----------------------|----------------|---------------|
| 1      | 0.1890                                   | 39.6                 | 439 400        | 1.23          |
| 2      | 0.1890                                   | 19.8                 | 2 96 800       | 1.19          |
| 3      | 0.0945                                   | 19.8                 | 3 42 700       | 1.24          |

*aFrom GPC.*

Table 1. Molecular Weight Data of CCS Polymers
chloride group has been proved again from proton NMR spectroscopy, where a new peak of acrylate proton appeared at 5.65 ppm (doublet) and peaks of the other two protons merged with those of phenyl protons of the polymeric backbone (Figure 5). The GPC images of these polymers (P7a-e and P9a-e) showed a gradual increase in molecular weight upon addition of more and more amount of styrene to produce the second block of the copolymer in the second step (Figure 6). Low dispersity (Đ) values proved the controlled nature of the polymerization process. The dynamic light scattering (DLS) study revealed that the hydrodynamic diameter of these copolymers remained between 1 and 10 nm (Figure 7a,b). A slightly higher size in case of oxime copolymers than the corresponding acrylate copolymers was corroborated by the

Figure 4. 1H NMR spectra of click product obtained from the reaction of P2a and ethyl acrylate.

Scheme 2. (A) Synthesis of Oxime (P7a-e)- and (B) Acrylate (P9a-e)-Functionalized Triblock Copolymers
molecular weight data. The GPC and DLS data for the above set of polymers are tabulated in Table 2.

A series of reactions were carried out between acrylate- and oxime-containing polymers to synthesize CS polymers of polymer–polymer systems. Upon completion of a cross-linking reaction, the product was completely purified and DLS experiments were carried out using high-performance liquid chromatography (HPLC)-grade dimethylformamide (DMF) as solvent at 25 °C to measure the size of the CS produced. The size of the CS polymers increased as the size of the reactants, i.e., acrylate- and oxime-containing polymers, increased (Figure 7c and Table 3). We have also checked the feasibility of synthesizing cross-linked copolymers by reaction of oxime-containing copolymers (P7a–e) with CL. It was found that the synthesis of CS polymers was also possible this way. The size of the CS polymers produced this way was smaller than that of polymer–polymer systems. The data for the CS polymers synthesized by this route are presented in Table S1 and Figure S2 (Supporting Information).

From the data generated so far, the solubility behavior of the cross-linked polymeric systems studied in this work may be summarized as follows: (a) the CCS polymer systems from triblock copolymer were soluble in common organic solvents up to 40 mol % of cross-linker, whereas CCS polymer systems from random copolymer of styrene and 4-vinylbenzaldehyde were insoluble or very slightly soluble; (b) CS systems were generally soluble in DMF or dimethyl sulfoxide (DMSO), with the solubility observed to increase with the length of the polystyrene inner block. The CS systems were very poorly soluble.
soluble in THF, and the solubility in THF increased slightly with increasing “inert” polystyrene chain length.

One of these polymer–polymer CS polymeric systems was further explored to find its utility. CS 75 (Table 3) was added in an aqueous medium to find the solution behavior. It was found that the CS polymer produced nanoparticles (NP) in aqueous medium. The size and shape of the polymeric NP thus produced was confirmed by field emission scanning electron microscopy (FESEM) and transmission electron microscopy (TEM) measurements. The FESEM image of the nanoparticle confirmed the size around 300 nm, which closely matched the size obtained from TEM experiment (Figure 8).

Table 2. Characterization of Oxime-Functionalized (P7a–e) and Acrylate-Functionalized (P9a–e) Polymers

| polymer | $M_\text{n}$ (g mol$^{-1}$) | $D$ | hydrodynamic diameter (nm) |
|---------|-----------------|-----|-----------------------------|
| P7a     | 9000            | 1.24| 3.1                         |
| P7b     | 11 050          | 1.18| 3.6                         |
| P7c     | 11 750          | 1.33| 4.2                         |
| P7d     | 13 000          | 1.40| 4.9                         |
| P7e     | 13 850          | 1.32| 4.9                         |
| P9a     | 3700            | 1.38| 1.7                         |
| P9b     | 4550            | 1.20| 2.3                         |
| P9c     | 5100            | 1.23| 2.7                         |
| P9d     | 5850            | 1.25| 3.6                         |
| P9e     | 6100            | 1.31| 4.2                         |

Table 3. Variation of Size of the CS Polymers Synthesized from Oxime- and Acrylate-Functionalized Polymers

| CS system | reacting polymers | hydrodynamic diameter (nm) |
|-----------|-------------------|-----------------------------|
| CS 25     | P7b–P9b           | 190.1                       |
| CS 50     | P7c–P9c           | 220.2                       |
| CS 75     | P7d–P9d           | 255.0                       |
| CS 100    | P7e–P9e           | 295.3                       |

Encapsulation of Hydrophobic Dyes and Drug in the Polymer NPs Produced from CS. The hydrophobic drug-loading capacity of the prepared polymeric NPs from CS polymer (CS 75) was investigated using steady-state and time-resolved spectroscopic techniques. Various coumarin molecules (C153, C480, and C343) were chosen as model drug molecules to ensure the efficacy of drug loading inside the polymeric core of the NPs. Coumarins are well-known hydrophobic molecules, and their hydrophobicity differs depending on the various functional groups present in the molecules. The literature reports show the following hydrophobicity order of the used coumarin molecules: $C_{153} > C_{480} > C_{343}$.$^{50}$ Hence, we could expect that if the synthesized polymeric NPs are well enough to carry water-insoluble drug then the incorporation of the coumarin dyes would also follow a similar trend, i.e., the incorporation of C153 should be higher compared to the other two coumarin dyes (C480 and C343).

To get the preliminary idea about the incorporation of the coumarin molecules inside the polymeric NPs, UV–vis absorption measurements were performed. Absorption spectra of the coumarin molecules inside the polymeric NP are shown in Figure S3 (Supporting Information). The absorption spectra for all of the coumarin molecules were different. C153 and C480 showed absorption peaks at around 404 and 379 nm, respectively, but no sharp peak was observed in case of C343, indicating no incorporation of C343 into the polymeric NP. To
ascertaining hydrophobicity-driven incorporation of coumarin dyes, steady-state emission measurements were also executed, and the corresponding data are presented in Table S2 (Supporting Information). In pure water, C153 exhibits an emission peak at \( \sim 549 \text{ nm} \) and inside the polymeric NP it showed emission peak at around 495 nm \( (\lambda_{em} = 408 \text{ nm}) \) (Figure 9). This large blue shift \( (\sim 54 \text{ nm}) \) of the emission maximum indicates the incorporation of C153 into the hydrophobic domains of the polymeric NP. The emission peak of C480 in pure water is nearly at 492 nm \(^52\) and inside the polymeric NP it shifted to 486 nm. The lower blue shift of C480 was due to its less incorporation in hydrophobic domains of NPs driven by its lower hydrophobicity than C153. We have also performed a similar experiment with another coumarin dye, C343, which is considered to be hydrophilic due to its anionic carboxylate moiety at neutral pH. The emission peak of C343 in water is found to be 490 nm \(^55\) which remained unchanged in the presence of polymeric NP, indicating no incorporation of the investigated C343 dye inside the NP. Hence, from the above results, we can conclude that the synthesized polymeric NP has the ability to incorporate hydrophobic molecules and the extent of incorporation depends on the molecules’ hydrophobicity.

The stability of incorporated hydrophobic dye molecules is also an important factor for drug-delivery applications. The stability of the incorporated model drug/dye molecules can be understood by measuring the fluorescence lifetime of the respective dye molecules in polymeric NPs. The obtained lifetime values are listed in Table 4, and the lifetime decays are shown in Figure 10. From Table 4, it is clear that both the coumarin molecules, i.e., C153 and C480, show higher lifetime inside the polymeric NP compared to that in water. The average lifetime value for C153 is 4.01 ns with components of 1.77 ns (43%) and 5.70 ns (57%) inside the polymeric NP, whereas the lifetime values of C153 were reported to be around 1.6–1.7 ns depending upon the pH of the solution. \(^44\) In case of C480, the average lifetime was found to be 4.02 ns with components 1.52 ns (35%) and 5.45 ns (65%). The higher lifetime values inside the polymeric NP suggest preferable incorporation as well as higher stability of the dye molecules. We did not measure the lifetime of C343 as it was not incorporated inside the polymeric NP, as discussed previously.

Once it was certain that the polymeric NPs could potentially encapsulate hydrophobic molecules, we tried to encapsulate a hydrophobic anticancer drug doxorubicin (DOX) inside the polymeric NP. A homogeneous solution of HPLC-grade DMF containing both polymer and DOX was added dropwise to 5 mL of Milli-Q water. After stirring for 30 min, the solution was dialyzed against Milli-Q water for 24 h and then the DOX-loaded polymeric NP was collected from the dialysis bag and UV measurement was carried out. The absorption maxima of DOX appeared at 504 nm (Figure 11) and upon comparing the absorbance value with the standard graph, the drug-loading content (LC) was calculated following the equation provided later and it is found to be 17.1%. This confirmed the drug-encapsulating ability of the polymeric NPs produced from CS systems.

### EXPERIMENTAL SECTION

**Materials, Methods, and Instrumentation.** Styrene, 4-vinylbenzyl chloride, \( \alpha, \alpha’- \)azoisobutyronitrile (AIBN), pentaerythritol, and doxorubicin hydrochloride were purchased from Sigma-Aldrich and used as received. Coumarin 153, coumarin 343, and coumarin 480 (laser grade) were obtained from Exciton and also used as received. All of the other used chemicals and solvents were purchased from Sigma Chemical Laboratories Pvt. Ltd. (SRL, India) and Spectrochem (India) and purified following the standard procedure. \(^46\) 4′,4″-Bis(\( \alpha, \alpha’- \)dimethyl-\( \alpha’- \)acetic acid)trithiocarbonate (CTA, Scheme S1 in Supporting Information) was synthesized according to the literature procedure. \(^47\) Synthesis of 4-vinylbenzaldehyde is described in Supporting Information (Scheme S2).

FTIR spectra were obtained on a Bruker IFS 133V, wavenumber represented in cm\(^{-1}\); samples used as KBr pellets. \(^1\)H NMR spectra were obtained on Bruker DPX-200 and 400 MHz NMR spectrometers, and tetramethylsilane was used as the internal standard to calibrate the spectra. Molecular weight and dispersity \((D)\) of the polymers were determined by GPC instrument (Viscotek) via a refractive index detector and THF as eluent. The flow rate of the system was 1 mL min\(^{-1}\). The molecular weights were calculated using polystyrene standards. Dynamic light scattering (DLS) measurements were performed using Malvern Zetasizer Nano equipment with a 3.0 mW He–Ne laser operated at 633 nm. Experiments were carried out at an angle of 173° and a constant temperature of 25 °C. Transmission electron microscopy (TEM) was performed using a transmission electron microscope (JEOL-JEM 2100, Japan), which operates at an accelerating voltage of 80 kV at 25 °C. Field emission scanning electron microscopy (FESEM) was performed using FEI NOVA NANOSEM 450. The absorption spectra were recorded using a Shimadzu (model no. UV-2450) spectrophotometer, and fluorescence spectra were recorded using a Hitachi (model no. F-7000) spectrofluorimeter. For steady-state study, all samples were excited at 408 nm. We obtained time-resolved fluorescence spectra through a time-correlated single photon counting instrument from IBH, U.K., in which the signals were recorded at the magic angle \((54.7°)\) using a Hamamatsu microchannel plate photomultiplier tube (3809U), and the instrument response was 100 ps. Decay analysis was carried out by IBH DAS, version 6 software. The long- and

![Figure 9](image-url)

**Figure 9.** Fluorescence spectra of the various coumarin dyes inside polymeric NPs.

**Table 4. Lifetime Values of the Probe Molecules**

| dyes     | \( \tau_1 (a_1) \) (ns) | \( \tau_2 (a_2) \) (ns) | \( \langle \tau \rangle \) (ns) | \( \chi^2 \) |
|----------|----------------|----------------|----------------|------|
| C153     | 1.77 (0.43)    | 5.70 (0.57)    | 4.01           | 1.10 |
| C343     | 1.52 (0.35)    | 5.45 (0.64)    | 4.02           | 0.98 |
short-wavelength decays were fitted biexponentially by reckoning $\chi^2$ close to 1, indicating a good fit.

**Synthetic Procedures.** *Synthesis of Polystyrene Macro-CTA (P1, Scheme 1A).* S,S'-Bis(α,α'-dimethyl-α''-acetic acid)-trithiocarbonate (CTA) (0.136 g, 0.481 mmol) and AIBN (0.20 mg, 0.12 mmol) were taken in a 25 mL single-neck round-bottom flask. Styrene (5 g, 48 mmol) diluted in 1.5 mL of 1,4-dioxane was then added along with a magnetic bar. The reaction mixture was degassed and purged thoroughly with nitrogen, and this process was repeated thrice. The reaction vessel was then placed in an oil bath at 70°C and stirred for 12 h. Thereafter, the polymerization was quenched by cooling in liquid nitrogen, followed by precipitation of the product in ice-cold methanol. The product was then filtered and dried under high vacuum to obtain polymer P1 as a yellow solid (~89% yield).

**Synthesis of Aldehyde-Functionalized Block Copolymer (P2, Scheme 1A).** P1 (0.4 g, 0.041 mmol) and AIBN (1.8 mg, 0.12 mmol) were taken in a single-neck round-bottom flask. 4-Vinylbenzaldehyde (0.38 g, 2.86 mmol) diluted in 1,4-dioxane (1.0 mL) was then added to the mixture. The reaction vessel was then degassed and purged with nitrogen, and this process was repeated thrice, followed by heating in a preheated oil bath at 70°C for 16 h. Thereafter, the polymerization was quenched and the polymer was obtained by precipitating out from ice-cold methanol, filtered, and then dried under high vacuum to obtain P2 as a pale yellow solid (78% yield). $^1$H NMR (CDCl$_3$): δ 0.96 (br, (CH$_3$)$_2$S(C=S)S(CH$_3$)$_2$), 1.43 (br, CHCH$_2$ polymer backbone), 1.73 (br, CHCH$_2$ polymer backbone), 6.58 (br, Ar, polymer), 7.06 (br, Ar, polymer), 7.51 (br, Ar, polymer), 9.87 (br, Ar, CHO, polymer) [Figure S5, Supporting Information (SI)].

**Synthesis of Oxime-Functionalized Triblock Copolymer (P2a, Scheme 1A).** Copolymer P2 (0.4 g, ~1.2 mmol) was dissolved in THF (8 mL), then hydroxylamine hydrochloride (0.226 g, 3.256 mmol) and sodium acetate (0.44 g, 5.32 mmol) were added to it, and the reaction mixture was stirred overnight at 50°C. After completion of the reaction, the product was obtained through precipitation in cold hexane, washed, and dried under high vacuum for 6 h. The complete conversion of the aldehyde group to oxime was confirmed by $^1$H NMR spectrum. $^1$H NMR (DMSO-d$_6$): δ 0.82 (br, (CH$_3$)$_2$S(C=S)S(CH$_3$)$_2$), 1.37 (br, CHCH$_2$ polymer backbone), 1.52 (br, CHCH$_2$ polymer backbone), 6.47 (br, Ar, polymer), 7.18 (br, Ar, polymer), 7.96 (br, CH(═N)OH polymer), 11.01 (br, Ar, CH(═N)OH, polymer) [Figure 1].

![Image](attachment:Figure_10.png)

**Figure 10.** Time-resolved fluorescence decay of (a) C153 and (b) C480 in polymeric nanoparticle.

![Image](attachment:Figure_11.png)

**Figure 11.** Absorption and emission spectra of doxorubicin confined in polymeric NPs.
Synthesis of Poly(styrene-r-4-vinylbenzaldehyde) (P4, Scheme 1B). In a 10 mL round-bottom flask, styrene (1 g, 9.6 mmol), 4-vinylbenzaldehyde (1.27 g, 9.6 mmol), and \(S,S^\prime\)-bis(\(\alpha,\alpha^\prime\)-dimethyl-\(\alpha\)-acetic acid)trithiocarbonate (CTA) (0.054 g, 0.192 mmol) were taken along with a magnetic bar. AIBN (6.3 mg, 0.0384 mmol) was then added to the mixture, followed by addition of 1.5 mL of 1,4-dioxane.

The reaction mixture was then degassed for 5 min and purged thoroughly with nitrogen, and this process was repeated thrice. The reaction vessel was then placed in a preheated oil bath at 70 °C and stirred for 24 h. Thereafter, the polymerization was quenched by cooling in liquid nitrogen, followed by precipitation of the product in ice-cold hexane. The product was then collected by filtration, washed thoroughly with hexane, and dried under high vacuum for 4 h to obtain polymer P4 as a yellowish solid (~85% yield). 1H NMR (CDCl\(_3\)): \(\delta\) 0.834 (br, \(-\text{CH}_2\) \(\text{S}(\text{C}=\text{S})(\text{CH}_3)\)), 1.396 (br, CH\(_2\) polymer backbone), 1.2 (br, CH\(_2\)CH\(_2\) polymer backbone), 6.496 (br, Ar, polymer), 6.981 (br, Ar, polymer), 7.391 (br, Ar, polymer) [Figure 4].

Synthesis of Poly(styrene-r-4-vinylbenzaldehyde oxime) (P5, Scheme 1B). Previously synthesized P4 (0.25 g, 0.025 mmol) was dissolved in THF (4 mL) in a 25 mL single-neck round-bottom flask, then NH\(_4\)OH-HCl (0.1 g, 1.43 mmol) and sodium acetate (0.157 g, 1.9 mmol) in 4 mL of water were added to it, and the reaction mixture was stirred overnight at room temperature. After the completion of the reaction, the aqueous part was discarded and the product was collected by precipitating the THF part in cold hexane, filtered, washed thoroughly, and then dried under high vacuum for 6 h to obtain oxime-based random copolymer P5 as a yellow solid. The complete conversion of the aldehyde group to oxime was confirmed by 1H NMR spectrum. 1H NMR (DMSO-d\(_6\)): \(\delta\) 8.26 (br, \(-\text{CH}(\equiv\text{N})\text{OH}\) polymer), 1.553 (br, CH\(_2\)CH\(_2\) polymer backbone), 6.537 (br, Ar, polymer), 7.071 and 7.252 (br, Ar, polymer), 8.03 (br, CH(\equiv\text{N})OH polymer), 11.013 (br, Ar, CH(\equiv\text{N})OH polymer). The polymerization conditions and the resultant molecular weights of the synthesized copolymers are provided in Table 5.

2,2-Bis(acryloyloxy)methylpropane-1,3-diyldiacrylate (CL, Scheme 1C). Pentacyrthritol (0.5 g, 3.67 mmol) in 15 mL of dry DMF was taken in a 50 mL double-neck round-bottom flask under nitrogen atmosphere. It was then placed in an ice bath at 0 °C with vigorous stirring and addition of triethylamine (1.48 g, 14.7 mmol). Acryloyl chloride (1.33 g, 14.7 mmol) was then added very slowly for 2 h at 0 °C, and the mixture was further stirred for 1 h under the same condition and at 60 °C for the next 48 h. Then, the reaction mixture was cooled to room temperature and ice-cold water was added to it; the product was extracted with chloroform, the organic part was repeatedly washed with ice-cold water and then dried over MgSO\(_4\), and the solvent was removed to afford CL as viscous oil. The crude product was purified through column chromatography, and pure CL was obtained as colorless oil (1.10 g, 85%). 1H NMR (CDCl\(_3\)): \(\delta\) 5.424 (s, 8H), 5.81 (d, 4H, \(J = 8.8\) Hz), 6.04 (dd, 4H, \(J = 6.6\) Hz), 6.35 (d, 4H, \(J = 16\) Hz) [Figure S7, SI]. 13C NMR (CDCl\(_3\)): \(\delta\) 31.2, 62.7, 127.7, 131.7, 165.5 [Figure S8, SI].

Table 5. Polymerization Conditions and Characterization Data of P1, P2, and P4

| polymer | CTA agent | monomer | initiator | temp (°C) | time (h) | \(M_n\) (g mol\(^{-1}\)) | \(M_w\) (g mol\(^{-1}\)) | \(M_z\) (g mol\(^{-1}\)) | \(\%\) conversion |
|---------|-----------|---------|-----------|-----------|-----------|-----------------|-----------------|-----------------|-----------------|
| P1      | CTA 1     | styrene | AIBN      | 80        | 24        | 8900            | 10 700          | 10 400          | 1.06            | 89              |
| P2      | P1        | 4-vinylbenzaldehyde | AIBN | 80 | 12 | 14 300 | 15 400 | 1.15           | 78              |
| P4      | CTA 1     | styrene + 4-vinylbenzaldehyde | AIBN | 70 | 24 | 8800  | 1.85            | 85              |

*aStatistical value. bEstimated from \(^1\)H NMR. cFrom gel permeation chromatography (GPC); solvent used for polymerization: 1,4-dioxane.

Synthesis of CS Polymer from P2a and CL. P2a (0.063 g, 0.189 mmol) was dissolved in dry dichloromethane (DCM) (5 mL) under nitrogen atmosphere. Magnesium sulfate (0.043 g, 0.36 mmol) was added to it, and the reaction mixture was placed on ice bath. Iodobenzenediacetate (0.114 g, 0.36 mmol) was added to the polymer solution at 0 °C, and the reaction mixture was stirred for 30 min. Then, CL (0.024 g, 0.075 mmol) in dry DCM (3 mL) was added slowly for 15 min at 0 °C, and the reaction mixture was left to stirring overnight at room temperature. The reaction mixture was filtered and concentrated, the polymer was precipitated from ice-cold hexane/methanol mixture, and the pure CS polymer was obtained by reprecipitation method.

Formation of Isoxazoline Polymer from P5 and CL. Four-arm CL (0.101 g, 0.287 mmol), iodobenzenediacetate (0.369 g, 1.14 mmol), and MgSO\(_4\) (0.138 g, 1.14 mmol) were taken in a 25 mL double-neck round-bottom flask under N\(_2\) atmosphere. Then, 5 mL of dry DMF was added to it and the reaction mixture was put in an ice bath. After stirring for 30 min, P5 (0.15 g, 0.015 mmol) in dry DMF (1.0 mL) was added dropwise for 15 min at 0 °C. Then, the reaction mixture was kept in 0 °C for further 1 h and finally left to stirring at room temperature for 24 h. Unreacted MgSO\(_4\) was removed by filtration, the polymer was precipitated from ice-cold hexane/methanol mixture, and the residue was repeatedly washed with hexane/methanol for complete removal of unreacted CL and iodobenzenediacetate. The residue was then collected and dried under high vacuum.

Formation of Click Product from P2a and Ethyl Acrylate. Iodobenzenediacetate (0.159 g, 0.494 mmol) and MgSO\(_4\) (0.059 g, 0.494 mmol) were taken in a 25 mL double-neck round-bottom flask under N\(_2\) atmosphere. Then, 5 mL of ethyl acrylate was added to it and the reaction mixture was put in an ice bath. After stirring for 15 min, P2a (0.1 g, 0.3 mmol) in dry DMF (1.0 mL) was added dropwise for 30 min at 0 °C. Then, the reaction mixture was kept in 0 °C for further 1 h and finally left to stirring at room temperature for 24 h. MgSO\(_4\) was removed by filtration, the polymer was precipitated from ice-cold hexane/methanol mixture, and the residue was repeatedly washed with hexane/methanol for complete removal of unreacted ethyl acrylate and iodobenzenediacetate. The residue was then collected and dried completely under high vacuum.

The formation of isoxazoline ring was confirmed by proton NMR analysis. 1H NMR (DMSO-d\(_6\)): \(\delta\) 1.565 (br, CH\(_2\)CH\(_2\) polymer backbone), 1.887 (br, CH\(_2\)CH\(_2\) polymer backbone), 4.153 (br, \(-\text{CHCH}=\text{NOH}\)polymer), 5.225 (br, \(-\text{CHO}\)polymer), 6.625 (br, Ar, polymer), 7.066 (br, Ar, polymer), 7.391 (br, Ar, polymer) [Figure 4].
Synthesis of Poly(styrene-r-4-vinylbenzaldehyde) (P6). P6 was synthesized by the same procedure as that of P4. Styrene (2.0 g, 0.019 mol), 4-vinylbenzaldehyde (0.132 g, 0.001 mol), and CTA (54 mg, 0.20 mmol) were taken in a 25 mL single-neck round-bottom flask with a magnetic bar. AIBN (9.77 mg, 0.059 mmol) and 2.0 mL of 1,4-dioxane were then added to it. The reaction mixture was then degassed, purged thoroughly with nitrogen, like before, and stirred at 70 °C for 24 h. Upon increase of viscosity of the reaction mixture, the polymerization was then quenched and the polymer was recovered by precipitating in ice-cold hexane. The precipitation was filtered, washed with ice-cold hexane, and dried to obtain polymer P6 as a yellow solid (80% yield). 1H NMR (CDCl3): δ 0.843 (br, -(CH3)2S(C=S)S(CH3)2), 1.317 (br, CHCH2 polymer backbone), 1.834 (br, CHCH2 polymer backbone), 6.512 (br, Ar, polymer), 7.023 (br, Ar, polymer), 7.533 (br, Ar, polymer), 9.873 (br, CH(==N)OH polymer).

Synthesis of Poly[styrene-b-(styrene-r-4-vinylbenzaldehyde)] (P6a−e) and Their Corresponding Oximes (P7a−e, Scheme 2A). The synthetic route to prepare block copolymer containing aldehyde and oxime groups is similar to the synthesis of P2 and P2a, as shown in Scheme 1A. P6 (0.25 g) was taken along with 25, 50, 75, and 100 equiv of styrene monomer in the presence of AIBN (0.2 equiv) and 1 mL of 1,4-dioxane. After degassing the reactor properly, the reaction mixture was stirred at 70−72 °C for 30 h. The reactions were quenched once the viscosity increased, and the polymer was precipitated out in ice-cold hexane/methanol mixture.

Table 6A. Characterization Table of Oxime-Based Polymers (P7a−e)

| Polymer | Addition of Styrene | Molecular Weight (g mol⁻¹) | D (Mw/Mn) |
|---------|---------------------|---------------------------|-----------|
| P7a     | _                   | 11150                     | 9000      | 1.24       |
| P7b     | 25 eq. (0.078 g)    | 13800                     | 11050     | 1.25       |
| P7c     | 50 eq. (0.156 g)    | 13850                     | 11750     | 1.18       |
| P7d     | 75 eq. (0.234 g)    | 18200                     | 13000     | 1.40       |
| P7e     | 100 eq. (0.312 g)   | 18700                     | 13850     | 1.35       |

Synthesis of Poly(styrene-r-4-vinylbenzyl chloride) (P8, Scheme 2B). Styrene (2.0 g, 0.019 mol), 4-vinylbenzyl chloride (0.154 g, 0.001 mol), and CTA (54 mg, 0.20 mmol) were taken in a single-neck round-bottom flask. AIBN (9.77 mg, 0.059 mmol) and 2 mL of 1,4-dioxane were then added to the flask. The flask was then degassed, purged with nitrogen, in the usual manner, and stirred at 70 °C for 20 h. Upon increase in the viscosity of the reaction mixture, the polymerization was quenched and the polymer was recovered by precipitating in ice-cold hexane. The precipitation was filtered, washed with ice-cold hexane, and dried thoroughly to obtain polymer P8 as a yellow solid (78% yield).

Synthesis of Poly[styrene-b-(styrene-r-4-vinylbenzyl chloride)] (P8a−e). P8 (0.2 g) was taken along with 25, 50, 75, and 100 equiv of styrene monomer in the presence of AIBN (0.2 equiv) and 1 mL of 1,4-dioxane. After degassing the reactor properly, the reaction mixture was stirred at 70−72 °C for 30 h. The reactions were quenched once the viscosity increased, and the polymer was precipitated out in ice-cold hexane.
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