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## Two Colour Photoflow Chemistry for Macromolecular Design

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**Abstract:** We report a photochemical flow setup that exploits  $\lambda$ -orthogonal reactions using two different colours of light ( $\lambda_1$  = 350 nm and  $\lambda_2$  = 410 nm) in sequential on-line irradiation steps. Critically, both photochemically reactive units (a visible light reactive chalcone and a UV-activated photo-caged diene) are present in the reaction mixture. We demonstrate the power of two colour photoflow by the wavelength-selective end group modification of photo-caged polymer end groups and the subsequent polymer ring closure driven by a [2+2] cycloaddition. Importantly, we evidence that the high energy gate does not induce the visible light reaction of the chalcone, which attests the true  $\lambda$ -orthogonal nature of the flow reactions to  $\lambda$ -orthogonal photochemistry.

In 1920, Hermann Staudinger postulated that covalent bonds between repeating monomeric units are the key element in synthetic high molecular weight molecules.<sup>[11]</sup> The introduction of this concept into the field of chemistry and organic synthesis has laid the foundation of today's understanding of macromolecules. Since this discovery, precision macromolecular design has become a key field, targeting advanced properties and applications on a macromolecular level. A large synthetic toolbox has been established over the last decades, enabling the selective generation and cleavage of bonds to design novel polymeric structures.<sup>[2]</sup> Importantly, not only size, but also polymer shape and morphology can be finely tuned, with control of these structural properties being possible utilising a number of different synthesis methodologies.<sup>[3]</sup>

Amongst the many systems that have been developed to form larger molecular entities through covalent bonds, light-driven reactions have become increasingly popular.<sup>[4]</sup> Not only can they be executed under catalyst-free and ambient conditions (reducing the chance of inducing any side reactions), yet more importantly, they allow the precise spatial and temporal control over chemical reactivity.<sup>[5]</sup> Furthermore, chemical selectivity can be achieved by tuning the wavelength and light intensity.<sup>[6]</sup> Moreover, photoreactions executed in a photoflow system can even further enhance reactivity, selectivity, reaction control and scalability, and have been demonstrated to be of critical value in the field of macromolecular design and organic synthesis.<sup>[7]</sup>

Through the use of flow setups, spatial control can be readily achieved with light, as different segments of the reactor tubing can be irradiated separately at the same time without mutual interference.<sup>[8]</sup> Such a strategy allows to induce reactivity of a reactant mixture at a certain interval of the reactor with one light source, followed by the initiation of another reaction, independent of the former process, with a second source.<sup>[9]</sup> Subsequent reactions can be triggered with other wavelengths, without interfering with the former irradiation paths. Therefore, the flow

**Scheme 1.** Overview of the two-colour photoflow setup. Consecutive irradiation of the compounds with UV-A light ( $\lambda_1$  = 350 nm) and violet-blue light ( $\lambda_2$  = 410 nm), respectively, selectively folds the polymeric chains into macrocycles.

setup can facilitate multi-step processes comparable to a 'one-pot' synthesis strategy by allowing controlled and efficient irradiation of the reactant mixture at all time.<sup>[10]</sup>

Herein, we introduce a photoflow system that can trigger two consecutive photochemical reactions with disparate wavelengths (Scheme 1). The photoligation of o-methylbenzaldehydes (MBA) in flow has been proven to be very efficient and fast in the presence of suitable dienophiles such as maleimides.<sup>[7d]</sup> The generation of reactive dienes upon irradiation with UV-light is therefore a very suitable strategy for chain-end modification using irreversible, light-driven reactions. In addition, a second photoreactive system is introduced at both chain ends that can undergo self-dimerisation, compacting the macromolecular chain into its corresponding cyclic structure. Importantly, the latter visible-light-reactive moiety remains unreacted during the first UV-induced photochemical process under the employed photoflow setup and can be addressed separately upon irradiation with visible light. This constitutes a key example of true  $\lambda$ -orthogonality, where a UV induced photoligation can be triggered without activating a visible-light-reactive chromophore that is present in the same reaction mixture.

We developed a [2+2]-cycloaddition system based on pyrenechalcones that can be activated with violet-blue light close to 410 nm and is unreactive in its monomeric state upon irradiation with UV-light ( $\lambda_{max}$  = 350 nm). Pyrene-chalcones (PC) are therefore ideally suited for the purpose of selective photoligation in combination with MBA-systems. A solution of methoxyfunctionalised pyrene-chalcone (PC-OMe) in a mixture of

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**Scheme 2.** Reaction of *o*-methylbenzaldehyde and maleimide triggered by UV-A light ( $\lambda_{max}$  = 350 nm) in the presence of pyrene-chalcone, resulting in the corresponding Diels-Alder adduct (top). [2+2]-Cycloaddition of pyrene-chalcone after irradiation with violet-blue light ( $\lambda_{max}$  = 410 nm)

acetonitrile and toluene was irradiated with a 10 W 415 nm LED (Scheme 2, Figure S1). UV-Vis spectroscopy confirmed the reactivity of the conjugated m-system upon irradiation with violetblue light. The typical absorbance spectrum of pyrene-chalcone with a maximum around 390 nm changed into an absorbance spectrum with two new maxima around 330 nm and 350 nm (Figure 1b). The new pattern matched with the absorbance spectrum of pyrene, showing two similar maxima in its absorbance spectrum. Therefore, we conclude that the conjugated bond between the pyrene and carbonyl species has undergone photoreaction. Additionally, <sup>1</sup>H-NMR spectroscopy evidences that the resonances of the protons of the conjugated system shifted or disappeared and the newly formed resonances are in good agreement with the formation of a cyclobutane moiety after [2+2]-cycloaddition (Figure 1a). Notably, the cycloaddition of pyrene-chalcones is reversible upon irradiation with UV-light. UV-Vis spectroscopy measurements were performed and the reversibility over time was analysed (Figure 1b). By increasing the irradiation time under UV-B light ( $\lambda_{max}$  = 313 nm), the absorbance peak close to 390 nm becomes more prominent, showing the reoccurrence of the single pyrene-chalcone species. However,

the maxima close between 330 nm and 350 nm remain visible. Therefore, the dimerisation of PC is not entirely reversible and, with time, reaches a certain equilibrium (Supporting Information, Figure S1-2).

In order to assess the  $\lambda$ -orthogonality between the pyrenephotodimerisation and the MBA-maleimide chalcone photoligation, initial small-molecule tests were performed. Equimolar mixtures of 2-methoxy-4,6-dimethylbenzaldehyde (MeO-MBA) and maleimide-functional pyrene-chalcone (PC-Mal) in a mixture of acetonitrile and toluene were irradiated with UV-A light ( $\lambda_{max}$  = 350 nm) under inert conditions (Scheme 2). Experiments were performed in a Luzchem LZC-4V photoreactor setup (refer to Supporting Information Figure S3). The reaction was monitored over time via LC-MS (Figure S4). Full conversion of the starting components over longer irradiation time was observed in LC, while a new species was simultaneously formed that was identified via mass spectrometry as the desired Diels-Alder photoadduct PC-DA with an exact mass of 788.28 Da ([M+Na]<sup>+</sup>). The stability of the pyrene-chalcone functionality was confirmed via UV-Vis spectroscopy, as the absorbance profile showed the presence of the latter moiety (refer to Supporting Information Figure S5). In addition, <sup>1</sup>H-NMR spectroscopy (Figure S6) revealed that the protons corresponding with the maleimide molety and MBA group reacted and that the Diels-Alder adduct was generated.

As we evidence that both reactions can be executed with clean product formation, subsequent experiments were performed combining both reactions to establish  $\lambda$ -orthogonality on the small molecule level. Equimolar mixtures of MeO-MBA and PC-Mal were irradiated with UV-light under the same conditions as before, followed by irradiation with violet-blue light ( $\lambda_{max}$  = 415 nm), while the UV-light was switched off. It must be noted that the sequence of irradiation is critical since pyrene-chalcones can undergo cycloreversion. Cleavage of the covalent bonds can be triggered with UV-light, similar to the conditions employed for MBAmaleimide ligation (Scheme 1). Reversing the order of irradiation might therefore cleave the PC-linkage again, not initiating macrocyclisation when built onto linear chain ends. The reaction was again followed via LC-MS measurements and it was confirmed that both reactions can be executed consecutively without any purification or intermediate step (Figure S7).



Figure 1. a) <sup>1</sup>H-NMR spectra (DMSO-d<sub>6</sub>, 600 MHz) of PC-OMe and the corresponding dimer. Upon dimerisation, a shift can be observed for the aromatic resonances as well as new resonances appearing at 5.15 and 5.35 ppm, identified as the protons of the cyclobutane ring formed after cycloaddition. b) UV-VIS absorption spectra of PC-OMe and the corresponding dimer. Irradiating the dimer with UV-B light regenerates single PC-OMe over time, as the absorbance peak at 390 nm becomes more prominent. All spectra are normalised to the isosbestic point at 360 nm.

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As the  $\lambda$ -orthogonality was proven for the two-chromophore reaction system, the dual-wavelength experimental design was translated to a photoflow reactor setup (Figure S8). Initially, the flow parameters for the individual reactions were investigated. The MBA-maleimide coupling was performed using a self-built photoflow coil with a residence volume of 1 mL that was wrapped around a Luzchem UV-A lamp emitting at 350 nm. Full conversion of the Diels-Alder adduct was achieved at a flow rate of 0.5 mL min<sup>-1</sup> with concentrations close to 0.1 mg mL<sup>-1</sup> of crude starting material. Similarly, the dimerisation of PC-OMe was optimised using a Vapourtec E2 Flow Reactor with a UV-150 module equipped with 410 nm LEDs. Using a 5 mL flow coil, full conversion of the starting compound (1 mg mL<sup>-1</sup>) was achieved within 1 minute. We thus conclude that both photo-active systems can be activated separately in flow, which bodes well for our aim of establishing a dual colour  $\lambda$ -orthogonal flow system.

Subsequently, we translated the dual-wavelength-selective concept to the macromolecular realm by incorporating the photoreactive functionalities onto linear polymers to selectively fold the chains into macrocycles. Poly(ethylene glycol) (PEG) was chosen as the polymer backbone because of the straightforward end-group modification and the good solubility in the solvents used for the photochemical reactions Firstly, PEG ( $M_{\rm p}$  = 2050 g mol<sup>-1</sup>) was end-capped with tosylate moieties and subsequently substituted with MBA functionalities, with an overall yield of 71%. The product was analysed and confirmed via <sup>1</sup>H-NMR spectroscopy and mass spectrometry (Figure S9-10). The modified PEG was further employed for photoflow synthesis. It is critical to keep the concentration of the chains low during the photoreactions. Indeed, at low concentrations, intramolecular [2+2]-cycloadditions are favoured when PEG is end-capped with PC moieties and irradiated with violet-blue light, resulting in the desired macrocycle. However, when the concentration of polymers exceeds a certain level, intermolecular reactions become more favourable, resulting in larger polymers via photopolyaddition. To overcome uncontrolled addition into larger chains, polymer concentrations were kept at 0.025 mg mL<sup>-1</sup> for all photoflow reactions. A solution of bisMBA-PEG with 2.05 equivalents of PC-Mal in acetonitrile/toluene (3:1) was irradiated in flow with UV-A light (Figure 2a). The same setup was used as described before. The reaction progress was monitored via size exclusion chromatography (SEC). The intermediate product after  $\lambda_1$ -irradiation was analysed. Comparing the size distribution of the starting compound (bisMBA-PEG) to the distribution of the obtained flow product shows a shift towards higher hydrodynamic



**Figure 2.** a) Reaction scheme of the dual-wavelength photoflow setup. Consecutive irradiation of the starting compounds selectively folds the PEG chains into macrocycles. b) SEC elugrams of the reaction mixture at each stage of the flow setup (before, after  $\lambda_1$  irradiation and after  $\lambda_2$  irradiation). Starting from bisMBA, a shift towards higher hydrodynamic volume could be observed upon irradiation with UV-A light (bisPC;  $\lambda_1$ ,  $\lambda_{max} = 350$  nm). Consecutive irradiation with violetblue light causes the chain to collapse, indicated by a shift back towards smaller hydrodynamic volume (folded cycle;  $\lambda_2$ ,  $\lambda_{max} = 410$  nm). c) UV-Vis absorption spectra after each irradiation step. The absorption spectrum of pyrene-chalcone can be recognised on the end-capped PEG-chain. The spectrum shifts towards the [2+2]-cycloadduct upon chain folding.

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volume after the photoreaction (Figure 2b). The shift is well in line with expectations, as introducing new moieties on both ends of the chains increases the size of the molecule and therefore also its volume. Additionally, mass spectrometry confirmed the formation of the new bis-substituted PEG-species (Figure S11). Subsequently, the pyrene-chalcone end capped polymer was irradiated with 410 nm LEDs. Again, SEC was employed to determine the change in size distribution occurring due to the irradiation in flow. Specifically, a shift towards lower hydrodynamic volume was observed after the second irradiation compared to the size distribution of the PC end-capped polymer (Figure 2b). A smaller hydrodynamic volume implies that the single chains collapsed during irradiation, which was achieved by covalent bond formation of the respective chain ends. The [2+2]cycloaddition reaction therefore effected the intramolecular cyclisation, resulting in macrocycles. The small side distribution at lower retention time is the result of minimal polyaddition during the second irradiation. This was minimalised by employing low concentrations but could not be prevented entirely as lower concentrations would require very long reaction times. It was shown that higher concentrations of polymer significantly increase the amount of polyaddition product (refer to Supporting Information Figure S12). In addition, UV-VIS spectroscopy revealed the presence of the [2+2]-cycloadduct after inducing the chain folding (Figure 2c).

As additional proof of cyclisation, a third light source was used to cleave the photo-adduct. As noted earlier, pyrene-chalcones can undergo cycloreversion, depending on the irradiation wavelength. Therefore, irradiating the macrocycles with UV-B light results in the opening of the cyclic structure, regenerating the chalconeend-capped PEG linear polymer. The UV-VIS spectra (Figure S13) of the macrocycles before and after irradiation with UV-B light indicate that the typical absorption maximum of the pyrenechalcone at 390 nm reappeared after irradiation, showing that the macrocyclic structure can be cleaved again to regenerate linear PEG chains.

In conclusion, we introduce a true  $\lambda$ -orthogonal continuous photoflow system that can initiate multiple reactions. A new [2+2]cycloaddition system was developed based on pyrene-chalcones, triggered upon irradiation with violet-blue light. We demonstrate that this functionality remains unreacted under UV-A light and can be reacted orthogonally with MBA-maleimide ligation. By incorporating o-methylbenzaldehyde functionalities on a small PEG chain, we show that the polymer can selectively be endcapped with one light source emitting at 350 nm, and subsequently cyclised by employing a second light source emitting at 410 nm – a remarkable example of triggering the high energy gate without affecting the low energy activated system. To the best of our knowledge, this is the first multi-step  $\lambda$ -orthogonal photoflow setup on a macromolecular level. Our system facilitates multi-step modifications with several photo-induced reactions. In addition, the flow setup facilitates the scalable synthesis of multistep processes by merely increasing the amount of material and the flow reaction time, without any further modifications or optimisation. While maintaining efficient and homogeneous irradiation in photoflow, scaling is significantly more difficult in a batch process. Increasing light gradients would reduce the irradiation efficiency, requiring optimisation for each different

batch size. The flexibility of the reactor design allows adaptation towards different chemical photosystems and light sources, as well as facile expansion with multiple flow coils.

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**Keywords:** flow photochemistry • continuous flow • orthogonal reactivity • multi-step synthesis • macrocycles

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Going with the Flow: True λorthogonality in a photochemical reaction system becomes possible in a photoflow system, able to control polymer end groups and topology, based on a photo-caged diene and [2+2] reaction system.



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