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Photocurable hard and porous biomaterials from ROMP precursors cross-linked with diyl radicals

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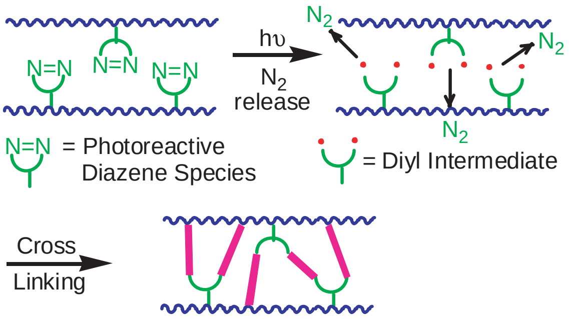
Abstract—A combination of (ROMP) ring-opening metathesis polymerization and diradical (diyl) cross-linking provides a new access to hard biomaterials and potential artificial bone replacements. ROMP was used to construct soft and pliable linear polymers bearing photolabile diazene functions. After treatment with light, a nitrogen aerosol is released throughout the polymer to create desirable porosity, cross-linking, and hardening in a single step. Nonpolymeric mechanistic work supporting these studies was also examined.

Olefin metathesis with well-defined ruthenium catalysts can provide a wide range of possibilities for hard materials' synthesis.[1,2] Increasing knowledge about these reasonably stable catalysts, promulgated by Grubbs and co-workers, has led to an improved understanding of ring-opening metathesis polymerization (ROMP) of substituted norbornyl compounds with a high toleration for a variety of functional groups and substrates.[3–5] We recently began a study of combining ROMP chemistry with novel cross-linking methods to create hard biomaterials.[6] A useful application of porous biomaterials is for the sustained delivery of biologically active agents such as drug molecules, nutrients, growth factors, and hard tissue replacements.[7–9] Many current hard tissue substitutes are nonporous and not ideal for irregularly shaped or hard to reach defects such as those found in many bone injuries.

In this paper, we investigated the chemical synthesis of new materials using ring-opening metathesis polymerization (ROMP) to construct linear polymers bearing photolabile diazene substituents as shown in Scheme 1.[10] It was not clear from the outset if a diazo function would survive the polymerization or Grubbs' ruthenium catalyst. These polymers would need to be soft and pliable enough to mold into any shape needed (i.e., like toothpaste), yet maintain this form until treated with light.



Scheme 1. Release of N_2 and cross-linking.

During the photocuring process, we hoped that nitrogen would be released and escape throughout the polymer as it hardened. There are two important processes taking place here. First, as the N_2 aerosol escapes, it creates the porosity we needed by boring holes through the soft polymer. Second, the diradicals (diyls) cause the linear ROMP chains to cross-link and solidify. The diyls could react with other diyl radicals in the same or an adjacent polymer chain and/or could react with carbon–hydrogen bonds in the backbones. Some mechanistic studies discussed below, were carried out to shed some light on this event. Once cross-linked, the polymer becomes intractable and insoluble in solvents; hence, mechanistic data had to be obtained in an indirect fashion.

The light-induced hardening process was selected because we wanted to utilize conditions that specifically

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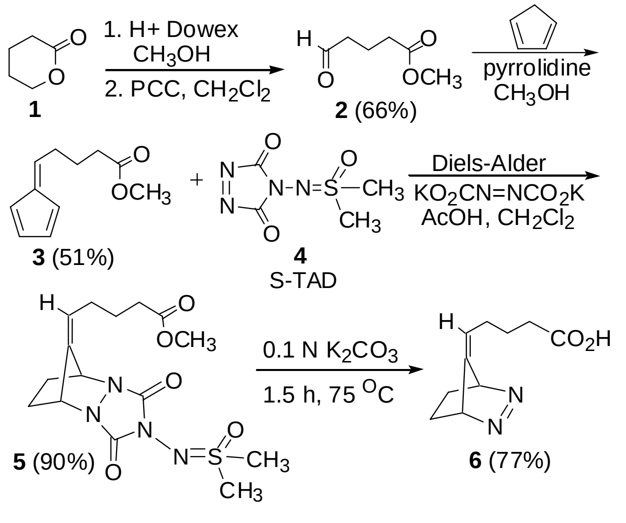
avoid physiologically incompatible acid, base, and highly exothermic methods. The diyl chemistry was adopted from extensive studies on trimethylene methane trapping reactions.[11] For our chemistry to be successful, it was modified to allow a diazo moiety to be attached to a ROMP polymer backbone. The work herein, discusses the first example of an internal nitrogen aerosol to prepare a porous architecture in a hard polymer.

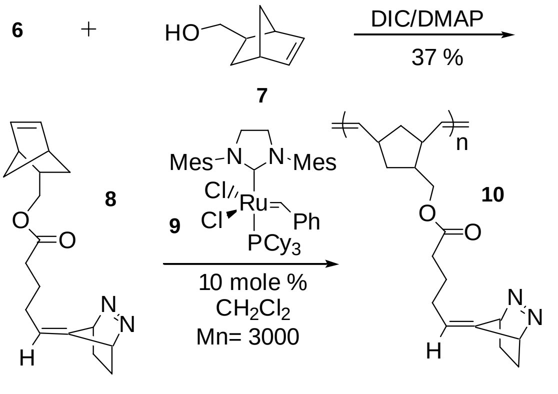
Thus, a norbornyl ring system was envisioned that could be constructed bearing a light sensitive diazene bridge. Another norbornyl residue would be appended by an ester linkage to expedite ROMP reactions with Grubbs' catalyst. The synthesis was initiated in Scheme 2. Commercially available δ-valerolactone **1** was ring-opened to an acyclic methyl ester with a catalytic amount of acidic Dowex resin in methanol and subsequently oxidized with pyridinium chlorochromate to aldehyde **2** in 66% yield. The standard method for the construction of fulvenes was adopted when **2** was treated with cyclopentadiene and a base.[12] The desired fulvene **3** was obtained in 51% yield.

We chose the chemistry of 4-(*S*,*S*-dimethylsulfoximino)-1,2,4-triazoline-3,5-dione (*S*-TAD), as described by Meehan and Little,[13] as an ideal method that could be adopted for the construction of a diazene bridge. The Diels–Alder cycloadduct **5** was prepared via the reaction of *S*-TAD **4** with a fulvene **3** in 90% yield, followed by a subsequent in situ reduction of the π-bond of the resulting Diels–Alder adduct using diimide at low temperature. Conversion of **5** to the corresponding diazene–acid **6** involved treating it under mildly basic conditions with hot water, in 77% yield.

The synthesis was continued in Scheme 3 with a *N′N* diisopropylcarbodiimide-mediated (DIC) esterification of diazene–acid **6** and norbornene alcohol **7** to give the desired ROMP monomer **8** in 37% yield after purification. The ROMP of **8** was then examined using Grubbs' second-generation catalyst **9**. We were pleased to observe that the catalyst led to ROMP polymer **10** without the worrisome degradation of the diazene function (vide infra). Upon addition of ethylvinyl ether to the reaction mixture, the polymerization was halted. Some precipitate was formed in the flask after the ether was added. The mixture was poured into rapidly stirring methanol at room temperature to obtain all of the remaining precipitate. The precipitate was washed several times with excess methanol to remove unwanted byproducts. A GPC analysis was obtained to elucidate the extent of polymerization. The analysis indicated an average molecular weight of 3000, which indicated short polymer chains, and a polydispersity of 1.19 for **10**.



Scheme 2. Synthesis of the diazene–acid.



Scheme 3. ROMP reaction of norbornene **8**.

Polymer **10** was then photocross-linked using a 400 W Hanovia lamp with a Pyrex filter for 3 h at a distance of 2 in. from the lamp. The polymer was observed to undergo gel–solid transformation. A cross-section of the polymer using scanning electron microscopy (SEM) is shown in Figure 1. This view shows the porous nature of the interior of the polymer.[14] The cross-section images clearly indicate that the nitrogen aerosol creates several holes (some being 40 μm) throughout the poly-

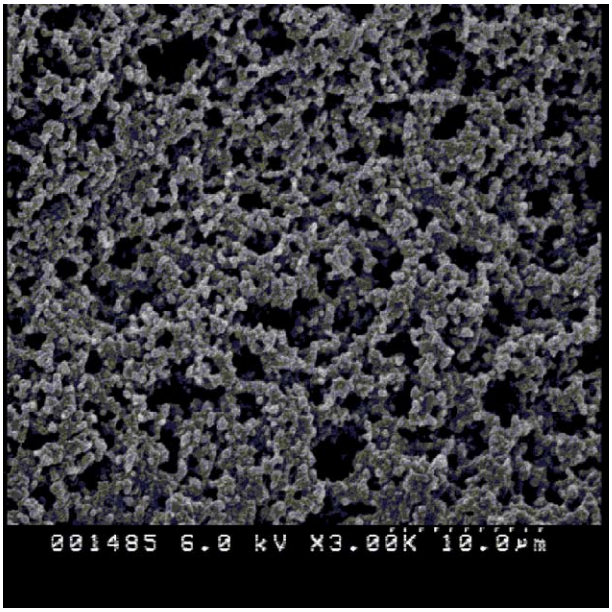
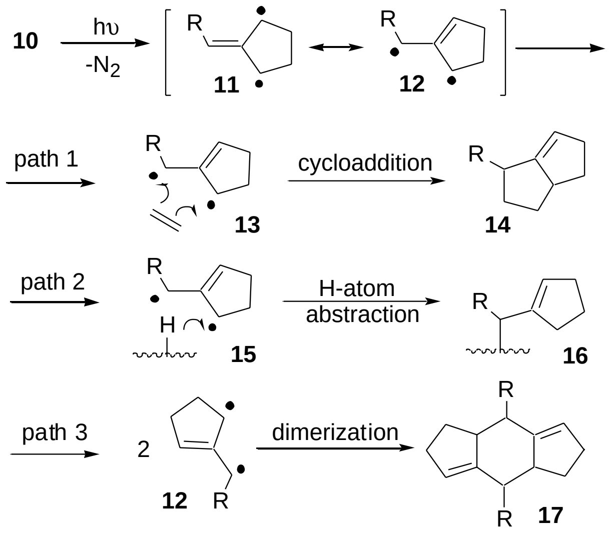


Figure 1. Cross-section of porous cross-linked material **10** (10 μm per division on lower scale).



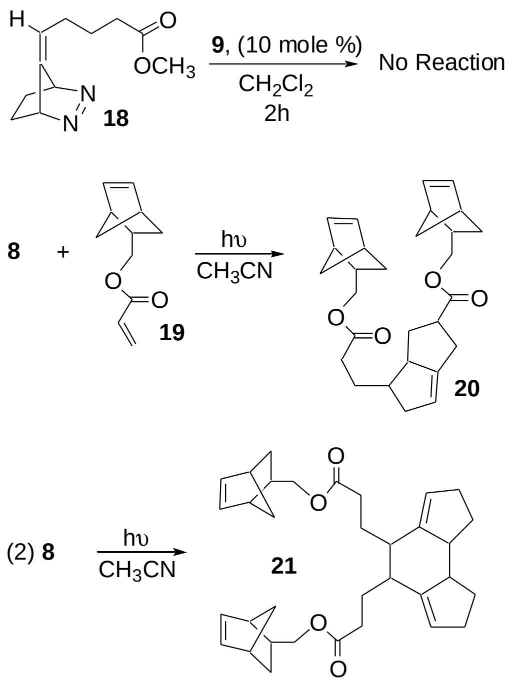
Scheme 4. Cross-linking mechanisms.

mer, capable of carrying water, nutrients, and blood cells through the hard, sponge-like material.[15] Ideally, the size of the pores should enable migration of water and blood, with an average of 10 μm width per red blood cell.[16]

Several cross-linking mechanisms are proposed in Scheme 4. Upon photochemical extrusion of nitrogen from **10**, diyl species **11** ↔ **12** is formed, which can react minimally via three pathways. These reactivity pathways have been observed with other 1,3-diyls in solution.[11a] Path 1 features a cycloaddition reaction with an alkene, while path 2 shows how a diyl can insert in a C–H bond (atom transfer). Both reactions can lead to cross-linked polymer and with the diyl species. A third path 3 involves direct dimerization to the tricyclic product **17** from two diradical precursors.

To further understand the photocross-linking step, three mechanistic studies were conducted to confirm the extrusion of nitrogen and diyl formation upon photoirradiation, as shown in Scheme 5. We synthesized methyl ester **18** without the norbornene group to confirm that a diazene moiety can survive a ROMP. This compound was easily formed by the reaction of acid **6** with diazomethane. Ester **18** was reacted with 0.1 equiv of Grubbs' second-generation catalyst in CH_2Cl_2 for 2 h and it was recovered unchanged. The lack of reactivity by the diazene π-bond precludes any metathesis at this site.[17]

It is also noteworthy that no cross-metathesis products formed from the trisubstituted alkene in **18**.[18] Unsymmetrically substituted alkenes usually readily undergo cross-metathesis and can give up to three products.[19] That this outcome was not observed can be rationalized by considering that the alkene is located in an apical position on a norbornyl ring system and very much hindered; thus, the bulky catalyst **9** could not readily access it. Second, the electron-rich diazene could coordinate to the catalyst and deactivate it, as has been observed in related cases. Third, we noted that no olefin migration was observed, a common occurrence with alkenes subjected to Grubbs' catalysts.[20] Because no chemical reaction was observed, we conclude that diazenes are stable to Grubbs' catalyst, a facet of their reactivity not clearly delineated prior to these studies.



Scheme 5. Metathesis studies.

In a second study, monomer **8** was dissolved in spectral grade acetonitrile and was photolyzed with **19** (Scheme 5) to obtain a cycloaddition reaction. The intermolecular cycloaddition product was obtained in 66% yield. This shows that the 1,3-diyls formed by photoextrusion can react with electron-deficient alkenes. Co-polymers of **19** and **10** are possible with **19** acting a spacer in a polymer chain.[21]

In a third study, compound **8** was dissolved in acetonitrile and irradiated for 3 h; the resulting dimerization product **21** was isolated in 95% yield. It is noteworthy that in the absence of the olefin, the diyl simply reacted with itself via the 1,3-diradical coupling.

In conclusion, ring-opening metathesis polymerization (ROMP) and diradical (diyl) cross-linking provided new access to hard biomaterials. ROMP was used to construct soft and pliable linear polymers, that extruded a nitrogen aerosol when photolyzed. The nitrogen gas created porosity, cross-linking, and hardening.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmcl.2005.08.060.

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