Straightforward Access to Block and Gradient Light-Responsive Poly(2-Oxazoline)S via Cationic Ring Opening Polymerization Of 2-Azobenzenyl-2-Oxazoline

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Light-responsive polymers are a prospective area of smart materials. The increasing number of potential applications of these materials require the development of new polymers sensitive to external irradiation. However, most of the polymers reported so far are represented by poly(meth)acrylates. In this work, the straightforward approach is proposed to the synthesis of light-responsive poly(2-oxazoline)s via cationic ring-opening polymerization of 2-azobenzenyl-2-oxazoline (2-(4-(phenyldiazenyl)phenyl)-2-oxazoline). Polymerization kinetics studies reveal significant activity of the new monomer in both homopolymerization and copolymerization with 2-ethyl-2-oxazoline. The difference in monomer reactivity allows obtaining both gradient and block copolymers via simultaneous or subsequent one-pot polymerization, respectively, leading to a set of well-defined gradient and block copoly(2-oxazoline)s with 10–40% of azobenzene units. Due to their amphiphilic nature, the materials self-assemble in water, which is proven by dynamic light scattering and transmission electron microscopy. The change in polarity caused by the isomerization of azobenzene fragments in response to UV light irradiation results in a change of nanoparticle size. The obtained results provide a new impulse for the development of light-responsive materials based on poly(2-oxazoline)s.

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1. Introduction

The term "smart polymer material" implies the adaptation of its properties – such as solubility, size, chemical reactivity, etc. – to the surrounding conditions. This behavior may occur as a response to a chemical, biochemical, or physical trigger.[1] The last group of stimuli attracts special attention because it allows remote control over the material behavior.[2] In particular, the introduction of light-sensitive moieties into the polymer structure allows one to tune its properties by applying light of a specific wavelength. Such light-responsive polymers have a broad field of potential applications in liquid crystal devices, smart surfaces, membranes, photochromic textiles, or in temporally and spatially controlled drug delivery.[3–7]

The reversibility of the properties of the light-responsive polymer is an important parameter determining its functionality. To date, azobenzene is a chromophore of the primary choice for the synthesis of light-responsive polymers.[8] The thermodynamically stable and nonpolar *trans*-azobenzene isomerizes into *cis*-azobenzene under UV-light irradiation, which is accompanied by a significant increase in its dipole moment (μ_{cis} = 3 D).[9] *Cis*-azobenzene, in turn, undergoes the reverse transition under blue light exposure or heating (45–50 °C).[10,11] The introduction of azobenzene into a given polymer structure provides a reversible change in the polarity of the final material under spatiotemporal control. Although the harmfulness of UV light limits the usage of azobenzene-containing polymers in bio-related applications, it is still highly attractive for other fields.[12–14]

The majority of to-date described polymers with azobenzene units in the side chain are based on poly(meth)acrylates obtained via controlled radical polymerization of the respective monomers. Only a few examples of other classes of polymers containing azobenzene are known.[15,16] Over the decades, poly(2-oxazoline)s have proven themselves as a prospective platform for the preparation of smart materials.[17,18] Narrow molar mass distribution, achievable via cationic ring-opening polymerization (CROP), and wide availability of the monomers provide a huge playground for polymer design. However, the demands placed on functional groups of monomers and reaction conditions make it less attractive compared to other polymerization

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techniques. This fact might explain why only a few examples of light-responsive materials based on poly(2-oxazoline)s exist, and yet here the introduction of the chromophore was performed via chain end or post-polymerization functionalization.[19–22] In the current work, we explore and investigate an alternative route to the synthesis of light-responsive polymers via direct polymerization of 2-(4-(phenyldiazenyl)phenyl)-2-oxazoline (2-azobenzenyl-2-oxazoline, AzBenOx). Although several examples of azo-benzene containing poly(2-oxazoline)s are known, this chromophore was never incorporated directly via CROP. The introduction of the chromophore in the monomeric unit provides more precise control over the structure of the final material, and it opens prospects for the synthesis of new stimuli-responsive poly(2-oxazoline)s.

2. Results and Discussion

AzBenOx was synthesized via cyclization of β-haloamide, as shown in Scheme S1 (Supporting Information). Because of the significant electron-withdrawing effect of the azobenzene fragment, 2-bromoethylamine hydrobromide was used instead of the more common 2-chloroethylamine hydrochloride. This, in turn, results in the direct formation of the desired 2-oxazoline with high yield and purity, obviously due to the high reactivity of the intermediate N-bromoethylamide.

Homo- and copolymerization kinetics studies were conducted in a microwave reactor according to a standard protocol at 140 °C in chlorobenzene using p-toluenesulfonate (MeOTos) as an initiator (see Sections S3.1 and S3.2, Supporting Information for details).[23] The homopolymerization kinetic plot clearly shows an increase in monomer conversion with time (Figure S3, Supporting Information). However, while at a short reaction time the linear fit holds, the deviation from the linearity increases with conversion, which might be caused by slow initiation. Moreover, due to strong $\pi-\pi$ interactions, the solubility of growing chains decreases, and at a conversion above ≈30% (DP ≈15), the polymer precipitates making further polymerization impossible.

The kinetics of the copolymerization of EtOx and AzBenOx were recorded at the ratio EtOx:AzBenOx:MeOTos = 25:25:1, with a total monomer concentration of 1 mol L⁻¹. As could be seen from the kinetic plot (**Figure 1**), the consumption of EtOx proceeds with a linear trend, typical for living CROP. The k_p value calculated from the slope is 0.115 L•mol⁻¹•s⁻¹, which is in good agreement with the literature.[24] On the kinetic plot of AzBenOx two regions could be distinguished. The first belongs to simultaneous polymerization with EtOx and is characterized by a higher polymerization rate (Figure 1, solid line; k_p ≈ 0.025 L•mol⁻¹•s⁻¹). The accelerated consumption of the less reactive comonomer is well known for the CROP of 2-oxazolines and attributed to increasing of the k_p value after the first propagation step due to intramolecular ion-dipole stabilization of the reactive center, and higher nucleophilicity of EtOx terminal units, which shifts the equilibrium toward reactive cationic species and promotes for attachment of less nucleophilic AzBenOx.[24,25] After the full conversion of EtOx the slope noticeably decreases, while remaining significantly higher than for the homopolymerization of AzBenOx (Figure 1, dashed line). The SEC traces also show an increase in molecular weight with conversion while the dispersity remains below 1.2 (Figure S4, Supporting Information).
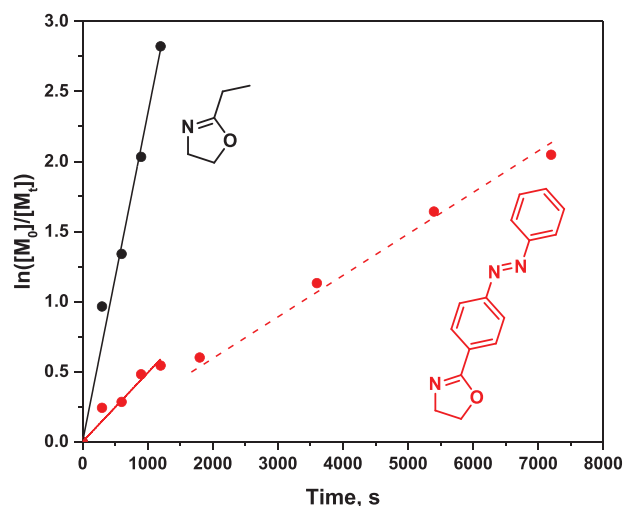

Figure 1. Polymerization kinetics of copolymerization of EtOx and AzBenOx.

The k_p value of AzBenOx determined from the slope after the full conversion of EtOx (0.015 L•mol⁻¹•s⁻¹) could be considered as a "quasi-homopolymerization" rate constant of AzBenOx.
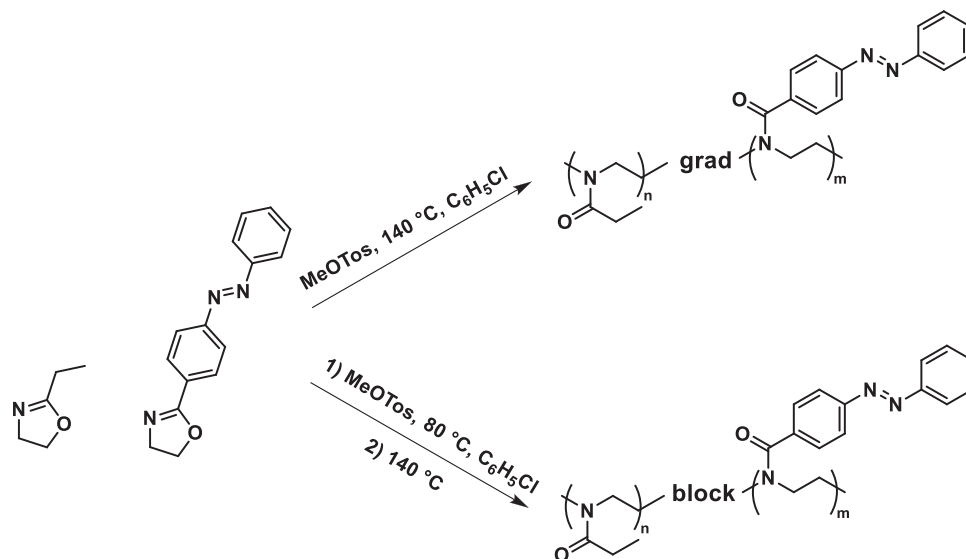
As could be concluded from the kinetic studies, the simultaneous copolymerization of the monomers results in the spontaneous formation of gradient copolymers.[26,27] On that basis, a library of P(EtOx-grad-AzBenOx) copolymers with different monomer ratios was synthesized (**Scheme 1**). The block copolymers of the same composition could be prepared by subsequent polymerization of monomers.[28] However, the significant differences in the reactivity of the monomers allow the application of "One-Shot" copolymerization, when the more reactive comonomer (EtOx) could be polymerized in the presence of the second comonomer (AzBenOx) without its significant involvement in the polymerization reaction.[29,30] Thus, three block copolymers of different compositions were synthesized in two stages, as presented in Scheme 1.

According to Hoogenboom et al., k_p value for EtOx at 80 °C is 0.0015 L•mol⁻¹•s⁻¹, which allows for achieving full conversion in a reasonable time, while the conversion of AzBenOx remains negligible.[25] As could be seen from the NMR after the first step there are no leftover signals from EtOx, while AzBenOx remains in the reaction mixture (Figure S7A, Supporting Information). After the second step (140 °C), the signals from the azobenzene monomer vanished, while broad signals of aromatic units at 7.5–8.5 ppm appeared, indicating successful copolymerization. The formation of block copolymers was also proven by SEC, exhibiting an increase in molecular weight after the second step (**Figure 2**; Figure S8, Supporting Information).
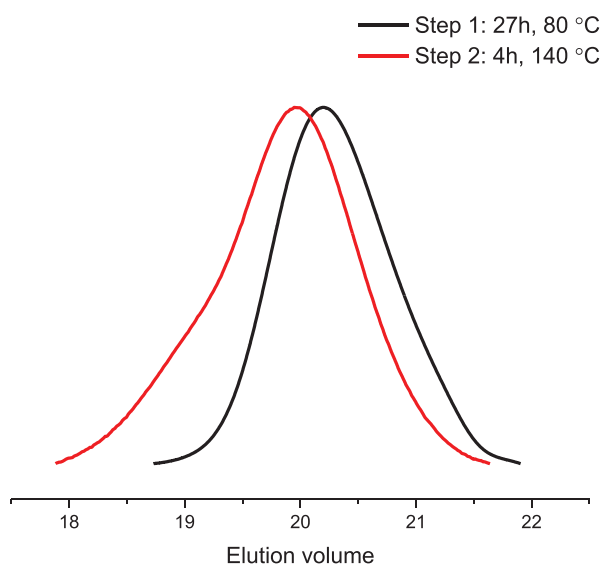
It should be noted, that despite the huge difference in the reactivities of EtOx and AzBenOx, the incorporation of AzBenOx units during the first step cannot be completely excluded.[31] Therefore, hereinafter under the term "block" we refer to steep gradient or quasi-block copolymers.

The characteristics of the obtained quasi-block and gradient copolymers are summarized in **Table 1**.

In the next stage, the ability of the obtained copolymers to form micelles in water was studied by dynamic light scattering. As

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Scheme 1. Synthetic route to P(EtOx-grad-AzBenOx) and P(EtOx-block-AzBenOx).

Figure 2. SEC (DMAc / LiCl) – Elugram of PEtOx$_{0.82}$-block-PAzBenOx$_{0.18}$ after first (80 °C, 27 h, black curve) and second step (140 °C, 4 h, red curve).

Table 1. Comparison of different gradient and block copolymers.

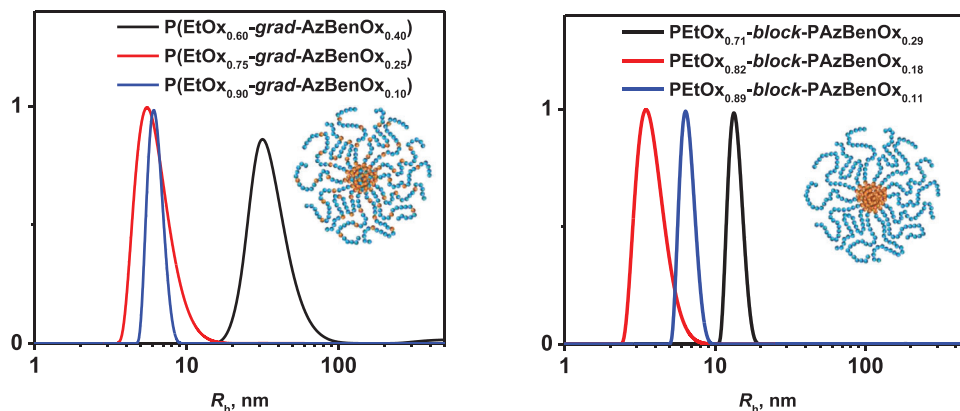| Copolymers composition	M_n, g mol^{-1} [α]	Đ [α]	AzBenOx, mol % [β]
P(EtOx$_{0.60}$-grad-AzBenOx$_{0.40}$)	5700	1.16	40
P(EtOx$_{0.75}$-grad-AzBenOx$_{0.25}$)	7300	1.22	25
P(EtOx$_{0.90}$-grad-AzBenOx$_{0.10}$)	7700	1.21	10
PEtOx$_{0.71}$-block-PAzBenOx$_{0.29}$	7000	1.22	29
PEtOx$_{0.82}$-block-PAzBenOx$_{0.18}$	5600	1.20	18
PEtOx$_{0.89}$-block-PAzBenOx$_{0.11}$	8600	1.17	11

[α] obtained by SEC; [β] obtained by ^{1}H NMR.

expected, the distribution functions of R_h confirm the presence of nanosized aggregates in solutions of both block and gradient copolymers (**Figure 3**). For both sets, there is a tendency to increase the radius of the particles with increasing of AzBenOx content. Although these observations are consistent with a general trend for amphiphilic copolymers, it is worth noting that this is different from that reported in Milonaki et al., where the authors find that a higher hydrophobic content corresponds to smaller particle sizes in case of similar gradient copolymers of 2-methyl-2-oxazoline and 2-phenyl-2-oxazoline.[32]
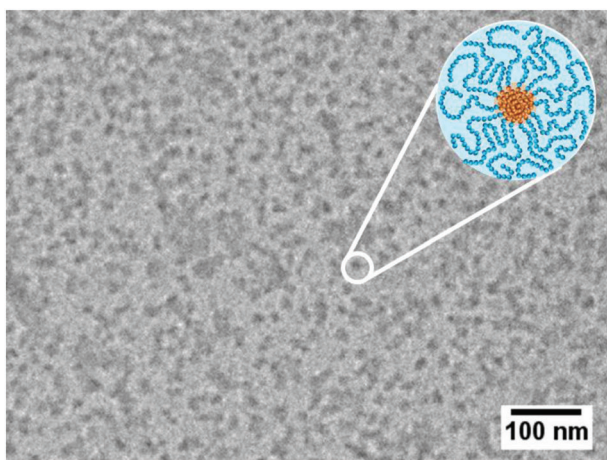
The TEM image of PEtOx$_{0.71}$-block-PAzBenOx$_{0.29}$ shows spherical micelles with a narrow radius distribution (**Figure 4**), that could be attributed to nanostructures with an azobenzene core and a hydrophilic PEtOx corona.

The reversible isomerization of azobenzene units under UV (365 nm) and visible light (450 nm) irradiation in the herein obtained copoly(2-oxazoline)s was confirmed by UV/vis spectroscopy (Figures S9 and S10, Supporting Information). Since *cis*-azobenzene possesses a significantly increased polarity compared to the *trans*-isomer, one can expect changes in the size or structure of nanoparticles in solution in response to irradiation. To explore this effect, additional DLS experiments under UV irradiation (LED 365 nm) were performed for PEtOx$_{0.71}$-block-PAzBenOx$_{0.29}$ and P(EtOx$_{0.75}$-grad-AzBenOx$_{0.25}$). As can be seen from the distribution function, after 1 h of UV irradiation, the hydrodynamic radius of the nanoparticles in the solution of PEtOx$_{0.71}$-block-PAzBenOx$_{0.29}$ decreased from ≈14 to ≈7 nm (**Figure 5**). The gradient copolymer of similar composition also shows a response to UV irradiation. However, in this case, the R_h increases from ≈5 to ≈9 nm.

These opposite effects should be attributed to the difference in the distribution of monomeric units in block and gradient copolymers. According to recent studies, there is a clear difference in the microstructure of the hydrophobic core of block and gradient copolymer micelles. The block copolymers have a distinct border between the hydrophilic and the hydrophobic part. Therefore, the distribution of hydrophobic units in the core of the respective

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Figure 3. Distribution functions of hydrodynamic radius R_h of gradient- (left) and block-copolymers (right) in aqueous solution.

Figure 4. TEM micrograph of PEtOx$_{0.71}$-block-PAzBenOx$_{0.29}$ nanoparticles from aqueous solution at a concentration of 1 mg mL^{-1}.

micelle is constant with smooth decay when approaching from the center of the micelle to its periphery.[33,34] UV light-induced isomerization of azobenzene units in the core increases their polarity, and, therefore, affinity to water. This, in turn, entails restructuring of the micelles and results in a decrease of their radius. In contrast, the core of gradient copolymer micelles is characterized by a significant content of hydrophilic units with a maximum at the core–corona interface, which is explained by the formation of hydrophilic loops.[33,34] When exposed to UV light, some fraction of azobenzene units "escape" from the core–corona interface, contributing to unfolding of the loops and "rolling out" of the gradient micelle. The opposite – "roll-in" effect – was described for gradient copolymer micelles containing thermoresponsive units in the core.[35] Besides that, the higher polarity of *cis*-azobenzene units might also induce swelling of the core.

Thus, the difference in the microstructure determines the behavior of nanoparticles in an aqueous solution under irradiation. Despite varying trends in size upon irradiation, the DLS results clearly confirm the light-responsiveness of the herein-described copolymers.
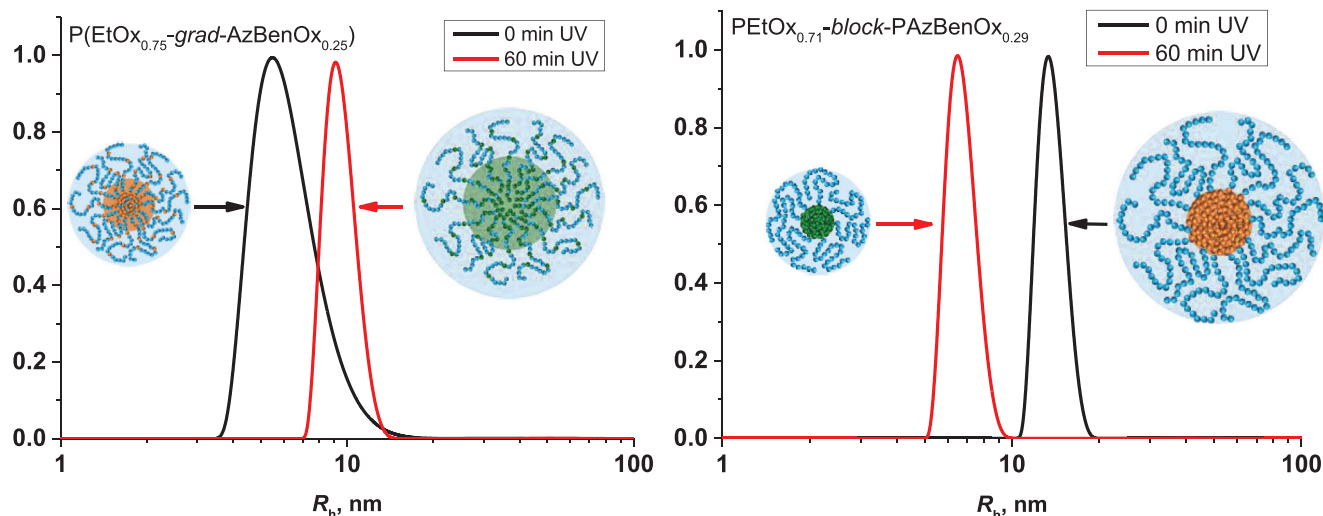
Figure 5. Distribution functions of hydrodynamic radius R_h after LED (365 nm) irradiation of 1 h, in aqueous solution. (DLS laser wavelength = 532 nm) Left: gradient copolymer P(EtOx$_{0.75}$-grad-AzBenOx$_{0.25}$). Right: block copolymer PEtOx$_{0.71}$-block-PAzBenOx$_{0.29}$.

3. Conclusions

In conclusion, we successfully performed the synthesis and polymerization of a new 2-oxazoline monomer with an azobenzene substituent. The polymerization kinetics show the activity of this monomer in cationic ring-opening copolymerization with 2-ethyl-2-oxazoline and the spontaneous formation of gradient copolymers. This allows the direct incorporation of the chromophore into the structure of poly(2-oxazoline)s. Furthermore, a significant difference in the reactivity of these monomers allows the synthesis of quasi-block copolymers via subsequent polymerization of a mixture of comonomers at varying reaction temperatures, leading to a small library of light-responsive poly(2-oxazoline)s with low dispersity in the range of 1.16–1.22. Self-assembly in aqueous media was confirmed by dynamic light scattering and we also demonstrated that the size of nanoparticles in solution changes in response to external UV irradiation. Our herein presented approach for direct incorporation of azobenzene provides a strategy for the development of new poly(2-oxazoline)-based materials for such fields as drug delivery, smart surfaces, or liquid crystalline polymers for optics and electronics.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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