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Painting Supramolecular Polymers in Organic Solvents by Super-resolution Microscopy

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ABSTRACT: Despite the rapid development of complex functional supramolecular systems, visualization of these architectures under native conditions at high resolution has remained a challenging endeavor. Super-resolution microscopy was recently proposed as an effective tool to unveil one-dimensional nanoscale structures in aqueous media upon chemical functionalization with suitable fluorescent probes. Building upon our previous work, which enabled photoactivation localization microscopy in organic solvents, herein, we present the imaging of one-dimensional supramolecular polymers in their native environment by interface point accumulation for imaging in nanoscale topography (iPAINT). The noncovalent staining, typical of iPAINT, allows the investigation of supramolecular polymers’ structure in situ without any chemical modification. The quasi-permanent adsorption of the dye to the polymer is exploited to identify block-like arrangements within supramolecular fibers, which were obtained upon mixing homopolymers that were prestained with different colors. The staining of the blocks, maintained by the lack of exchange of the dyes, permits the imaging of complex structures for multiple days. This study showcases the potential of PAINT-like strategies such as iPAINT to visualize multicomponent dynamic systems in their native environment with an easy, synthesis-free approach and high spatial resolution.

KEYWORDS: self-assembly, super-resolution microscopy, supramolecular block copolymers, single-molecule localization microscopy, multicomponent unidimensional aggregates, iPAINT

Complex supramolecular systems have fascinated chemists, biologists, physicists, and material scientists for decades.1 In biological and synthetic materials, control over the architecture of multicomponent systems is pivotal for their performance, such as storing information,2–4 generating motion,5–8 performing catalytic reactions,9,10 and enhancing optoelectronic properties.11–13 Recently, the emerging class of supramolecular polymers established its role as versatile systems for a broad range of functionalities.14 Despite considerable progress, visualization and in-depth understanding of the microstructure of such dynamic self-assembled polymers remains a formidable challenge.15 Conventional tools, such as spectroscopy and light scattering, are powerful yet insufficient to unambiguously determine supramolecular organization in a direct manner without modeling. By contrast, microscopy offers direct access to real-space information but often not at the required spatial resolution nor without perturbation of the object of interest. This latter impediment is particularly relevant for intrinsically dynamic systems, such as supramolecular fibers where molecular components are held together by noncovalent interactions. Recently, super-resolution microscopy has been introduced as an effective tool to overcome these obstacles.17–20 The widespread employment of single-molecule localization microscopy (SMLM) to image in situ natural20–23 and synthetic24–29 supramolecular polymers is a testament to its great utility. Indeed, it has opened the door to a better understanding of the exchange dynamics and formation pathways of one-dimensional aggregates.28,30–33 Unfortunately, most SMLM strategies applied to supramolecular fibers require chemical functionalization of the systems with dyes, which involves time-consuming synthesis and can potentially influence the supramolecular structure. Instead, PAINT (point accumulation for imaging in nanoscale topography)36 microscopy circumvents this requirement as it exploits

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(transient) aspecific\textsuperscript{18} or specific\textsuperscript{19,20} physisorption of fluorescent dyes onto the surfaces of objects of interest.

Inspired by (DNA-)PAINT and photoactivation localization microscopy (PALM) approaches, we recently introduced a combinatorial extension of these techniques coined iPAINT (interface point accumulation for imaging in nanoscale topography) featuring higher control over dye photoswitching and more general applicability.\textsuperscript{35} This method has since been used to visualize interfaces of water–oil emulsions, air nanobubbles,\textsuperscript{37} and micelles,\textsuperscript{38} rendering it a promising strategy for imaging of supramolecular polymers. iPAINT utilizes caged rhodamine dyes as fluorophores (Scheme S1).\textsuperscript{39,40} It exploits the uncaging and subsequent localization of a small subpopulation of photoactivatable rhodamine dyes to improve spatial resolution. The uncaging of these fluorophores involves the photolysis of the photoactivatable moiety with low-power ultraviolet light, a Wolff rearrangement, followed by a nucleophile attack on the resulting ketene.\textsuperscript{39,40} This last step requires the presence of an auxiliary nucleophile, which has thus far limited iPAINT’s utility to aqueous media. However, recent works by the groups of Kaminski and Manners\textsuperscript{\textsuperscript{9}} and Voets\textsuperscript{\textsuperscript{2}} have pointed out a potential solution. It was found that caged rhodamine dyes may be used in organic solvents for PALM (photoactivated localization microscopy) in the presence of a small percentage of alcohols that acts as a source of nucleophiles for uncaging the dyes. To evaluate the applicability of this advance in iPAINT, we explore herein its employment in the investigation of dynamic supramolecular systems in nonpolar organic media. Through a comprehensive series of control experiments, we establish that the quasi-permanent labeling of the fibers is critical to yielding remarkable fidelity in resolving supramolecular microstructures. The versatility of this approach is finally demonstrated in twocolor iPAINT experiments that unveil nanometer thin, micrometer long supramolecular block copolymers.

**RESULTS AND DISCUSSION**

To optimize iPAINT for imaging supramolecular polymers in organic solvents, we adapted the previously reported strategy\textsuperscript{37} in the following manner (Figure 1). First, we added 1% (v/v) isopropyl alcohol (i-PrOH) to sample solutions to ensure the formation of the fluorescent species. Second, we chose not to attach the dyes to polyethylene glycol chains, as described in previous iPAINT protocols,\textsuperscript{35} to enhance solubility in organic media and to minimize interference with supramolecular fiber formation. We first performed single-color iPAINT experiments on several hydrogen-bond-based supramolecular polymers in methylcyclohexane (MCH) with the aim to establish a reliable imaging routine. In addition to the classical chiral benzene tricarboxamide (S-4),\textsuperscript{43} we selected chiral (S-1) and achiral (A-1) tripyridylamine tricarboxamides;\textsuperscript{44} chiral (S-2) and achiral (A-2) triphenylamine tricarboxamides; and chiral biphrenyl tetracarboxamide (S-3) (Figure 2a). All chiral derivatives bear (S)-3,7-dimethyloctyl chains, whereas the achiral analogues possess n-dodecyl chains. Each monomer was allowed to self-assemble in MCH to form one-dimensional supramolecular homopolymers (e.g., poly(S-1)) via slow cooling from 100 to 20 °C at either 15 or 60 °C h\textsuperscript{-1}. For imaging purposes, approximately 0.5–1% (v/v) caged dye (Cage-SS2 or Cage-635, 10 mM in DMSO) (Scheme S1) and 1% (v/v) i-PrOH were added. As a result, the dyes “stain” the fibers through noncovalent, nonspecific interactions (Figure 1).

Because a small amount of polar solvent, such as DMSO and i-PrOH, can denature H-bond-based networks of supramolecular polymers,\textsuperscript{45–47} we performed spectroscopic control experiments that confirmed the stability of the fibers under iPAINT conditions (Figure S1). For clarity, the dye used to visualize each respective polymer is denoted by a superscript label (e.g., poly(S-1))\textsuperscript{C635}. Once immobilized on the microscope coverslip, the stained fibers can be imaged by iPAINT. This is because the translational motion and the monomer exchange\textsuperscript{30} are effectively arrested upon physisorption onto the substrate, allowing for single-molecule localization with high precision. iPAINT imaging reveals the formation of micrometer long and 26–100 nm thick fibers for poly(S-1)\textsuperscript{C635}, poly(S-2)\textsuperscript{C635}, and poly(A-2)\textsuperscript{C552}. Poly(S-3)\textsuperscript{C552} and poly(S-4)\textsuperscript{C552} samples were ~26 nm thick (Figures 2 and S2–S4), whereas poly(A-1)\textsuperscript{C552} exhibits bundles of multiple fibers (25 nm up to hundreds of nanometers thick), likely driven by its scarce solubility in MCH (Figure 2d). These results illustrate the potential of iPAINT imaging to visualize supramolecular fibers in organic solvents—without any chemical modification of their respective monomer units—and to discern between one-dimensional polymers and bundled aggregates, with a spatial resolution down to ~20 nm (Figure S2). Additionally, to demonstrate the applicability of iPAINT imaging in both organic and aqueous solvents, we visualized water-soluble 1,3,5benzenetricarboxamide-based supramolecular polymer poly(W-4)\textsuperscript{33} by iPAINT in water (Figure S5a). In agreement with what we previously observed by STORM microscopy\textsuperscript{30} on poly(W-4) covalently labeled with Cy-5 dyes, we visualize micrometer long and nanometer thin fibers (Figure S5b,c), confirming the broad applicability of iPAINT.

Although physisorption onto a surface is well-known to hamper the monomer exchange of supramolecular fibers in water,\textsuperscript{30} the dynamics of these polymers dissolved in organic solvents in the absence as well as in the presence of dyes remains unclear. We hence sought to elucidate the effect of dye physisorption on the dynamics of the homopolymers in solution. To do so, we performed two-color iPAINT experiments on fibers formed by mixing chemically equivalent, but differently stained, supramolecular homopolymers as poly(S-1)\textsuperscript{C635} and poly(S-1)\textsuperscript{C552} (Figure 3a). Imaging reveals essentially equivalent poly(S-1) fibers in both red and green channels (Figure 3b,c). This indicates that the resulting fibers are randomly stained with red and green dyes, labeled as poly(S-1)\textsuperscript{C635/C552} (Figure 3d) and implies a fast exchange between poly(S-1)\textsuperscript{C635} and poly(S-1)\textsuperscript{C552} in organic media. Monomer exchange takes place within tens of seconds—that is, the time between mixing the solutions and the adsorption of the fibers on the coverslip, at which point monomer exchange is suppressed. We repeated this experiment with poly(S-2) and observed the same effect (Figures 3f–i). We verified these observations by quantifying the single-molecule localizations in both channels for several fibers, which revealed a high number of localizations in both channels (>70%) along the fibers (Figure 3ej). Moreover, the same set of experiments was performed after heating stained polymers (Figure S6) to 90 °C and then cooling them back to 20 °C, thereby disassembling and reassembling the fibers. In all cases, fiber formation was observed, and dye–polymer correspondence was lost, demonstrating that the dyes do not self-sort nor hamper exchange among supramolecular polymer chains.

We next demonstrate the simplicity and versatility of this technique by visualizing more advanced supramolecular fibers.
in two-color experiments. We focused on imaging the supramolecular block copolymer poly[\((S-1)\)-co-\((S-2)\)], which can be formed by the addition of poly\((S-1)\) to poly\((S-2)\) at 40 °C, as we recently discovered (unpublished work). Before mixing the homopolymers for iPAINT imaging, we selectively stained poly\((S-1)\) with Cage-635 (red dye), giving poly\((S-1)\) C-635, and poly\((S-2)\) with Cage-552 (green dye) to give poly\((S-2)\) C-552, and then we added 1% v/v i-PrOH to each solution. The prestained homopolymers were thus mixed in a 1:1 ratio at 40 °C (Figure 4a). iPAINT imaging revealed a distinct block-like arrangement of red- and green-stained segments within the supramolecular fibers (Figure 4b–d). We observed a preference for the formation of di- and triblock copolymers with a mean block length of roughly 3–4 μm, consistent with the formation of poly[(S-1) C-635-co-(S-2) C-552]. A similar segregation has only been observed for supracolloidal polymeric chains and supramolecular amyloid fibers. To quantify the segregation of blocks within single fibers, we counted the number of red and green single-molecule localizations in each block. In the red blocks, we have 9% green localizations, whereas in the green blocks, we calculated 18% red localizations (Figure 4e). Given the overlap of the absorption spectra of the two probes at the excitation wavelengths used (Figure S7a) and the uncaging mechanism.
The occurrence of green localizations in the red segments (and red localizations in the green segments) is likely a result of crosstalk of the two-color experiments (Figure S7b) and not due to incorporation of, for example, (S)-1-C635C-552 monomers into poly((S)-2)-C635C-552. Under \( \lambda = 561 \) nm irradiation, Cage-552 shows a non-negligible spectral overlap in the absorption spectrum at that wavelength (\( \sim 20\% \), Figure S7a). Conversely, upon \( \lambda = 647 \) nm irradiation, Cage-552 shows \( \sim 3\% \) spectral overlap in the absorption spectrum (Figure S7a). To quantify the extent of crosstalk at the single-molecule level, we prepared single-color stained fibers and imaged them by iPAINT. We illuminated the sample with both lasers at \( \lambda = 561 \) nm and \( \lambda = 647 \) nm. We calculated that 16% of "false positives" are registered as red localizations on poly((S)-2)-C552 (Figure S8a–c). Conversely, 32% of green localizations have been found on poly((S)-1)-C635 (Figure S8d–f). The percentage of "false positives" calculated at the single-molecule level is higher than when compared to the spectral overlap values, which is due to a prolonged emission of dye molecules in two consecutive frames during the alternate illumination of the sample with two laser lines (see Supporting Information for further details). This results in the localization of the same molecule twice, namely, as red in the first and green in the second frame or vice versa. These extra localizations contribute to an increase of "false positives" registered in the same supramolecular block. For the copolymers displayed in Figure 4, we have less red localizations in the green blocks (and green...
localizations in the red blocks) than these “false positive” threshold values, quantitatively confirming the presence of the block-like architectures.

The remarkable clarity achieved in visualizing these supramolecular architectures was surprising given the dependence of iPAINT on reversible staining and dye exchange. As previously reported, reversible physisorption of fluorescent probes ensures prolonged acquisition times, which in turn leads to a high number of precise localizations, enough to allow the full reconstruction of the object. This is granted by the continuous exchange between the physisorbed dyes and those freely dispersed in solution, permitting a continuous supply of nonbleached dyes at the interface of interest. Interestingly, this feature would have been detrimental for imaging supramolecular block copolymers because the dye–polymer correspondence imposed by prestaining would have been lost. Precisely because we are able here to visualize the block-like architecture of poly[(S-1)-C-635-co-(S-2)-C-635], we suspected dye exchange to be suppressed in organic solvents. This motivated us to investigate in more detail the behavior of physisorbed dyes onto supramolecular fibers. To this end, we quantified the number of localizations along the single-color stained fibers in time (Figure 5) and observed that both caged dyes exhibit an exponential decrease in counts as a function of acquisition time. For fibers stained with Cage-552, no localizations were found after ~200 s (Figure 5a), whereas for the ones stained with Cage-635, localizations are no longer registered after ~80 s (Figure 5b). We attribute this behavior to a lack of dye exchange between supramolecular polymers and the reservoir in organic solvents. In sharp contrast, a continuous replacement of the probes adsorbed onto the fibers with those in solution is maintained in water, where a constant number of localizations is observed throughout the iPAINT experiment (Figure S9). As a consequence of the photobleaching of the quasi-permanently physisorbed dyes, we find an exponential decrease of the localizations in time (Figure 5c). We attribute this behavior to the low solubility of the dye in MCH, which is consequently found to adsorb onto the coverslip. Indeed, when we calculate the number of localizations on the coverslip (i.e., where no fibers are absorbed), we register a mean value of 500 loc/μm². This value is 5 times higher than what is reported for iPAINT in water, consistent with the lower solubility of the dyes in organic solvents.
alkanes and hence their depletion from the reservoir. We thus posit that the observed dye–polymer correspondence is ultimately a consequence of the unexpected noncontinuous labeling of the supramolecular structure.

Additionally, the high visual fidelity of the block-like segments in the two-color experiment requires not only that the physisorbed dyes do not exchange with reservoir dyes but also that the physisorbed dyes do not migrate into neighboring domains—for example, Cage-635 remains primarily in the poly(S-1) segments of poly[(S-1)C<sub>635</sub>-co-(S-2)C<sub>552</sub>]. To evaluate this, we monitored in time the number of single-molecule localizations in the red and green blocks of selected fibers of poly[(S-1)C<sub>635</sub>-co-(S-2)C<sub>552</sub>]. We observed that the decay rates of the red and green localizations within the red block are similar (Figure 5e), and likewise, so they are for the green block (Figure 5f). This suggests there is little or no dye migration along the fiber as this would reduce the correlation between the two signals (Figure 5g).

Once we established that the dynamicity of the supramolecular polymers is maintained upon staining (vide supra, Figure 3) and that the dyes do not self-sort spontaneously (Figure S6a,b), nor exchange with the reservoir, nor migrate along the polymer (Figure S5), we then verified that the dyes have no preferential interaction with one of the two supramolecular homopolymers. To this end, we disassembled poly[(S-1)C<sub>635</sub>-co-(S-2)C<sub>552</sub>]) by heating the solution to 90 °C and reassembled the copolymer by cooling it to 20 °C. This disassembly brings the system to the molecularly dissolved state, which results in the loss of the dye–polymer correspondence. Upon reassembly, the dye molecules randomly adsorb onto the newly formed fibers, resulting in fully green and red stained architectures. This thermal cycle demonstrates the lack of a preferential interaction of the two probes with a specific homopolymer (Figure S6g–i) and confirms the veracity of the imaged block architectures.

Finally, we probed the limits of dye–polymer correspondence in a time-lapse iPAINT imaging series. Spectroscopic experiments revealed that the addition of poly(S-1) to poly(S-2) at 20 °C results in a metastable self-sorted state; the dynamicity of the codissolved homopolymers is evidently low at this temperature. Copolymerization is initiated by either heating the mixture to 27 °C or equilibrating for long periods of time at 20 °C. Intrigued by the possibility of visualizing the progression of self-sorted to blocky supramolecular polymers, we performed iPAINT measurements over the course of 1 week on poly(S-1)C<sub>635</sub> and poly(S-2)C<sub>552</sub> that were mixed at 20 °C. iPAINT images acquired immediately after mixing confirm the presence of self-sorted homopolymers (Figure 6a and Figure S10). After 1 h, iPAINT imaging reveals that poly(S-1)C<sub>635</sub> and poly(S-2)C<sub>552</sub> interact to form supramolecular block copolymers (Figure 6b). The block-like structures obtained are due to a balance between the favorable hydrogen bonding interactions, which support the heterointeractions, and the mismatch penalty that suppresses the complete mixing of the two monomers. This architecture is also observed after allowing the sample to equilibrate for 8 h (Figure 6c) and 3 days (Figure 6d). However, after 1 week, we observed a complete intermixing of the dyes (Figure 6e).

To validate the observed stability of the blocks over time, we evaluated the percentage of green localizations in the red blocks (and red localizations in the green blocks) at each time point. Within the first 3 days of measurements, the percentage of red counts in the green blocks falls below the “false positive” threshold of Cage-635 (Figure 6f). Likewise, the percentage of green localizations in the red blocks falls below the crosstalk threshold of Cage-552 (Figure 6f). After 1 week, however, the percentage of red localizations in the green blocks, and vice

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**Figure 6.** iPAINT imaging at different time-lapses of the mix of poly[(S-1)C<sub>635</sub>] to poly[(S-2)C<sub>552</sub>] at 20 °C. Directly after the mixing, (a) poly[(S-1)C<sub>635</sub>] and poly[(S-2)C<sub>552</sub>] are in a self-sorted state. After 1 h, (b) the system evolves in block copolymers poly[(S-1)C<sub>635</sub>-co-(S-2)C<sub>552</sub>]; (c) 8 h and (d) 3 days after the mixing, iPAINT can still accurately visualize the block architecture. One week after the mixing, (f) iPAINT displays random organization of Cage-635 and Cage-552 along the fiber. (f) Percentage of red counts in green blocks, and vice versa, as a function of time, after 1 week the percentage results are higher than the fluorescence crosstalk of the dyes (dashed line for false green and dashed-dotted line for false red positives). (g) Schematic representation of the migration of the dyes originating the loss of dye–polymer correspondence after 3 days. Imaging performed with 98.5% c<sub>1</sub> = c<sub>2</sub> = 200 μM in MCH, 0.5% caged dye ε = 10 nM in DMSO, 1% i-ProOH.
versa, exceeds the respective crosstalk thresholds, indicating a mixing of the dyes physisorbed along the fibers. Because poly[(S-1)$_{C-635}$-co-(S-2)$_{C-552}$] exhibits stable spectroscopic features for over 1 week in the same imaging conditions (Figure S11), we hypothesize that the mixing observed by iPAINT after 1 week is due to a loss of dye–polymer correspondence. Hence, iPAINT successfully reports on the microstructure of supramolecular block copolymers as long as dye solubility is low and dye–polymer correspondence is maintained.

CONCLUSIONS

In conclusion, we report on the visualization of one-dimensional supramolecular polymers using iPAINT microscopy with a resolution down to ~20 nm. By adapting iPAINT microscopy to image structures in apolar solvents, we introduce a facile, synthesis-free technique that allows for imaging of dynamic supramolecular architectures. The hindered exchange of dyes between the reservoir and the stained interface, as well as the hampered migration of dyes along the fibers, grants the dye–polymer correspondence imposed by pre-staining the supramolecular homopolymers. This ensures the investigation of the arrangement of microstructure in poly[(S-1)$_{C-635}$ and poly[(S-2)$_{C-552}$] mixtures. We visually confirmed the existence of poly[(S-1)$_{C-635}$-co-(S-2)$_{C-552}$] as a block-like supramolecular architecture, which is consistent with extensive spectroscopic characterization. A thorough analysis of “false positive” localizations has been carried out to ascribe the red/green characterizations. A thorough analysis of architecture, which is consistent with extensive spectroscopic microcrosopic grade solvents were employed, and different cells were employed. For CD and UV/vis measurements, a sealable quartz cuvette with an optic path of 1 cm × 1 mm was used. Solutions were prepared by weighing the necessary amount of compound for the given concentration and dissolved with a weighted amount of solvent based on its density. The stock solutions were heated, sonicated until completely dissolved, and slowly cooled to room temperature every time before use unless otherwise specified. The spectroscopic measurements were performed on solutions prepared within the same day. The CD measurement performed after 1 month was carried out on the same sample stored in the dark in a sealable cuvette at 20 °C.

ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsnano.8b00396.

Materials and methods; CD spectroscopy; fiber thickness analysis; fluorescence crosstalk analysis (PDF)

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Notes
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