Stability of Diels-Alder Photoadducts in Macromolecules

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Complete List of Authors:	Petit, Charlotte; Karlsruhe Institute of Technology, Institute of Chemical Technology and Polymer Chemistry Bangert, Lukas; Karlsruhe Institute of Technology, Institute of Chemical Technology and Polymer Chemistry Abbasi, Mahdi; Karlsruhe Institute of Technology, Polymer Materials Wilhelm, Manfred; Karlsruhe Institut of Technology, Goldmann, Anja; Karlsruhe Institute of Technology, Institute of Chemical Technology and Polymer Chemistry; Queensland University of Technology Faculty of Science and Engineering, Barner-Kowollik, Christopher; Queensland Universtiy of Technology, School of Chemistry, Physics and Mechanical Engineering; Karlsruhe Institute of Technology, Institut für Technische Chemie und Polymerchemie

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Stability of Diels-Alder Photoadducts in Macromolecules †

Charlotte Petit,[ab] Lukas D. Bangert,[ab] Mahdi Abbasi,[c] Manfred Wilhelm,[c] Anja S. Goldmann,*[ab] Christopher Barner-Kowollik*[ab]

We explore the stability of *o*-quinodimethane-based ligation points generated by a popular photo-induced Diels-Alder reaction, assessing their ability to withstand challenging environments. Our molecular assessment includes size-exclusion chromatography as well as high resolution electrospray ionization mass spectrometry (SEC-ESI MS), finding that their stability is dependent on the macromolecular chain length.

Using light as an energy source to induce chemical reactions has inspired chemists for at least the last 100 years.[1] Light-induced chemistries offer a wider range of opportunities to construct complex molecules in a spatially and temporally gated fashion. Photosensitive organic molecules can be activated or excited by the absorption of photons (or light).[2] In macromolecular chemistry, photo-induced ligations are exploited for the design of sophisticated polymer topologies,[3-5] advanced macromolecular interfaces,[6] or photoresists for two photon 3D laser lithography with micro- and even nanometer features,[3] as well as 3D printed materials on the meso[7] and macroscale.[8, 9] Although photochemistry is used in a wide range of applications, in-depth insights into the stability of the generated molecular adducts critically lacks, is however of key importance for the final performance of the generated material under real life conditions. In the literature, investigations into the stability of thermally generated linkages can be found. For example, we investigated the stability of polymers linked by 3,6-dihydro-2H-thiopyran rings under various thermal and pH conditions, generated via a hetero Diels-Alder (DA) reaction.[10, 11] Similarly, the thermal stability of the triazole group used as linkage points in macromolecules was explored by Altintas *et al*.[12] In both thermally and photochemically induced [2+4] cycloadditions (in the photochemical case the precursor is photochemical generated), maleimides constitute a powerful counter reactivity due to their electron-poor C=C double bond and the nitrogen atom allowing for varied substitution. One of the most employed photo-induced DA reactions[13] proceeds via an *o*-quinodimethane structure (a so-called photoenol) by photochemically uncaging methylbenz-aldehydes (MBAs) and subsequent reaction with a maleimide. In the herein explored case, the reaction of a photo-generated diene has a strong driving force to react with an activated ene, driven by the rearomatization of the adjacent phenyl ring, and should lead to an enhanced thermal stability of the Diels-Alder adduct compared to thermally generated adducts. Critically, however, despite its widespread usage, the stability of the resulting DA adduct has never been probed. This comes as a surprise, given the use of the linkage in varied materials science applications.
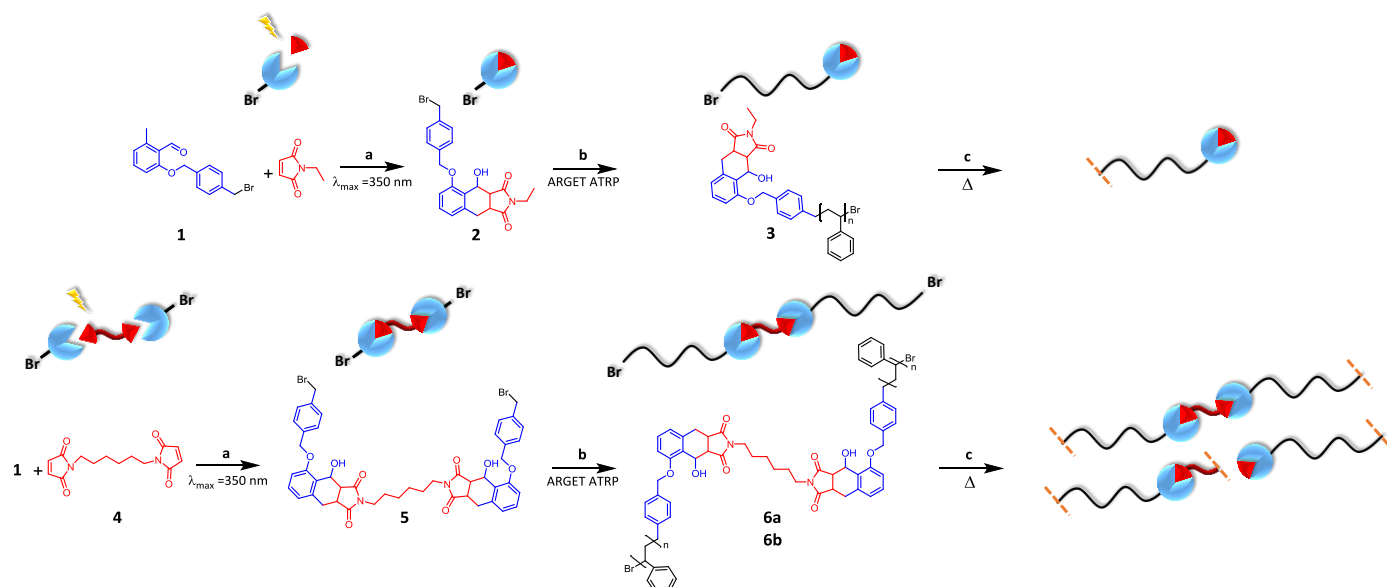
Herein, we close this critical gap and assess the thermal stability of the photoenol cycloadduct resulting from the reaction of an *o*-methylbenzaldehyde derivative with a maleimide group as end chain or mid chain functionality in linear macromolecules prepared via Activator ReGenerated by Electron Transfer Atom Transfer Radical Polymerization (ARGET ATRP). In order to avoid end-group modifications, our molecular construct features the photochemical ligation point as part of ARGET ATRP initiators. To enable assessing the photoadduct's stability, the absence of potentially unstable functional groups in the respective photo-functional polymer, e.g. ester bonds, is of key importance. Esterification is one of the most employed chemical transformations to generate covalent bonds, yet – as previously noted – ester moieties are prone to degradation upon thermal insult in the presence of bromine terminated polymers (due to HBr formation) and, thus, need to be excluded.[12] Incorporating only the group of interest in the (macro)molecule and no other potentially labile structural elements makes the ATRP initiator design challenging. Thus, we herein employ polystyrenes as inert polymer entailing only the photo-cycloadduct alongside

[a] School of Chemistry, Physics and Mechanical Engineering, Queensland University of Technology (QUT), 2 George Street, Brisbane, QLD 4000, Australia. E-Mail: a.goldmann@qut.edu.au; christopher.barnerkowollik@qut.edu.au

[b] Macromolecular Architectures, Institut für Technische Chemie und Polymerchemie, Karlsruhe Institute of Technology (KIT), Engesserstr. 18, 76128 Karlsruhe, Germany. E-Mail: anja.goldmann@kit.edu; christopher.barner-kowollik@kit.edu

[c] Polymeric Materials, Institut für Technische Chemie und Polymerchemie, Karlsruhe Institute of Technology (KIT), Engesserstr. 18, 76128 Karlsruhe, Germany.

Scheme 1 Synthetic strategy for the preparation of monofunctional **2** and bisfunctional **5** ATRP initiators bearing 9,9a-dihydro-1H-benzo[f]isoindole-1,3,4(2H,3aH)-trione (photoenol cycloadduct) functionalities as well as the resulting polystyrene synthesized via ARGET ATRP. **(a)** Photochemically-induced initiator synthesis: 5 mM solution in acetonitrile, irradiation at λ_{max} = 350 nm, 1.5 h, **(b)** synthesis of variable molecular mass polystyrenes carrying the photoenol cycloadduct at the chain terminus or at the centre of the polymer chain: Styrene, CuBr$_2$, Me$_6$TREN, Sn(EH)$_2$, anisole, 90 °C, **(c)** schematic representation of the structures obtained after thermal treatment of the polymers at 150 °C (or 180°C) under inert atmosphere.

thermally stable ether linkages. We introduce two new ATRP initiators, synthesized via photoenol chemistry, to obtain initiators carrying the photoenol-derived cycloadduct. One initiator is monofunctional (**Scheme 1, 2**), affording a polymer bearing the photoenol cycloadduct as end-group, serving as the reference system (**Scheme 1**, **3**). Employing the other bifunctional initiator (**Scheme 1, 5**) results in a polymer featuring two mid-chain photoenol ligation points (**Scheme 1, 6a and 6b**).

The synthesis of the *o*-methylbenzaldehyde precursor **1** (**Scheme 1**) has been adapted from the literature.[14] For the new ATRP initiators (**Scheme 1, 2** and **5**), a 10 mM solution of MBA and maleimide (stoichiometric ratio of maleimide and MBA functions) in dry acetonitrile was prepared, respectively separated in capped photovials and freed of oxygen. The vials were irradiated for 1.5 h (λ_{max} = 350 nm) in a custom-built photoreactor (**Figure S1, S2**). After solvent removal at reduced pressure, yellow crystals were obtained without further purification. ^{1}H-NMR, ^{13}C-NMR and MS data (**Figure S7, S10, S11, S13**) confirm the target initiators in high purity.

Styrene was polymerized using ARGET ATRP conditions at 90°C in anisole with CuBr$_2$ as catalyst, Me$_6$TREN as reductive agent and Sn(EH)$_2$ as ligand.[12] Initially, end-chain photoadduct functionalized polystyrene was obtained using **2** as initiator. Next, **5** led to polystyrenes featuring two mid-chain photoadducts functionalities. The chemical structures of the synthesized polymers with varying position of the photochemical ligation points are depicted in **Scheme 1**. The polystyrenes (1.7 kg·mol^{-1} ≤ M_n ≤ 6.3 kg·mol^{-1}, Đ = 1.1-1.4) were analysed via SEC revealing monomodal molecular weight distributions as well as low dispersities. The associated molecular weight distribution are depicted in **Figure 1**.

Our stability assay commences with the linear end-chain photoadduct functional polystyrene **3** carrying a Br functionality as reference system. High resolution SEC-ESI MS was used to determine the impact of the bromine group on the photoadduct during the thermal treatment on the molecular level. The SEC-ESI MS spectrum of the parent molecule **3** is depicted in **Figure S14**. Note that the imaging of non-polar polymers such as polystyrenes via ESI-MS requires negative ion protocols for high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) recently pioneered by our team, which we adapted for the current study.[15] Due to the limited *m/z* range of the Orbitrap ESI mass spectrometer (max. *m/z* 6000), we targeted molecular weights below 10 kg·mol^{-1}, exploiting up to doubly charged polystyrenes. Note that MALDI is not a viable alternative as ionization method, as the inherent laser irradiation makes it unsuitable for the assessment of photochemically reactive entities. The linear α,ω-dibromo mid-chain functional polystyrenes **6a** (M_n = 1.7 kg·mol^{-1}; Đ = 1.3) and **6b** (M_n = 6.3 kg·mol^{-1}; Đ = 1.1) were also analysed via SEC-ESI MS to investigate − on a molecular level − the impact of the chain length and position of the photochemical ligation point within the polymer chain on the stability during thermal treatment. Interestingly, Pahnke *et al.*[16] reported the impact of the position of the functionality of interest within the polymer on the cleavage process, citing entropic effect leading to an enhanced cleavage propensity with increasing chain length. Further, they demonstrated that the cleavage of macromolecules at the linkage point is entropically more favoured when the functionality is located in the middle rather than at the end of the polymer. The SEC-ESI MS spectra of the initial polymers **6a** and **6b** are depicted in **Figure S16**. For both polymers (**6a** and **6b**), the experimental isotopic patterns are in excellent agreement with the theoretical patterns, simulated based on their expected structures including two mid chain photoadduct ligation points and α,ω-dibromine end chains (molecular masses and dispersities are depicted in the caption of **Figure 1**).

The behaviour of well-defined polymers under thermal stress is a complex process under an oxygen rich atmosphere.[17, 18]
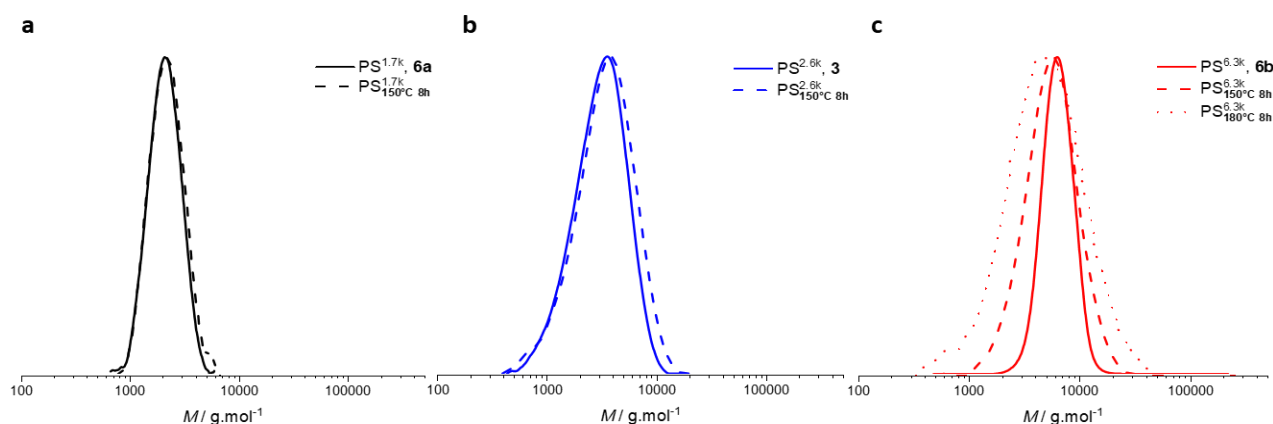

Figure 1 SEC traces of the polymers **(a) 6a, (b) 3** and **(c) 6b** before (**6a**: M_n = 1.7 kg·mol^{-1}, Đ = 1.2, **3**, M_n = 2.6 kg·mol^{-1}, Đ = 1.3, **6b**: M_n = 6.3 kg·mol^{-1}, Đ = 1.1) and after thermal treatment (**6a**: M_n = 2.0 kg·mol^{-1}, Đ = 1.3, **3**, M_n = 2.7 kg·mol^{-1}, Đ = 1.4, **6b**: M_n = 5.2 kg·mol^{-1}, Đ = 1.4) for 8 h at 150°C, and **6b** after thermal treatment at 180°C (M_n = 3.4 kg·mol^{-1}, Đ = 1.9) under N_2 atmosphere.

Moreover, during typical extrusion processes, polymers are subjected to high temperature and pressure, e.g. 150 to 200°C and up to 300 bar in a closed extrude system, thus limiting the amount of present oxygen. Thus, herein, the thermal stability of the synthesized polymers has been assessed under an inert atmosphere (N_2) at 150°C or 180°C.

Initially, the reference system **3** bearing both a bromine and a photo cycloadduct at the respective chain termini, was subjected to thermal stress for 8 h at 150°C under inert conditions. The resulting SEC trace after thermal treatment is depicted in **Figure 1b** (blue dashed line) as well as the initial polymer **3** (blue full line). These two traces elute at approximately identical retention times, suggesting the absence of cleavage events within the main chain. The effect of thermal stress on the molecular level has been followed via SEC-ESI MS analysis. The resulting spectra are shown in **Figure S15**. The main distribution after thermal stress of **3** appears at *m/z* 2779 with one single negative charge (I$^-$) and is attributed to a mixture of unsaturated species resulting from the elimination of HBr (*m/z* 2779) and saturated species resulting from the opening of the maleimide moiety, leading to the addition of two mass units (*m/z* 2781). The appearance of an additional signal with a lower intensity can be attributed to species at 16 and 18 mass units heavier (*m/z* 2795 and *m/z* 2797). According to Altintas *et al.*, the species at 18 mass units higher is associated with halides (e.g. Br) formed prior MS analysis.[12] The species at 16 mass units higher are assigned to the species of both the oxidation of the alcohol formed during the photoenol-maleimide DA reaction and the halide formation. No starting material was found in the spectrum, revealing the complete elimination of HBr. Since the photoenol cycloadduct remains intact after thermal treatment of polystyrene **3**, we conclude that the position of the function at the chain end is both chemically and entropically unfavoured for decomposition. In addition, the presence of a bromine end-group has no influence on the stability of the photoenol cycloadduct, in agreement with the findings of Altintas *et al.* for triazole groups.[12] The polystyrenes **6a** and **6b** resulting from the polymerization initiated by **5** have been submitted to thermal stress at 150°C for 8 h in an N_2 atmosphere, too. On the one hand, the SEC trace of polymer **6a** after thermal treatment (depicted in **Figure 1a**) shows a slight broadening along with a slight increase of dispersity from 1.2 to 1.3 before (black

full line) and after (black dashed line) treatment, respectively. We thus propose that the mid-chain ligation point is still intact after thermal treatment. On the other hand, the SEC trace of polymer **6b** (**Figure 1c** in red) after thermal treatment at 150°C for 8 h under N_2 displays a clear broadening to lower molecular weights, thus suggesting cleavage of the polymer. These observations emphasize the correlation between the chain length and the cleavage propensity of macromolecules. As noted by Pahnke *et al.*,[19] the increase of entropy leads to a decrease of intact ligation points within the macromolecules at a given temperature, accompanied by a faster cleavage for longer chains. To confirm this notion for our systems on the molecular level, polymers **6a** and **6b** were analysed via SEC-ESI MS after thermal treatment. The spectra obtained are depicted in **Figure 2** (**a-e**), in which n_1 and n_2 represent the chain length on each side of the photochemical ligation point, respectively (n_1+n_2 is used for the MS spectra simulation). The full spectra are available in **Figures S17** and **S18** for polymers **6a** and **6b**, respectively. For both polymers **6a** and **6b**, the ESI-MS spectra are in agreement with the observations obtained for the reference system **3**: (*i*) HBr elimination and double bond formation, (*ii*) opening of the maleimide[20] and (*iii*) halide formation leading to the formation of a species at 18 mass units higher (*m/z* 2143 and *m/z* 2696 for **6a** and **6b**, respectively, shown in **Figure 2**, **a and b** accordingly). However, the fraction corresponding to the lower molecular weight of **6b** – detected in SEC and attributed to decomposition – could not be detected via MS, most probably due to the low concentration of the cleavage products formed by dissociation of the photochemical linkage point. In order to increase their concentration and, thus, visualize the decomposition products via ESI-MS, the temperature was increased to 180°C (for 8 h under N_2 atmosphere). The SEC trace of **6b** after thermal treatment at 180°C under N_2 atmosphere for 8 h is presented in **Figure 1c** (red dots), showing a very clear shift to lower molecular weights confirming the decomposition of the polymer under these conditions (before thermal treatment: M_n = 6.3 kg·mol^{-1}, Đ = 1.1; after thermal treatment at 180°C, 8h, N_2: M_n = 3.4 kg·mol^{-1}, Đ = 1.9). The careful SEC-ESI MS analysis of **6b** allows identifying the two fractions resulting from the thermal treatment. The mass spectrum obtained is depicted in **Figure 2f** (for the full spectrum refer to **Figure S19**). The assignment of the structures presented
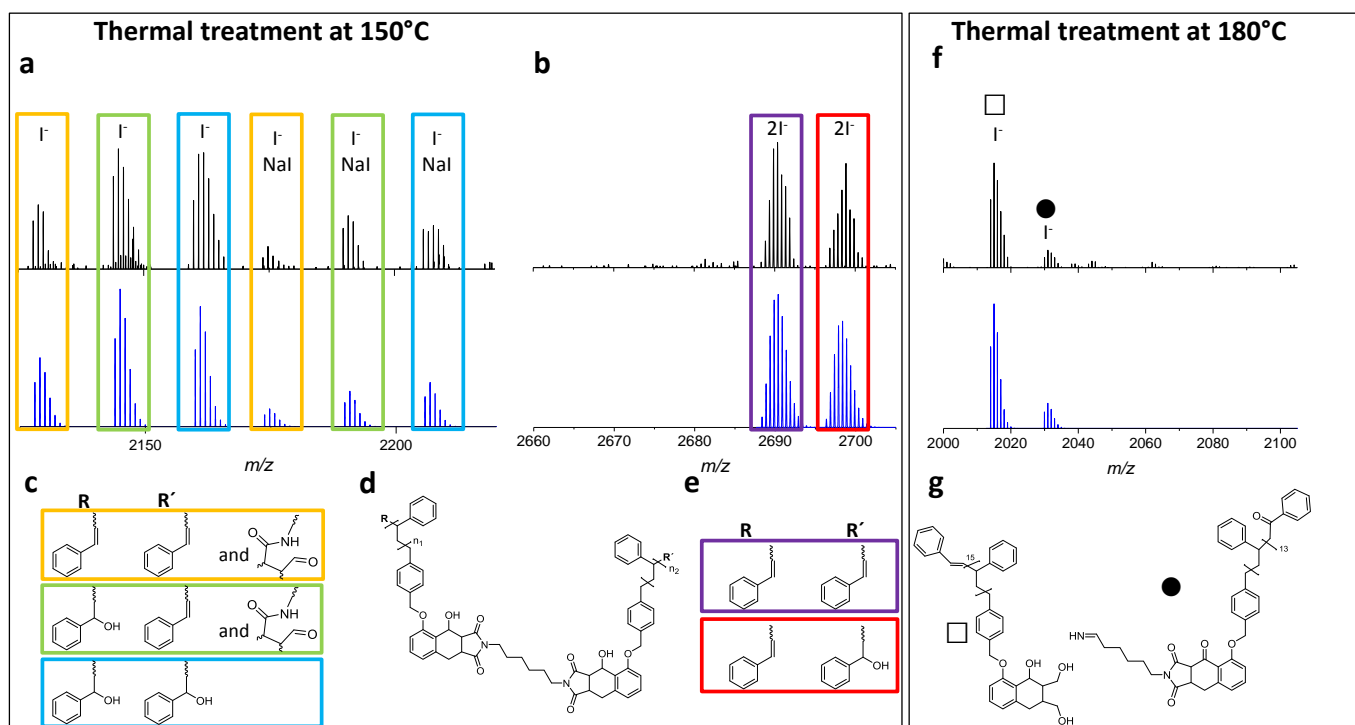
Figure 2 High resolution SEC-HR-ESI-MS zoom spectra of **6a** and **6b** (**a**-**e**) recorded after 8h at 150°C and at 180°C for **6b** (**f, g**) within an N_2 atmosphere, recorded in negative ion mode (doped with NaI). **(a)** and **(b)**: Zoom of one repetitive unit of **6a** and **6b**, respectively; top (black): experimental, bottom (blue): simulated spectra **(c)** Structures of the end-group assigned to the species resulting from the thermal treatment of **6a** with $n_1+n_2=10$ and singly charged species **(d)** General structure assigned to the spectra for the thermal stability of both **6a** and **6b**. **(e)** Structures of the end-group assigned to the species resulting from the thermal treatment of polymer **6b** with $n_1+n_2=40$ and doubly charged species. **(f)** Zoom of one repetitive unit of the analysis of the polymers **6b** after thermal treatment at 180°C for 8 h. **(g)** Structures assigned to the species □ and ● highlighted in the spectrum **f)**. For the full spectra of the SEC-HR-ESI-MS please refer to **Figure S17-19** in the supporting information.

in **Figure 2g** confirms the cleavage of the polymer by opening of the maleimide ring, thus leading to two distinct fractions: one carrying a carbaldehyde and a second one bearing an imine function that reveal an intact DA linkage.

Our molecular investigation into the stability of *o*-quinodimethane based photo-adducts thus demonstrates that: (*i*) Cleavage in the molecular vicinity of the mid chain positioned photoadduct is favoured over cleavage at the chain end, in agreement with the studies of Pahnke *et al.* noting that debonding in a mid-chain position is entropically favoured over chain end cleavage.[16] (*ii*) The thermal stability of the polystyrenes is highly dependent on the chain length on either side of the ligation point, which is also in agreement with the observations of Pahnke *et al.*[19] (*iii*) Critically, we find that the photochemical ligation points themselves are stable when exposed up to 180 °C for up to 8 h, with cleavage occurring at the maleimide rather than the Diels-Alder adduct. Harking back to the importance of having stable ligation points resulting from photochemical reactions, we submit that photochemically derived DA adducts based on *o*-methylbenzaldehydes show superior stabilities likely due to the rearomatization of the phenyl ring during the DA reaction disallowing cycloreversion, yet the ene component with which they ligate needs to be judiciously selected.

Conflicts of interest
There are no conflicts to declare.

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C. Petit,[ab] L. D. Bangert,[ab] M. Abbasi,[c] M. Wilhelm,[c] A. S. Goldmann,*[ab] C. Barner-Kowollik*[ab]

[a]School of Chemistry, Physics and Mechanical Engineering, Queensland University of Technology (QUT), 2 George Street, Brisbane, QLD 4000, Australia. E-Mail: a.goldmann@qut.edu.au; christopher.barnerkowollik@qut.edu.au

[b]Macromolecular Architectures, Institut für Technische Chemie and Polymerchemie, Karlsruhe Institute of Technology (KIT), Engesserstr. 18, 76128 Karlsruhe, Germany. E-Mail: anja.goldmann@kit.edu; christopher.barner-kowollik@kit.edu

[c]Polymeric Materials, Institut für Technische Chemie und Polymerchemie, Karlsruhe Institute of Technology (KIT), Engesserstr. 18, 76128 Karlsruhe, Germany.

The study investigates the thermal stability of ligation points resulting from photochemically induced Diels-Alder reactions within soft matter materials on the molecular level.