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► **To cite this version:**

Théo Pesenti, Julien Nicolas. 100 th Anniversary of Macromolecular Science Viewpoint: Degradable Polymers from Radical Ring-Opening Polymerization (rROP): Latest Advances, New Directions and Ongoing Challenges. ACS Macro Letters, In press, 10.1021/acsmacrolett.0c00676 . hal-03022543

HAL Id: hal-03022543

<https://hal.science/hal-03022543>

Submitted on 24 Nov 2020

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100th Anniversary of Macromolecular Science

Viewpoint: Degradable Polymers from Radical
Ring-Opening Polymerization (rROP): Latest
Advances, New Directions and Ongoing
Challenges

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Abstract

Radical ring-opening polymerization (rROP) allows facile incorporation of labile groups (e.g., ester) into the main chain of vinyl polymers to obtain (bio)degradable materials. rROP has focused a lot of attention especially since the advent of reversible deactivation radical polymerization (RDRP) techniques and is still incredibly moving forward, as attested by the numerous achievements in terms of monomer synthesis, macromolecular engineering and potential biomedical applications of the resulting degradable polymers. In the present Viewpoint, we will cover the latest progress made in rROP in the last ~ 5 years, such as its recent directions, its remaining limitations and the ongoing challenges. More specifically, this will be achieved through the three different classes of monomers that recently caught most of the attention: cyclic ketene acetals (CKA), thionolactones and macrocyclic monomers.

Introduction

Radical ring-opening polymerization (rROP)^{1,2} is a chain-growth polymerization process involving cyclic monomers that can polymerize through a radical ring-opening mechanism. rROP allows facile incorporation of heteroatoms and functional groups into the polymer backbone, conversely to the radical polymerization of traditional vinyl monomers that is restricted to side chain and chain-end functionalization. Therefore, it is possible to insert labile bonds (e.g., esters, thioesters, etc.) into the main chain to obtain (bio)degradable (co)polymers whose degradation can be triggered by different degradation pathways (e.g., hydrolytic, enzymatic, redox, etc.).² This polymerization method is therefore of great interest when persistence and structural integrity of vinyl polymers are an issue, for instance regarding accumulation of plastic waste in the environment which is a huge environmental concern, or for biomedical applications where safety of the injected materials and their excretion must be ensured.³

Even though rROP has been discovered in the 80s,⁴⁻⁶ there has been a recent resurgence of interest in this technique especially since the advent of reversible deactivation radical polymerization (RDRP).⁷⁻¹² Contrary to free-radical polymerization (FRP), RDRP indeed allows the preparation of well-defined, functional and complex macromolecular architectures and has been the focus of considerable attention.⁷⁻¹² Therefore, combining RDRP and rROP has opened new avenues not achievable with traditional polyesters, towards advanced, degradable polymeric materials, by a simple, yet efficient radical polymerization process.

Consequently, rROP exhibits important advantages when compared to other ring-opening polymerization (ROP) methods, such as the ROP of lactones^{13,14} or the ring-opening metathesis polymerization (ROMP) of cyclic olefins:¹⁵ (i) the high diversity of polymeric structures that can be synthesized, given the broad range of different vinyl monomers that can

be copolymerized with rROP monomers; (ii) its ability to interface with many different RDRP methods to produce well-defined, functional, degradable macromolecular architectures and (iii) the absence of metal-based catalyst during the polymerization process, which can be crucial for further developments and biomedical purposes. In a way, rROP efficiently combines the simplicity and robustness of the radical polymerization of traditional vinyl monomers together with the possibility to form (bio)degradable materials like those obtained from ROP of lactones. However, traditional polyesters are still considered gold standards for biomedical applications given their high biocompatibility and biodegradability, and their approval for use in humans.

In this challenging context, rROP has benefited from substantial development and progress in multiple directions;² from new monomer and polymer syntheses, to new materials with different degradation modalities and promising use in various (biomedical) applications.² Interestingly, thanks to the intense effort and enthusiasm of the polymer community, the field of rROP is still incredibly moving forward as it still has not reached its full potential. Therefore, we believe that a recent snapshot of the field could help capture the latest progress made in rROP, its new directions, its remaining limitations and ongoing challenges. In the present Viewpoint, we will cover all these aspects in the last ~ 5 years by specifically focusing on degradable materials from rROP. This will be achieved through three different classes of monomers that caught most of the attention from the polymer community lately: cyclic ketene acetals (CKA), thionolactones and macrocyclic monomers. To help the readers catching the recent trends in each section, a brief overview of the literature will be given, followed by the recent discoveries and new directions.

1. Pushing the limits of cyclic ketene acetals

Originated from the pioneering work from Endo, Bailey and others, many different classes of cyclic monomers have been studied to prepare degradable (co)polymers, such as unsaturated spiro orthocarbonates, unsaturated spiro orthoesters, vinylcyclopropanone cyclic acetals, CKAs and their derivatives (e.g., fluorinated, thioacetals, dithioacetals, hemiaminal ethers, vinylketene cyclic acetals).² In fact, CKAs are nowadays the most representative and used rROP monomers. They are indeed being intensively investigated not only to prepare degradable homopolymers but also to confer degradability to traditional vinyl polymers. The ideal polymerization mechanism is based on a radical addition of the exo-methylene group and the subsequent ring-opening process to form an ester group in the main chain (Figure 1a).

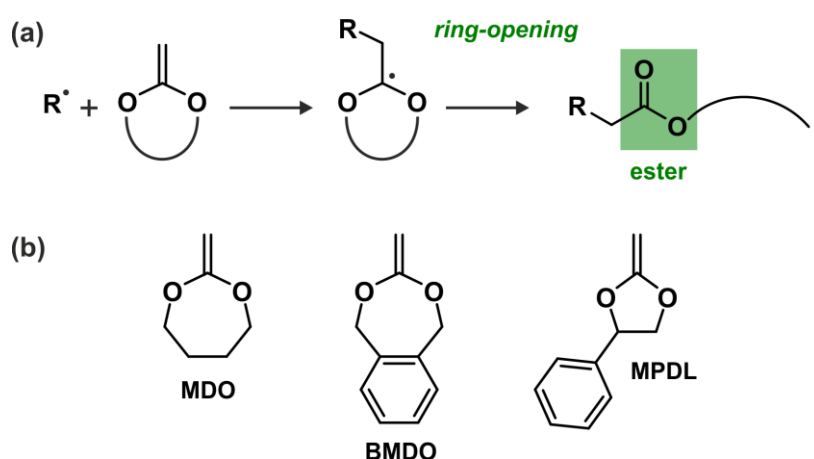


Figure 1. (a) General mechanism for the rROP of CKA monomers. (b) Structures of 2-methylene-1,3-dioxepane (MDO), 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) and 2-methylene-4-phenyl-1,3-dioxolane (MPDL).

1.1. Optimized synthesis and new CKAs

Even though many different CKAs have been developed so far, it appears that only two of them, namely 2-methylene-1,3-dioxepane (MDO) and 5,6-benzo-2-methylene-1,3-dioxepane (BMDO), became very popular (Figure 1b).¹ 2-Methylene-4-phenyl-1,3-dioxolane (MPDL) has however been recently revisited given its styrene-like propagating radical and has met

some success to yield various degradable copolymers by RDRP (Figure 1b).² Some of the reasons that explain the somewhat limited range of CKAs effectively used in the literature are certainly the relatively harsh, tricky and poorly described synthetic conditions to obtain those monomers, the difficulty to easily modify their structure and properties, and their relative instability and high susceptibility to hydrolysis.

Traditionally, CKAs are synthesized through the haloacetal route originally described by McElvain et al. in 1948.¹⁶ This two-step route consists in a transacetalisation between a diol and a haloacetal followed by an elimination reaction. This synthetic pathway is compatible with many different CKAs and has been extensively used, as recently to yield 4,7-dimethyl-5,6-benzo-2-methylene-1,3-dioxepane (MeBMDO),¹⁷ a dimethylated BMDO with a styryl propagating radical. Nevertheless, the classic conditions of the elimination step for this route require high temperatures (typically 100-115 °C in *t*BuOH^{18,19} or 90 °C in THF¹⁷) over long reaction times (initially 24 h in *t*BuOH¹⁹ further reduced to 4 h in THF¹⁷) and purification by fractional distillation under reduced pressure.²⁰ These conditions can be detrimental to achieve high yields or some CKA structures. These monomers are indeed highly sensitive as they can be quickly hydrolyzed under acidic conditions likewise traditional acetals, but they can also undergo nucleophilic attacks due to the electrophilicity induced by the C=C bond.² Moreover, CKAs can self-polymerize by cationic polymerization upon glass contact during distillation²¹ but also upon storage during which pyridine (1–2 %) can be added to improve their stability.¹⁹

In this context, some effort has recently been put in reporting optimized and reliable synthetic routes for CKAs. Building on suggested alternative protocols,²² the synthesis of MPDL was optimized to reach higher conversion and greater purity under mild reaction conditions.²⁰ The elimination step was carried out at 0 °C for only 2 h by using dry THF as a solvent and a phase-transfer catalyst in the presence of the haloacetal. Among the three

different haloacetals tested, the bromoacetal gave the best results and led to pure MPDL with 65 % overall yield (Figure 2a). Another recent improvement of the haloacetal route has been proposed and consisted in using CoCl_2 /trimethylsilyl chloride as a catalytic system during the transacetalisation step,²³⁻²⁵ which allowed the reaction to be performed at room temperature with high reproducibility. When applied to 4,7-dimethyl-2-methylene-1,3-dioxepane (DMMDO), the yield of the transacetalisation step reached 61 %, despite an overall yield of 20 %.

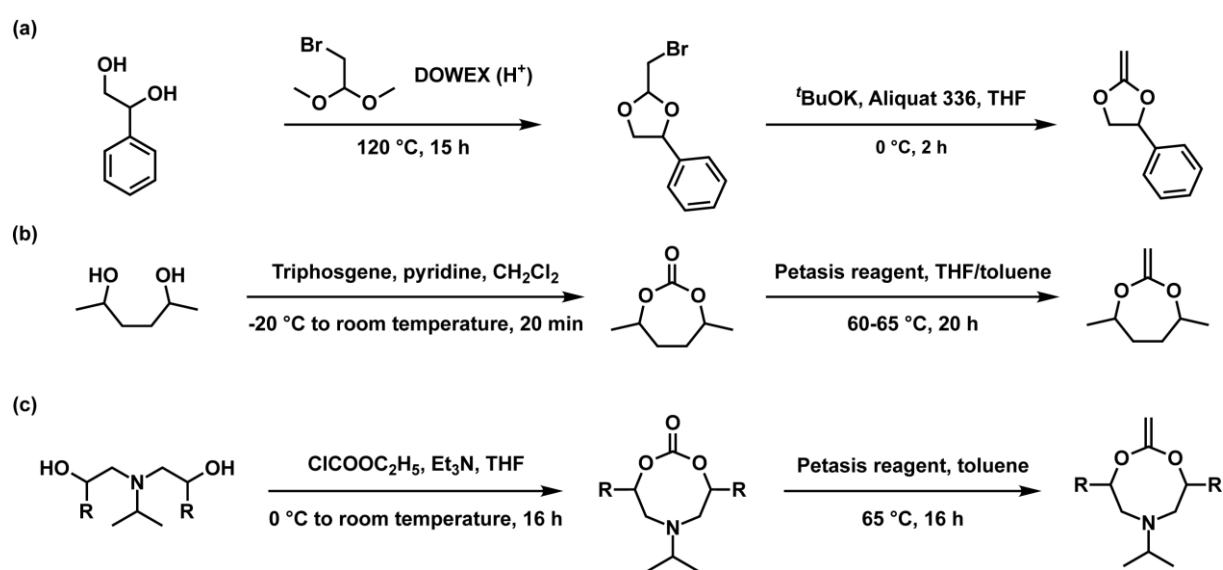


Figure 2. (a) Optimized haloacetal route for the synthesis of MPDL;²⁰ Carbonate route using (b) triphosgene to obtain DMMDO or (c) ethylchloroformate for the synthesis of *i*-MAC (R = H) and *i*-DMMAC (R = CH_3).^{24,26}

Even though the haloacetal route is most popular, other routes have been investigated but with less success. Among them, the carbonate route, whose second step was initially proposed by Petasis,²⁷ was however recently revisited and improved.^{24,26} It relies on a carbonate intermediate formed by treatment of a diol with triphosgene or ethylchloroformate, followed by olefination using the Petasis reagent (Figure 2b and 2c). Reaction conditions appeared rather delicate but did not necessitate any purification by distillation during DMMDO synthesis and led to a 39 % overall yield.²⁴ The authors also successfully applied this route to

the synthesis of amine-bearing CKAs; namely 6-isopropyl-4,8-dimethyl-2-methylene-1,3,6-dioxazocane (i-DMMAC) and 6-isopropyl-2-methylene-1,3,6-dioxazocane (i-MAC) that allowed the synthesis of pH-sensitive copolymers (see sections 1.2 and 1.4).²⁶

i-DMMAC and i-MAC are an interesting addition to the limited library of heteroatom-bearing CKAs which was only composed of 2-methylene-1,3,6-trioxocane.²⁸ Unfortunately, although these three CKAs are synthesized *via* two different pathways, they were obtained with modest yields, mainly because of the final elimination step (24 %, 12 % and 10-54 % elimination yield for i-DMMAC, i-MAC and MTC, respectively).

Despite continuous progress on CKA synthesis, obtaining useful structures with a broad range of different properties is still challenging as insertion of functional groups on the ring appears very limited. The most used CKAs are indeed all hydrophobic (Figure 1b), which limits their use especially for biomedical applications where water-soluble materials can be preferred when it comes to toxicity and excretion. A great deal of effort should therefore be made in this direction in order to significantly broaden the range of CKAs and gain access to new degradable vinyl polymers with innovative and unprecedented properties.

1.2. Homopolymerization of CKAs

Radical homopolymerization of CKAs was extensively studied in the 80s mainly by Bailey and co-workers.² A well-known feature of CKAs is their ability to polymerize through two different mechanisms (Figure 3): (i) a radical ring-opening mechanism, during which the radical addition onto the double bond leads to β -scission of the C-O bond, resulting in the formation of an ester moiety along with a radical able to further propagate to give a degradable polyester and (ii) a ring-retaining vinylic propagation leading to a non-degradable polyacetal. When (bio)degradable materials are envisioned, the former pathway is obviously preferred. In many cases, however, a mixture of ring-opened and ring-retained propagating

species is obtained, resulting in poly(ester-co-acetal) copolymers whose degradation can be significantly affected depending on the proportion of ester units.

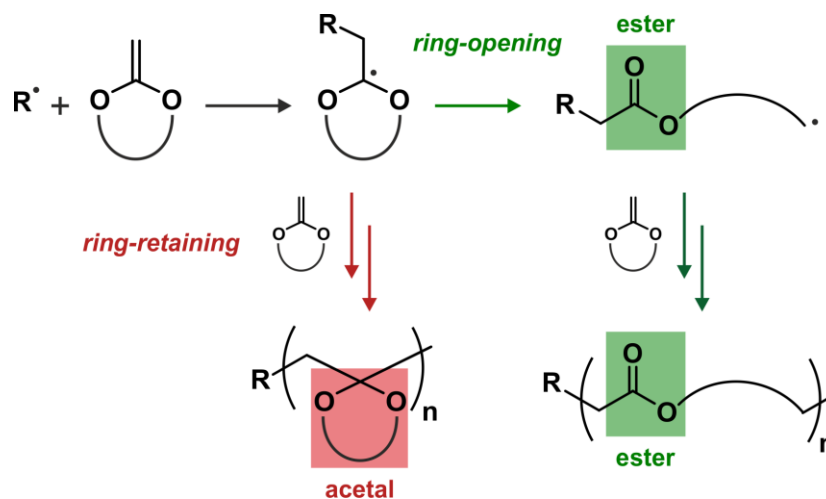


Figure 3. The two main propagation mechanisms during the rROP of CKAs.

It has indeed been shown that several parameters can impact the ring-opening ability of CKAs.^{2,29} For instance, it is generally observed that the ring-opening process is facilitated by increasing the temperature and performing the polymerization in solution instead of in bulk. Influence of the CKA structure (e.g., ring size, steric hindrance, substitutive group on the ring) was also the focus of great attention and the radical ring-opening ability of the most common CKA monomers can be summarized as in Figure 4.

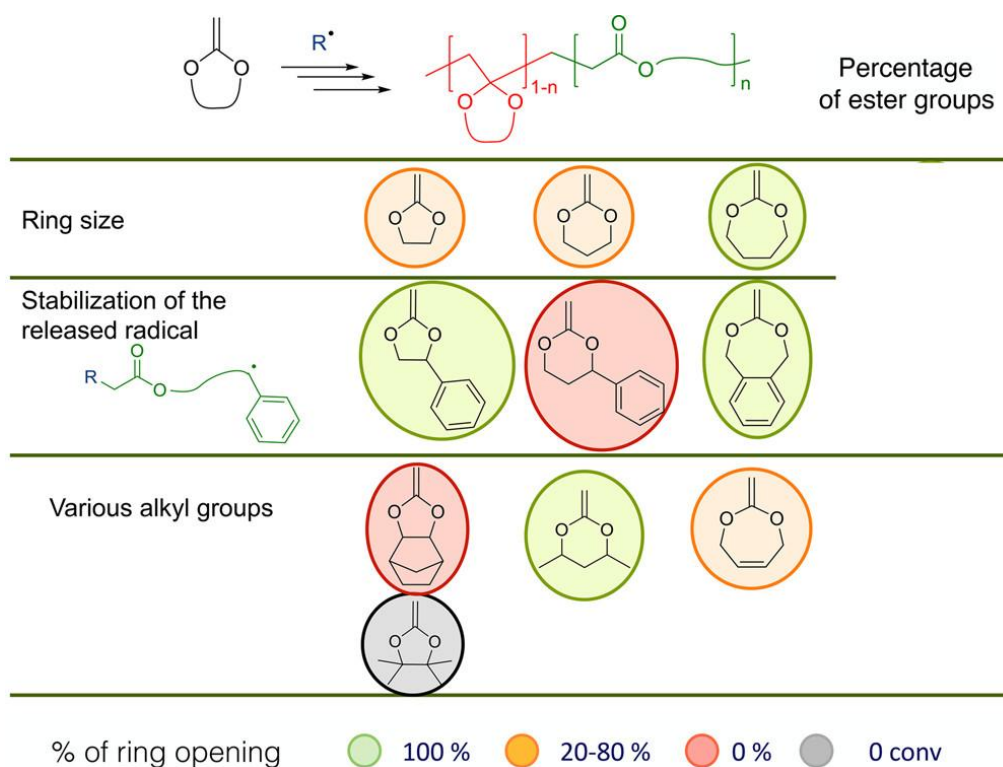


Figure 4. Ring-opening behavior of the most common CKA monomers as function of the ring size, the stabilization of the formed radical and the nature of the alkyl group (Reproduced with permission from ref ². Copyright 2017 American Chemical Society).

However, it is only very recently that a rationalization of the ring-opening ability of CKA monomers was developed.³⁰ The behavior of model CKAs was successfully predicted using a combination of density functional theory (DFT) calculations and kinetic modeling *via* PREDICI, which was further supported by an experimental study. This represents an important step towards the discovery of optimized CKA structures for efficient synthesis of aliphatic polyesters by rROP.

The vast majority of CKAs developed so far, if not all, are still very difficult to homopolymerize by FRP resulting in harsh polymerization conditions, slow polymerizations and low molar masses,² even though the macromolecular characteristics can be slightly tuned by adjusting the initiator's nature and concentration, the polymerization time and the reaction temperature. Unfortunately, the newly developed CKAs have not brought about major changes. For instance, DMMDO was polymerized by FRP during 66 h at 85 °C to yield

polymers with M_n in the 2.9–5.2 kg.mol⁻¹ range, whose degradation was only complete in acetonitrile with NaOH 1M at 80 °C for 24 h.²⁴ This system was nevertheless applied to the synthesis of PEG-*b*-PDMMDO from a PEG-azo initiator by FRP, leading after formulation to PEGylated nanoparticles and able to encapsulate horseradish peroxidase whose activity was maintained for 1 week.

Even if recently synthesized MeBMDO has been able to polymerize by a quantitative ring-opening mechanism, the polymerization temperature had to be increased up to 160 °C (compared to 70-120 °C for BMDO) to counterbalance its poor reactivity. Another newly obtained CKA, *i*-MAC, was polymerized at 85 °C in toluene for 24 h using azobisisobutyronitrile (AIBN) as an initiator, but generated oligomers ($M_n = 1700$ g.mol⁻¹) with a ring-opening content of 70 %.²⁶ On the other hand, *i*-DMMAC did not polymerize in the presence of different thermal radical initiators and solvents. This drawback has been overcome by performing photopolymerization (365 nm at 25 °C for 12 h), where pH-sensitive oligomers ($M_n = 1500$ g.mol⁻¹) of undefined structure were obtained.²⁶ Additionally to photopolymerization, ultrasound-mediated rROP of CKAs has been also investigated as a way to impact the M_n and the ring-opening ability of each CKA.²⁵

RDRP of CKAs³¹ was attempted to overcome limitations of CKA FRP, but with limited success.³²⁻³⁴ Whereas early achievements on nitroxide-mediated polymerization (NMP) of MDO using TEMPO as a nitroxide were not conclusive due to several inconsistencies, atom transfer radical polymerization (ATRP) of MPDL led to significant amount of acetal units in the polymer. The proportion of non-degradable units was however significantly reduced by using BMDO instead, while maintaining a good control of the polymerization.³⁵ Similar results were obtained with the same monomer by reversible addition-fragmentation chain transfer (RAFT) polymerization.³⁶ However, the polymerization

was performed in solution to avoid significant increase of the dispersity and the polymer livingness was not investigated.

By selecting *O-p*-methoxyphenyl-*S*-methylacetylthioacetate as a chain transfer agent (CTA), the first RAFT homopolymerization of MDO was recently reported.³⁷ This CTA was indeed able to reduce fragmentation and electron rearrangement during rROP, conversely to other structures. It yielded good control over molecular weight and rather low dispersity ($\mathcal{D} = 1.55$), together with high retention onto the polymer chain-end, even though moderate conversions and M_n were obtained. Hyperbranched PMDO was also obtained from [(ethoxycarbonothioyl) sulfanyl] propanoate as a polymerizable RAFT agent.³⁸ Interestingly, hyperbranched PMDO exhibited lower crystallinity than PMDO obtained using a non-polymerizable RAFT agent (2-ethoxythiocarbonylsulfanyl-propionic acid ethyl ester) and therefore a faster degradation than its linear counterpart. However, polymerization of DMMDO could not be controlled neither by ATRP using ethyl- α -bromoisobutyrate, 2,2'-bipyridyl/CuBr nor by RAFT/MADIX using 2-cyano-2-propyl benzodithiotate or 2-((ethoxycarbonothioyl)thio)-2-methylpropanoic acid.²⁴ This emphasizes the tremendous impact of slight structural changes in CKAs and RAFT agents on the outcome of the homopolymerizations.

More recently, NMP of CKAs was revisited by using the SG1-based BlocBuilder MA alkoxyamine. BMDO and MPDL were homopolymerized at 140 °C leading to a quite good control of the polymerization ($M_n < 10 \text{ kg}\cdot\text{mol}^{-1}$, $\mathcal{D} < 1.5$).³⁹ However, it revealed the occurrence of side reactions preventing high monomer conversion to be reached and highly living polymers to be synthesized, despite a broad range of different experimental conditions explored (i.e., reaction temperature, nature of solvent, and nature of the alkyl initiating radical). By ³¹P NMR spectroscopy, ESI-MS together with DFT calculations and PREDICI modeling, it was hypothesized that ketal-based macroradicals were irreversibly trapped by the

SG1 nitroxide, followed by cleavage of CO–N bond of the corresponding macroalkoxyamines.

RDRP methods suitable for CKA homopolymerization have been broadened to cobalt-mediated radical polymerization (CMRP) of MTC.⁴⁰ Performing homopolymerization in bulk at 75 °C for 22 h using cobalt(II) [*N,N'*-bis(3,5-ditert-butylsalicylidene)-1,2-cyclohexanediamine] as cobalt complex gave a PMTC of $M_n = 16\,300\text{ g}\cdot\text{mol}^{-1}$ with a low dispersity ($D = 1.25$).

These few recent achievements tend to show that homopolymerization of CKA under RDRP conditions remains somewhat challenging, especially to reach high M_n and well-defined macromolecular architectures containing PCKA blocks. Future effort should therefore focus on those directions to better challenge aliphatic polyesters made by ROP. Designing new CKAs (especially hydrophilic, or at least less hydrophobic than the handful of CKAs commonly used) and/or perhaps more efficient controlling/chain transfer agents, while finding optimized polymerization conditions are likely the leads that should be followed to achieve these goals.

1.3. Copolymerization of CKAs with vinyl monomers

Whereas little progress has been made in the past few years on the homopolymerization of CKAs, their copolymerization with common vinyl monomers, by either FRP or RDRP, has become an incredibly productive research field. This can be explained by the great interest in endowing vinyl polymers with degradability,³ which is key for biomedical applications where this feature is essential (e.g., drug delivery), or to make degradable vinyl materials for a more sustainable world. As an illustration, the past few decades have witnessed the development of a broad range of different vinyl polymer-based drug delivery systems with promising properties.^{41,42} However, their non-degradability represents an important drawback because such materials may accumulate in the body and lead to severe toxicity, for instance in case of

chronic administration. Therefore, incorporating ester groups into their backbone by a simple copolymerization approach quickly appeared as a very appealing strategy. This renewed success in copolymerizing CKA with vinyl monomers also emerged thanks to the recent advent of RDRP which, contrary to ROP, enables functional macromolecular architectures to be readily synthesized. Therefore, the possibility to prepare degradable RDRP-derived materials to surpass, or at least challenge traditional polyesters also attracted a lot of attention.³¹

CKA have been copolymerized with the main types of vinyl monomers by both FRP and RDRP.^{2,31} However, this was achieved with more or less success depending on the reactivity ratios of each CKA/vinyl monomer pair, that eventually govern the molar fraction of CKA units (and therefore of ester groups) into the copolymer.^{2,43} In fact, the recent years have seen most of the research effort and innovation focused on four different vinyl monomer types: methacrylates, vinyl acetates, maleimides and vinyl ethers.

1.3.1 Methacrylates

Methyl methacrylate (MMA) was one of first vinyl monomers to be copolymerized with CKAs.¹⁹ Despite reactivity ratios comparable to those of acrylates and acrylamides, copolymerization of CKAs with methacrylates became much more popular, especially since RDRP techniques went mainstream. This can be explained by the numerous commercially available methacrylate monomers, the easy synthesis of methacrylates bearing a broad range of different functionalities (e.g., OH, OEG, carbohydrate, etc.) and their efficient (controlled) polymerization under relatively mild conditions.

Various copolymers based on CKAs and methacrylates have been synthesized by FRP and RDRP techniques (mainly ATRP and RAFT) and exhibited high ring-opening abilities (typically from 70 to 100 %).² Insertions of CKA units into the copolymers were in line with the associated reactivity ratios: for instance, when the initial molar fractions of CKA in the

monomer feed, $f_{\text{CKA},0}$, was 0.5, the molar fractions of the CKA in the copolymer, F_{CKA} , were typically in the 0.1–0.4 range, depending on the CKA and methacrylate used.² Even though such copolymerization systems were compatible with ATRP and RAFT, increasing $f_{\text{CKA},0}$ values up to 0.6–0.8 led to a significant increase in the dispersity, thus indicating a partial loss of control. Beyond fundamental studies to investigate the feasibility of their synthesis and the degradation properties of the obtained copolymers, different applications were envisioned: (i) degradable materials with new properties; (ii) degradable nanoparticles; (iii) degradable marine antibiofouling coatings; (iv) nanocarriers for drug delivery; (v) biomaterials for gene/DNA transfection; (vi) materials for tissue engineering and some others.

In the past few years, important effort has been directed towards the design of degradable polymethacrylates with new properties. In this context, the synthesis of degradable fluorinated polymers by ruthenium-catalyzed living radical terpolymerization of BMDO with fluorinated methacrylates (1*H*,1*H*,2*H*,2*H*-perfluorooctyl or 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoropentyl methacrylate) and oligo(ethylene glycol) methacrylate (OEGMA) has been recently reported for potential use in medicine and other applications (Figure 5).⁴⁴ It was demonstrated that increasing the fluorinated monomer content led to: (i) enhanced BMDO incorporation in the resulting terpolymer and (ii) a 100-fold higher hydrolytic stability compared to the non-fluorinated counterpart.

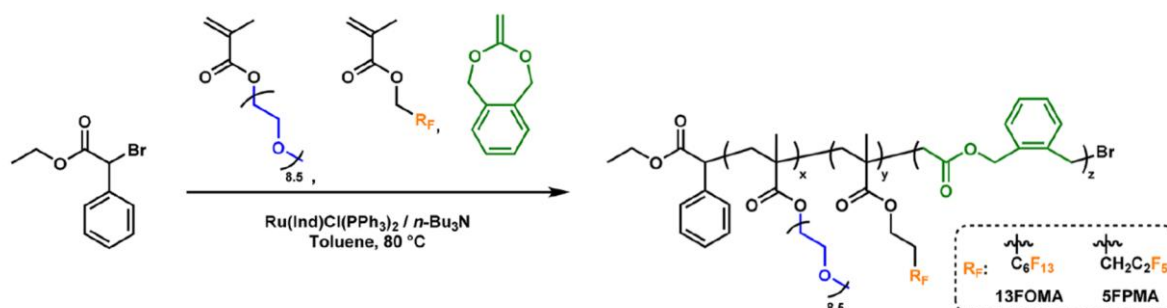


Figure 5. Ruthenium-catalyzed terpolymerization of BMDO with fluorinated alkyl methacrylates and OEGMA (Adapted with permission from ref⁴⁴. Copyright 2017 American Chemical Society).

A great deal of effort was also directed towards marine antibiofouling coatings, whose surface need to be self-polishing and able to release biocides for optimized properties. P(MMA-*co*-MDO) copolymers ($M_n = 19\text{--}27 \text{ kg}\cdot\text{mol}^{-1}$, $D > 2$) made by FRP showed good adhesion properties compared to PMDO, owing to the presence of MMA units, and exhibited both hydrolysis and enzymatic degradation.⁴⁵ They demonstrated antifouling properties during marine field tests for 3 months thanks to the renewal of the coating surface caused by the copolymer degradation, that allowed the release of encapsulated 4,5-dichloro-2-octylisothiazolone (DCOIT) as the antifoulant molecule (Figure 6).

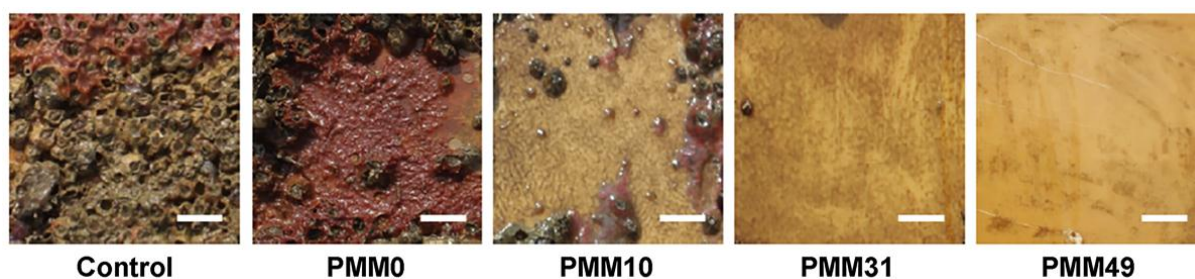


Figure 6. Images of tested panels with P(MMA-*co*-MDO) coatings or without, after immersion in seawater for three months (control: epoxy panel; PMM0: $F_{\text{MDO}} = 0$; PMM10: $F_{\text{MDO}} = 0.1$; PMM31: $F_{\text{MDO}} = 0.31$; PMM49: $F_{\text{MDO}} = 0.49$) with 5 wt.% of DCOIT. Scale bar: 2 cm (Adapted with permission from ref ⁴⁵. Copyright 2018 Elsevier).

This system was further optimized by grafting the antifoulants onto the polymer backbone in order to better control its release and to improve the antifouling ability. This was achieved by copolymerizing MDO and MMA with *N*-methacryloyloxy methyl benzoisothiazolinone (V-BIT), an antifoulant pending group with a broad-spectrum antimicrobial property.⁴⁶ The release of the antifoulant can therefore be adjusted by modulating the main-chain degradation as well as the side-group hydrolysis. The coating was able to generate a constantly renewed

surface while releasing antifoulant molecules, leading to good antifouling efficacy for more than 6 months.

Another approach consisted in the copolymerization of MDO with silyl methacrylates that led to copolymers whose pending silyl ester group hydrolysis on contact with artificial seawater (ASW) was used as a leverage to tune the degradation of the main-chain ester groups of the copolymers.⁴⁷ From the three silyl methacrylates investigated (bis(trimethylsiloxy)methylsilyl methacrylate (MATM2), triisopropylsilyl methacrylate (TIPSiMA) and tributylsilyl methacrylate (TBSiMA)), MATM2 and TBSiMA gave the highest water uptake and degradation kinetics (M_n decrease of 90 % and 86 % after immersion in ASW at room temperature for 7 weeks) than TIPSiMA, that led to insignificant degradation.

Crosslinking strategies have also been reported to improve the coating ability and overall properties of MDO-containing antibiofouling copolymers; for example by copolymerizing MDO with: (i) 2-(dimethylamino) ethyl methacrylate (DMAEMA) and 3-(methacryloxypropyl) trimethoxysilane (KH570),⁴⁸ to make the materials protein resistant and self-crosslinkable, respectively or (ii) tertiary carboxybetaine ester (TCB) to confer protein resistance features and 7-methacryloxy-4-methylcoumarin (MAMC) to allow photo-cross-linking (Figure 7a).⁴⁹ Interestingly in the latter case, the copolymer film can produce oligo-zwitterions with antibacterial activity resulting from surface hydrolysis in ASW (Figure 7b).

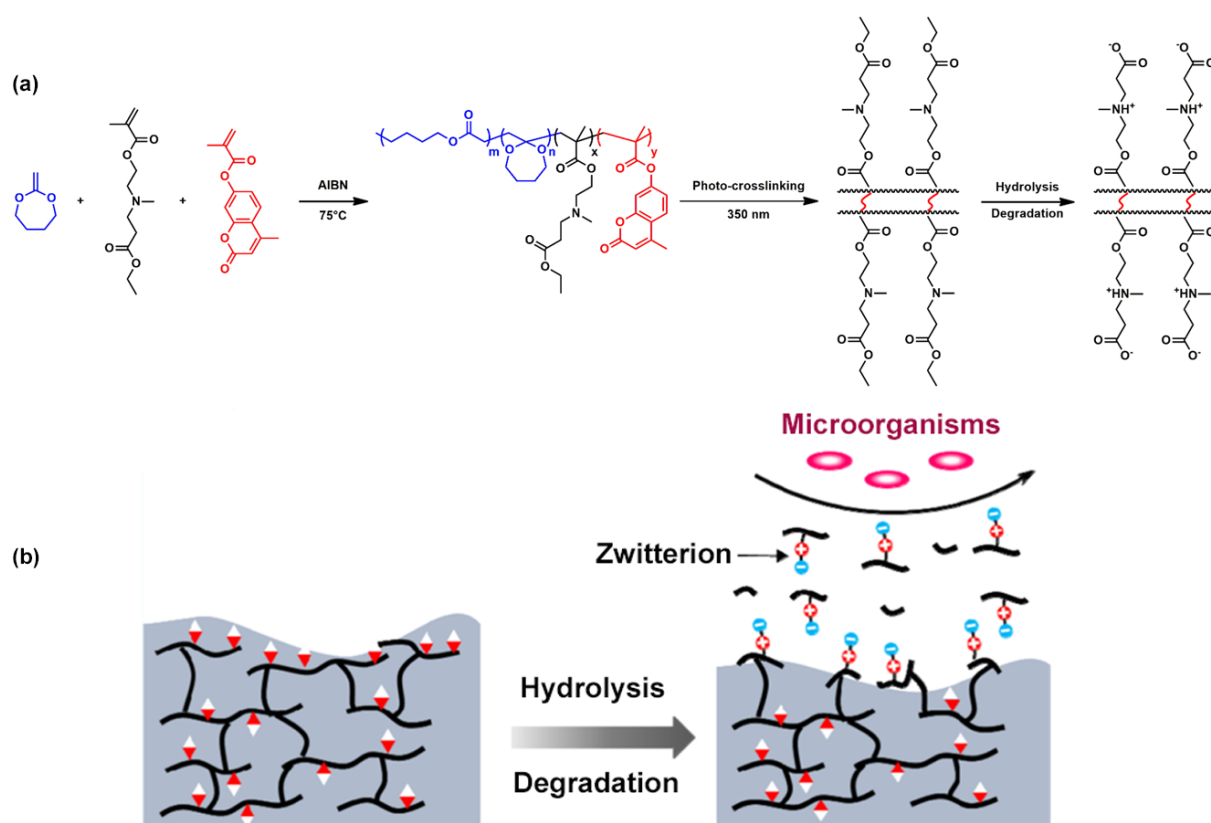


Figure 7. Marine antibiofouling coating synthesized from MDO-based terpolymer. (a) Synthesis of P(MDO-*co*-TCB-*co*-MAMC) copolymers by FRP. (b) Upon water contact, degradation of the copolymer backbone produces oligo-zwitterions with protein resistance and antibacterial activity (Adapted with permission from ref ⁴⁹. Copyright 2018 American Chemical Society).

New developments have also been reported in biotechnology, biomaterials and drug delivery. For instance, in the field of polymer-protein bioconjugates,^{50,51} degradable, PEGylated P(OEGMA-*co*-BMDO)-lysozyme ($F_{\text{BMDO}} \sim 0.1$) containing a disulfide linker has been prepared by RAFT polymerization and showed an increase in activity of the lysozyme after reductive cleavage of the polymer.⁵² A recent study also concerned the design of new protein stabilizing polymers for cryopreservation. A copolymer with trehalose side chains was obtained by RAFT-mediated copolymerization of but-3-enyl methacrylate (BMA) and BMDO.⁵³ The subsequent thiol-ene modification with trehalose gave a P(BMDO-*co*-BMA-

trehalose) copolymer that showed 66 % retention of activity of the therapeutic protein G-CSF after heat stress.

In the field of biomaterials, terpolymers composed of MDO, *n*-butyl methacrylate (*n*BMA) and 2-methacryloyloxyethylphosphorylcholine (MPC) were obtained by FRP and investigated as cardiovascular drug-eluting stent coatings that showed good blood compatibility, anti-adhesion properties and biodegradability.⁵⁴ P(MDO-*co*-MMA) copolymers ($F_{\text{MDO}} = 0.05$) loaded with *N*-acetyl cysteine have also been investigated as bone filling material given their identical morphology than conventional PMMA bone cement and their good biocompatibility, mechanical (e.g., compressive strength) and mineralization properties.⁵⁵

Stimuli-responsive materials are of great interest notably for biomedical applications.^{56,57} Dual stimuli-responsiveness and main-chain degradation were successfully combined through the synthesis of degradable star hyperbranched polymers comprising of pH-responsive hyperbranched cores and thermoresponsive PEG-based coronas.⁵⁸ MDO was first copolymerized with DMAEMA and di(ethylene glycol) dimethacrylate (DEGDMA) by RAFT to constitute the hyperbranched core, which was further chain extended with OEGMA and MDO to produce a linear PEG-based corona (Figure 8). Main-chain degradation was therefore incorporated throughout the whole structure and hydrolysis was confirmed by degradation under accelerated conditions ($\text{NaOH}_{\text{aq}} \sim 1 \text{ wt.}\%$) on linear copolymers.

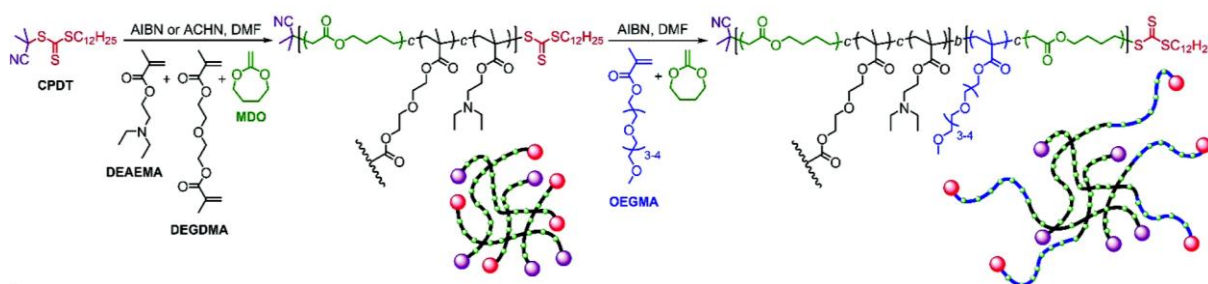


Figure 8. Synthesis of degradable star hyperbranched copolymers with a pH-responsive hyperbranched core and a thermoresponsive PEG-based corona (Adapted with permission from ref ⁵⁸. Copyright 2018 Royal Society of Society).

Interestingly, when similar linear copolymers are prepared (i.e., copolymers obtained by RAFT polymerization of DMAEMA and MDO from a PEG-based macro CTA), they can undergo pH-triggered self-assembly into degradable nanoparticles of average diameters ranging from 20 to 60 nm (Figure 9a–c).⁵⁹ *N*-hydroxysuccinimide ester methacrylic acid (NHSMA), whose ability to be copolymerized with MDO has been recently established,⁶⁰ was also added into the monomer feed allowing crosslinking of the resulting nanoparticles *via* amide bond formation (Figure 9d) and the production of branched oligomers upon hydrolysis under alkaline conditions. These nanoparticles were also able to reversibly swell and contract from ~ 80 nm to ~ 160 nm with changes in pH; a potentially useful feature for triggered drug delivery.

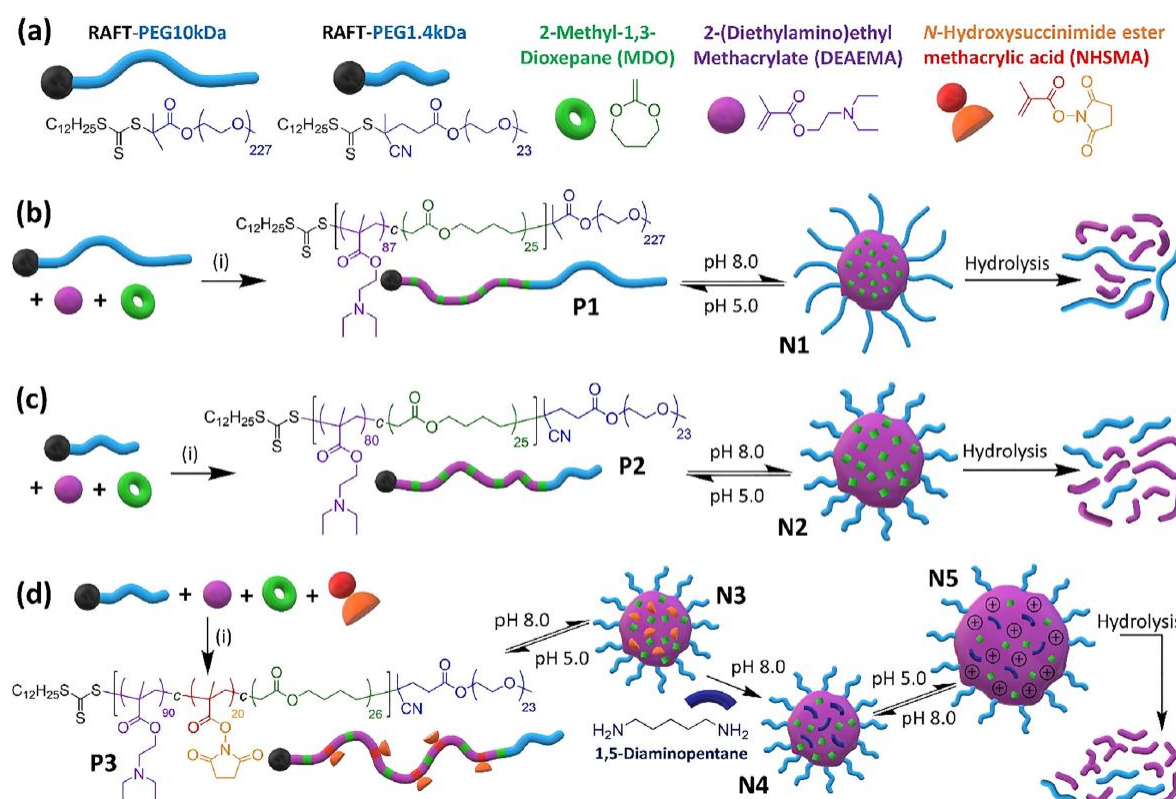


Figure 9. Synthesis of pH-responsive nanoparticles by rROP. (a) Structures of the main building blocks; (b) and (c) Copolymerization of MDO and 2-(dimethylamino) ethyl

methacrylate (DMAEMA) from PEG-based macro-RAFT agents; (d) Terpolymerization of MDO, DMAEMA and *N*-hydroxysuccinimide ester methacrylic acid (NHSMA) followed by crosslinking with 1,5-diaminopentane (Reproduced with permission from ref ⁵⁹. Copyright 2020 Elsevier).

Whereas ATRP and RAFT have been largely employed as RDRP technique to synthesize CKA-containing polymers, the recent years has witnessed the rise of NMP to produce well-defined, degradable CKA-containing polymethacrylates for different applications. Nitroxide-mediated terpolymerization of OEGMA, CKAs and acrylonitrile (AN) was initially reported using the SG1 nitroxide as a way to prepare well-defined, degradable PEG-based polymethacrylates.⁶¹ Given the well-known difficulty for NMP to control the homopolymerization of methacrylates, AN was used here as controlling comonomer.⁶² Among the different CKAs tested (BMDO, MDO and MPDL), it was shown that MPDL gave the best control of the polymerization ($M_n \sim 10 \text{ kg}\cdot\text{mol}^{-1}$, $D \sim 1.3$) and tunable MPDL amounts in the copolymer ($F_{\text{MPDL}} = 0.07\text{--}0.29$), presumably because of its styrene-like ring-opened structure which enabled homolytic cleavage of MPDL-SG1 bonds under optimized NMP conditions. In-depth chain-end characterization of those terpolymers by ³¹P NMR spectroscopy revealed that most of the copolymer chains were terminated by MPDL-SG1 sequences,⁶³ similarly to other controlling comonomers like styrene (S)⁶⁴ and AN.⁶⁵ This observation then prompted the use of MPDL as a 2-in-1 comonomer; that is able to both confer degradability and help controlling of the copolymerization on its own (Figure 10a). Indeed, in absence of AN, SG1-mediated copolymerization between OEGMA⁶⁶ (or MMA)²⁰ and MPDL yielded well-defined P(MMA-*co*-MPDL) and P(OEGMA-*co*-MPDL) copolymers with the following trend: the higher $f_{\text{MPDL},0}$, the lower D .

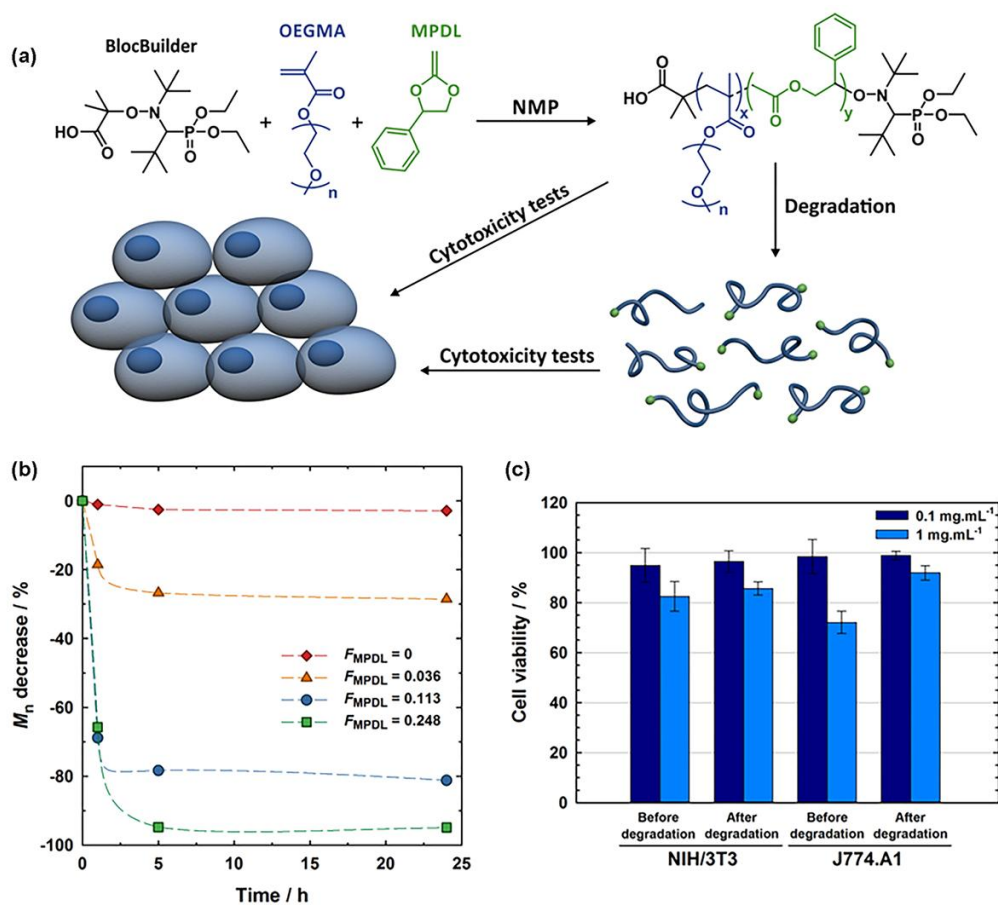


Figure 10. (a) Synthesis of degradable P(OEGMA-*co*-MPDL) copolymers by NMP and cytotoxicity evaluation. (b) Hydrolytic degradation in 5 wt.% KOH of P(OEGMA-*co*-MPDL) as a function of the MPDL content (F_{MPDL}). (c) Cell viability (MTT assay) after incubation of NIH/3T3 cells and J774.A1 cells with P(OEGMA-*co*-MPDL) copolymer ($F_{MPDL} = 0.113$) at 0.1 and 1 mg.mL⁻¹ (Adapted with permission from ref ⁶⁶. Copyright 2015 Royal Society of Chemistry).

The copolymers were living and their degradability was assessed under accelerated conditions (5 % KOH) (Figure 10b). Given their water-solubility, P(OEGMA-*co*-MPDL) copolymers were tested for their cytocompatibility during which both the original copolymers and their degradation products showed high cell viability up to 1 mg.mL⁻¹ on NIH/3T3 cells and J774.A1 cells (Figure 10c), which represents a promising step towards their biocompatibility.

Hydrolytic degradation of P(MMA-*co*-MPDL) and P(OEGMA-*co*-MPDL) copolymers under physiological conditions (PBS 0.1 M, pH 7.4, 37 °C) was then benchmarked with traditional aliphatic polyesters such as poly(lactide-*co*-glycolide) (PLGA), polylactide (PLA) and polycaprolactone (PCL), which are considered the gold standards in terms of degradable materials for biomedical applications.⁶⁷ Whereas degradation of P(MMA-*co*-MPDL) was slower than that of PCL whatever F_{MPDL} , likely because of its high hydrophobicity and rigidity, P(OEGMA-*co*-MPDL) had a tunable degradation kinetics as function of F_{MPDL} , that was comprised in between that of PCL (for $F_{\text{MPDL}} = 0.09$) and PLA (for $F_{\text{MPDL}} = 0.27$). Interestingly, pH of P(OEGMA-*co*-MPDL) solution stayed higher than 6.8 during degradation, whereas PLA reached pH 5.5. However, enzymatic degradation in the presence of lipases (*Candida antarctica*) was negligible for P(MMA-*co*-MPDL) and moderate for P(OEGMA-*co*-MPDL), presumably because of the high hydrophobicity of MMA and MPDL, the high steric hindrance of MPDL, and potential steric repulsion of PEG chains.

Polymer prodrug nanocarriers⁶⁸ are also of great interest in drug delivery as a way to circumvent the limitations associated to the physical encapsulation of drugs (e.g., poor drug loading, burst release, etc.). In this context, P(MMA-*co*-MPDL) and P(OEGMA-*co*-MPDL) copolymers were grown from an anticancer drug-bearing SG1-based alkoxyamine by the “*drug-initiated*” method (also called “*grafting-from*” approach),^{69,70} to generate degradable polymer prodrug nanocarriers. By using gemcitabine (Gem) as the drug, water-soluble Gem-P(OEGMA-*co*-MPDL) prodrugs and Gem-P(MMA-*co*-MPDL) prodrug nanoparticles ($D_z = 100\text{--}200$ nm) were obtained (Figure 11a).⁷¹ Interestingly, cytotoxicity experiments demonstrated that the anticancer activity can be governed by independently manipulating three structural parameters: (i) the nature of the comonomer used (MMA or OEGMA); (ii) the nature of the drug-polymer linker (amide or diglycolate) and (iii) the MPDL content, that was varied from ~ 7 to ~ 25 mol.%. Indeed, water-soluble POEGMA-based prodrugs were

significantly more cytotoxic than PMMA-based counterparts. Also, the lower the MPDL content, the greater the cytotoxicity. Eventually, the more labile diglycolate linker yielded higher cytotoxicity compared to a simple amide bond because of a greater drug release kinetics (Figure 11b and 11c).

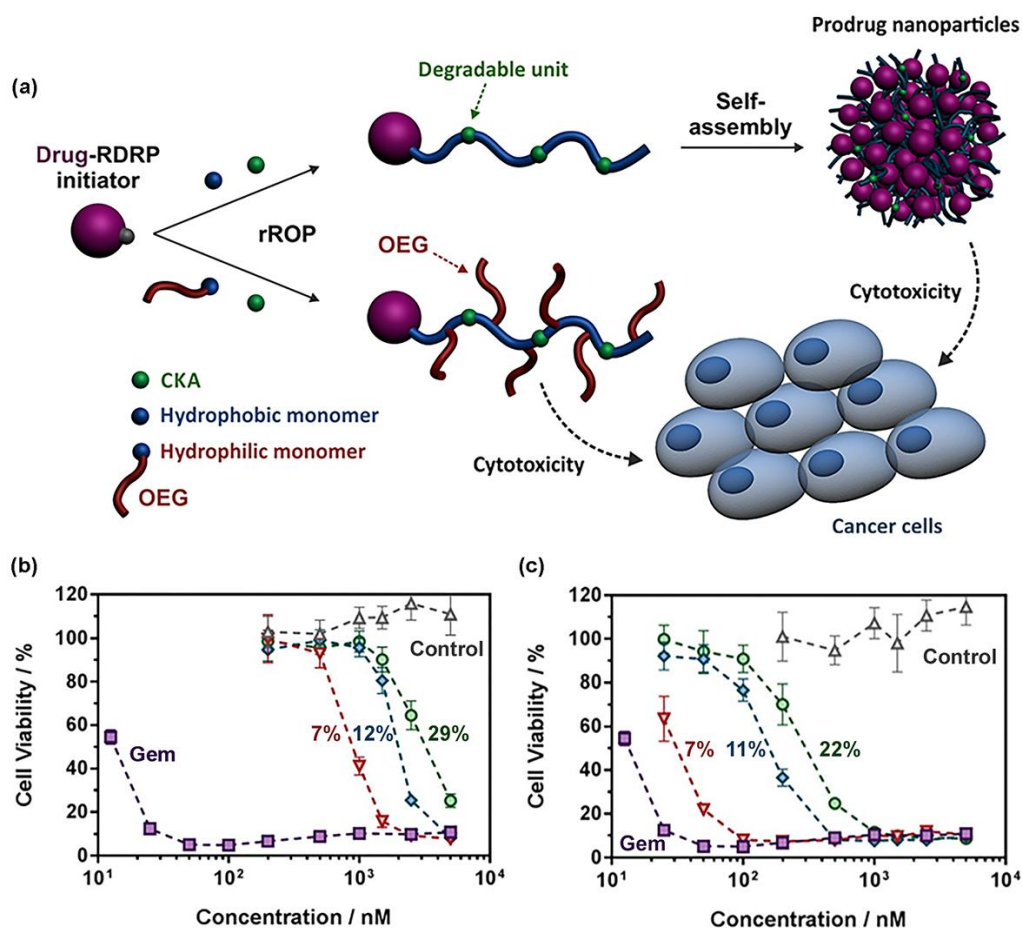


Figure 11. (a) Synthesis of degradable, hydrophobic and hydrophilic polymer prodrugs by NMP using the “drug-initiated” method. Cell viability (MTT assay) on MiaPaCa-2 cells with (b) Gem, Gem-P(MMA-co-MPDL) of variable F_{MPDL} and P(MMA-co-MPDL) as a control and (c) Gem, Gem-P(OEGMA-co-MPDL) of variable F_{MPDL} and P(OEGMA-co-MPDL) as a control (Adapted with permission from ref⁷¹. Copyright 2018 Royal Society of Chemistry).

Other polymer prodrugs constructed by rROP via a “grafting-through” approach were subsequently reported, whose synthesis relied on the RAFT-mediated copolymerization of MDO and a methacrylate monomer bearing Gem.⁷² The resulting copolymer exhibited hydrolytic degradation under accelerated conditions (pH 11, 40 °C) and was formulated into

nanoparticles that showed sustained Gem release in the presence of Cathepsin at pH 5.2 and some cytotoxicity on pancreatic cancer cells.

1.3.2 Vinyl acetates

Like methacrylate monomers, vinyl acetate (VAc) was also extensively studied as comonomer with CKAs.^{1,2} Consequently, this copolymerization system has been largely investigated over the past few decades, in particular by FRP^{73,74} and RAFT^{37,75} to make degradable vinyl copolymers. A notable difference with methacrylates is, however, the more favorable reactivity ratios observed for VAc:CKA monomer pairs (for instance with MDO: $r_{\text{VAc}} = 1.53$ and $r_{\text{MDO}} = 0.47$)⁷³ than for methacrylate:CKA monomer pairs, thus leading to greater CKA incorporations into the final copolymers than for methacrylate-based counterparts.

The recent years have seen the development of copolymerization systems involving CKAs and new VAc derivatives. For instance, a degradable PVA with high ice recrystallization inhibition activity was obtained by FRP of vinyl chloroacetate (VClAc) and MDO ($F_{\text{MDO}} = 0.05$), followed by selective hydrolysis of the chloroacetate groups to yield the alcohol units.⁷⁶

In another study, vinyl bromobutanoate (VBr) was copolymerized with MDO under RAFT control.⁷⁷ It yielded well-defined P(MDO-*co*-VBr) copolymers, whose pendent bromine functional groups could be further modified *via* post-polymerization modification (e.g., azidation, copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC)), as a general way to access functional, degradable polymers. A series of oligo(ethylene glycol) vinyl acetates (MeO_nVAc; n = 1–3) was also reported and successfully copolymerized with MDO by RAFT (Figure 12a). The resulting copolymers were non-cytotoxic and exhibited tunable degradability and thermosensitivity (i.e., adjustable lower critical solution temperatures (LCST)/degradation as function of F_{MDO}), and can thus be seen as an alternative to poly(*N*-

isopropylacrylamide) (PNIPAAm) and POEGMA (Figure 12b).⁷⁸ These copolymers also served to make polymer-protein bioconjugates *via* coupling of chain-end thiol groups (generated from aminolyzed xanthate moieties) onto a iodoacyl functionalized human lysozyme.

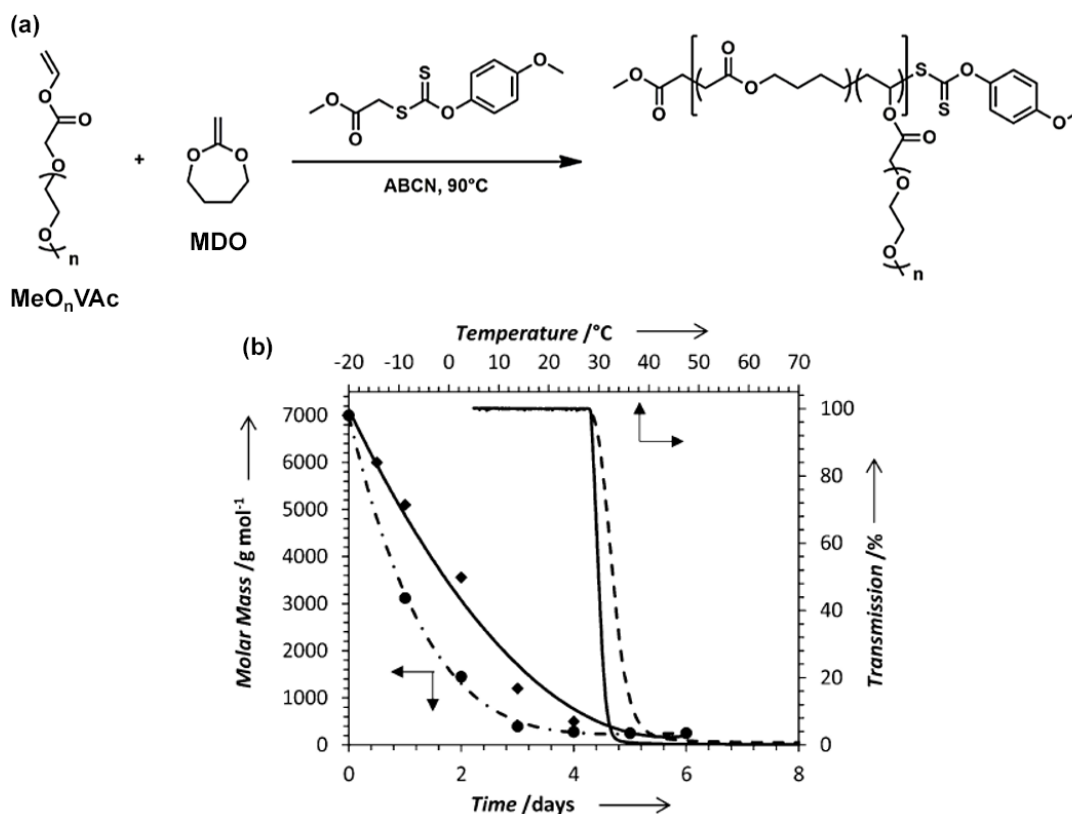


Figure 12. (a) Synthesis of P(MDO-co-MeO_nVAc) copolymers by RAFT polymerization. (b) Enzymatic degradation and thermoresponsiveness of P(MDO-co-MeO₂VAc) with $F_{\text{MDO}} = 0.33$ (solid lines) and P(MDO-co-MeOVAc) with $F_{\text{MDO}} = 0.10$ (dot/dash lines) (Adapted with permission from ref⁷⁸. Copyright 2017 Wiley-VCH).

Implementation of other RDRP techniques, such as photo-induced CMRP,⁷⁹ has also been reported to readily control the copolymerization of MDO and VAc at room temperature. It gave well-controlled, living copolymers ($M_n \sim 15 \text{ kg}\cdot\text{mol}^{-1}$ and $D = 1.26\text{--}1.45$) despite less favorable reactivity ratios ($r_{\text{VAc}} = 1.89$ and $r_{\text{MDO}} = 0.14$), likely due to the low polymerization temperature used.

One can note that, while CKA units incorporation into P(CKA-*co*-VAc) copolymers is relatively easy, such a copolymerization system brought less attention over the years compared to CKA-containing polymethacrylates. This could be explained by lower availability of vinyl acetates compared to methacrylates and by the not so straightforward synthetic pathways (i.e., Pd-catalyzed reactions) to access VAc derivatives. Future development should perhaps focus on broadening the range of VAc derivatives to enhance the structural diversity of the resulting copolymers and access new applications.

1.3.3 Maleimides

Copolymerizing CKA with maleimides (MI) is a copolymerization system that has recently come into the spotlight. Its particularity is that it allows alternating copolymers to be made thanks to reactivity ratios close to zero for both monomers resulting from radical copolymerization of donor-acceptor (D-A) monomer pairs.⁸⁰ First results focused on the FRP of MDO and *N*-phenyl maleimide (PhMI) either by simple heating thanks to the formation of charge-transfer complex between MDO and PhMI, or under conventional radical initiation (Figure 13a).⁸⁰ The obtained P(MDO-*alt*-PhMI) copolymer reached high M_n (~ 55–200 kg.mol⁻¹) with $F_{\text{MDO}} \sim 0.5$ (except when $f_{\text{MDO},0} = 0.1$ that gave $F_{\text{MDO}} = 0.25$) and high transparency. Nevertheless, a maximum of ~ 50 % MDO were eventually ring-opened which represented a serious limitation.

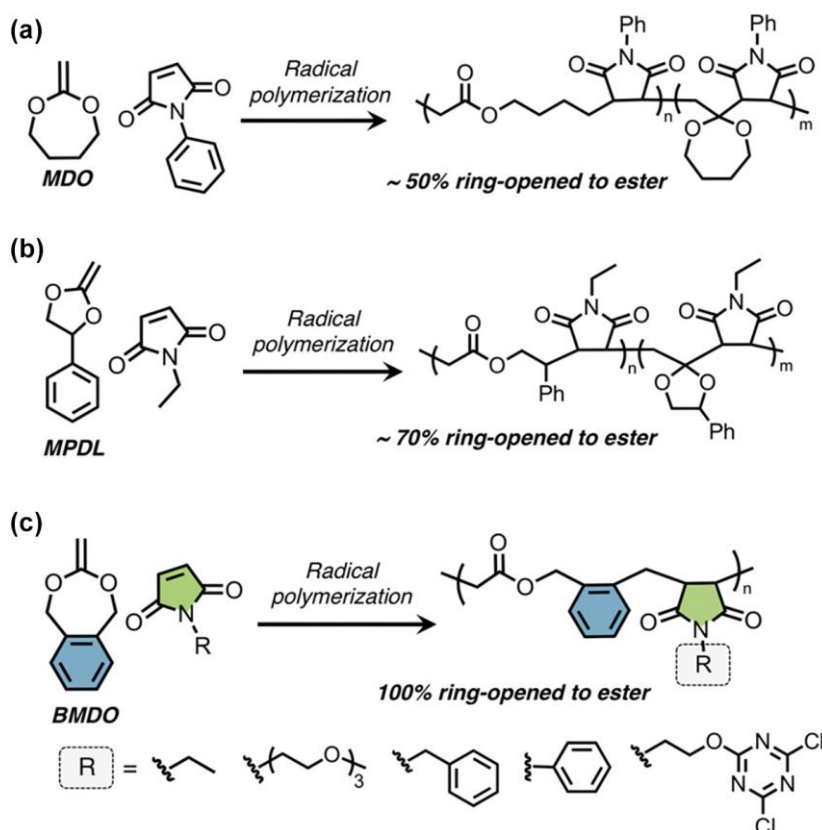


Figure 13. Synthesis of alternating (a) P(MDO-*alt*-PhMI), (b) P(MPDL-*alt*-NEtMI) and (c) P(BMDO-*alt*-MI) copolymers by copolymerization between MI derivatives and different CKAs (Adapted with permission from ref ⁸¹. Copyright 2018 American Chemical Society).

Recent developments significantly improved this copolymerization system, notably by showing its compatibility with RAFT polymerization for the production of well-defined copolymers based on *N*-ethyl maleimide (NEtMI) (Figure 13b).^{81,82} Moreover, a drastic increase in the ring-opening ability of the CKA was achieved by performing copolymerization of NEtMI with MPDL⁸² and BMDO,⁸¹ leading to 70 % and ~ 100 % ring-opened NEtMI units, respectively. Some efforts were also directed towards broadening the structural diversity of the copolymers by changing the *N*-substituent of the MI *via* substituting the Et moiety by EG₃, Ph, Bn and 2,4,6-trichloro-1,3,5-triazine (TCT) groups (Figure 13c). Not only did this strategy successfully produce well-defined degradable, alternating copolymers with different pendent functionalities, but also allowed the fine tuning of their thermal properties, as T_g values ranged from -17 to 147 °C. Diblock copolymers comprising a degradable

P(CKA-*alt*-MI) block were also synthesized.^{81,82} In particular, when a poly(*N,N*-dimethylacrylamide) macro-CTA was chain extended by BMDO/MI, the resulting amphiphilic diblock copolymers could be formulated into degradable nanoparticles.⁸¹

1.3.4 Vinyl ethers

From all the copolymerization systems investigated so far, the best results in terms of CKAs insertion were obtained with VAc as comonomer. However, the maximum amount of ester groups in the copolymer that has been experimentally reached seems to be ca. 65 %.⁷⁴ Moreover, as previously discussed, the poor diversity of available VAc structures appears to be a limitation for future developments. Therefore, an ideal copolymerization system that would give polyester-like copolymers (typically $F_{CKA} > 0.9$) and at the same time, would be highly versatile in terms of properties, functionalities and structural variations is still the missing link.

It was recently discovered by DFT calculations that the addition rate of the vinyl radical onto the vinyl monomer (and not the rate of cross-addition between the vinyl radical and the CKAs) explains the difference in reactivity between vinyl monomers when copolymerized with CKAs.⁸³ Such a finding helped to discover that vinyl ether (VE) derivatives can be ideally copolymerized by FRP with MDO.⁸³ The resulting P(MDO-*co*-VE) copolymers ($M_n \sim 15000 \text{ g.mol}^{-1}$, $D \sim 2$) exhibited tunable MDO contents, quantitative ring-opened MDO and could be finely tuned in terms of properties favored by the broad range of commercially available VE derivatives and readily post-functionalized to access advanced materials. Given the very favorable reactivity ratios of such a copolymerization system ($r_{BVE} = 1.61$ and $r_{MDO} = 0.73$),⁸³ copolymers with very high amount of MDO (typically $F_{CKA} \sim 0.95$) could be obtained, which readily enabled functional polyester-like (PCL-like in the present case) copolymers to be obtained by a radical process (Figure 14).

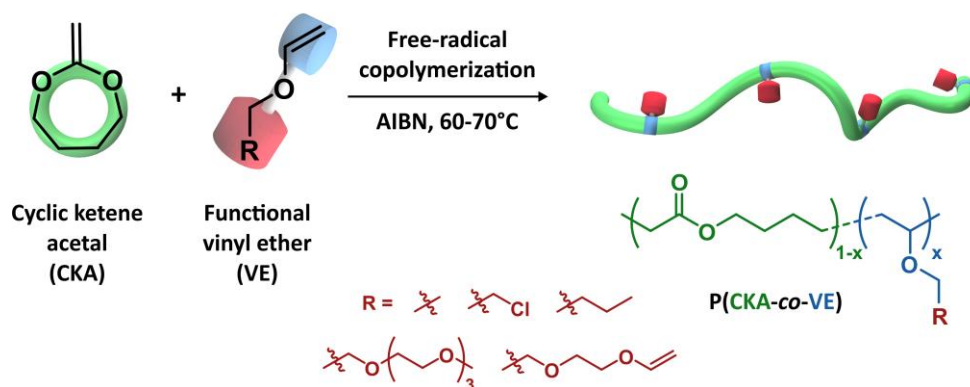


Figure 14. Synthesis of functionalized aliphatic polyester by rROP of MDO as a CKA and vinyl ether (VE) derivatives (Reproduced with permission from ref ⁸³. Copyright 2017 Wiley-VCH).

This robust, yet simple route was used to prepare a broad range of different functional polyesters. For instance, copolymers obtained by copolymerization between MDO and 2-chloroethyl vinyl ether (CEVE), were successfully functionalized, either through direct nucleophilic substitution with a fluorescent probe, or by azidation followed by CuAAC to graft PEG chains, whose length governed the final solubility of the copolymer.⁸³ A small library of PEGylated nanoparticles were also prepared by formulation of such copolymers and exhibited high colloidal stability up to 6 months together with good cytocompatibility on three representative cell lines.⁸⁴ Copolymers showed hydrolytic degradation in physiological condition similar to that of traditional PCL and were rapidly degraded in the presence of lipases (*Candida antarctica*). Interestingly, two other applications were envisioned:⁸³ (i) the preparation of degradable films with antibacterial properties, simply by surface casting of a traditional PCL/P(MDO-co-CEVE) blend followed by surface quaternization (Figure 15a) and (ii) degradable bioelastomers obtained by copolymerization of MDO with di(ethylene glycol) divinyl ether (DIVE) (Figure 15b and 15c), with mechanical properties similar to that of poly(glycerol sebacate), a polymer widely used in tissue engineering.

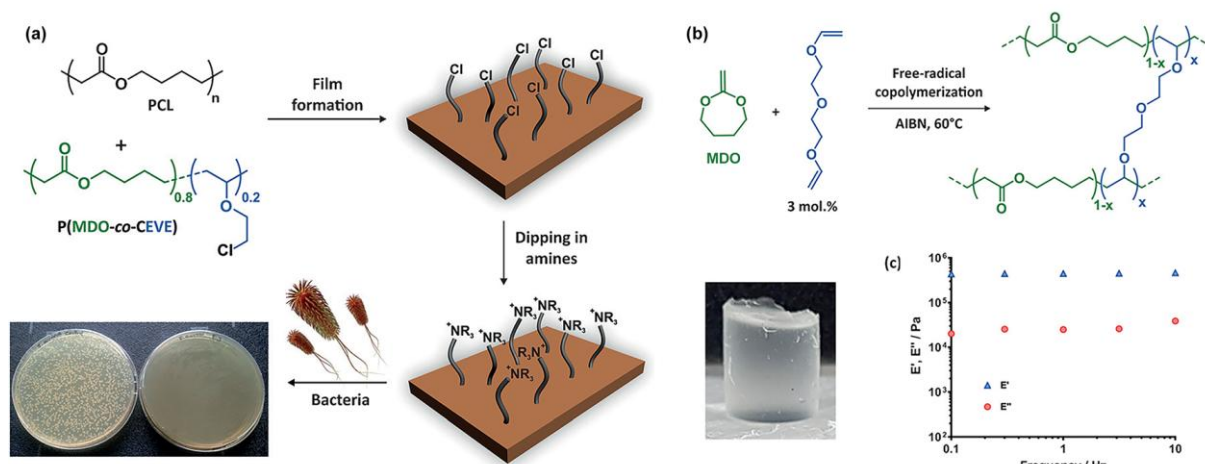


Figure 15. (a) Preparation of a biodegradable antibacterial surface by solvent casting from a 1:1 blend of commercially available PCL and P(MDO-co-CEVE). (b) Synthesis of degradable bioelastomers by rROP of MDO and DIVE (MDO:DIVE = 97:3). Insert: picture of the obtained material. (c) Plot of storage E' and loss E'' moduli as a function of frequency.

Given all the advantages of this copolymerization system, future development should be focused on developing RDRP methods compatible with it to produce well-defined and more complex architectures with more sophisticated properties.

1.3.5 Other vinyl comonomers

Whereas S and its derivatives are very popular vinyl monomers, they are usually associated with very unfavorable reactivity ratios when copolymerized with CKAs; in particular 5- and 7-membered CKAs such as MDO,^{18,85} MPDL,¹⁹ BMDO⁸⁵⁻⁸⁸ and DMMDO.⁸⁹ They have therefore known little success for the synthesis of degradable styrenic polymers. Notable exceptions are copolymerizations of MDO with 2,3,4,5,6-pentafluorostyrene⁸⁷ and MTC with S,⁹⁰ that gave higher incorporations of CKA units. Interestingly, recent in-depth ¹H-NMR analysis of BMDO/MDO copolymers enabled a more accurate determination of the MDO content and highlighted some overestimation of several published values.⁸⁵

Copolymerization of CKAs with acrylates is more favorable than with styrenics but similar or slightly less favorable than with methacrylates, depending on the experimental

conditions^{2,91} Such copolymerization systems were also associated with a relatively low ring-opening ability; typically, from 30 to 80 % at best. In fact, this system did not know much success, despite some interesting achievements by FRP⁹¹⁻⁹⁶ and RDRP.^{89,97-99} In particular it was recently shown that a semi-batch approach increased the maximum F_{MDO} value and improved the homogeneity of the MDO insertion during free-radical copolymerization with various acrylates.⁹¹ Consequently, it may create a renewed interest for this copolymerization system. Also, P(MDO-*co*-propargyl acrylate) copolymers made by FRP have been successfully grafted with PEG chains by CuAAC to give a biocompatible and non-cytotoxic material.⁹² In the field of material design, a fructose acrylate derivative was used to prepare PCL-*b*-P(fructose acrylate-*co*-BMDO) diblock copolymers by RAFT, that gave enzymatically degradable BMDO-based glycopolymer micelles whose degradation products and parent polymer led to good cell viability (> 75 %) at a concentration up to 0.1 mg.mL⁻¹.⁹⁸ The same copolymer also gave two-dimensional lamellar platelet structures by crystallization-driven self-assembly.⁹⁹

Given their unique properties in water, acrylamide derivatives have also been the focus of attention in recent years as rROP comonomers. Copolymerization of NIPAAm and CKAs by either FRP or RDRP exhibited rather unfavorable reactivity ratios, but such systems successfully led to the preparation of thermosensitive, degradable P(BMDO-*co*-NIPAAm) copolymers^{100,101} and degradable hydrogels.¹⁰¹⁻¹⁰⁴ Copolymerization of acrylamide (AAm) and MDO by FRP yielded copolymers with upper critical solution temperatures (UCST) thanks to the hydrophobicity and branching of PMDO units.¹⁰⁵

More specific monomers have also been investigated. *N*-vinylcaprolactam (NVCL) yielded degradable, thermosensitive copolymers when copolymerized with BMDO but were characterized by a low amount of incorporated BMDO ($F_{\text{BMDO}} \leq 0.04$).¹⁰⁶ Degradable polyethylene (PE) was also recently synthesized by copolymerizing ethylene with MDO or

MTC by CMRP.⁴⁰ This system produced well-controlled copolymers ($M_n \sim 12 \text{ kg}\cdot\text{mol}^{-1}$, $\mathcal{D} \sim 1.25$) with 100 % opened CKA and was further applied to the synthesis of diblock copolymers by chain extension from P(MDO-*co*-E) with VAc or VBr to allow CuAAC reactions to be performed.

Side-chain functionalization was also achieved by copolymerizing 2-vinyl-4,4-dimethylazlactone (VDMA) and MDO by FRP or RAFT, to yield degradable copolymers containing azlactone pendent functionalities.¹⁰⁷ Despite partial ring-opening of MDO (27–69 %), the copolymers exhibited higher incorporation of MDO units than for copolymerizations based on S, methyl acrylate (MA) and even MMA (e.g., for $f_{\text{MDO}} = 0.7$, $F_{\text{MDO}} \sim 0.5$). Pendent azlactone moieties have then been exploited to graft various primary amines under mild conditions (stoichiometric reaction, no byproduct, room temperature, no catalyst). In particular, the use of branched polyethyleneimine and tris(2-aminoethyl)amine produced degradable gels, microcapsules and DNA-containing multi-layers films.

1.4. Copolymerization between two CKAs

Whereas copolymerization of CKA with vinyl monomers has been extensively studied, copolymerizing two CKAs has, in contrast, been scarcely investigated. Initial work reported the synthesis by FRP of P(MTC-*co*-MDO) copolymers with rather limited M_n (2200–8600 $\text{g}\cdot\text{mol}^{-1}$), high dispersity ($\mathcal{D} = 2.1\text{--}12.4$) and MTC fractions always higher than MDO fractions regardless of the initial feed and without any clear trend.²⁸

Recent studies in this area focused on trying other CKAs combinations. For instance, P(MDO-*co*-BMDO) obtained in bulk FRP of a 1:1 MDO:BMDO mixture showed quantitative ring-opening but very limited M_n (ca. 1000 $\text{g}\cdot\text{mol}^{-1}$),¹⁷ which was assigned to the two labile benzylic hydrogens of BMDO repeating unit and the strong abstracting propagating radical of MDO. Copolymerization of *i*-MAC and DMMDO was also attempted by FRP from a PEG-azo initiator and yielded PEG-*b*-P(*i*-MAC-*co*-DMMDO) copolymer with also quantitative

ring-opening of both CKAs despite a short hydrophobic block that suggests a low M_n .²⁶ Even if impurities (e.g., homopolymers) were present, this copolymer was formulated into nanoparticles that can be degraded in the presence of esterases (porcine liver).

1.5. Polymerization processes

While most (co)polymerizations involving CKAs are performed in bulk or in solution, other processes have been investigated. Chemical vapor deposition (CVD) is a well-known technique to prepare polymeric structures.¹⁰⁸ It uses the delivery of vapor- phase monomers to form chemically well- defined polymeric films directly on the surface of a substrate. The first degradable copolymer synthesized by CVD was obtained from reaction between [2.2]para-cyclophane and BMDO (Figure 16a).¹⁰⁹ After consecutive sublimation, pyrolysis and adsorption steps, they were polymerized on a substrate at 15 °C. CVD was further extended to the synthesis of fluorescent, CKA-containing films by copolymerizing hydroxyl- and alkyne-functionalized [2.2]para-cyclophane with BMDO. The resulting materials were then modified *via* CuAAC using microcontact printing with azide-modified Alexa Fluor488 (Figure 16b) or biotin-PEG₃-azide subsequently reacted with streptavidin-Cy3 (Figure 16c).

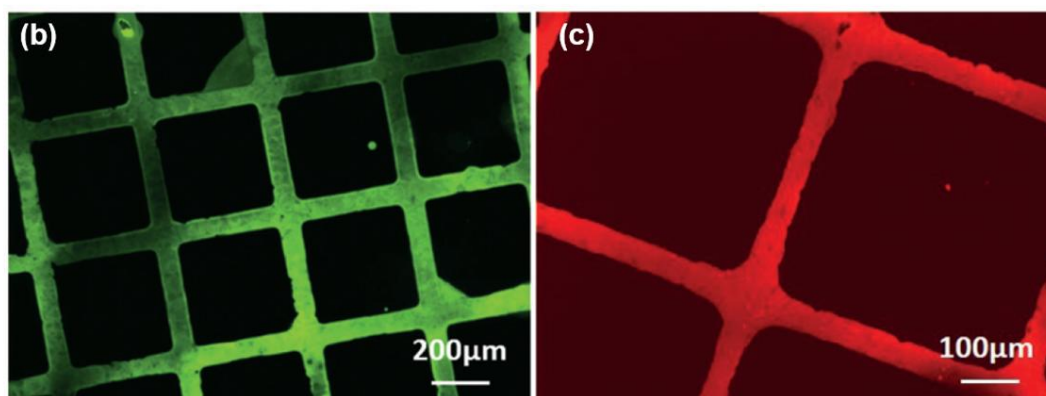
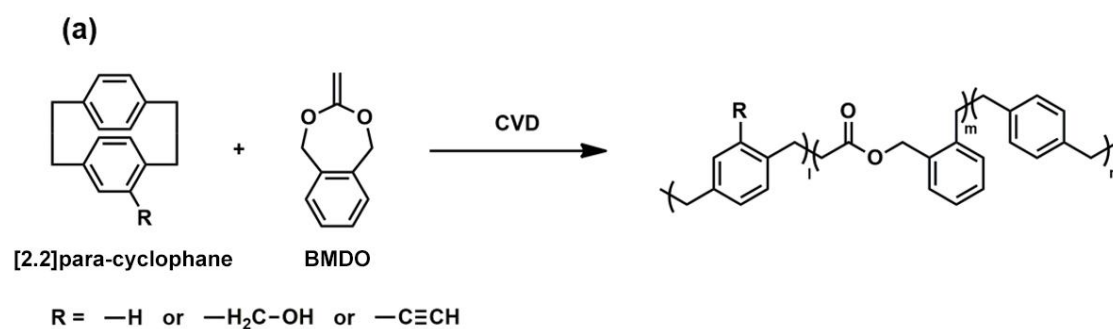


Figure 16. (a) Copolymerization between BMDO and [2.2]para-cyclophane by CVD. BMDO-containing fluorescent coatings obtained from alkyne-functionalized copolymers synthesized by CVD onto which (b) azide-modified Alexa Fluor488 or (c) biotin-PEG₃-azide followed by incubation with streptavidin-Cy3, were grafted by CuAAC (Adapted with permission from ref¹⁰⁹. Copyright 2017 Wiley-VCH).

A polymerization process that caught up enormous attention in the past decade is polymerization-induced self-assembly (PISA).^{110,111} Despite tremendous development in many different directions, PISA has always been used to produce nondegradable polymer particles. Recently, a new polymerization technique that combined the rROP of CKA and the PISA process, called radical ring-opening copolymerization-induced self-assembly (rROPISA), was developed (Figure 17).¹¹²

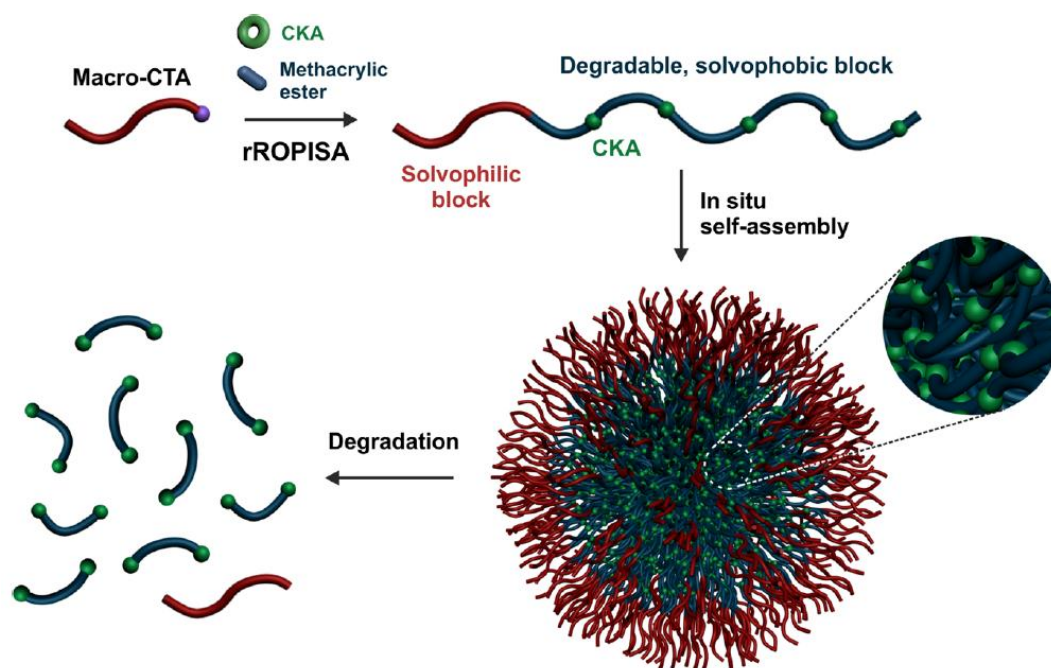


Figure 17. Synthesis of core degradable block copolymer nanoparticles by RAFT-mediated radical ring-opening copolymerization-induced self-assembly (rROPISA) (Reproduced with permission from ref ¹¹². Copyright 2019 American Chemical Society).

In brief, MPDL or BMDO were copolymerized with benzyl methacrylate (BzMA) in heptane at 90 °C by RAFT polymerization from a poly(lauryl methacrylate) (PLMA) macro-RAFT agent (Figure 18a). The amount of CKA in the copolymers ranged from 4 to ~ 40 mol.% by adjusting the monomer stoichiometry, and the resulting nanoparticles were very stable and narrowly dispersed, whose average diameters ranged from 40 to 500 nm, depending on the experimental conditions but with a strong impact of F_{MPDL} (Figure 18c). Hydrolytic degradation of the different copolymers (Figure 18b) and of copolymer films obtained by solvent casting was assessed in accelerated conditions (2.5 % KOH), which was in good agreement with their CKA content. Interestingly, incorporation of CKA units prevented the formation of other morphologies than spheres.

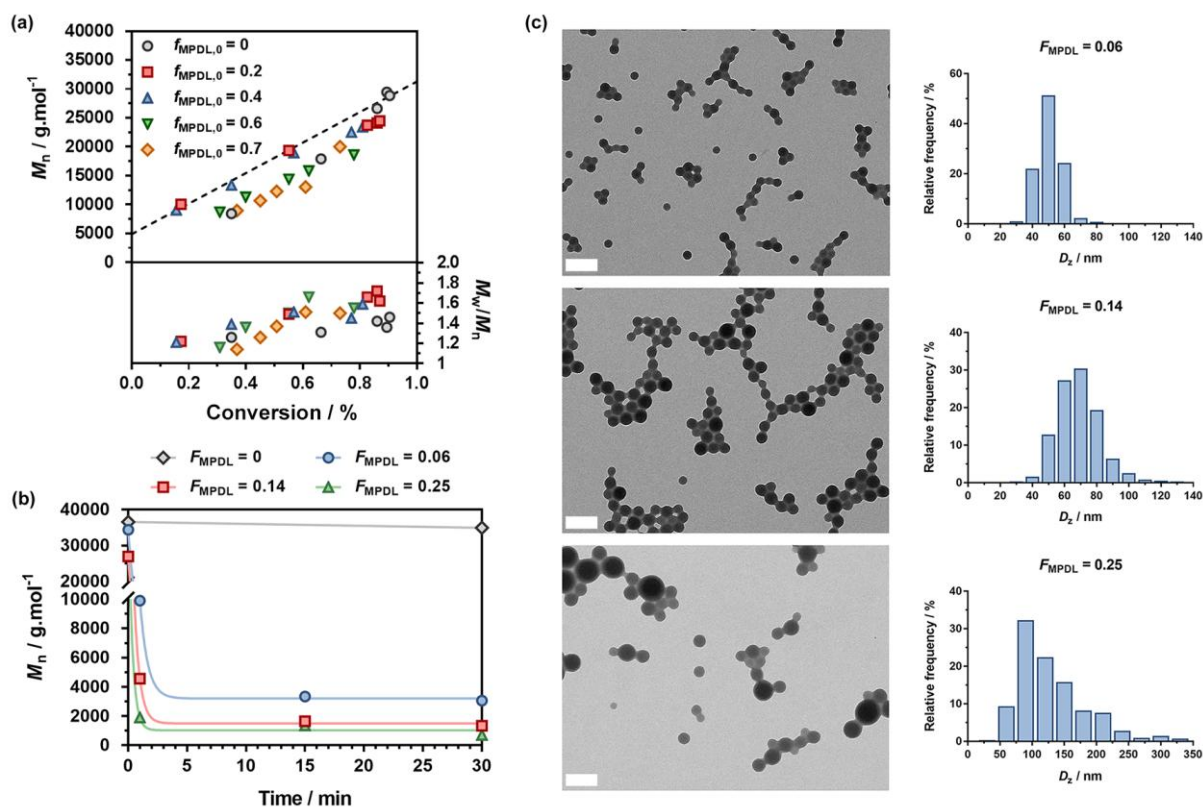


Figure 18. (a) Evolution of M_n and M_w/M_n vs BzMA conversion during the rROPISA from a PLMA macro-CTA of BzMA and MPDL as function of $f_{\text{MPDL},0}$. (b) Evolution with time of M_n during degradation under accelerated conditions (THF/MeOH, 2.5 % KOH) of PLMA₁₈-*b*-P(BzMA₁₅₀-*co*-MPDL) copolymers as function of F_{MPDL} . (c) Representative TEM images and particle size distributions of PLMA₁₈-*b*-P(BzMA₁₅₀-*co*-MPDL) copolymer nanoparticles as a function of F_{MPDL} in the copolymer. Scale bars = 200 nm (Adapted with permission from ref ¹¹². Copyright 2019 American Chemical Society).

1.6. Composition drift and microstructure

During copolymerization between CKAs and vinyl monomers, their reactivity ratios govern the CKA incorporation into the copolymer and the final microstructure. For instance, for CKA/S, CKA/acrylate or CKA/methacrylate pairs, the vinyl monomer is incorporated faster, resulting in a composition drift and therefore a gradient-type copolymer (i.e., a copolymer being strongly enriched in vinyl monomer units at the beginning while progressively being richer in CKA units

along the chain). In contrast, for CKA/VE and CKA/VAc pairs, both monomers are incorporated nearly homogeneously during the copolymerization and almost no composition drift is observed (i.e., random copolymer). A schematic representation of the achievable range of CKA content and microstructure observed for each type of copolymer is presented in Figure 19.

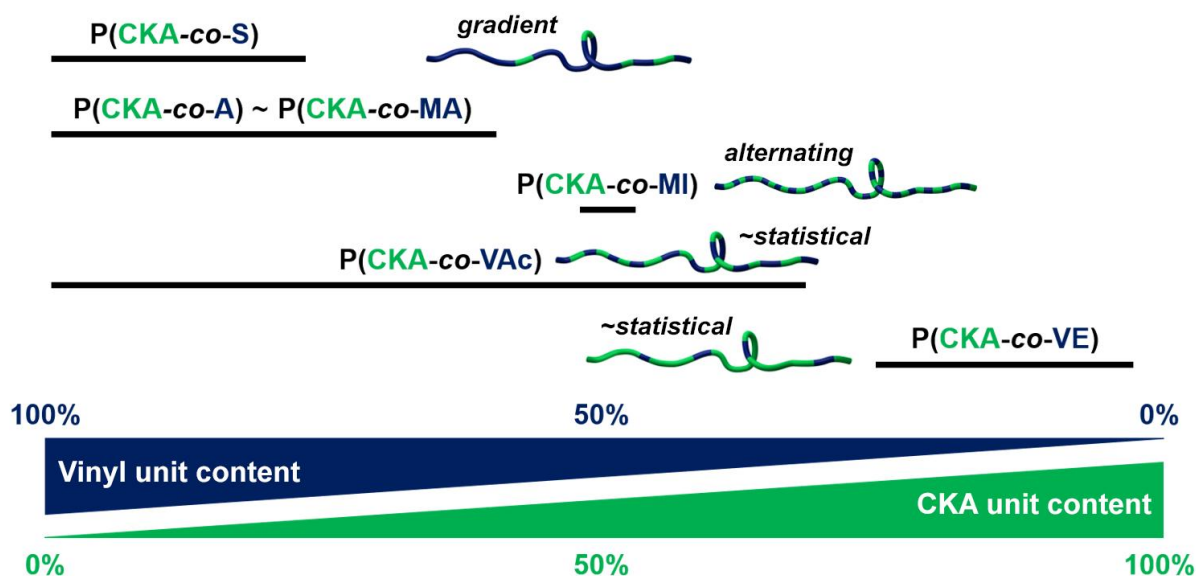


Figure 19. Schematic representation of vinyl and CKA unit average contents reported in the literature (horizontal black lines) together with the typical microstructures of copolymers obtained from the most used copolymerization systems between CKAs and main vinyl monomers (A = acrylates, S = styrenics, MA = methacrylates, MI = maleimides, VAc = vinyl acetates and VE = vinyl ethers). Note that microstructures are for copolymers obtained by RDRP with S, A, MA and VAc as comonomers, FRP and RDRP with MI and FRP with VE.

These differences in microstructures have important consequences on the copolymers degradation and especially on the nature and homogeneity of the degradation products, as recently highlighted.^{113,114} Interestingly, kinetic Monte Carlo simulations have predicted, at a macromolecular level (i.e., allowing differentiation between the monomer sequences of individual chains), the importance of the microstructure on the degradation properties for different MDO-containing copolymers based on S, MMA, VAc and VE as comonomers.¹¹³ This approach enabled complete description of the composition of the original copolymers

and of the degraded chains (Figure 20). In a nutshell, very different reactivity ratios (as for CKA/S, CKA/MMA, etc.) can give heterogeneous degradation products conversely to copolymerization systems with similar reactivity ratios (e.g., CKA/VE, CKA/VAc, etc.). The polymerization technique used (i.e., FRP or RDRP) had however no impact on the nature of the degraded products.

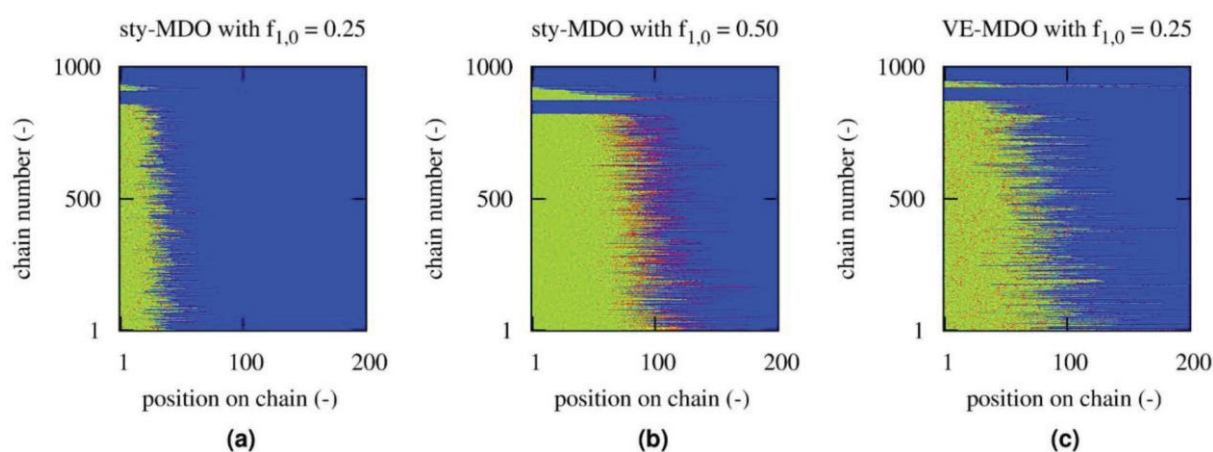


Figure 20. Visualization of individual chains for RDRP of CKA/vinyl monomer (red: CKA monomer unit; green: vinyl monomer unit; blue: absence of monomer) before hydrolysis at $F_{\text{vinyl}} = 0.8$. (a) S/MDO; (b) S/MDO and (c) VE/MDO (Reproduced with permission from ref ¹¹³. Copyright 2018 Wiley-VCH).

Precise determination of reactivity ratios is therefore essential to better estimate/predict the microstructure of the obtained copolymer. In such a context, the importance of the determination method was recently emphasized *via* re-evaluation of reactivity ratios for a series of different CKA/vinyl monomer pairs using nonlinear least-square method (NLLS).⁴³ It was concluded that the NLLS method should be used instead of Fineman–Ross or Kellen–Tudos methods to reach better accuracy.

2. Thionolactones: opening new perspectives for rROP

The use of CKAs has been dominating past and current research about degradable materials prepared by rROP.² Even though important achievements have been witnessed with CKAs, they still possess some strong limitations (e.g., complex synthesis, poor structural variation, high susceptibility to hydrolysis, unfavorable reactivity ratios, etc.). Seeking new types of suitable monomers for rROP is thus a topic of great interest that could considerably broaden the scope and application of this polymerization technique.

The thiocarbonyl moiety is extensively used in polymer chemistry as part of the structure of RAFT agents. Using a thiocarbonyl-based molecule as a monomer can therefore lead to the insertion of a sulfur-based functional group into the polymer backbone (Figure 21). Among the different potential structures containing a thiocarbonyl group, thionoester-containing cyclic monomers, namely thionolactone, have recently emerged as good candidates to prepare degradable polymers by rROP. The polymerization proceeds *via* insertion of thioester groups into the polymer backbone¹¹⁵ (also termed thiocarbonyl addition–ring-opening (TARO) polymerization),¹¹⁶ that could be cleaved through different degradation conditions (e.g., aminolysis, methanolysis, hydrolysis, thiol-thioester exchange, etc.).

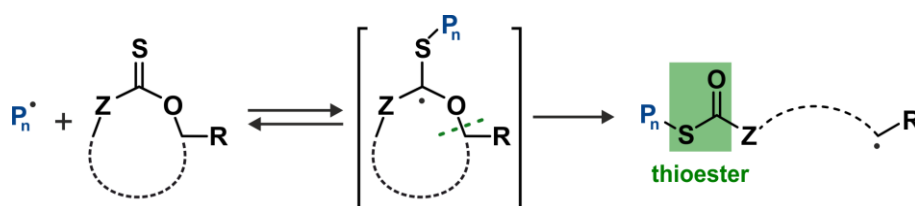


Figure 21. General polymerization mechanism of thiocarbonyl-mediated radical ring-opening polymerization (Adapted with permission from ref ¹¹⁵. Copyright 2019 American Chemical Society).

2.1. Synthesis

From the different thionolactones developed so far, only dibenzo[c,e]oxepane-5-thione (DOT) was successfully polymerized by rROP. It is obtained by reduction of diphenic anhydride

followed by the thiation of the resulting lactone using Lawesson's reagent (Figure 22).^{115,116} The overall yield of this two-step route is similar to that of traditional CKAs. Other thionolactones were synthesized under similar conditions by thiation of the corresponding lactone, demonstrating the versatility of this pathway to obtain other structures.¹¹⁶ Interestingly, DOT showed high stability upon storage (10 months at 5 °C in the dark and 45 days at room temperature under day light). To that extent, DOT seems easier to be routinely handled than CKAs, but harsh heating can be detrimental as it could induce isomerization of the thionoester into thioester.

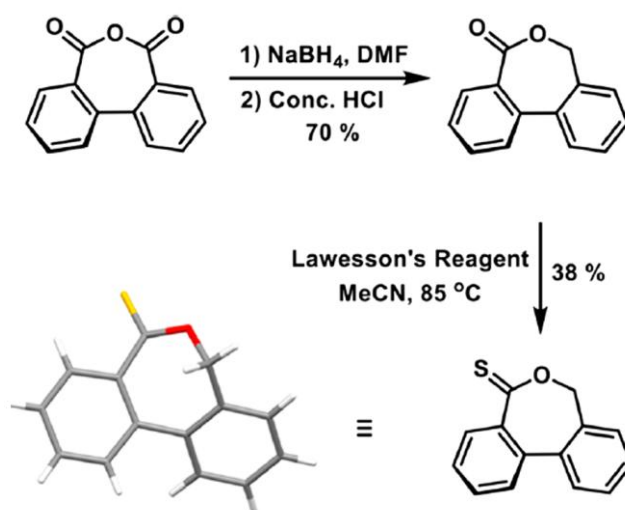


Figure 22. Synthetic route for dibenzo[*c,e*]oxepane-5-thione (DOT) (Reproduced with permission from ref ¹¹⁵. Copyright 2019 American Chemical Society).

Another key specificity of DOT and of thionolactones in general, is the absence of side-reaction during the ring-opening propagation step (Figure 23). Indeed, conversely to CKA, no ring-retaining propagation can occur due to the reversible reaction of thiocarbonyl moiety with radical species. Consequently, each inserted DOT monomer will generate a cleavable thioester unit.

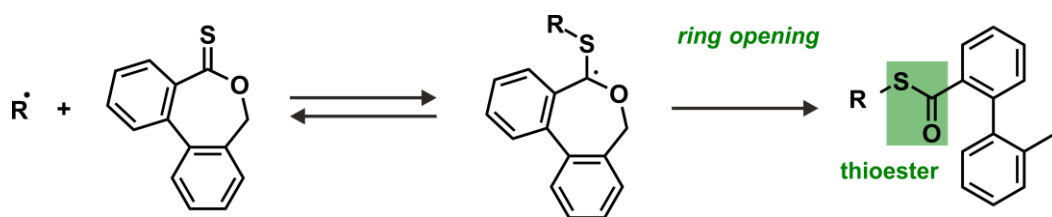


Figure 23. Proposed mechanism for the radical ring-opening polymerization of DOT leading to an exclusive ring-opening mechanism and absence of ring-retaining side reaction.

2.2. Homopolymerization

However, conversely to CKAs, DOT does not readily homopolymerize, even upon long heating periods in presence of a radical initiator. Only < 1–2 % monomer conversion was obtained by FRP using AIBN either in acetonitrile at 80 °C overnight¹¹⁶ or in DMF at 70 °C for 70 h.¹¹⁵ Performing the polymerization in DMSO with sequential addition of AIBN over 27 days at 60 °C however provided some improvement (conversion = 22 %, $M_n = 3.1\text{--}4.9$ kg.mol⁻¹).¹¹⁷ RAFT homopolymerization of DOT was also attempted, but without success (< 2 % DOT conversion).¹¹⁵

2.3. Copolymerization

DOT appeared as the most successful thionolactone for the copolymerization with vinyl monomers. Initial copolymerizations were indeed conducted with γ -phenyl- γ -butyrolthionolactone and some thionophthalides with S, MA, MMA and VAc, but all gave poor results (e.g., polymerization inhibition, poor incorporation).¹¹⁶

2.3.1 Acrylates

DOT, whose two aromatic rings stabilize the propagating radicals and induce ring-strain and steric hindrance, was however rapidly copolymerized with a variety of acrylates (MA, *n*-butyl acrylate (*n*BA), *tert*-butyl acrylate (*t*BA), benzyl acrylate (BnA), trifluoroethyl acrylate (TFEA) and PEG acrylate (PEGA))^{115,116} by FRP or by RAFT (Figure 24a). For instance by RAFT of *t*BA, $M_{n,SEC}$ reached 4.4–32.6 kg.mol⁻¹ with relatively low dispersities ($D = 1.05\text{--}$

1.27) and a broad range of DOT fractions ($F_{\text{DOT}} = 0.05\text{--}0.50$). Nevertheless, further increasing in the initial DOT molar fraction resulted in significant retardation. Well-defined $P(t\text{BA-}co\text{-DOT})\text{-}b\text{-}P(n\text{BA-}co\text{-DOT})$ diblock copolymers were also synthesized, demonstrating the livingness of the system (Figure 24b). Reactivity ratios with acrylates were found to be favorable (for instance with MA: $r_{\text{DOT}} = 0.003$ and $r_{\text{MA}} = 0.424$),¹¹⁶ leading to rapid copolymerization of DOT and the formation of alternating sequences, although a slight gradient composition should be observed.

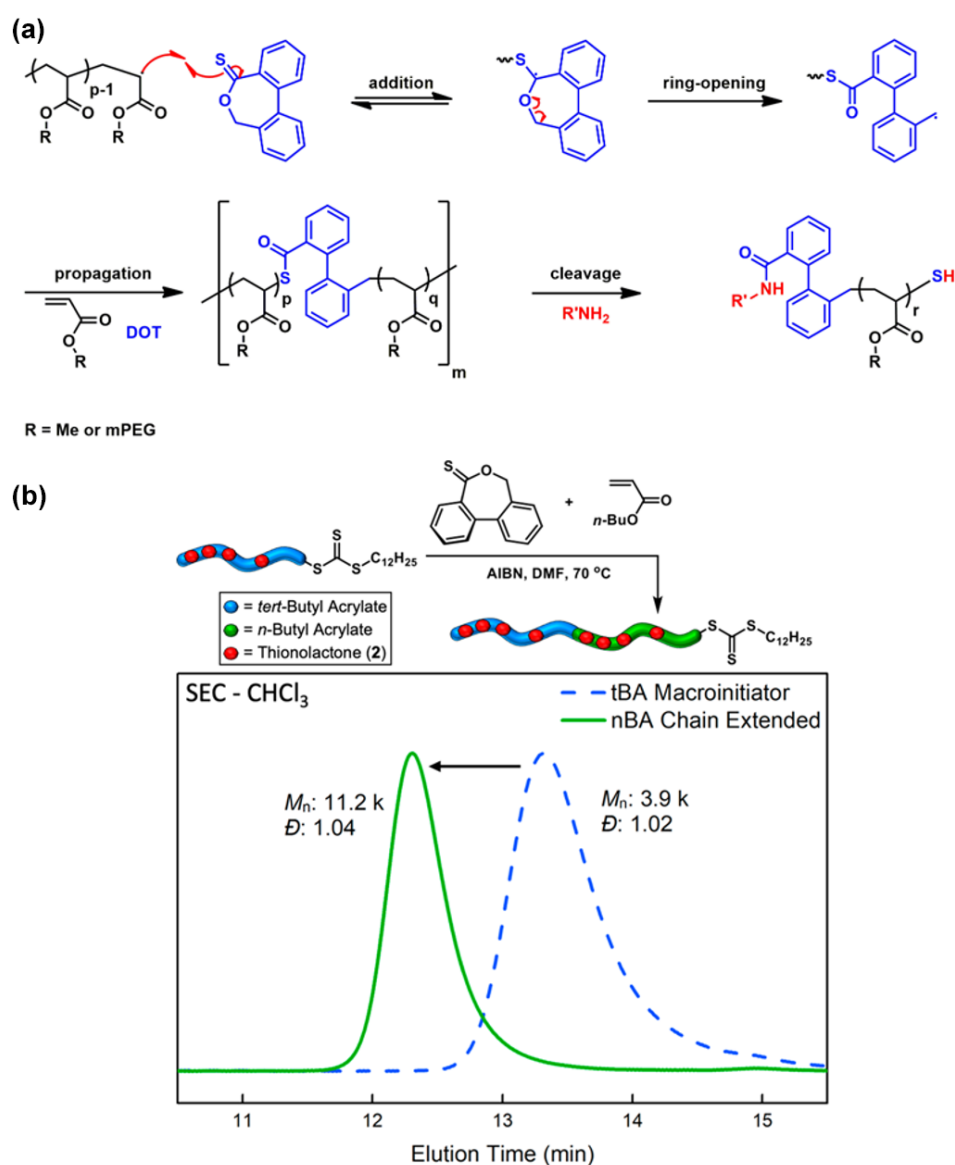


Figure 24. (a) Proposed mechanism of ring-opening copolymerization of DOT with acrylate monomers and degradation *via* aminolysis. (b) Synthesis of $P(t\text{BA-}co\text{-DOT})\text{-}b\text{-}P(n\text{BA-}co\text{-DOT})$ diblock copolymer ($F_{\text{DOT}} = 0.05$) by RAFT polymerization of $n\text{BA}$ and DOT from a

P(*t*BA-*co*-DOT) macro-CTA ($F_{\text{DOT}} = 0.05$), and corresponding SEC traces (Adapted with permission from ref ¹¹⁵. Copyright 2019 American Chemical Society).

Degradation experiments of the DOT-containing copolymers were successfully performed by methanolysis (with NaOMe),¹¹⁵ aminolysis (with *N*-isopropylamine)¹¹⁶ and through thiol-thioester exchange reaction (with cysteine methyl ester).¹¹⁵ For example, degradation of P(*t*BA-*co*-DOT) gave much lower M_n values (35 vs. 1.75 kg.mol⁻¹ for $F_{\text{DOT}} = 0.05$) after methanolysis.

2.3.2 Maleimides

Copolymerization of DOT with maleic anhydride, fumaronitrile or diethyl fumarate were not successful and resulted in no or very low monomer conversion (< 10 %). FRP or RAFT copolymerizations of DOT with *N*-functional maleimides (*N*-methylmaleimide (MeMI), PhMI and *N*-2,3,4,5,6-pentafluorophenylmaleimide (PFPMI)) were also investigated and produced (well-defined) copolymers with the tendency to form alternating sequences in the following order: MeMI \ll PhMI < PFPMI ($r_{\text{DOT}} = 0.198$; $r_{\text{PFPMI}} = 0.0078$).¹¹⁷ Degradation of the copolymers by aminolysis was assessed (Figure 25) and gave a broad range of different degradation products owing to cleavage/chemical modification of maleimide units and/or their side groups during degradation.

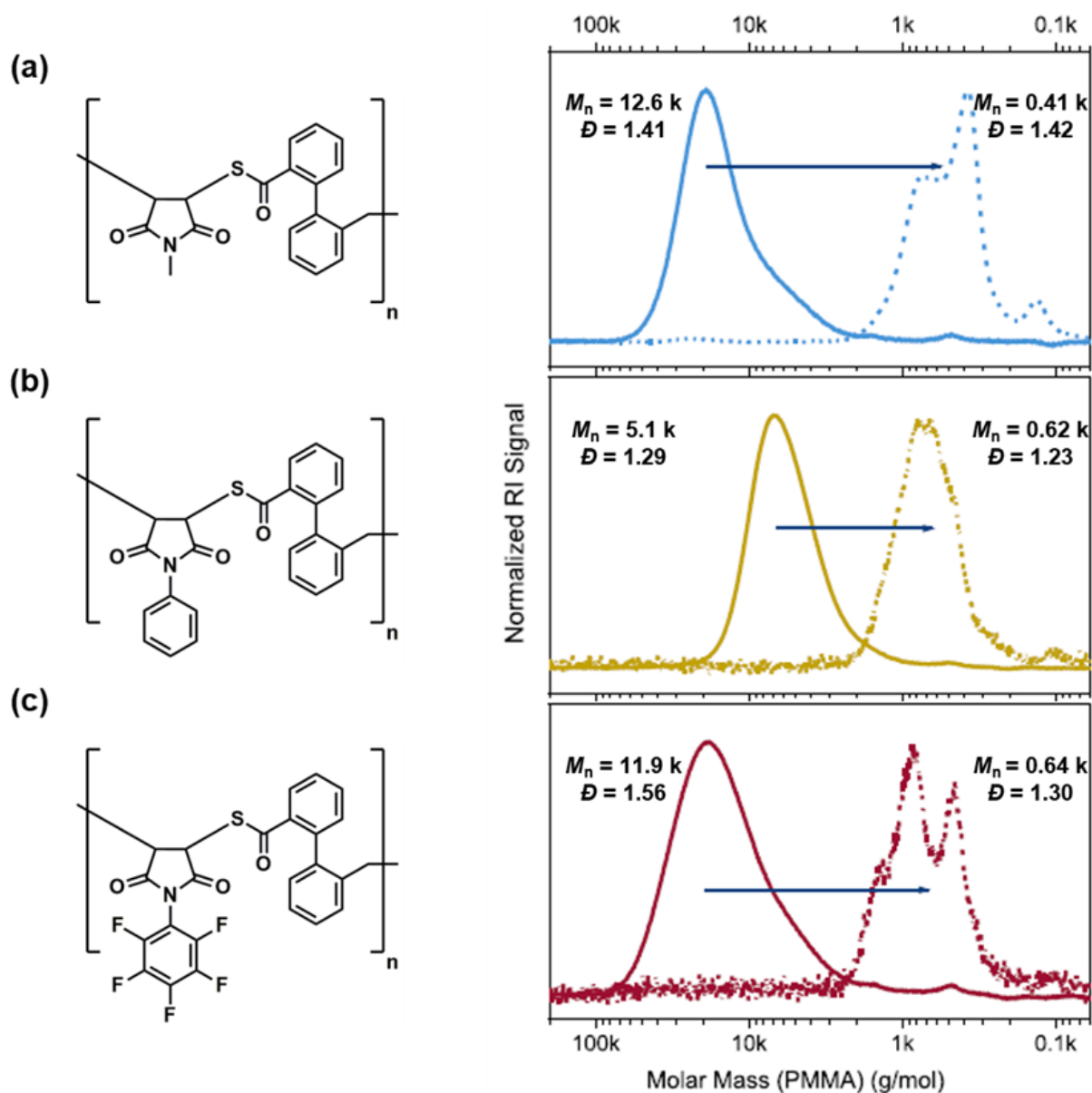


Figure 25. Structure of the different copolymers and their SEC traces before (solid lines) and after treatment (dashed lines) with *N*-isopropylamine in THF: (a) P(DOT-*alt*-MeMI); (b) P(DOT-*alt*-PhMI) and (c) P(DOT-*alt*-PFPMI) (Adapted with permission from ref ¹¹⁷. Copyright 2020 American Chemical Society).

2.3.4 Other monomers

Successful copolymerizations of DOT with other monomers such as AN¹¹⁶ and acrylamides (e.g., NIPAAm, AAm, *N,N*-dimethylacrylamide (DMAm), *N,N*-diethylacrylamide (DEAm) and *N*-3-(*N*-4-sulfobutyl-*N,N*-dimethylammonium)propylacrylamide (SBBAm))^{116,118} have also recently been reported. Interestingly with acrylamides, incorporation of DOT into

polyacrylamide backbones ($F_{\text{DOT}} = 0.08$) still enabled temperature-responsive materials to be obtained and tunable thermal and solubility properties depending on the degradation conditions applied (e.g., hydrolysis, aminolysis, transthioesterification and oxidative hydrolysis).¹¹⁸ For instance, the LCST of P(DMAm-*co*-DOT) copolymer was shifted from 25 to 41 °C after hydrolysis with ammonia whereas it reached 76 °C after transthioesterification *via* cysteonolysis.

By FRP, DOT was however found to inhibit the polymerization of VAc and *N*-vinylcarbazole, to retard the polymerization of S while not being incorporated and to act as a bystander with MMA.¹¹⁶

3. Macrocyclic monomers: expanding rROP possibilities

Cyclic monomers used for rROP typically contain a 5- to 8-membered ring in their structures. Nevertheless, a new direction for rROP investigated the use of > 10-membered ring monomers. Given their much bigger ring size than CKA monomers and DOT, their ring-opening ability is therefore much less (or even not) impacted by the release of the ring strain, which is known to be one of the driving forces that could impact the ring opening ability of small cyclic monomers (note that some 6-membered ring monomers do not follow this trend). The following section will focus on two different families of macrocyclic monomers that recently attracted some attention for their use in rROP: macrocyclic allylic sulfides and macrocyclic allylic sulfones.

3.1. Macrocyclic allylic sulfide

(Macro)cyclic allylic sulfides were developed in the 90s¹¹⁹⁻¹²¹ and elegantly revisited a decade later to further expand the field of rROP *via* the polymerization of new structures.¹²² The ring-opening mechanism of such monomers relies on a radical addition to the alkene followed by

radical transfer to the sulfur atom, which results in the ring opening and formation of a thiyl radical that propagates (Figure 26a). When (macro)cyclic allylic sulfides contain an acrylate-like moiety into their structures, the ring-opening mechanism generates an ester group in the polymer backbone.

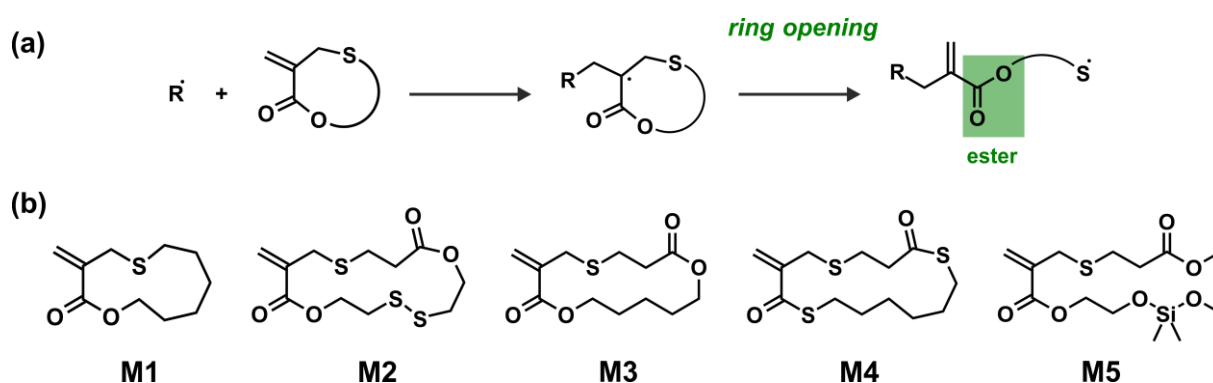


Figure 26. (a) General mechanism for the rROP of macrocyclic allyl sulfides. (b) Structures of the main macrocyclic allyl sulfides used in rROP.

3.1.1 Synthesis

One of the first ever developed macrocyclic allyl sulfides for use in radical polymerization was 1-oxa-3-methylene-5-thiacycloundecan-2-one (**M1** in Figure 26b)¹²¹ and a representative one is 3-methyldiene-1,9-dioxa-5,12,13-trithiacyclopentadecane-2,8-dione (MDTD or **M2** in Figure 26b). The synthesis of MDTD synthesis relies on nucleophilic substitution of α -bromomethyl acrylic acid with 6-mercapto-1-hexanol to give the hydroxyl acid, which is subsequently cyclized under high dilution conditions by the Mukaiyama's reagent to produce MDTD with 30 % yield. The synthetic pathway can be adapted to the preparation of a broader range of macrocyclic allyl sulfides bearing other functional groups into their structure (ester, disulfide, thioether or silyl-ether) by simply changing the nature of the hydroxyl acid intermediate and using the appropriate diol or dithiol (**M3–5**, see Figure 26b). Even though synthesis of macrocyclic allyl sulfides appears more tedious than that of CKAs, their structural diversity is a strong advantage to produce more advanced materials.

3.1.2 Copolymerization

RAFT copolymerizations of MMA with MDTD and other macrocyclic allylic sulfides (**M1–4**, Figure 27) were successfully performed.¹²² Overall, they showed good control over molar masses ($M_n \sim 30 \text{ kg.mol}^{-1}$) and tunable, but somewhat limited amount of macrocyclic allylic sulfide units in the final copolymer ($F_{\text{MDTD}} = 0.01\text{--}0.10$). Increasing dispersity however came from an increase of $f_{\text{MDTD},0}$ (e.g., $D \sim 1.2\text{--}1.3$ for $f_{\text{MDTD},0} = 0.01$ and $D \sim 1.4\text{--}1.5$ for $f_{\text{MDTD},0} = 0.05$). It reflected the cross-linking that occurs from pendent acrylate-like C=C bonds formed during copolymerization upon ring opening of macrocyclic allylic sulfides.

An advantage compared to CKA monomers was the approximately equal rates of consumption for both cyclic/vinyl monomers, which avoided using an excess of cyclic monomers. The ability to form well-defined copolymers with similar properties was also demonstrated with other vinyl monomers such as 2-hydroxyethyl methacrylate (HEMA) and DMAEMA. Interestingly, selecting macrocyclic allylic sulfides **M2–4** enabled incorporation of additional functional groups (e.g., ester, thioester and disulfide) into the polymer backbone compared to only one ester group per **M1** unit, thus giving copolymers with different degradation modalities such as basic/acidic, reductive or even enzymatic (Figure 27). Moreover, incorporating different macrocyclic allylic sulfides bearing dissimilar functional groups into the same copolymer backbone, gave stepwise, orthogonal degradations, resulting in systems exhibiting programmable degradation profiles.

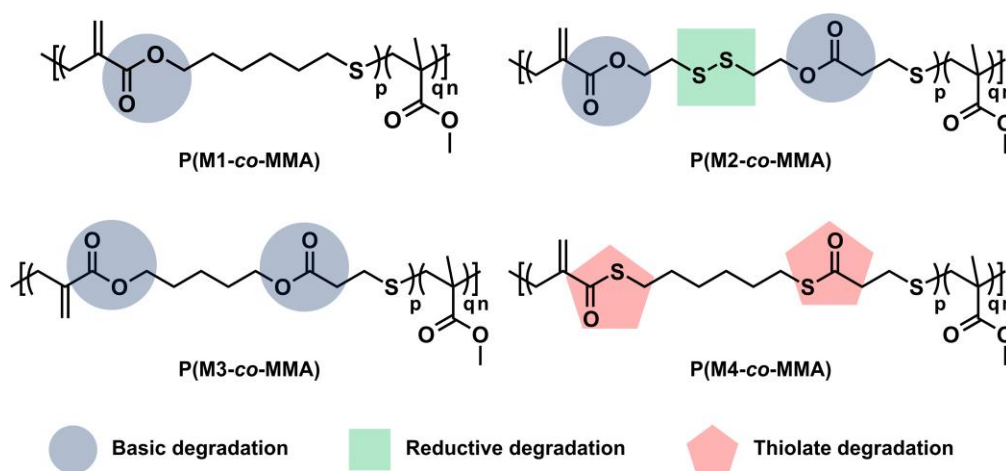


Figure 27. Copolymers based on MMA and various macrocyclic allylic sulfides (**M1–4**) and their specific degradation conditions (Adapted with permission from ref ¹²². Copyright 2009 American Chemical Society).

Recent researches built on these previous achievements focused on the development of more sophisticated materials and bio-related applications. The macrocyclic allylic sulfide **M2** was copolymerized at very low content ($F_{M2} \sim 0.01$) with 2-hydroxypropyl methacrylate (HPMA) by RAFT-mediated PISA from a poly(glycerol monomethacrylate) (PGMA) macro-CTA to yield different nano-objects.¹²³ Despite broad molar masses distributions, the obtained worm-like nano-objects were mainly transformed into spheres by cleavage of the disulfide bonds under reductive environment (i.e., tris(2-carboxyethyl)phosphine, TCEP) at pH 8–9, as a consequence of the reduction in the packing parameter (Figure 28). However, given the very low amount of MDTD in the copolymers, it was calculated that $\sim 40\%$ of the chain may not contain any MDTD unit. The MDTD content also appeared to be difficult to increase due to its propensity to undergo cross-linking or fragmentation at high feed ratio and may be detrimental for the material cytotoxicity.

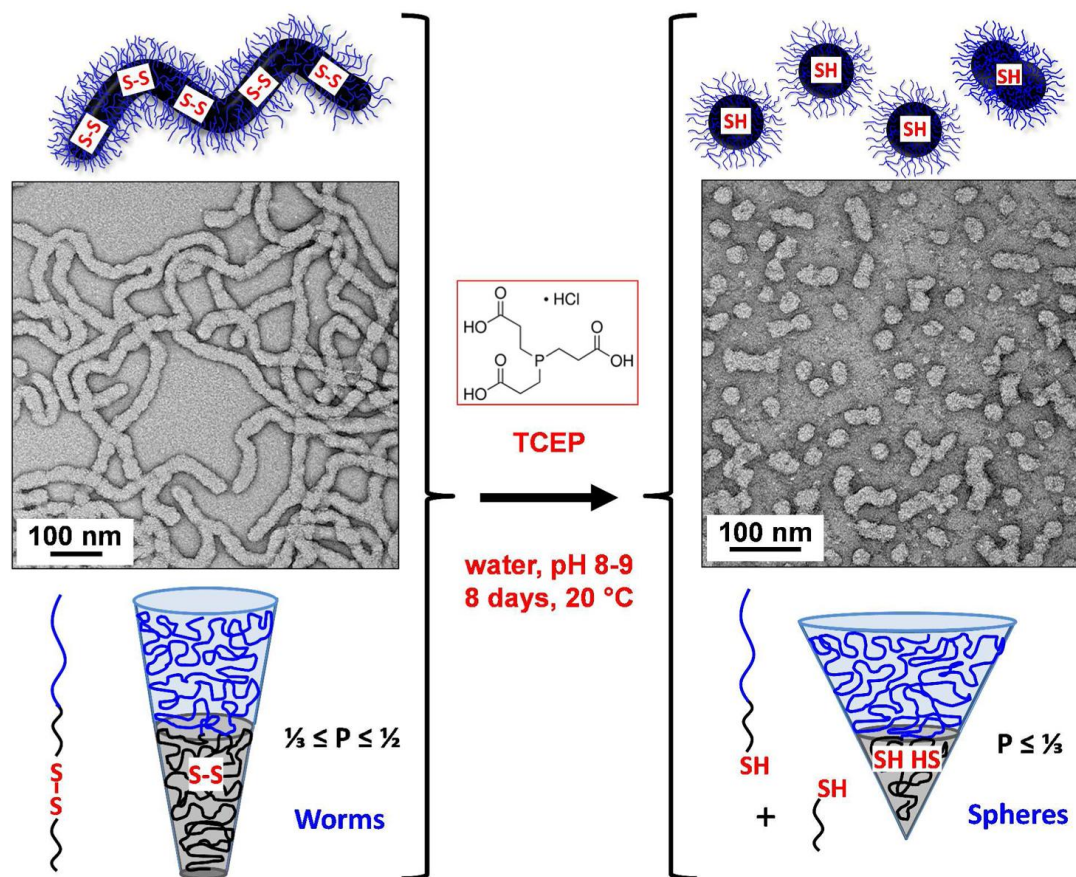


Figure 28. TEM images obtained for an aqueous dispersion of PGMA₅₆-*b*-P(HPMA₁₇₀-*co*-MDTD_{0.85}) before and after exposure to TCEP at pH 8–9 for 8 days at 20 °C, showing the worm-to-sphere transition. The below cartoons show the corresponding reduction in the packing parameter (Adapted with permission from ref ¹²³. Copyright 2016 American Chemical Society).

The same cyclic monomer was also used to confer degradability to single-chain polymeric nanoparticles. Those are usually made by RDRP of vinyl monomers in highly dilute solution and their persistence remains an issue especially when biomedical applications are envisioned. To tackle this challenge, a synthetic approach combining one-pot RAFT copolymerization of MDTD/DMAEMA and intramolecular cyclization (using tri(ethylene glycol) diacrylate (TEGDA) as a comonomer) under concentrated conditions was reported.¹²⁴ Backbone degradable single-chain polymer nanoparticles with $M_n \sim 10 \text{ kg}\cdot\text{mol}^{-1}$ and ~ 5 mol.% MDTD units were produced, and fully degraded in the presence of glutathione or

hydrazine, for potential use as gene transfection vectors. They exhibited superior transfection efficiencies than both non-degradable and crosslinked/degradable counterparts, thus highlighting the key role of a rapid and complete backbone degradation.

To design polymer prodrug nanocarriers, MDTD was incorporated at very low content ($F_{\text{MDTD}} < 0.01$) into POEGMA-*b*-P(DPAEMA-*co*-PTXMA-*co*-MDTD) diblock copolymers made by RAFT (Figure 29).¹²⁵ After formulation, degradable pH- and redox- dual responsive polymersomes of ~ 100 nm in diameter were produced whose disassembly and degradation could be independently triggered. Whereas treatment with TCEP as a reducing agent led to a reduction of the polymersome average diameter down to ~ 50 nm at pH = 7.0 due to disulfide bond cleavage, complete disassembly was obtained when pH was subsequently set at pH = 5.0. However, direct reduction of pH to 5.0 completely disassembled the polymersomes by releasing intact diblock copolymers. This approach could find potential application in cancer therapy given the lower pH and higher concentration of reducing agents observed in the tumor microenvironment and/or to induce site-specific degradation in endosomes or lysosomes.

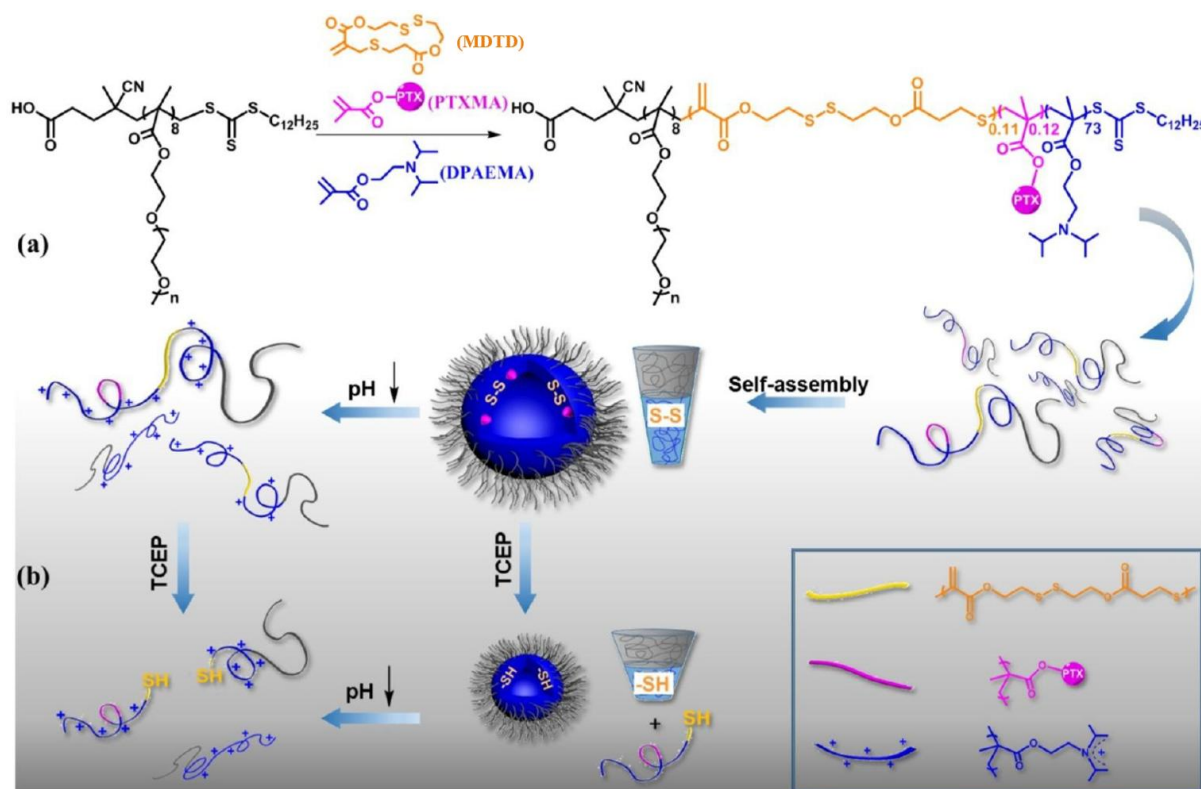


Figure 29. (a) Synthesis of POEGMA-*b*-P(DPAEMA-*co*-PTXMA-*co*-MDTD) diblock copolymers (DPAEMA = (2-(diisopropylamino) ethyl methacrylate); PTXMA = Paclitaxel methacrylate). (b) Schematic illustration of the fabrication of degradable pH/redox dual responsive drug conjugates *via* RAFT polymerization and their dual stimuli responsiveness (Adapted with permission from ref ¹²⁵. Copyright 2019 Royal Society of Chemistry).

Macrocyclic allylic sulfides allowed the insertion of different labile groups by a simple rROP approach, resulting in various degradation modalities and even programmable degradation pathways integrated into advanced nano-objects. Thiol-ene or Michael additions on the 1,1-disubstituted alkene units of the polymer backbone may also represent an additional opportunity for post-functionalization, which is a specificity of those monomers. However, it appeared that only a low amount of macrocyclic allylic sulfides could be effectively incorporated into the copolymers at the risk of dramatically increasing their dispersity because of a certain incompatibility between the thiyl propagating radical and the RAFT process. It would therefore be important to see the emergence of other structures and/or optimization of polymerization procedures to enhance the incorporation of those cyclic monomers.

3.2. Macrocyclic allylic sulfones

To circumvent the previously mentioned drawbacks associated to the rROP of macrocyclic allylic sulfides, a new ring-opening polymerization technique was recently developed. Its mechanism relies on a chain-growth cascade polymerization of 12- to 16-membered ring structures as a strong driving force for the ring-opening step and was therefore termed radical cascade-triggered ring-opening polymerization (RCT-ROP).¹²⁶ It consists in an allylic sulfone structure that can act as a “ring-opening trigger” *via* a radical cascade reaction, to form a sulfonyl radical intermediate, which subsequently expels SO₂ and generates a stabilized secondary alkyl radical (analogous to the propagating radical of polyacrylates), suitable for FRP and RDRP (Figure 30a).¹²⁷ Different structures able to be polymerized that way were synthesized (M6–M9, Figure 30b). They were engaged in RAFT polymerization to successfully generate well-defined homopolymers ($M_n \sim 12 \text{ kg.mol}^{-1}$, $D < 1.2$), poly(macrocyclic monomer)-*b*-PMA and all-macrocyclic diblock copolymers, that were then degraded under accelerated conditions (i.e., sodium methoxide).

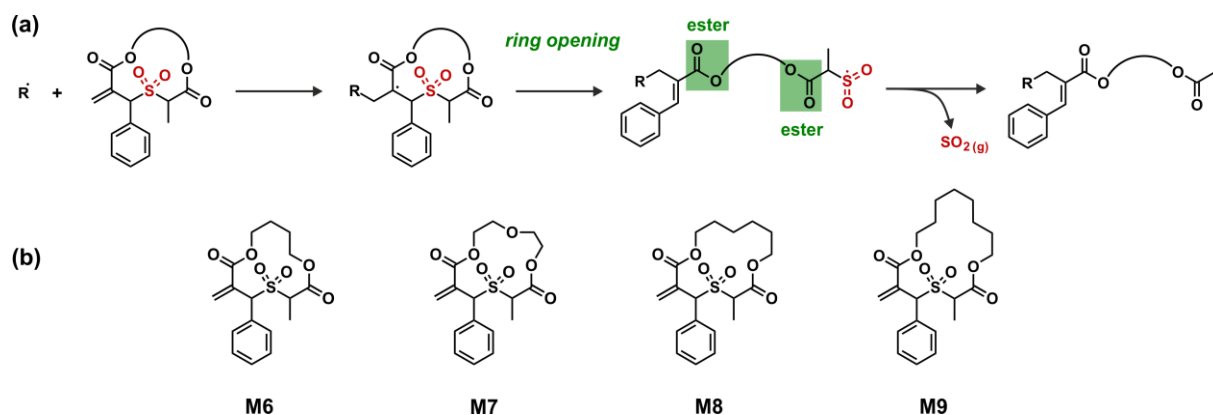


Figure 30. (a) Radical cascade-triggered ring-opening polymerization (RCT-ROP) from an allylic sulfone trigger and (b) structures of the different monomers polymerized by RCT-ROP.

To expand the scope of radical cascade polymerization and access macromolecules with more complex backbones, radical ring-closing/ring-opening cascade polymerization (rRCROCP) was then developed.¹²⁸ By taking inspiration from the structures used in RCT-ROP,

macrocyclic monomers of even larger ring sizes (26- to 31-membered ring) incorporating 1,6-diene-fused allylic sulfone motifs were proposed. They can undergo a radical addition to the vinyl group followed by consecutive cyclization of the 1,6-diene and formation of a propagating alkyl radical after β -elimination of the alkyl sulfone radical and loss of SO_2 (Figure 31a). Several macrocyclic structures were synthesized through a 7-step procedure (**M11**–**M13**, Figure 31b) and successfully polymerized by RAFT for 40–45 h at 85 °C ($M_n \sim 4.1$ – $20.1 \text{ kg}\cdot\text{mol}^{-1}$, $D = 1.21$ – 1.39). A control structure (**M10**, Figure 31b) was also synthesized to demonstrate the poor control of the polymerization in absence of the sulfone moiety. The polymers obtained from **M11**–**M13** exhibited good thermal stability ($\sim 5\%$ mass loss at 310–340 °C), variable glass transition temperature ($T_g = 48$ – 138 °C) and high livingness, allowing well-defined block copolymers to be made with high susceptibility to degradation *via* cleavage of ester groups by sodium methoxide.

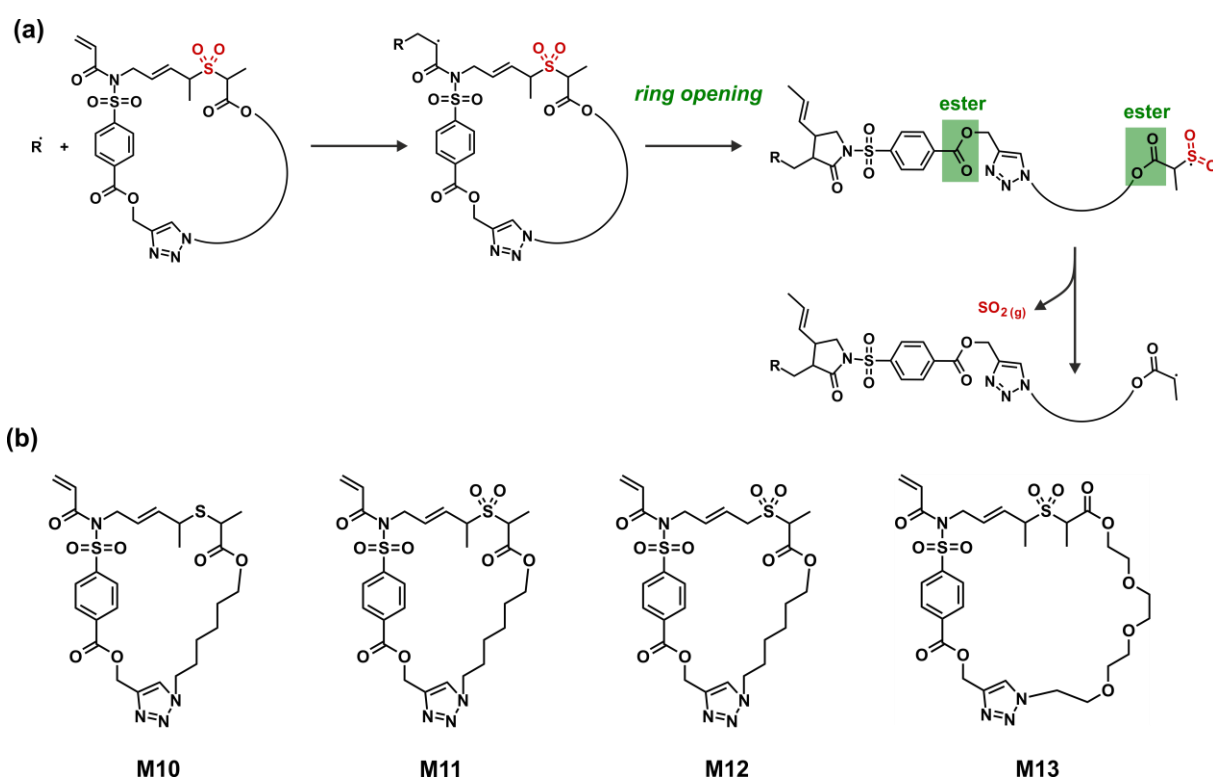


Figure 31. (a) Radical ring-closing/ring-opening cascade polymerization (rRCROCP) of 1,6-diene-fused allylic sulfone. (b) Structures of the different monomers polymerized by rRCROCP.

Conclusion

In this Viewpoint, we have summarized the recent progress observed in rROP through the three main monomer types that aggregated most of the research effort over the past few years. CKA monomers are still heavily investigated as rROP (co)monomers and most of their important limitations (e.g., tedious synthesis, poor structural diversity, difficult homopolymerization and unfavorable reactivity ratios with many comonomers) have been alleviated, but without being entirely solved though. Nevertheless, it did not prevent advanced and cutting-edge materials to be made by rROP of CKAs for many different applications including drug delivery, biomaterials, biotechnology, etc. For instance, the discovery and/or optimization of new copolymerization systems enabled the synthesis of (bio)degradable copolymers with high contents in labile groups and versatile functionalization, which is something that cannot be easily obtained from traditional polyesters. Future work should aim at diversifying even further the structure of CKAs, which currently prevent the synthesis of a broader range of materials with adjustable properties (e.g., degradability, solubility, etc.).

The recent use of DOT has rejuvenated the field of rROP by allowing the production of polyacrylates with tunable amounts of thioester units in the main chain, that can be degraded under different conditions (e.g., methanolysis, aminolysis and thiol-thioester exchange). Noteworthy is the fact that despite a reduced amount of compatible vinyl monomers to be copolymerized with, DOT is complementary to CKAs as, conversely to them, it can readily copolymerize with acrylates.

Eventually, macrocycles have been successfully (co)polymerized by rROP to access new degradable polymers. Macrocyclic allylic sulfides allowed various labile groups to be inserted (e.g., ester, disulfide, thioester) during free-radical and controlled copolymerization with vinyl monomers, thus resulting in different degradation pathways. Successful homopolymerization of macrocyclic allylic sulfones by FRP and RDRP appeared as a new

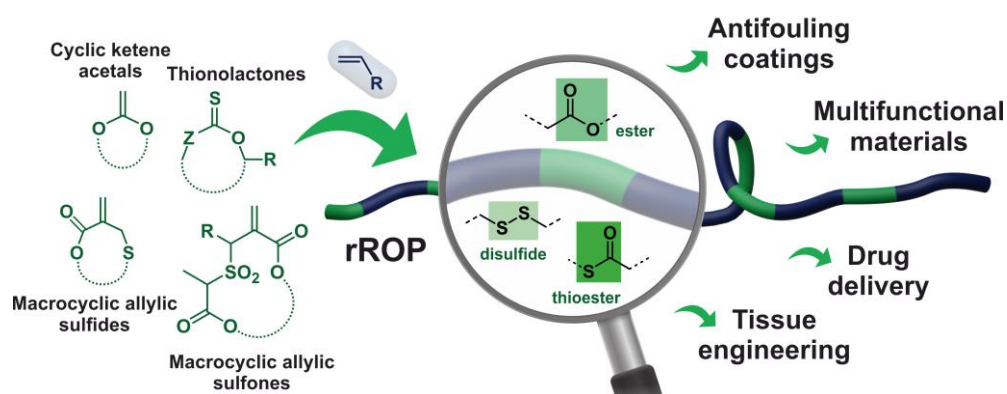
way to yield degradable materials with more complex main chains. The fact that macrocyclic allylic sulfones can be readily homopolymerized is also complementary to CKAs, whose homopolymerization is still rather limited and difficult.

To conclude, the field of rROP is still incredibly vivid and productive, and no doubt the forthcoming decade will be the theater of important innovations to push even further the boundaries of this exciting polymerization technique. Even though a lot of work remains to be done, the ultimate goal for rROP would be to challenge traditional polyesters in terms of biodegradation and biocompatibility and surpass them in terms of functionalization and sophistication.

Acknowledgments

We thank the French Ministry of Research for the financial support of the PhD thesis of TP. Some results described in this manuscript were obtained thanks to the French National Research Agency (ANR-11-JS08-0005 and ANR-15-CE08-0019) and the French Ministry of Research. The CNRS is also acknowledged for financial support. JN is indebted to all his past and present students from his group and collaborators involved in the field of rROP.

Graphical abstract



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