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Model Diels–Alder Studies for the Creation of Amphiphilic Cross-Linked Networks as Healable, Antibiofouling Coatings

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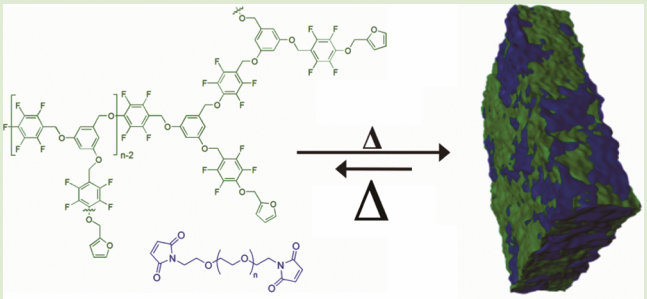
Supporting Information

ABSTRACT: Diels–Alder (DA) chemistry was used in the construction of amphiphilic cross-linked polymer networks comprised of furan-functionalized hyperbranched fluoropolymers and maleimide-functionalized linear poly(ethylene glycol)s, which were designed as antibiofouling coatings capable of repair. Discrete molecules and a linear polymer analog were studied as model systems to understand the nature of the thermally reversible [4 + 2] cycloaddition reaction involving a tetrafluorobenzylfuranyl ether unit, which was part of the structure for the incorporation of the DA functionalities into the composite network materials. Atomic force microscopy confirmed the complex, nanoscopically resolved topography needed for antibiofouling. Bright field and fluorescence imaging monitored healing at damage sites as well as the ability of the coatings to resist protein adsorption.



It has become ever more desirable to prepare smart polymers using increasingly simpler methods. A popular topic to emerge in the past decade is that of reversible chemistry, which has allowed the development of repairable or "self-healing" materials. A few truly elegant examples in this field include the work of Jen et al.,[1] Leibler et al.,[2] White et al.,[3,4] and Wudl et al.[5] Many of these healable systems use, or share the characteristics of, "click" chemistry,[6−10] which has received significant attention as it involves reactions that have led to highly efficient and diverse production of complex materials.[8] Chemistries such as azide–alkyne Huisgen cycloaddition,[6] thiol-ene,[11−13] Michael addition,[14] and *para*-fluoro-thiol click[15] are selective, orthogonal, and quantitative. Diels–Alder (DA) cycloadditions[5] not only provide the qualities of "click" reactions but have the added benefit of being reversible and provide an opportunity for self-healing. The use of DA chemistry in polymerizations is widespread and can be found in the synthesis of dendritic,[16−19] linear,[20−25] block,[26] graft,[27,28] star[29,30] and cross-linked polymers,[5,29,31−36] as has been reviewed recently.[37] DA chemistry is selective, yet versatile; the diene and dienophile are not restricted to one class of compounds. Indeed, some more exotic examples have been published under the title of hetero-Diels–Alder (HDA), where, for example, dithioesters have been coupled with butadiene and cyclopentadienyl moieties.[28,32] One of the most popular pairings for DA is that of a maleimide-type dienophile with a furfuryl-based diene.[18,19,24,33−36]

Having demonstrated that hyperbranched fluorinated polymers (HBFP, **1**) cross-linked with poly(ethylene glycol) (PEG), HBFP-PEG, exhibit unique antibiofouling capabilities yet lack adequate durability as coatings for application in the marine environment,[38] a current goal has been to incorporate a healable function for increased longevity. Based upon the thermally triggered reversibility of the DA reaction and the chemical versatility of dienes and dieneophiles, we chose to install DA-reactive furan and maleimide functionalities onto HBFP (**2**) and PEG (**3**), respectively, to utilize DA chemistry as the mechanism for healable antibiofouling coatings, **4**. However, because the chemical compositions and structures are difficult to characterize within cross-linked networks and unusual electronic effects were anticipated for the furfuryl group of the HBFP material, two model systems were designed by systematically deconstructing the HBFP and PEG components (Scheme 1) into A_2 (**5**) + B_2 (**3**) comonomers for linear polymer formation **6** (model reaction 2) and, further, into monofunctional small molecules, **7** and *N*-methylmaleimide, for coupling to a DA adduct **8** (model reaction 1). Studies were then performed to understand the reaction conditions to effect the reversible chemistry.

The first study involved small molecule reactions of *N*-methylmaleimide with a diene, **7**, that was built to model structural elements of the furan-functionalized HBFP, **2** (Scheme 1, right, and Figure 1). The furan-based diene was connected to a tetrafluorobenzylphenyl ether to approximate the electron-withdrawing characteristics that would be present in **2**. Reaction of 2,3,4,5,6-pentafluorobenzyl bromide with phenol in the presence of potassium carbonate and 18-crown-6 yielded **9**,[39] followed by nucleophilic aromatic substitution of the *para*-fluorine by reaction with furfuryl alcohol and sodium

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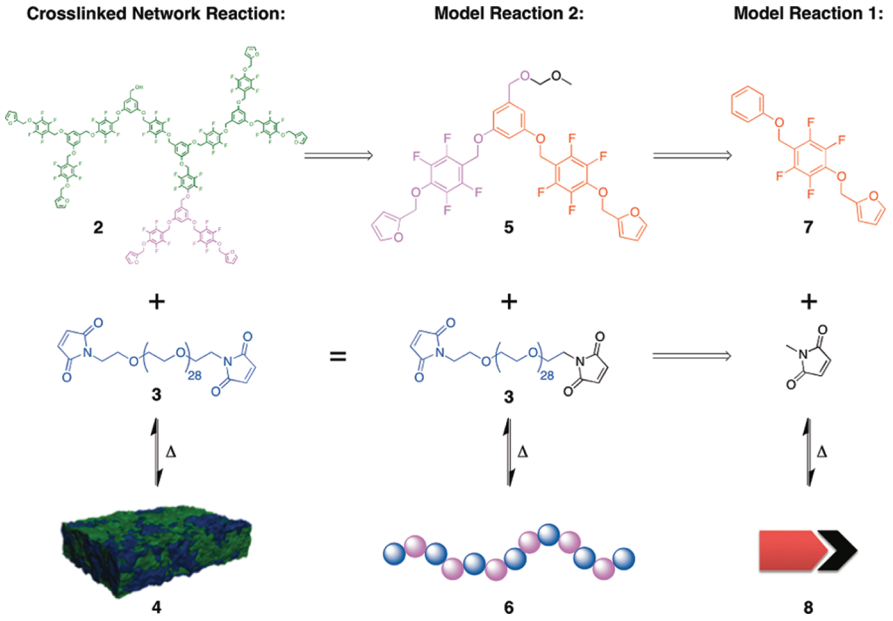
Scheme 1. Deconstruction of HBFP (left, upper) to an A_2 Monomer (middle, upper) and a Discrete Molecule (right, upper), To Understand the Reversible Nature of the Diels-Alder Reaction in the Substituted Diene and Dienophile Sub-Units of the Crosslinked Network System. Model Reaction 2 Involves a Linear Polymerization, and the Small Molecule Studies Are Model Reaction 1



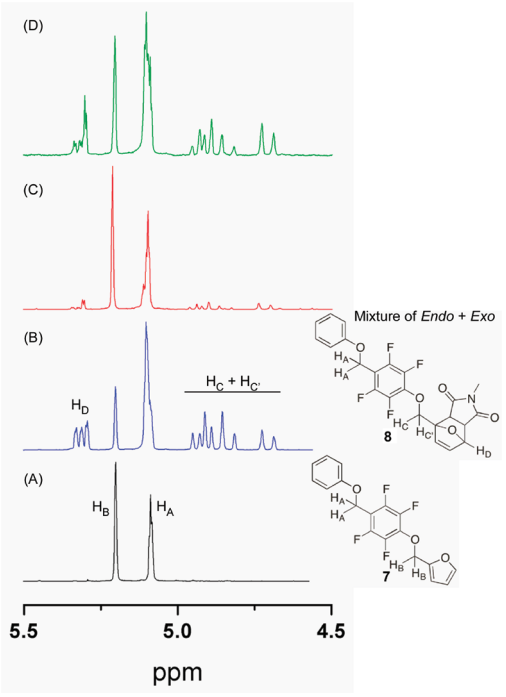


Figure 1. ^{1}H NMR spectra (300 MHz, $CDCl_3$) depicting model reaction 1 at various stages of the forward and reverse reaction conditions, performed in bulk: (A) starting materials; (B) DA adduct formation after heating at 60 °C for 24 h; (C) retro-Diels–Alder after heating at 90 °C for 5 h; (D) reformation by heating at 60 °C for 24 h.

hydride which afforded 1-benzyloxy-4-furfuryloxy-2,3,5,6-tetrafluoro-benzene, **7**, in 35% yield over the two synthetic steps. Analysis showed that, while *N*-methylmaleimide would undergo reaction with unmodified furfuryl alcohol in DCM under ambient conditions, no reaction was observed for *N*-methylmaleimide and **7** under ambient conditions, with or without solvent. The rapid reaction of maleimide with furfuryl derivatives is well-established, suggesting in this case that the substituent had contributed toward decreased diene reactivity. A tri(ethylene glycol) spacer was used to place the diene far from the fluoroaromatic group, therefore as a model study during peer review of this manuscript, which restored the furfuryl unit's DA reactivity with *N*-methylmaleimide (see the Supporting Information, SI).

Despite the reduced activity of the DA moieties, reversible bond formation/cleavage was achievable through alteration of the experimental conditions. By heating the reaction mixture to 60 °C in bulk, it was found that the reaction could be driven to achieve 65% conversion of **7** to **8** in 24 h. The reaction temperature could not be raised any further, due to the possibility of triggering the retro-Diels–Alder reaction. To demonstrate reversibility, the crude product **8** was heated at 90 °C for 5 h to return to **7**, analyzed, and then subsequently heated at 60 °C for another 24 h to reobtain **8**. The results were visualized by ^{1}H NMR spectroscopy, observing the appearance and disappearance of DA adduct signals in the 4.5–5.5 ppm range (Figure 1). Due to the nonquantitative reaction and generation of stereocenters in the product, NMR spectra of the crude product were complex.[24,35]

A second model system, that of a reversible, linear polymer (**6**), was studied, wherein a bis(furfuryl) A_2 monomer, **5**, was copolymerized with **3** to resemble the eventual cross-linked networks, yet afford soluble products for analyses (Scheme 1, middle). The A_2 monomer, **5**, was synthesized in three steps, according to previously reported literature,[40] followed by protection of the benzylic alcohol of the intermediate **10** (which actually serves as the A_2B monomer for the preparation of HBFP **1**, the precursor to **2**; see the SI) with methoxymethyl chloride to yield **11**, followed by substitution of the *para*-fluorines with furfuryl alcohol to give **5**, in an overall 43% yield.

Copolymerization of **5** and **3** was achieved by heating the bulk mixture of reagents at 60 °C for 24 h, the conditions that

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were identified from the small molecule model reaction 1. Accurate stoichiometry was attainted by first preparing stock solutions, mixing the components and allowing the solvent to evaporate before performing the polymerization. Gel permeation chromatography (GPC) was used to monitor the polymerization, showing formation of oligomers with a DP_n in the range 2−4 (Figure 2). Although slow, the growth of

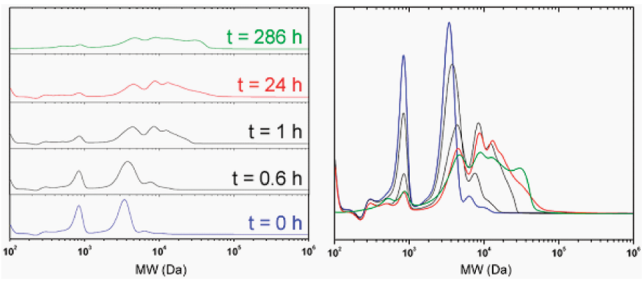

Figure 2. Stacked (left) and overlaid (right) GPC traces, depicting formation of oligomers of **6** from the copolymerization of **5** and **3**; t = 0 h, t = 0.6 h, t = 1 h, t = 24 h, t = 286 h.

higher molecular weight oligomers was observed beyond 24 h, with a concurrent decrease in the amount of lower molecular weight components. While there are some examples of DA-mediated step-growth polymerizations that proceed much faster,[32] it is nonetheless comparable to others.[18]

Reversibility was once again demonstrated in model system 2. However, the reverse reaction, or depolymerization, was not accomplished following the protocol defined for the small molecule study and, rather, resulted in a gradual conversion to a brown, insoluble residue. Depolymerization instead was attainable by dissolving the crude mixture in toluene and heating at reflux for 24 h. Repolymerization was established by heating again in bulk at 60 °C for 24 h. Each stage was confirmed by GPC (Figure 3).

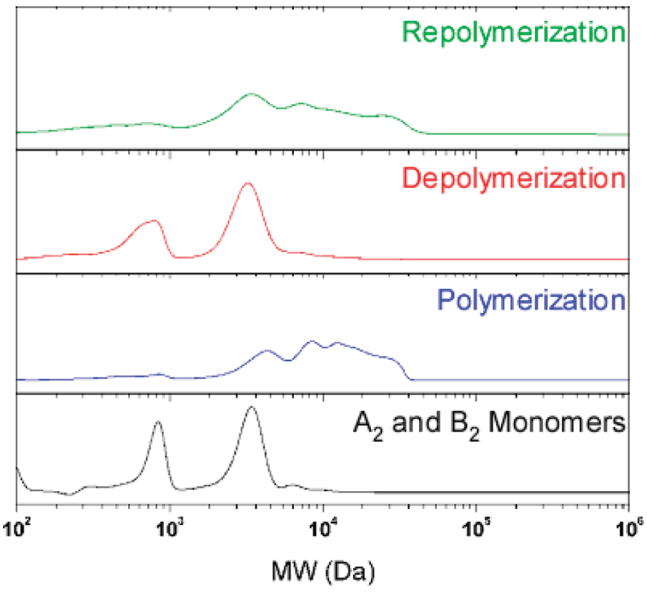

Figure 3. GPC spectra depicting forward and reverse reactions for a DA polymerization of the A_2 and B_2 monomers, **5** and **3**: polymerization in bulk at 60 °C for 24 h; depolymerization in toluene heated at reflux for 24 h; repolymerization in bulk at 60 °C for 24 h.

Given the amphiphilic nature of **6**, it was postulated that under the appropriate conditions the oligomers/polymers could self-assemble in aqueous solutions to form nanoaggregates. Two approaches were used to investigate the assembly behaviors of **6**: (i) direct dissolution of the crude oligomeric mixture in water and (ii) dissolution in tetrahydrofuran (THF), followed by the slow addition of water and dialysis to remove the organic solvent. Dynamic light scattering (DLS) analysis confirmed the presence of assemblies in both cases, with number-average hydrodynamic diameters of 37 ± 11 nm for method i (Figure S2 of the SI) and 70 ± 19 nm for method ii (Figure S3 of the SI), further demonstrating the versatility of these materials in potential applications.

Finally, DA-reversible amphiphilic cross-linked networks were studied. The first generation HBFP, **1**,[38,40] was modified to bear furfuryl moieties, **2**, and was codeposited along with bis(maleimide) PEG from dichloromethane, **3**, onto a glass slide to form a cross-linked network **4** (Scheme 1, left). After the solvent evaporated, the slides were cured at 60 °C for 24 h. Successful cross-linking was determined by immersing the cured films in separate baths of THF and water. Whereas an uncured film dissolved, the cured coatings merely delaminated as flexible, optically transparent films that remained intact. Atomic force microscopy (AFM) analysis indicated a complex nanoscopically resolved surface topography and comparison of dry cured films against water-immersed cured films revealed an increase in surface roughness, consistent with HBFP-PEG materials (Figure 4).[38]

Noting that **4** presented nanoscopic complexity and behaved in water similarly to the covalent counterpart obtained from cross-linking **1** and PEG, we believed that **4** would also resist protein adsorption and perform as an antibiofouling coating.[41] Therefore, a phosphate-buffered saline (PBS) solution containing bovine serum albumin (BSA) conjugated to a fluorescent dye, AlexaFluor-488, was incubated on the surfaces of **4** and HBFP-PEG.[41] The fluorescence was collected before and after exposure to the protein solution to elucidate how well these surfaces resisted protein adsorption. We found that the increase in fluorescence after the introduction of BSA was low and similar to that of the covalently cross-linked HBFP-PEG (Figures S4, S5, and S6 of the SI). This finding confirms that inclusion of the DA cross-linking moieties did not significantly decrease the ability of these healable coatings to resist protein adsorption.

Initial investigations into the ability for the surface to be repaired following a damaging event provided promising preliminary data. Coatings were scratched by a file to induce light surface abrasions as well as cut with a sharp knife to inflict deeper gashes and then placed in an oven at 60 °C to stimulate the forward DA reaction and re-establish cross-links.[5] After only 30 min, it was observed that the minor abrasions were healed. Deep cuts were partially healed after 3 h, but additional time at the elevated temperature did not appear to be of further benefit (Figure 5). A detailed analysis of the optical microscopy results can be found in the SI.

DA chemistry was used to produce a new generation of HBFP-PEG antibiofouling coatings that are capable of repair. Small molecule and linear polymer model studies investigated the reactivity of the substituted diene and dienophile. The reversible nature of the DA cycloaddition was demonstrated in these model systems and proved to be a viable option for re-establishment of cross-links in a damaged coating. HBFP-PEG coatings were produced through the curing of furan-modified

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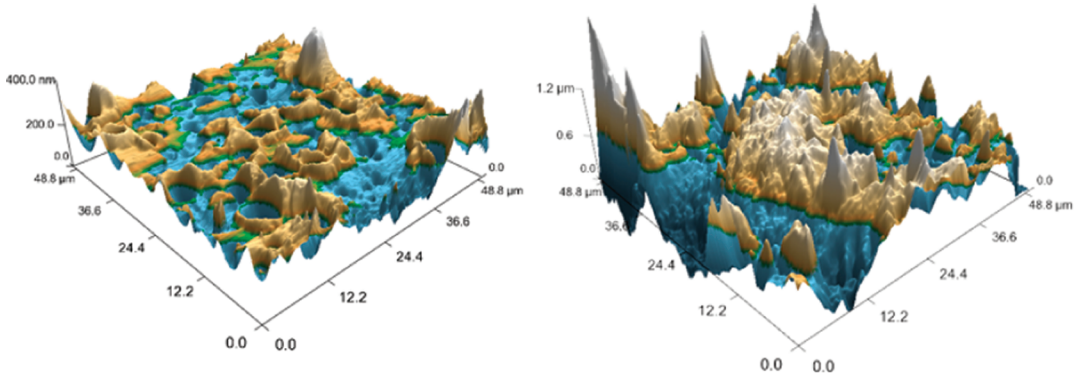

Figure 4. AFM images of DA-cross-linked HBFP-PEG film, **4**, dry (left) and after 24 h immersion in water (right).

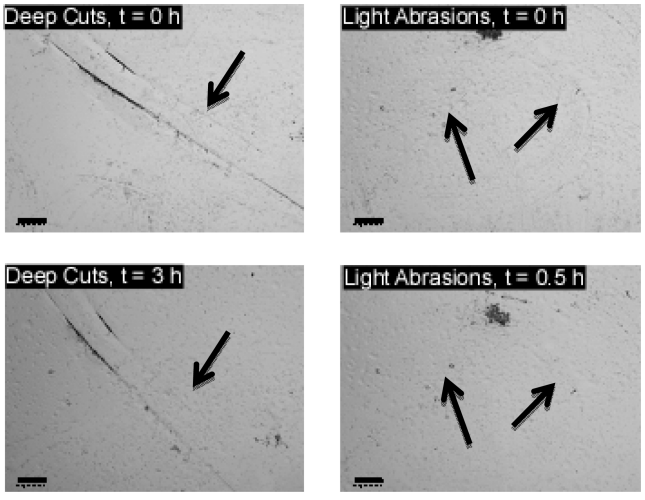

Figure 5. Images of DA cross-linked HBFP-PEG films damaged with deep cuts (upper left) and light abrasions (upper right) and at 60 °C, the partial damage healing of cuts after 3 h (lower left) and complete healing of abrasions after 0.5 h (lower right). Scale bars = 200 μm.

HBFP and maleimide-modified PEG. Testing of the scratch-healing ability of the coating surfaces revealed that small abrasions was healed in 30 min and large gashes were partially healed in 3 h. Without bulk flow, there is no mechanism to fill in large gaps and replace the material removed from serious damage. Future studies will consider localized heating above 100 °C to break all of the cross-links surrounding a surface wound, promoting the flow of oligomers to smooth out the surface, followed by heating at 60 °C to re-establish the cross-linked network. AFM revealed a topographically complex surface, which was shown to resist protein adsorption, as confirmed by a fluorescently labeled protein assay. The similarities between this system and the conventional HBFP-PEG, in terms of both chemical composition and resistance to protein adsorption, suggest similar antibiofouling behavior against marine microorganisms. This study provides a new strategy of combining materials of known antibiofouling ability with reversible cross-links to impart a healable trait into the material and functions as a guide for future formulations that optimize the effective application of these materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

All synthetic details, full characterization data, fluorescence, and optical microscopy. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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