Radical Ring-Opening Polymerization: Scope, Limitations, and Application to (Bio)Degradable Materials

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Abstract

Cyclic monomers bearing either vinyl or exomethylene groups have the ability to be polymerized through a radical pathway *via* a ring-opening mechanism (addition – fragmentation process), leading to the introduction of functionalities in the polymer backbone. Radical ring-opening polymerization (rROP) combines thus the advantages of both ring-opening polymerization and radical polymerization: that is the preparation of polymers bearing heteroatoms in the backbone but with the ease and robustness of a radical process. This current review presents a comprehensive description of rROP by detailing: (i) the various monomers that polymerize through rROP; (ii) the main parameters that govern the rROP mechanism; (iii) the copolymerization by conventional or controlled/living radical polymerization between rROP monomers and traditional vinyl monomers to obtain copolymers with advanced properties; (iv) the different applications (low shrinkage materials and preparation of (bio)degradable materials) of rROP monomer-containing materials and (v) the main alternatives to rROP to induce degradability to materials obtained by a radical polymerization.

1. Introduction

Among the various polymerization methods, ring-opening polymerization (ROP) is fascinating since it enables the incorporation of heteroatoms and also functional groups into the polymer backbone, thus giving access to a broad range of (bio)degradable materials, such as those deriving from the ROP of lactones and lactides.[1-4] In the last decade, many metal-based[5] or organic[6] catalysts have been developed to improve the characteristics of ROP-synthesized polymers in terms of kinetics, macromolecular architectures, incorporation of functionalities, process, etc.

Although polymerization of traditional vinyl monomers proceeds by chain addition with the creation of carbon-carbon bonds, some cyclic monomers bearing vinyl or exomethylene groups can be polymerized by a radical pathway through a ring-opening mechanism. The polymerization of cyclic monomers bearing a vinyl group leads to polymers with a double bond in the polymer backbone whereas the polymerization of cyclic compounds with an exomethylene group produces polymers with a pendant double bond. The functionality (e.g., ketone, ester, amide, thioester, etc.) derived from the nature of the X and W atoms in α position of the initial double bond (Figure 1).

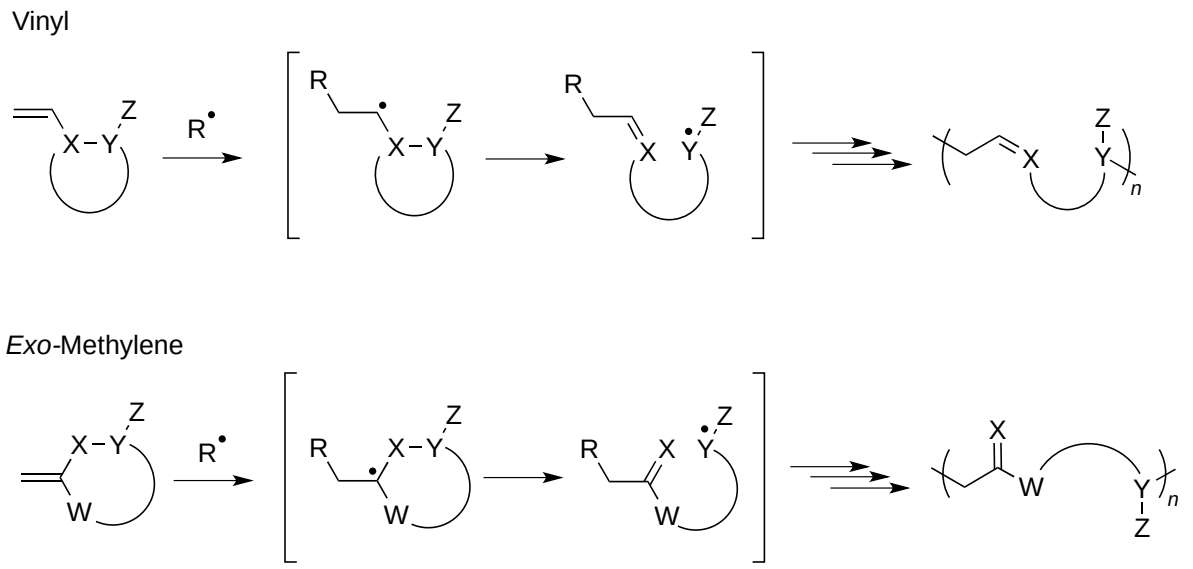


Figure 1. Structures of the two different cyclic monomers that can be polymerized by radical ring-opening polymerization (rROP).

Radical ring-opening polymerization (rROP) thus combines the advantages of both ring-opening polymerization and radical polymerization: that is the production of polymers having heteroatom and/or functional groups in the main chain together with the robustness, the ease of use and the mild polymerization conditions of a radical process. Since the first studies, it was believed that a few requirements were necessary for the design of cyclic monomers: (i) the strain of the ring must be high (or distorsion in the ring-structure must occur) to induce the ring cleavage; (ii) the ring-opening of the structure should be accompanied by isomerization processes that yield thermodynamically more favored functional groups (C=X in Figure 1), and (iii) the released alkyl radical after fragmentation has to be stabilized.

If those requirements were not fulfilled or if side-reactions occurred during the polymerization, a competition between ring-opening and ring-retaining processes could take

place, leading to different monomer units into the polymer backbone (Figure 2). The presence of ring-retaining units because of classic vinyl-type propagation leads to an aliphatic carbon-based skeleton, without no further possibility of degradation.

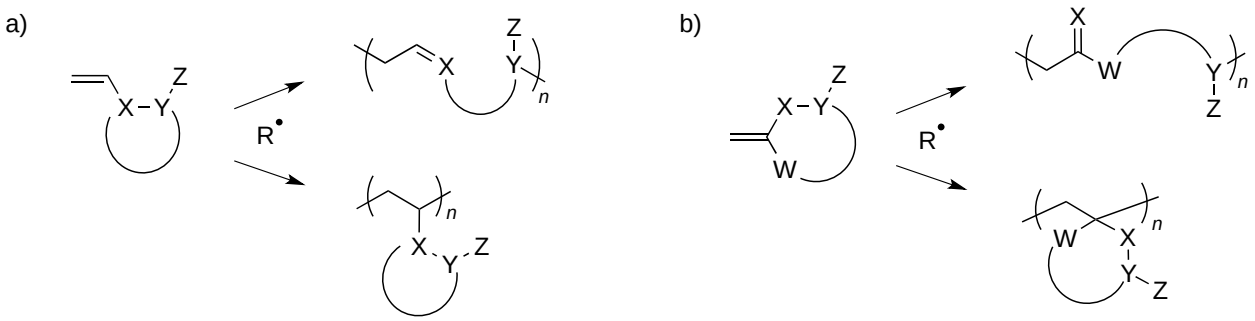


Figure 2. Competition between radical ring-opening and ring-retaining (vinyl type) polymerization for a) vinyl type and b) exomethylene type monomers.

The first report on rROP was published in the 60s with the polymerization of spiro-di-*o*-xylylene.[7] The polymerization of **AR1** was performed for few days at 50 °C in the presence of a radical initiator and led to semi-crystalline and low-T_g polymer **PAR1** (Figure 3). In the same period, Takahashi and coworkers[8-9] demonstrated that the polymerization of vinyl-cyclopropane **VCP1** proceeded by a radical mechanism since a 1,5 propagation occurred instead of the common vinyl 1,2 propagation that is reported for the cationic polymerization of such compounds.

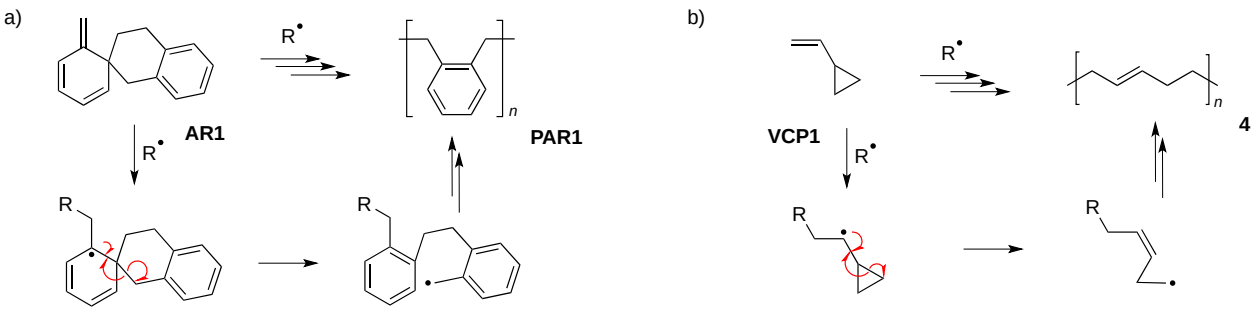


Figure 3. First monomers that historically underwent radical ring-opening polymerization.

Since then, many structures from totally different chemical families (e.g., spiro-*ortho*-carbonates, cyclic acrylates, unsaturated spiro-ortho-esters, etc.) were tested for their ring-opening ability. Among them, cyclic ketene acetals (CKA) were reported by Bailey and coworkers[10-11] in the early eighties as suitable monomers for rROP. This monomer family was then extensively studied as a way to produce similar polymers to classic aliphatic polyesters, but through a radical pathway.

Another feature that promoted the development of rROP during the 80s-90s was the development of low shrinkage materials for various applications including dental fillings and precision moldings.[12] Indeed, it is known that volume contraction during the polymerization is due the replacement of a Van der Walls distance between two monomer units by a shorter covalent bond along the polymer backbone. When bond formation is accompanied by bond breaking (due to β fragmentation for instance), the shrinkage is substantially reduced. Cyclic allylic sulfides was for example proved to be very efficient to obtain a complete ring-opening of the starting monomer[13] with very low shrinkage of the final materials.

One of the main challenges regarding rROP is the competition between the ring-opening process and the direct radical polymerization of the double bond (i.e., without ring opening). The present review aims at first establishing a complete and comprehensive overview of the various compounds that have been developed and tested for rROP and then identifying the various factors that led to the efficient ring-opening of the monomer. rROP was extensively studied in the 80s–90s but has been recently rejuvenated by the possibility to copolymerize cyclic vinyl monomers with classical vinyl monomers, leading to cleavable functions into the copolymer backbone (Figure 4a). This led to a broad range of novel (bio)degradable materials suitable for a large scope of applications, particularly in the biomedical field[14-21] where degradability and/or bioresorption are often required. It has to be noted that all these recent studies used well-known cyclic monomers (e.g., CKA, sulfide cyclic methacrylate, etc.) without newly developed compounds. Nevertheless the enthusiasm provoked by the use of rROP is likely to stimulate the design of new monomer structures in the near future.

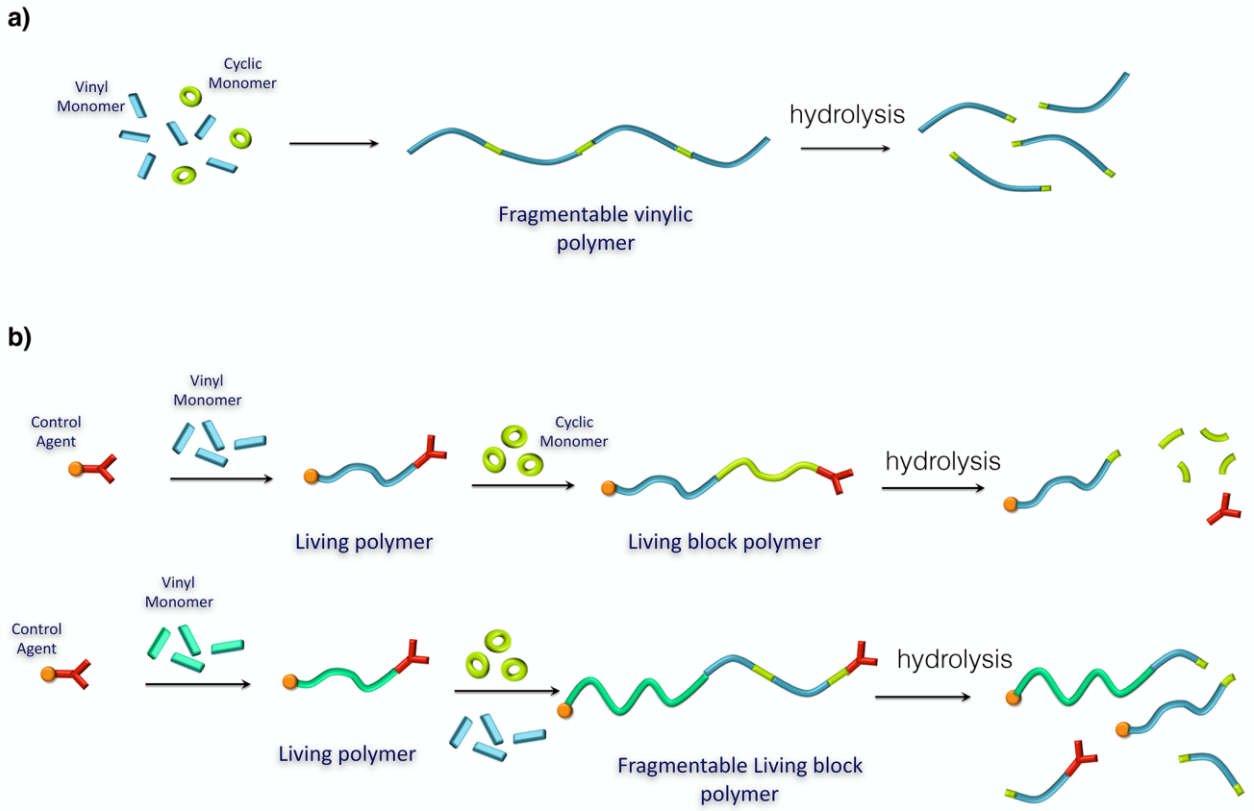


Figure 4. Complex macromolecular architectures that can be obtained *via* radical ring-opening (co)polymerization.

The interest towards rROP has also been renewed by the development of controlled/living radical polymerization (CLRP) techniques, now called reversible deactivation radical polymerization (RDRP). These techniques enables the preparation of complex macromolecular architectures (e.g., block, star, grafted copolymers, etc.) that could self-assemble at the nanoscale to create materials with advanced properties.[22] The combination of both RDRP and rROP makes now possible the preparation of block copolymers with different levels of degradability by a unique radical polymerization mechanism (Figure 4b).

Up to now, no comprehensive review on the rROP has been published. Only reviews on polymerization mechanism[23-28] or reviews published on specific families of cyclic monomers were performed (vinyl cyclopropane derivatives[29] and the use of cyclic ketene acetal in polymer science[30]). Due to the recent increase of publications in this field, the aim of this comprehensive review is to cover all aspects of rROP; from the reactivity of cyclic monomers, to the synthesis of (co)polymers and the different applications deriving from their use. The final section is devoted to the different alternatives to rROP that rely on a radical mechanism to produce degradable vinyl-based materials.

2. The various cyclic monomer structures

To be polymerized by radical ring-opening polymerization, cyclic monomers should fulfill various criteria: i) bearing a carbon-carbon double bond (radical acceptor); ii) having distorted ring structures to promote the ring-opening; iii) having a concomitant ring-opening mechanism with isomerization processes giving thermodynamically more favored structures and iv) having a stabilized radical deriving from the ring-opening process. Various families of monomers able to polymerize by rROP have been synthesized and are listed below:

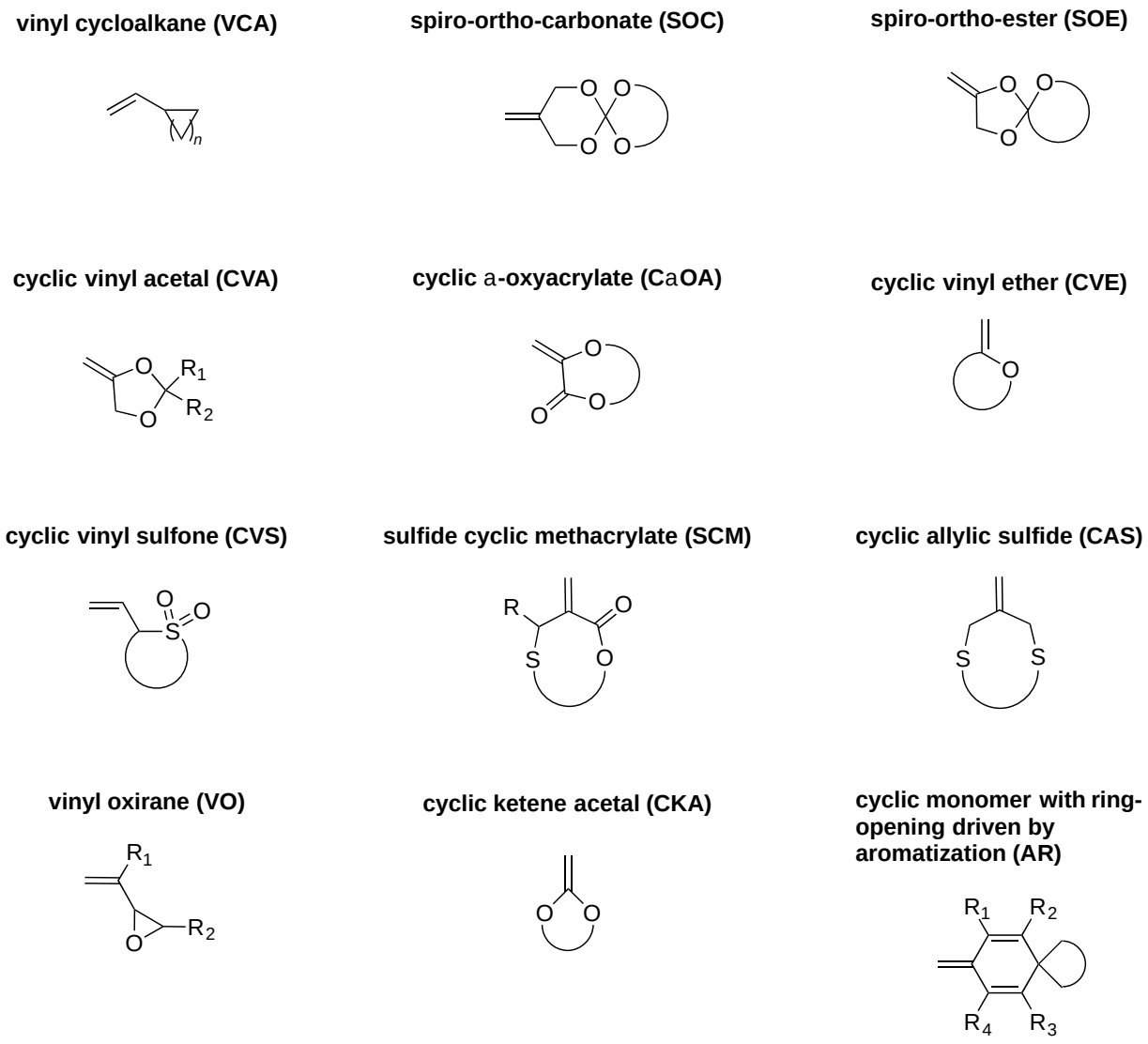


Figure 5. Structures of the different monomer families that can be polymerized by rROP.

2.1 Vinyl cycloalkane

As previously discussed, monomers suitable for rROP should have a double bond and also a strained cyclic structure. This explains why vinyl cyclopropane VCP derivatives have been the first monomers tested for rROP.

Based on the pioneering work of Van Volkenburgh[31] on the polymerization of vinylcyclopropane initiated by benzoyl peroxide under UV irradiation, Takahashi and co-workers[8-9] proved in the 60's that its radical polymerization proceeded *via* a 1,5 ring-opening mechanism followed by propagation (Figure 6). This mechanism was different from the 1,2-vinyl mechanism involved in cationic polymerization. More precisely, in the case of the rROP, the first step consisted in the addition of a radical species to the vinyl function followed by the ring-opening reaction of the highly distorted 3-membered ring. This reaction led to the formation of a radical and at the same time of a thermodynamically more stable internal olefin that promoted the ring-opening reaction.

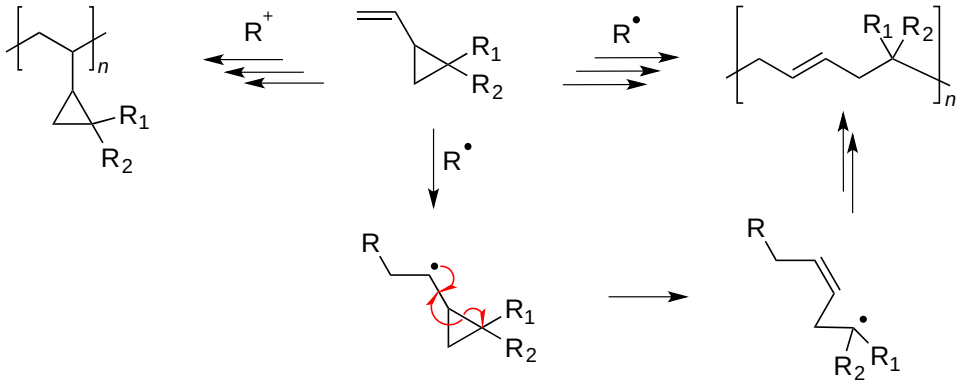


Figure 6. Vinyl cyclopropane radical and cationic polymerization mechanism.

The molar masses of the obtained polymers were low (1000 – 5000 g.mol^{-1}). Several studies were then conducted to prepare substituted and more reactive monomers to reach higher molar masses (Figure 7).[32] All these monomers were reviewed in details by Moszner in

1999[29] and Endo in 2015.[24] Contrary to the chain polymerization of conventional vinyl monomers such as styrenics, acrylates or methacrylates, the rROP of vinyl cyclopropanes presented the advantage of inducing low volume shrinkage. The resulting polymers can consequently be envisioned as shrinkage-free adhesives and void-free sealants.

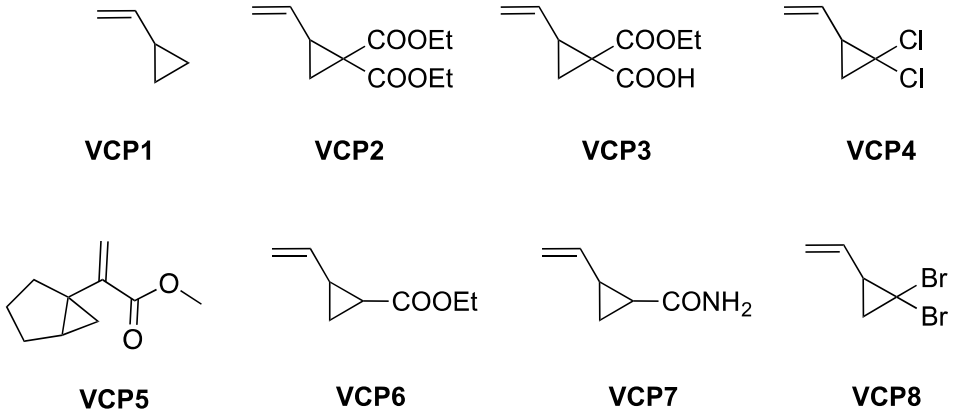


Figure 7. Structures of several vinyl cyclopropane reported in the literature.

Since this family of monomers has been widely studied in the literature, their synthesis and radical reactivity will be discussed in section 3. Their application as low shrinkage materials will be detailed in section 7.1 and the polymerization of the vinylcyclopropane acetal monomers will be detailed in subsection 4.7 (entitled hybrid CKA monomers).

In addition to cyclopropane structures, cyclobutane derivatives such as **VCB1** can undergo radical ring-opening (Figure 8).[33] The mechanism can be also decomposed into three steps: (i) addition of a radical species onto the carbon-carbon double bond; (ii) ring-opening of the cyclobutane ring and (iii) release of the four-membered ring. The ester group promoted the ring-opening reaction by stabilizing the newly formed radical.

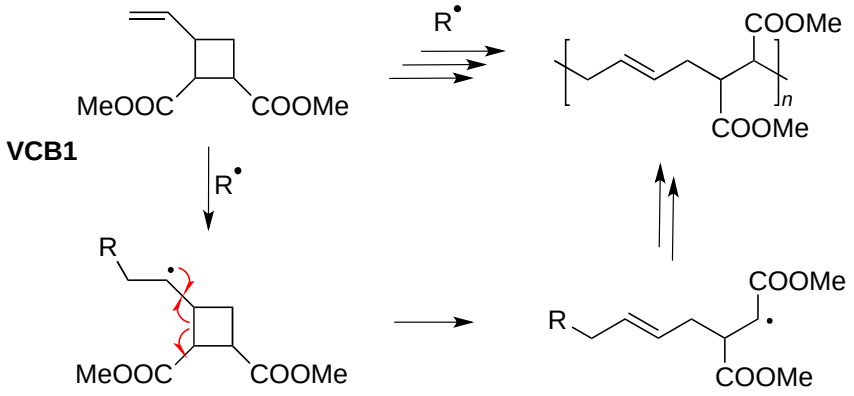


Figure 8. Mechanism of rROP of vinyl cyclobutane.

2.2 Unsaturated spiro-ortho-carbonates and unsaturated spiro-ortho-ester

Spiro-ortho-carbonates and spiro-ortho-esters are cyclic monomers that can be polymerized by cationic ring-opening polymerization. This polymerization is accompanied by a volume expansion because the acyclic polymer chains occupy a significant higher volume than the corresponding cyclic monomers. This property of volume expansion can be useful to elaborate sealants and adhesives that exhibit no void and crack.

The first rROP of such monomers was reported in 1975 by Bailey and Endo[34] who described the polymerization of the unsaturated spiro-ortho-carbonate **SOC1**. After 10 h at 130 °C with di-*tert*-butyl peroxide as initiator, the conversion reached 42 % and the obtained polymer was a polycarbonate-*alt*-polyether with pendant carbon double bonds (Figure 9).

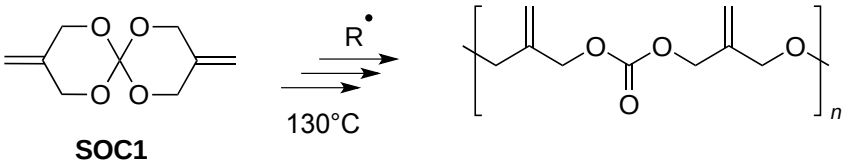


Figure 9. Polymerization of 3,9-dimethylene-1,5,7,11-tetraoxaspiro-(5,5)undecane **SOC1**.

The polymerization of similar monomers **SOC2-SOC4** gave the same polymer structure. The proposed mechanism was a double ring-opening: after the addition of the radical on the double bond, a β-scission gave a new C=C bond and an alkoxyl radical (Figure 10).[35]

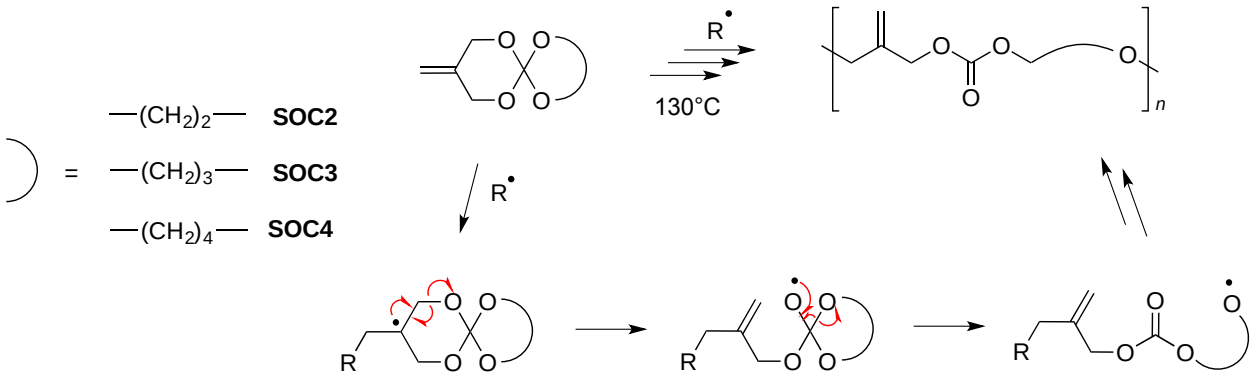


Figure 10. Polymerization mechanism of unsaturated spiro-ortho-carbonates.

Different spiro-ortho-carbonates similar to **SOC2-4** were studied to prepare new polycarbonates. By varying the size of the rings, adding aromatic group to stabilize the propagating radical or putting the exo-methylene group in α of oxygen, it was nevertheless difficult to clearly identify the involved mechanisms.[36] The advances in characterization techniques and in particular in NMR finally enabled to propose a polymerization mechanism in the case of cyclic β-exo-

methylene spiro-ortho-carbonates (Figure 11) and cyclic α-exo-methylene spiro-ortho-carbonates (Figure 12).

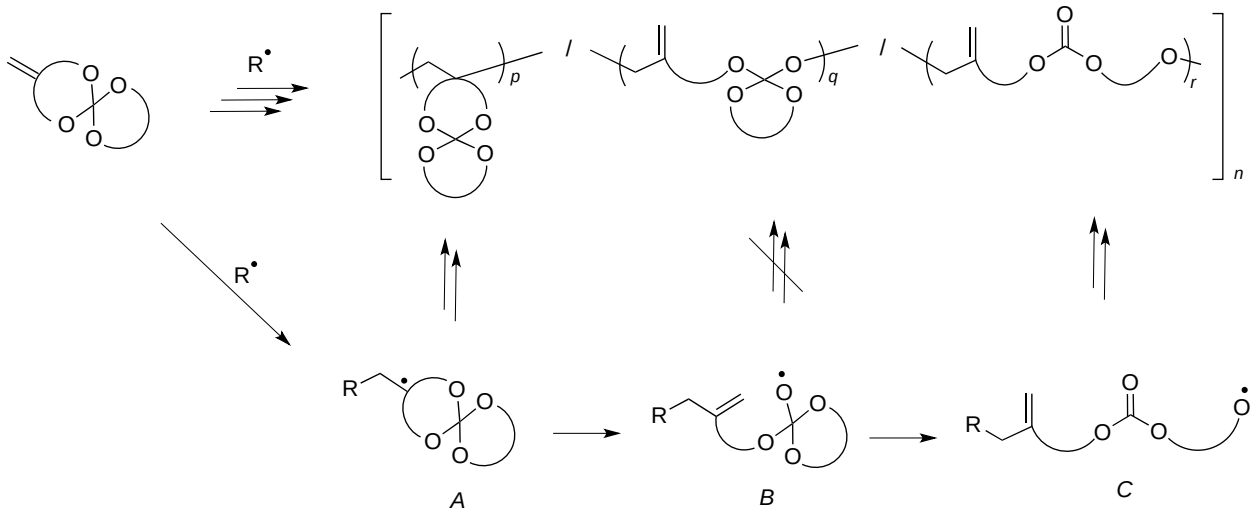


Figure 11. Polymerization mechanism of cyclic β-exo-methylene spiro-ortho-carbonates

In both cases (α or β-exo methylene spiro-ortho-carbonates), the resulting polymers were composed of repeat units from the vinyl polymerization or the double ROP but never from the mono ring-opening process (q = 0, see Figure 11 and 12). The radical B indeed quickly rearranged into the form C that is more stable because of the carbonate group formation.

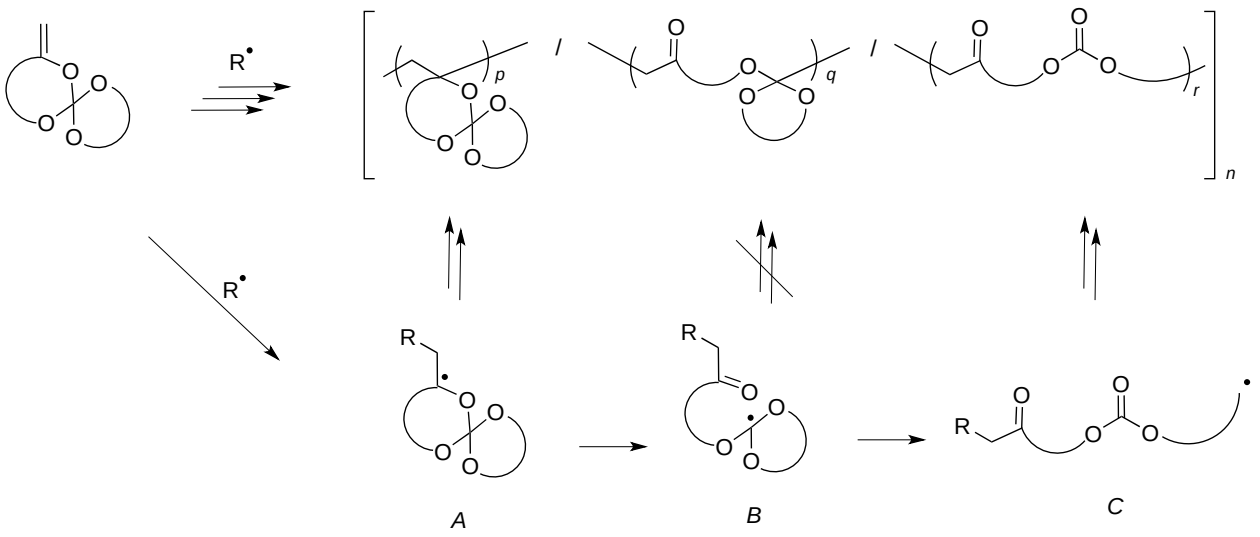
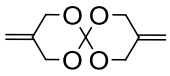
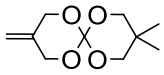
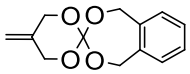
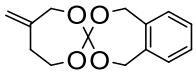


Figure 12. Polymerization mechanism of cyclic α-exo-methylene spiro-ortho-carbonates.

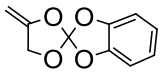
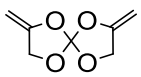
Unfortunately when in-depth NMR studies were conducted on the rROP of **SOC1**, the authors observed that the double rROP concerned only 5% of the consumed monomer (Table 1).[37] The main polymerization mechanism was indeed the polymerization of the C=C bond without ring-opening (i.e. the vinyl process). Moreover, the radical addition onto the pendant C=C bond was responsible for the cross-linking in the final polymer. If an increase of the temperature helped favoring the ring-opening mechanism towards the vinyl polymerization, the use of solvent had no effect and the molar masses were generally lower than 2000 $g.mol^{-1}$.

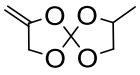
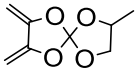
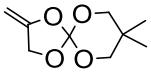
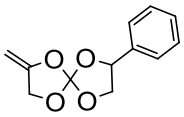
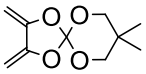
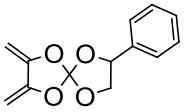
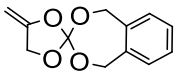
Table 1. Polymerization of β-exo methylene spiro-ortho-carbonates

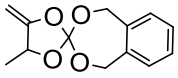
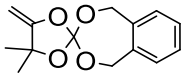
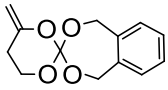
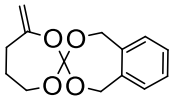
Number	Monomer	Polymerization conditions	Double ring-opening (% r)	Reference
SOC1		130 °C, sol.1.25M, 20h	5% , + cross-linking	[37]
SOC5		130 °C, bulk, 20h 180 °C, bulk, 20h	4% 24%	[38]
SOC6		130 °C, 20h 180 °C, bulk, 20h	8% bulk, 9%sol. 55%	[38]
SOC7		130 °C, bulk, 20h 180 °C, bulk, 20h	34% 86%	[38]

The monomers with the exo-methylene group in the α position to the oxygen formed by the double rROP poly(ketone-carbonate) without pendant C=C bond (Figure 12). The problem of cross-linking that occurred with monomers bearing a β exo-methylene group is therefore circumvented but the double ring-opening process is at the same time less promoted (Table 2).[39]

Table 2. Polymerization of α exo-methylene spiro-ortho-carbonates.

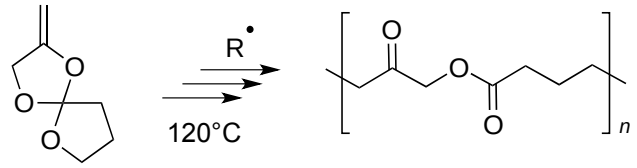
Number	Monomer	Polymerization conditions	Double ring-opening (% r)	Reference
SOC8		60-165 °C, solution, 48h	0%	[40]
SOC9		60-120 °C,	0%	[41]

		solution, 50h	cross-linking	
SOC10		copo MMA, 65-120 °C, solution, 20h	0%	[36]
SOC11		copo MMA, 65-120 °C, solution, 20h	0% cross-linking	[36]
SOC12		130 °C, solution	45-85%	[42]
SOC13		130 °C, solution	50-80%	[42]
SOC14		130 °C, solution	60-85%	[42]
SOC15		130 °C, solution	50-70%	[42]
SOC16		130 °C, bulk, 20h 180 °C, bulk, 20h	0% 20%	[39]

SOC17		130 °C, bulk, 20h 180 °C, bulk, 20h	10% 35%	[39]
SOC18		130 °C, bulk, 20h 180 °C, bulk, 20h	- -	[39]
SOC19		130 °C, bulk, 20h 180 °C, bulk, 20h	18% 89%	[39]
SOC20		130 °C, bulk, 20h 180 °C, bulk, 20h	29% 42%	[39]

Still with the objective of developing monomers with low shrinkage and/or liquid at room temperature for easy handling and after the successful synthesis of polycarbonate from spiro-ortho-carbonate, Endo and Bailey described in 1980[43] the synthesis of poly(ketone-ester) by the rROP of unsaturated cyclic spiro-ortho-esters. From the first results observed with **SOE1** (Figure 13a) and monomers with 6 or 7-membered second ring (**SOE2** and **SOE3**), the polymerization mechanism of spiro-ortho-ester proposed in 1981 was again a double ring-opening process (Figure 13b).[44]

a)



SOE1

b)

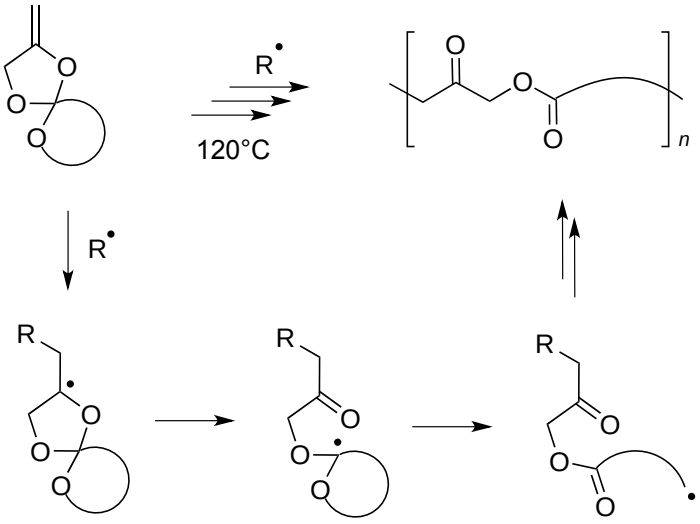


Figure 13. a) Polymerization of 2-methylene-1,4,6-trioxaspiro(4,4)nonane **SOE1**. b) First postulated polymerization mechanism of spiro-orhto-ester **SOE1-3**.

In depth investigations were later conducted on spiro-ortho-ester monomers and called this "simple" mechanism into question. Indeed, when polymerizing **SOE4** (Figure 14), Han and Choi[45] obtained a copolymer composed of poly(ketone-ester) from the double ring-opening process and poly(cyclic ortho-ester) from the vinyl polymerization of the C=C bond. Even if the quantification of each repeat unit was particularly difficult by NMR, the authors observed a clear change of the chemical structure with the temperature and they postulated that at 60 °C, the main

mechanism was the vinyl polymerization whereas at higher temperatures (90 and 120 °C), the main product was a poly(ketone-ester) deriving from the double ring-opening polymerization.

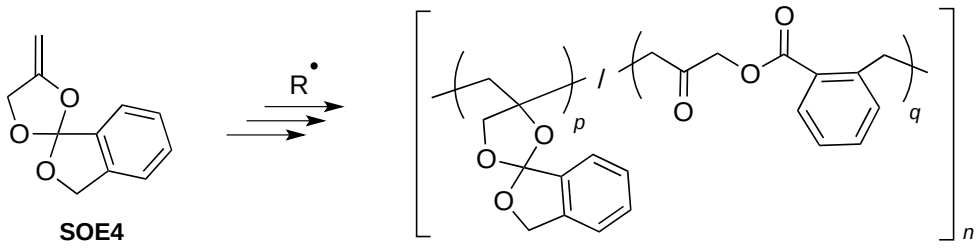


Figure 14. Polymerization of the cyclic spiro-ortho-ester **SOE4**.[45]

In 1985, Bailey had a new look at the polymerization of **SOE1** and reported that in fact, 90 % of the polymer synthesized at 120 °C were composed of poly(cyclic ortho-ester) implying that q = r = 5% (Figure 15).[11] The same results were also observed with 7-membered second ring spiro-ortho-ester monomers such as **SOE3**.[46]

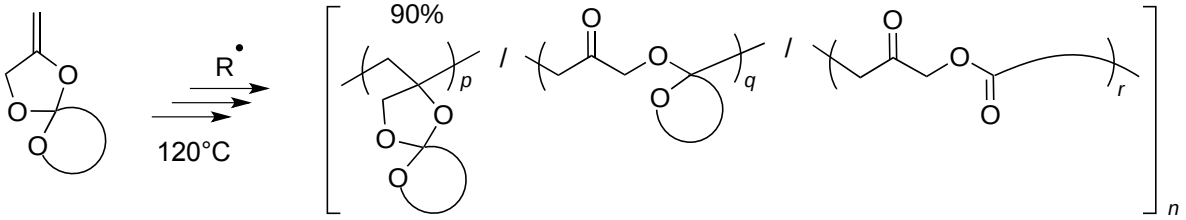
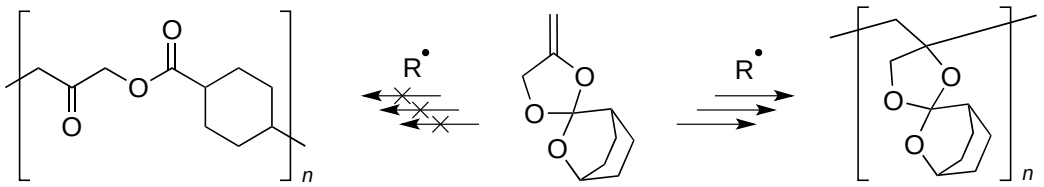


Figure 15. Polymerization of spiro-ortho-ester according to Ref. [11].

Similarly, the results concerning the radical polymerization by double ring-opening of **SOE5** were modified 6 years later to only consider the vinyl polymerization (Figure 16).[11, 46-47]



SOE5

Figure 16. Polymerization of monomer **SOE5**.

Based on the results obtained with the 4-methylene-1,3-dioxolane monomers and producing only polyketones, Pan and Bailey reassessed the results obtained from **SOE4**. It was observed that the polymerization mechanism was more complex that the one initially proposed and it was concluded that the rROP of these monomers did not produce poly(ester-ketone) but polyketone by phtalolactone elimination (Figure 17).[48] Even if the proportions of the different species and the influence of the temperature were not established, the ring-opening rate was estimated to be in the 2-4.5 × 10^4 mol.L^{-1}.min^{-1} range for a propagation rate of 2-8 × 10^4 mol.L^{-1}.min^{-1} at 75 °C.

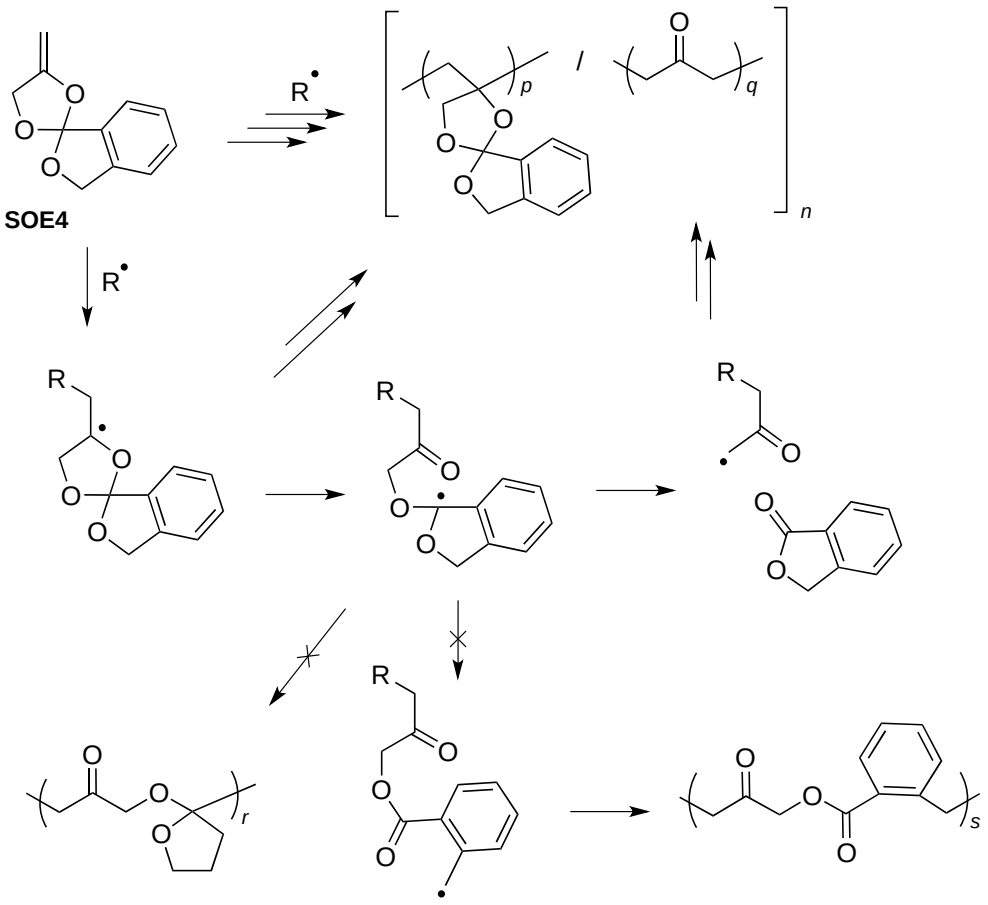


Figure 17. Updated mechanism of rROP for monomer **SOE4**.

Interestingly, the polymerization of spiro-ortho-esters with the exo-methylene group on the cycle bearing only one oxygen atom (called 7-methylene-spiro-ortho-esters, see Figure 18a) gave complex copolymers with repeat units coming from single and double ring-opening.[49-50]

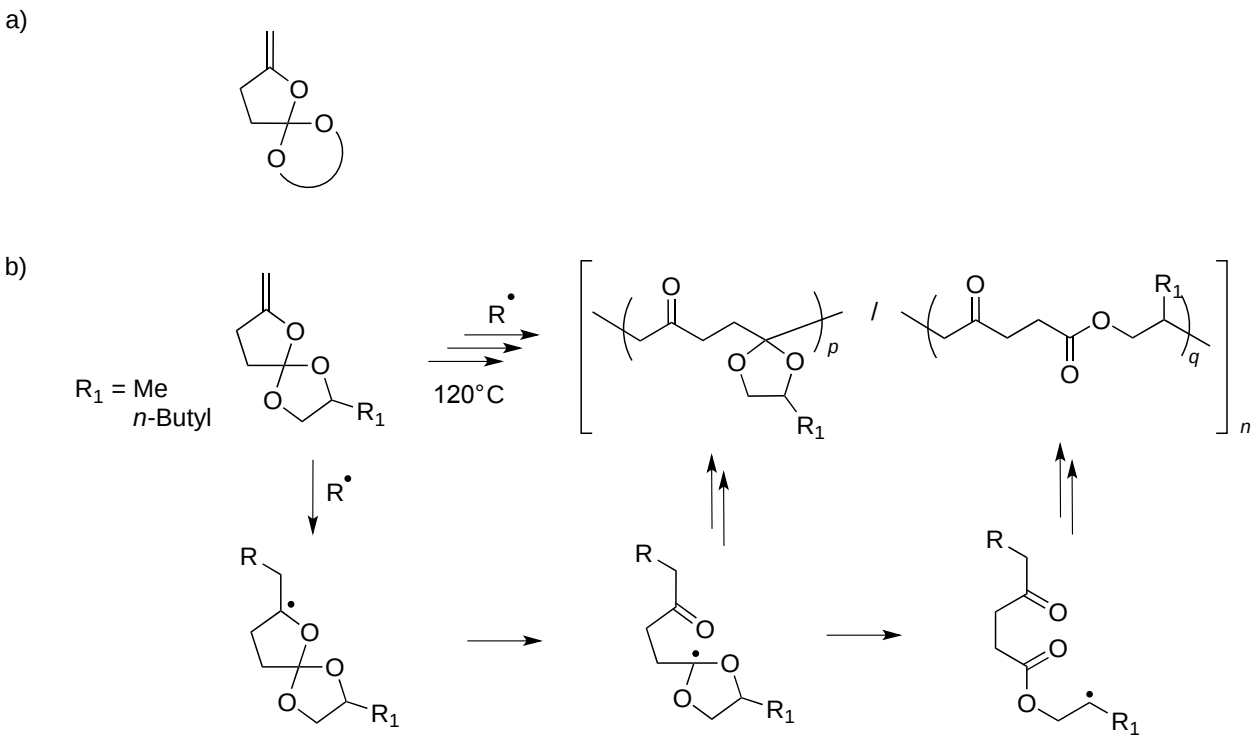


Figure 18. a) Structure of 7-methylene-spiro-ortho-ester monomers. b) Polymerization mechanism of 7-methylene-spiro-ortho-esters.

Pan and Bailey[49-50] studied the influence of the dilution, the temperature and the size of the R_1 substitute (Figure 18b) on the polymerization of different 7-methylene-spiro-ortho-oesters. They showed that at 60, 75 or 120 °C, the monomer with a methyl group in R_1 position gave a polymer only composed of repeat units coming from partial opening (p = 100%) whereas when solvent is used at 120 °C, the proportion of double ring-opening reaches 50 % (p<q>50%). The size of the R_1 substitute seemed to be important as well since 50% of double ring-opening was observed for R_1 = *n*-butyl and this whatever the temperature (Figure 18b).

2.3 Cyclic vinyl acetals

In the 60s, Goodman[51] reported on the cationic polymerization of several 4-methylene-1,3-dioxolane (cyclic vinyl acetal monomers) and mentioned that according to an American patent from 1947 it was believed that these monomers did not homopolymerize by a radical process as opposed to their copolymerization. In 1982, Fukuda[52] studied the polymerization of cyclic vinyl acetals with maleic anhydride and observed a spontaneous copolymerization *via* a charged transfer complex (CTC) giving an alternating copolymer but without ring-opening (Figure 19).

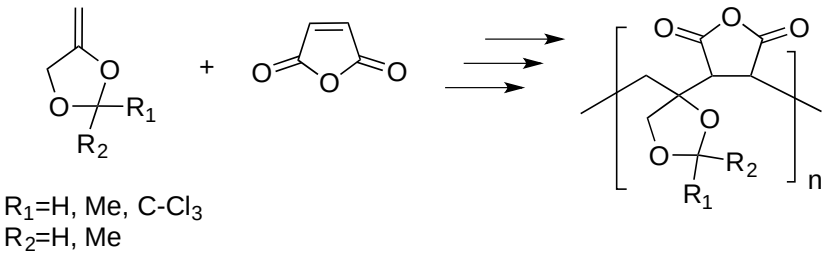


Figure 19. Copolymerization by CTC of 4-methylene-1,3-dioxolane and maleic anhydride.

This type of mechanism was confirmed in 1988[53] by studying the copolymerization of **CVA1** with acrylonitrile (AN), methyl methacrylate (MMA) and styrene (S). No copolymer was obtained with S whereas spontaneous copolymerization with MMA or AN gave copolymers but with no alternating structure (low CTC) and no ring-opening.

The radical homopolymerization of **CVA1** (Figure 20) was also studied.[54] The molar masses of the polymers were low (< 2000 g.mol^{-1}) and the structure rather complex since 3 types of repeat units were observed namely cyclic units *via* vinyl polymerization, poly(ketone-ester) units *via* ring-opening and polyketones resulting of β-scission followed by the elimination of benzaldehyde. It was shown that the temperature and the solvent played an important role in the proportion of ring-opening and elimination (Table 3).

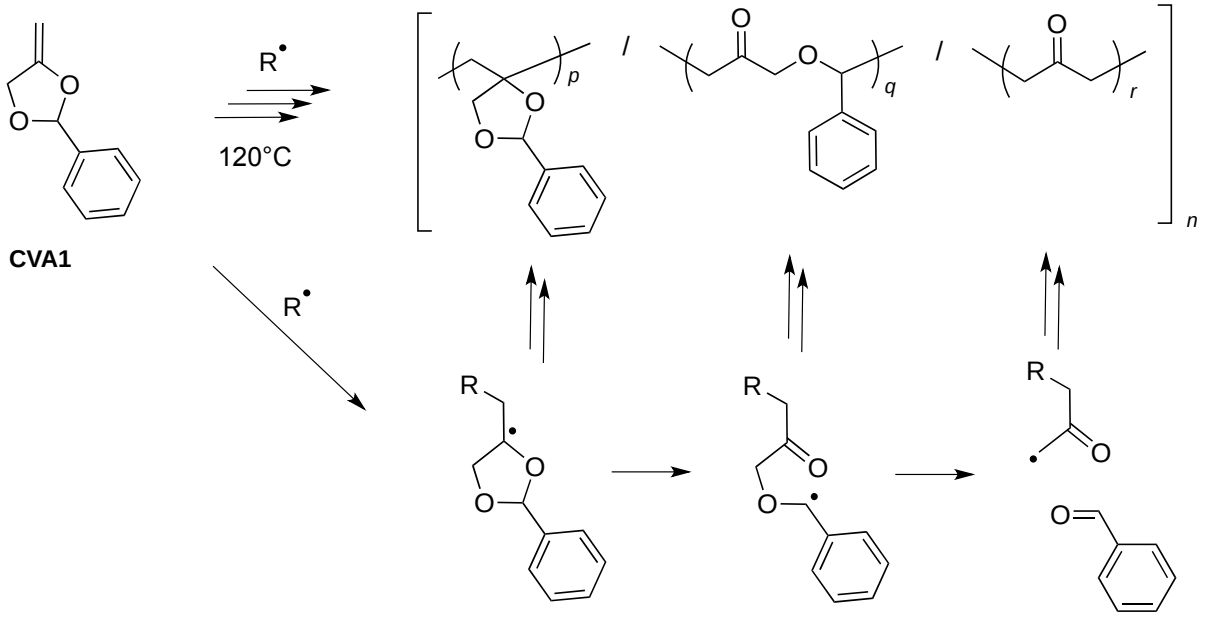
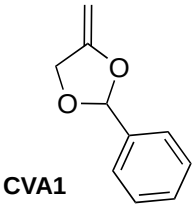
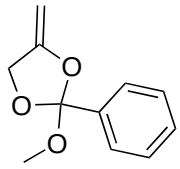


Figure 20. Polymerization mechanism of 4-methylene-2-phenyl-1,3-dioxolane **CVA1**.

These results were confirmed a few years later and poly(ketone-ester) of 5000 – 11,000 g.mol^{-1} were successfully obtained by ring-opening of **CVA1** at low temperature *via* radical photopolymerization in the presence of 2-methoxy-2-phenylacetophenone (BME) as initiator.[55]

Unfortunately intermediate radicals were formed when increasing the temperature that gave rise to a mixture of different structures.

Table 3. Results of the polymerization of 4-methylene-2-phenyl-1,3-dioxolanes.

Monomer	Initiator, Temperature (°C)	Solvent	% of the different units in the copolymer			Reference
			p	***q***	***r***	
 **CVA1**	DTBP, 120	-	27	47	26	54
	DTBP, 120	chlorobenzene (1:1 in vol)	14	52	36	
	DTBP, 120	chlorobenzene (1:3 in vol)	14	36	51	
	BPO, 80	-	47	40	13	
	AIBN, 65	-	25	63	12	
	BME, 25-50	-	0	100	0	55
	BME, 80	-	<10	80	<20	
 **CVA2**	AIBN, 65	-	30	70	0	56
	AIBN, 65	5 mL benzene/g CVA2	0	60	40	
	BPO, 85	5 mL benzene/g CVA2	0	40	60	
	DTBP, 125	1 mL benzene/g CVA2	0	40	60	
	DTBP, 125	5 mL benzene/g CVA2	0	20	80	

AIBN: azobisisobutyronitrile; BME: benzoin methyl ether; BPO: benzoyl peroxide; DTBP: di-*tert*-butyl peroxide

A similar influence of the temperature and the dilution on the polymerization of the same type of monomer but bearing a methoxy group (**CVA2**, see Table 3) was observed. The elimination of methyl benzoate increased with temperature and dilution (r = 40 – 80 %).[56]

More recently, Morariu and coworkers[57] described the polymerization of monomer **CVA3** bearing a chlorine group on the ortho position of the aromatic ring (Figure 21). In this case, the NMR analysis of the polymer indicated that the main structure corresponded to a β-scission on the side not stabilized by the aromatic ring, giving an exo-methylene group and an alkoxyl propagating radical. The proportion of repeat units coming from the ring-opening process could be increased by using the photopolymerization technique.

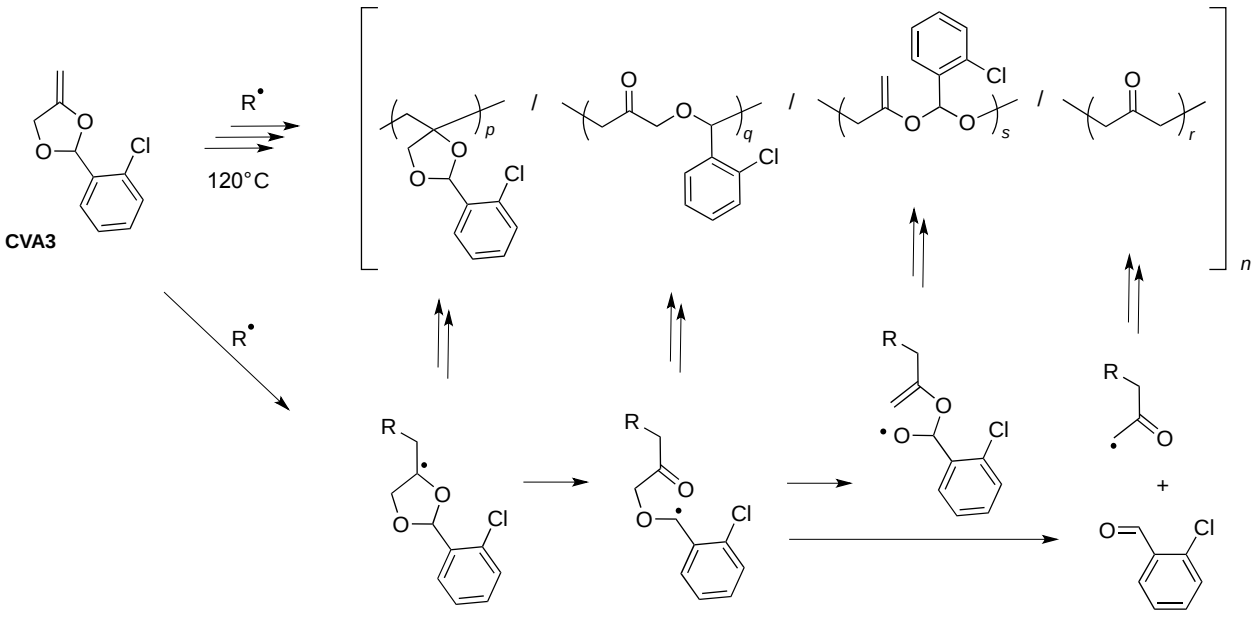


Figure 21. Polymerization of 2-(2-chlorophenyl)-4-methylene-1,3-dioxolane **CVA3**.

Table 4. Thermic and photochemical polymerization of 2-(2-chlorophenyl)-4-methylene-1,3-dioxolane **CVA3**.

Initiator, Temperature (°C)	Solvent	% of different repeat units in the polymer				Reference
		p	***q***	***r***	***s***	
AIBN, 70 °C	-	**<15**	**20**	**<5**	**60**	[57]
BME, 50 °C	-	**0**	**45**	**0**	**55**	

In 1987, Endo and Hiraguri[58] presented the polymerization of a monomer with 2 phenyl groups (**CVA4**), paving the way to a new method to prepare polyketone without any side reaction (Figure 22). The opened radical was significantly stabilized by the presence of two aromatic rings and therefore cannot propagate. Moreover the formation of polyketone along with benzophenone elimination was thermodynamically highly favored at 120 °C in solution. When performed in bulk at 60 °C, the polymerization yielded polyketone with up to 18% of repeat units coming from the vinyl polymerization and without repeat units coming from the single ring-opening.[59] The polymerization of monomers with a methyl group on the α position to the exomethylene group gave polyketone with a better solubility in usual organic solvents.[60]

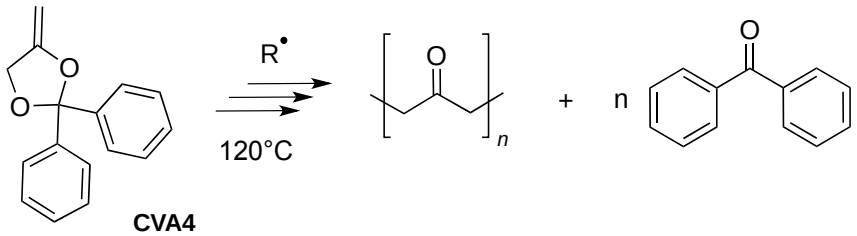


Figure 22. Polymerization of 4-methylene-2,2-diphenyl-1,3-dioxolane **CVA4**.

Several studies were then devoted to the synthesis of pure polyketone by varying the substituting alkyl groups on the acetal carbon (Figure 23). The proportion of polyketone and polymers coming from direct polymerization ranged between 50 and 100 %.[61-63] The presence of polar moieties that could be either electron withdrawing or electron donating groups on the para position of the aromatic ring had no influence on the copolymer structure.

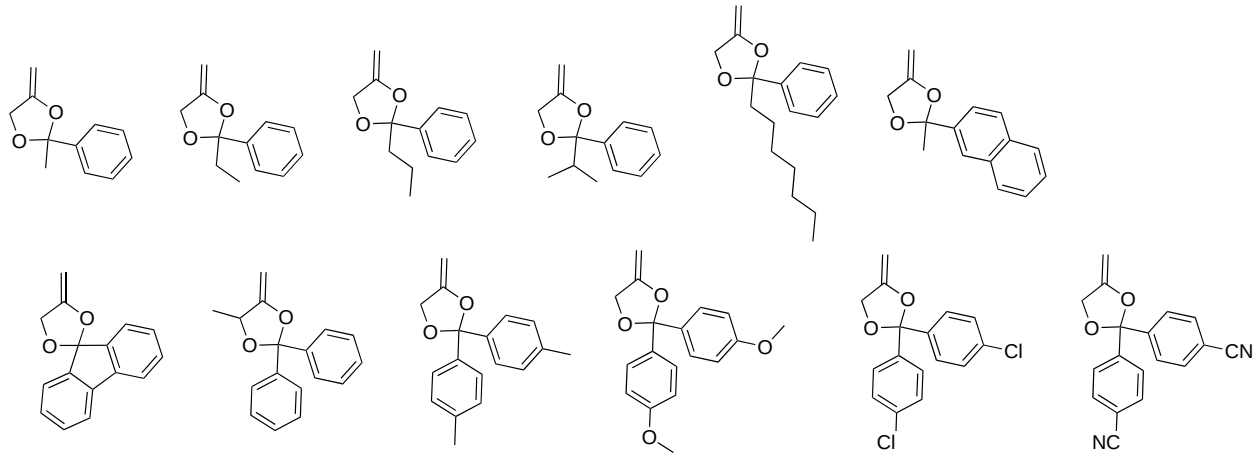


Figure 23. Monomers studied for the synthesis of polyketones.

More recently, the copolymerization of these monomers with styrene to get photodegradable copolymers thanks to the ketone function present in the main chain aroused interest. For example, a poly(4-hydroxystyrene-ketone) copolymer of 17,000 $g.mol^{-1}$ with 20% of ketone-based units was degraded into a 5,000 $g.mol^{-1}$ copolymer by photolysis.[64-65]

In 1998, Klemm and co-workers[66] studied the radical polymerization of 7-membered cyclic monomers (**CVA5** and **CVA6**, Figure 24). They concluded that at 60 and 90 °C, the polymerization only proceeded by a ring-opening process but with the formation of polyketones issued from aldehyde elimination (Figure 24, q = 9 – 16 % and q = 23 – 30 % for **CVA5** and **CVA6** respectively).

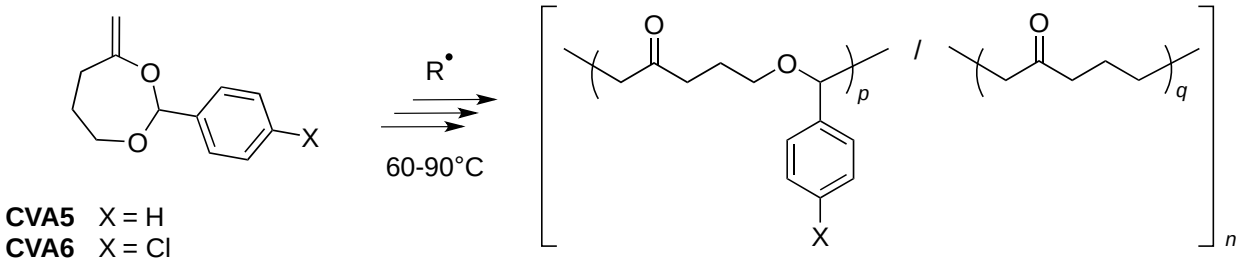


Figure 24. Polymerization of 4-methylene-2-phenyl-1,3-dioxepane (**CVA5**) and 4-methylene-2-(4-chlorophenyl)-1,3-dioxepane (**CVA6**).

2.4 Cyclic α-oxyacrylates (or α-exo-methylene lactones)

Cyclic α-oxyacrylates are cyclic lactones bearing an exo-methylene group in the α-position. The particularities of these monomers are that the acrylate-type function of the monomer is a good radical acceptor. The mechanism of radical polymerization of α-exo-methylene lactones is depicted in Figure 25. The route i) corresponds to the vinyl polymerization of the C=C bond and the route ii) to the radical ring-opening process. In this second pathway, the addition of a radical on the C=C bond formed a tertiary radical which is stabilized by the adjacent ester group. The ring-opening reaction then gave a thermodynamically stable α-ketoester moiety that favored the formation of photodegradable polymers thanks to the presence of this photosensitive linkage in their main chain.

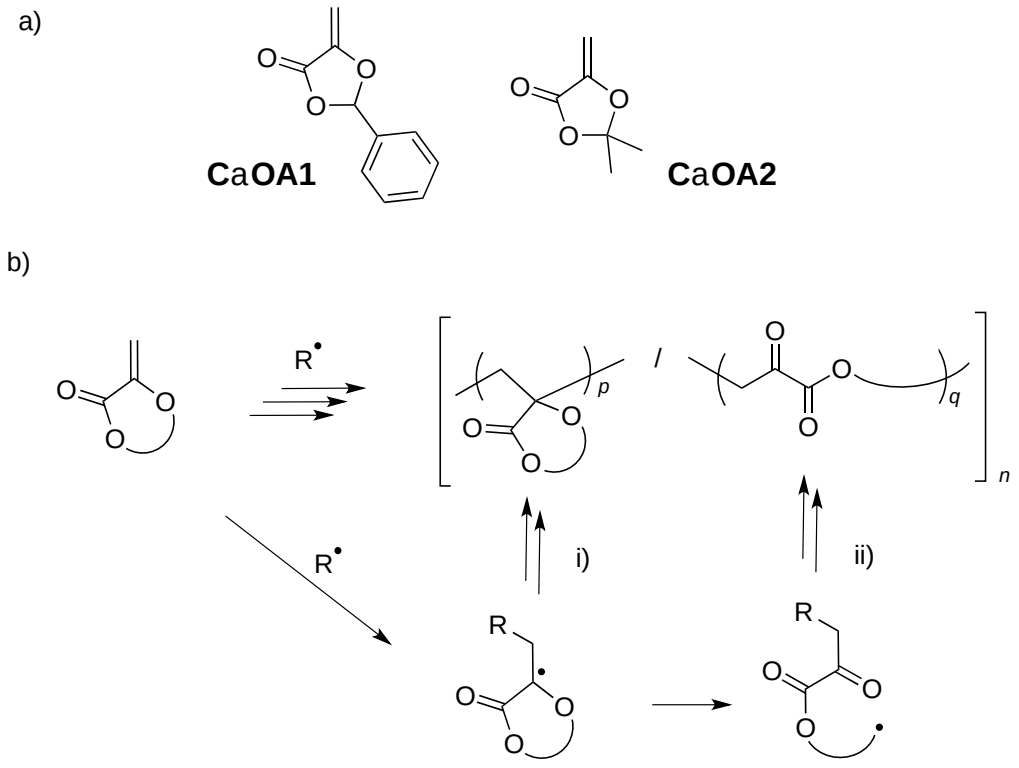
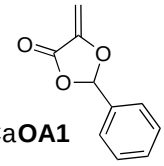
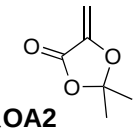
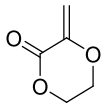
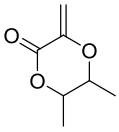
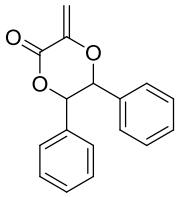
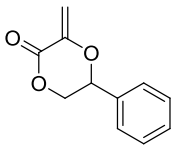
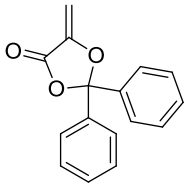


Figure 25. a) Structure of **CαOA1** and **CαOA2**. b) Mechanism of polymerization of cyclic α-oxyacrylate **CαOA**.

Different five and six-membered α-exo-methylene lactones were polymerized by rROP. More precisely, Bailey[67] published new results concerning the polymerization of different cyclic acrylates. He described copolymers with two types of repeat units and reported an easy rROP at high temperature (140 °C) and in solution for both monomers **CαOA1** and **CαOA2** (Figure 25). Nevertheless no experimental part gave the accurate characterization of the synthesized copolymers.[68] One year later, Bailey published a review on the rROP.[46] The main results are summarized in Table 5. Again, no detail was provided on the copolymer characterization.

Table 5. Results on the polymerization of different cyclic α-oxyacrylates.

Monomer	Temperature polym. (°C), solvent	% of ring-opening [68]	% of ring-opening [46]
 **CaOA1**	120, bulk	20%	"Almost entirely non ROP"
	140, tBuBZ	"essentially quantitative"	"Limited amount (10%)"
 **CaOA2**	120, bulk	50%	15%
	140, tBuBZ	"Nearly 100%"	50%
	BPO, 80 °C, benzene	20%	20%
	BPO, 80 °C, benzene	50%	30%
	BPO, 80 °C, benzene	100%	100%
	DTBP, 120 °C, t-BuBz	"nearly 100%" [69]	
	120, bulk	70% [23]	
	140, tBuBZ	100%	

A few years later, **CαOA1** and **CαOA2** were studied again and consistent results with those from Bailey were obtained:[70] in bulk, 80 and 50% of **CαOA1** and **CαOA2** respectively polymerize by rROP. In the case of **CαOA2**, 80% were obtained when the polymerization was performed in solution at 0.8 mol.L^{-1}.

The polymerization of several **CαOA1**derivatives was also described (Figure 26).[71] According to the authors, the monomers polymerized only by a ring-opening process in bulk at 60 °C but unfortunately, no detailed characterization supported these conclusions and the cross-linking observed in the case of some monomers was still unclear.

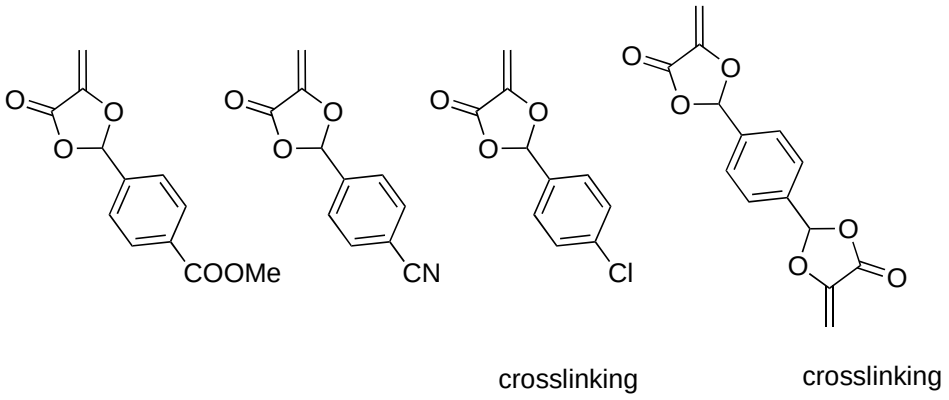


Figure 26. Cyclic α-oxyacrylates polymerized by Zeuner.[71]

2.5 Cyclic vinyl ether

Monomers with only one oxygen, called cyclic vinyl ethers, were also studied,[11] in the objective to get polyketones potentially photodegradable according to the mechanism depicted in Figure 27.

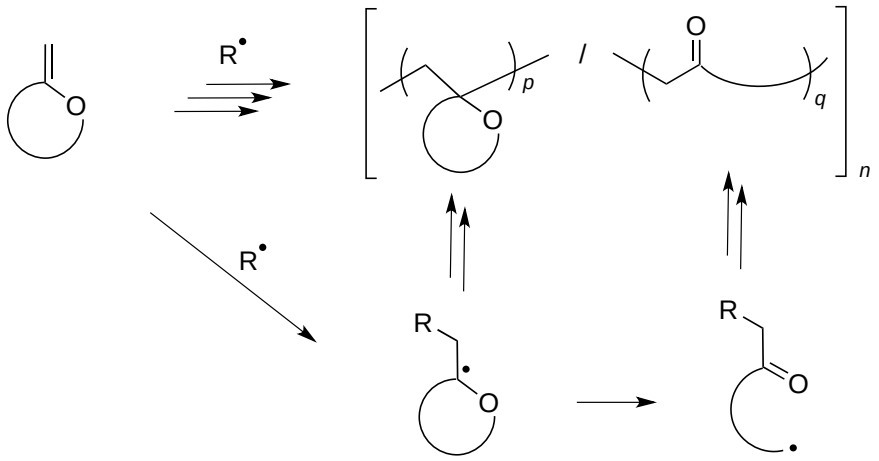


Figure 27. Mechanism of cyclic vinyl ethers polymerization.

According to the authors, cyclic vinyl ether monomers presented the advantage to be less prone to ring-opening than cyclic ketene acetal (CKA), enabling a better and easier study of the steric and stabilizing effects of substitutive groups on the radicals. The methylene oxetane **CVE1** (Table 6) both underwent rROP and the radical polymerization of the vinyl function. Consequently, the resulting polymer contained ketone and oxetane units (Figure 28a). After addition of a radical onto the exo-methylene group followed by the ring-opening of the strained oxirane ring, the formed radical was a non-stabilized primary radical. The rROP was nevertheless supported by both the appearance of a thermodynamically stable ketone group and by the release of the highly strain structure.

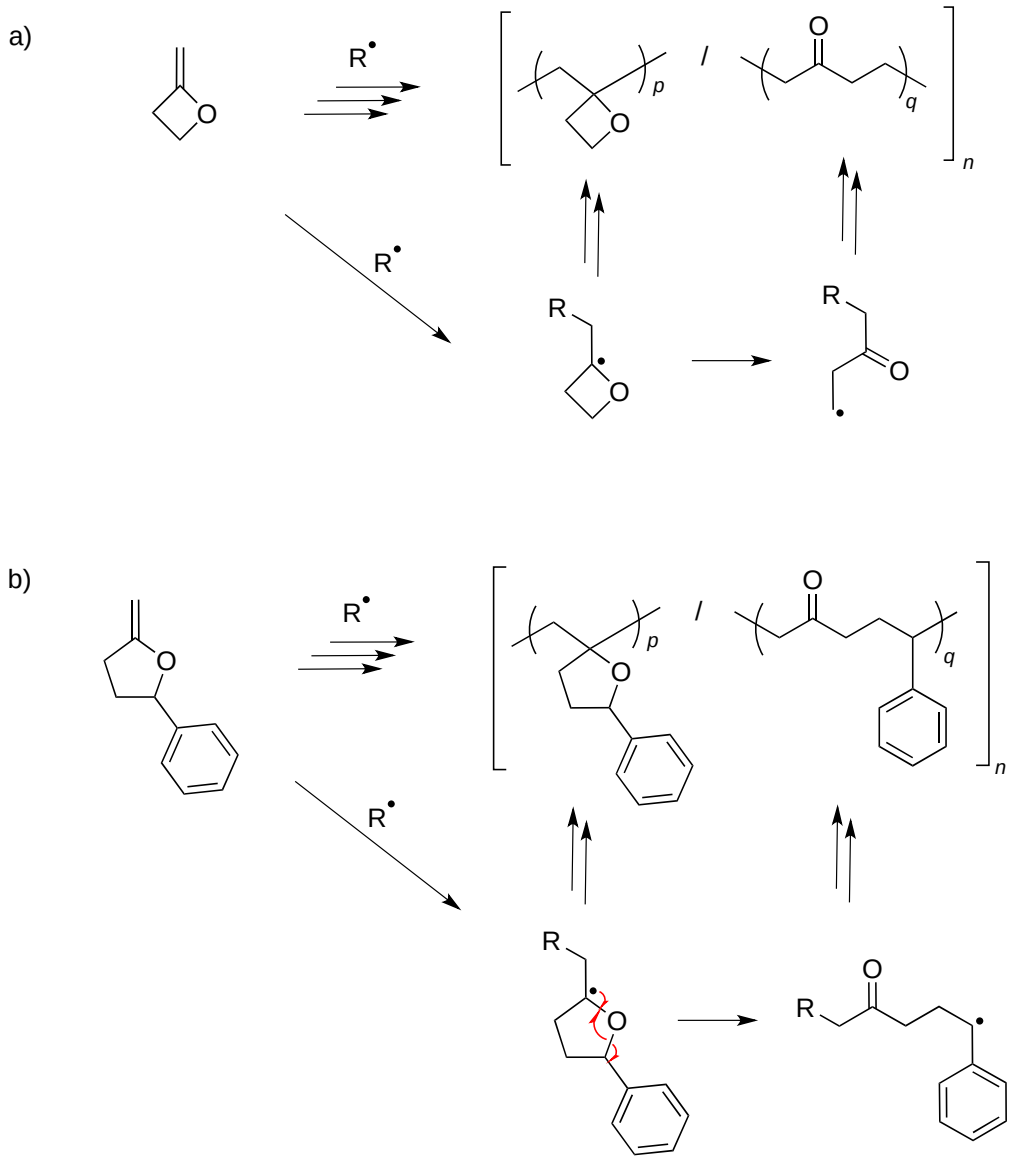
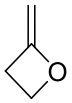
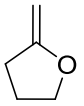
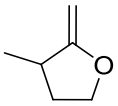
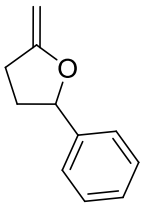


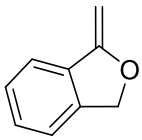
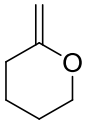
Figure 28. a) rROP of exo-methylene oxetane **CVE1**. b) rROP of exo-methylene tetrahydrofuran **CVE2**.

Concerning the five-membered cyclic ether **CVE2** (Table 6 and Figure 28b), the radical ring-opening reaction was promoted by the formation of a thermodynamically stable ketone and a relatively stable benzyl radical chain end.

According to the results presented in Table 6, it seemed that the aromatic group stabilized the opened radical and consequently favored the ring-opening (**CVE2**).[72] The opposite effect was observed when the aromatic ring stabilized the intermediate radical as well (**CVE3**). In addition, a higher ring tensile favored ring-opening as observed in the case of the 4-membered cyclic monomers (**CVE1)**, even if the steric hindrance could also play a role.

Table 6. Polymerization of different cyclic vinyl ether monomers.

Number	Monomer	Polymerization conditions	Ring-opening (% q)	References
CVE1		DTBP, 120 °C, solution	40	[72]
		DTBP, 120 °C	5	[73] [11]
		DTBP, 120 °C	15-20	[73] [11]
CVE2		DTBP, 120 °C, benzene	70	[73] [11]
		DTBP, 120 °C,	50	

CVE3		DTBP, 120 °C	0	[73] [11]
		DTBP, 120 °C	4-8	[73] [11]

2.6 Sulfur-containing monomers

2.6.1 Cyclic vinylsulfones

Cho[74] reported a new family of monomers called cyclic vinylsulfones that enabled the synthesis of polyalkylene sulfones by ring-opening and propagation *via* an alkylsulfonyl radical (Figure 29).

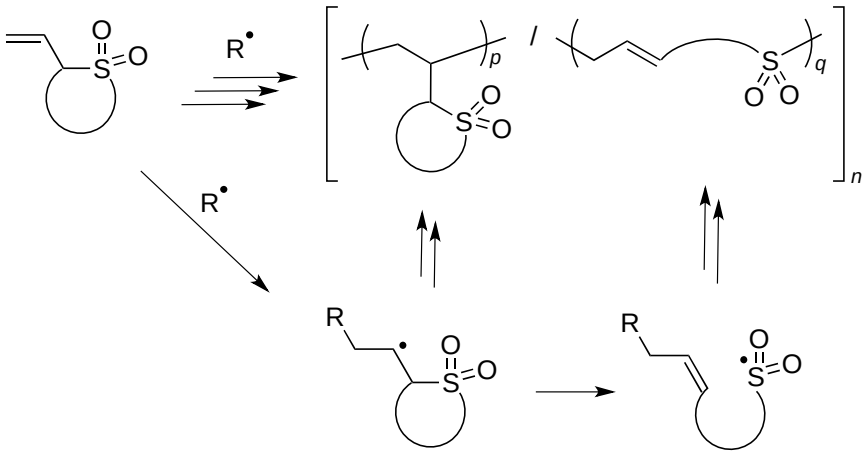
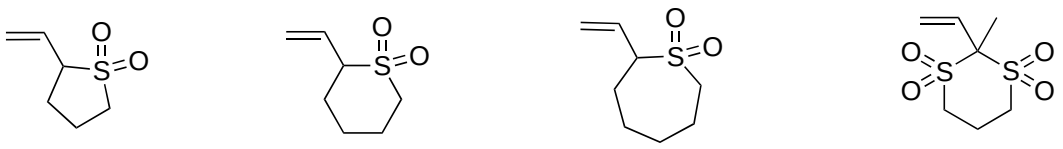


Figure 29. Polymerization mechanism of cyclic vinylsulfones.

The polymerization of **CVS1** (Figure 30) with AIBN at 60 °C reached high conversion in 20 h and gave a polymer only soluble in concentrated sulfuric acid or trifluoroacetic acid. The polymerization mechanism was clearly based on a ring-opening process.[75-76] Conversely, **CVS2** was more difficult to polymerize since only 60 % conversion were reached after 12h at 80 °C in the presence of BPO and with only 40% of ring-opening. **CVS3** was situated in between **CVS1** and **CVS2** as it partially polymerized by ring-opening like **CVS2** (85%) but reached high conversion, similarly to **CVS1**.[77] Compared to monomer **CVS2** and **CVS3,** the reactivity of the 6-membered cyclic **CVS4** bearing a quaternary carbon was largely higher and 100% of ring-opening were observed at 80 °C (together with high conversion).[78]



CVS1 **CVS2** **CVS3** **CVS4**

Figure 30. Cyclic vinylsulfone monomers **CVS1-CVS4**.

2.6.2 Sulfide cyclic methacrylates

In 1994, Rizzardo and co-workers[79] developed a new class of sulfurated cyclic monomers, namely sulfide cyclic methacrylates. The **SCM1-4** structures (Figure 31) were quite stable and presented a good solubility in usual organic solvents and vinyl monomers. Because of the high lability of the C-S bond, the β-scission is, in this case, favored and gives a C=C bond and a thiyl propagating radical. Sulfide cyclic methacrylate monomers were consequently exclusively polymerized *via* a ring-opening process. They also possessed a high reactivity both in homopolymerization (around 80% conversion in 3h at 70 °C) and copolymerization (quantitative insertion with MMA) but cross-linking was observed for **SCM1** after 20% conversion during homopolymerization. This problem was however not observed with **SCM2** because the methyl group on the formed double bond prevented radical addition. The copolymerization with styrene was also possible but the chemical degradation was not as good as expected.

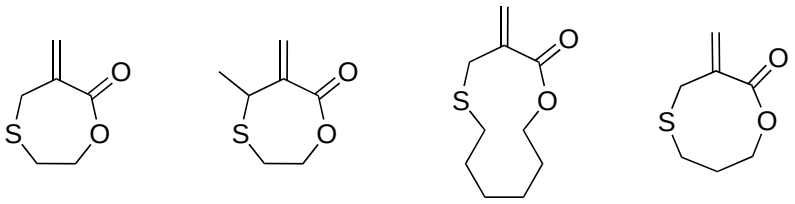


Figure 31. Structures of sulfide cyclic methacrylate monomers.

The polymerization mechanism of sulfide cyclic methacrylate monomers is given on Figure 32. A study focused on the elucidation of the polymerization mechanism showed a slight influence of the ring size on the monomer reactivity. The rate of polymerization of large cyclic monomers was then slightly higher.[80-81] Besides the cross-linking tendency seemed to decrease with an increase of the ring size.

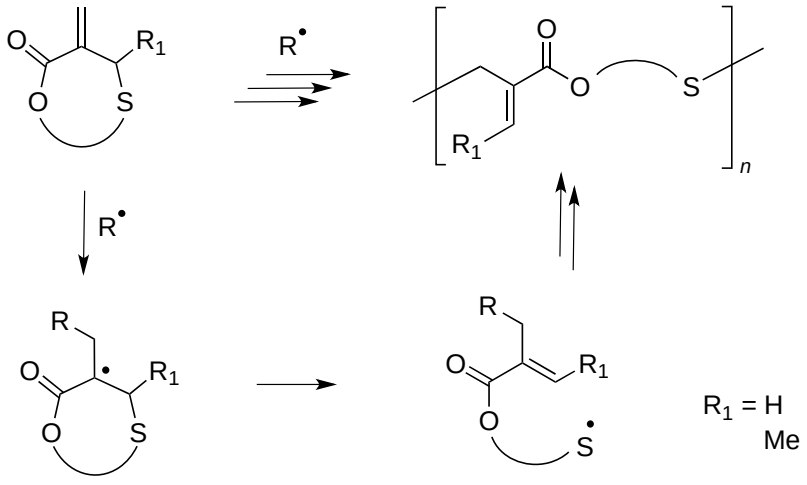
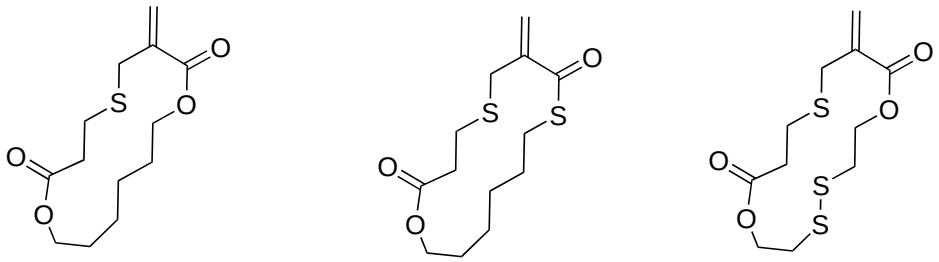


Figure 32. Polymerization mechanism of sulfide cyclic methacrylate monomers.

Hawker and co-workers[82] have then continued this work and extended the study to cyclic monomers with ester, thioester and disulfur functionalities (Figure 33). By a copolymerization approach with methacrylic monomers, copolymers with different modes of degradation were obtained: degradation in alkaline conditions, reductive degradation of disulfide bond (in the presence of hydrazine or tributylphosphine) or degradation of thioester groups with sodium thiomethoxide. The degradation properties are discussed in details in section 7.



SCM5 **SCM6** **SCM7**

Figure 33. Sulfide cyclic methacrylate monomers with ester, thioester and disulfur group.

2.6.3 Cyclic allylic sulfides

Cyclic allylic sulfide monomers presented the advantage of being highly reactive in various radical systems. The rROP of these monomers gives the corresponding polysulfides with a C=C bond in the main chain. The general rROP mechanism of cyclic allylic sulfides is depicted in Figure 34. The first step consisted in the addition of a radical on the exo-methylene function

forming a radical at the β-position of the sulfur atom. The ring-opening reaction of this radical produced a new acyclic allylic sulfide and a thiyl radical. One of the main advantages of cyclic allylic sulfides was the low volume shrinkage when polymerized by rROP.[24]

Rizzardo and co-workers[13] demonstrated that the radical polymerization of **CAS1** and **CAS2** exclusively occurred *via* a ring-opening process (Figure 34). At 70 °C, in solution or in bulk, the kinetics were very fast and could reach 100% conversion with polymers of high molar masses (> 500,000 $g.mol^{-1}$) insoluble in the monomer and in usual solvents (except in pyridine at 90 °C). The easy addition of thiyl radicals onto monomers without hydrogen abstraction (side reaction) gave well-defined and highly crystalline polymers.

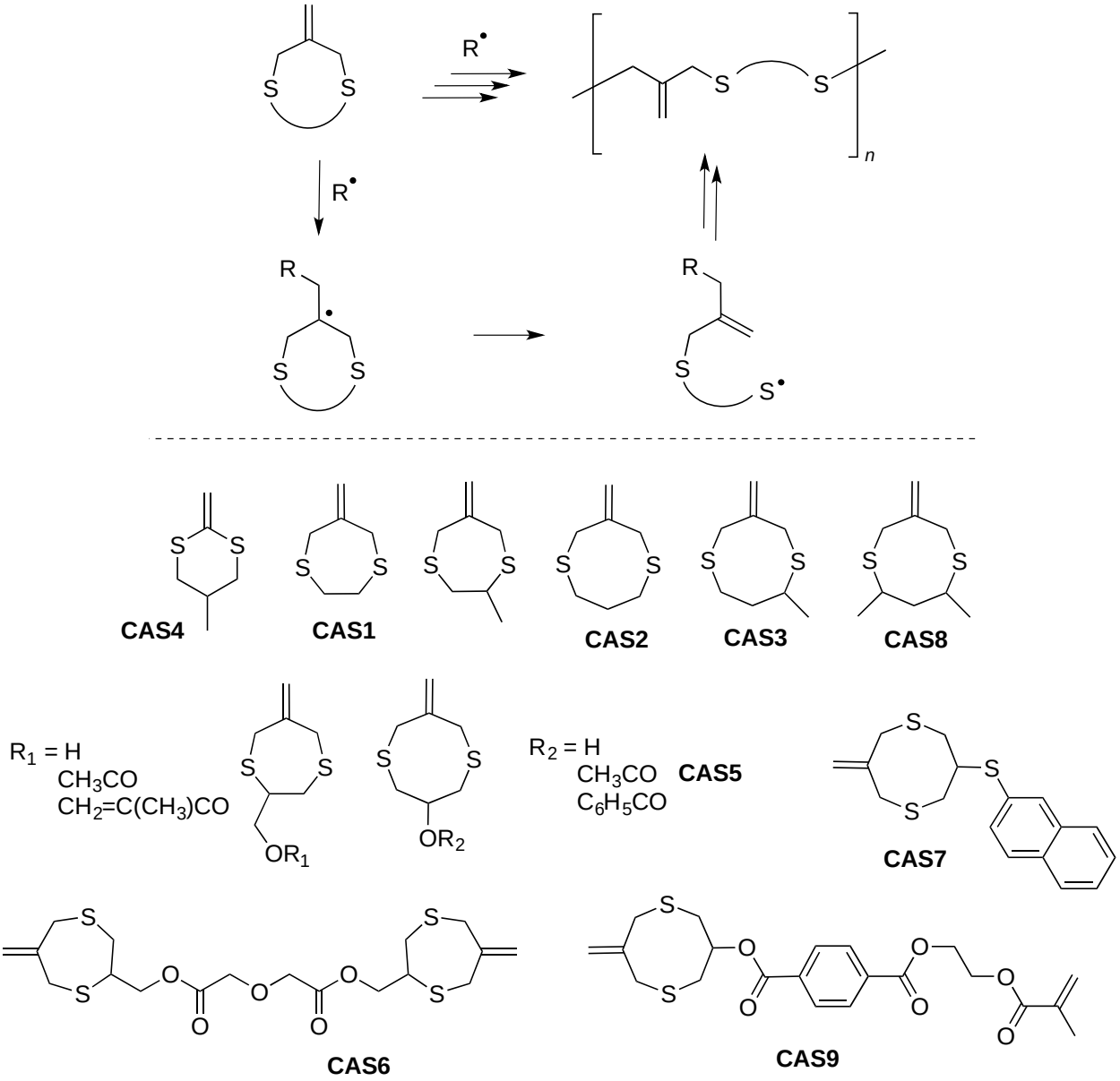


Figure 34. Polymerization mechanism of cyclic allylic sulfide monomers.

Several other articles studying the impact of the monomer structure on the polymer crystallinity confirmed the results obtained by Rizzardo.[83] For example, the polymerization of **CAS3** bearing a methyl group in the α position of one of the sulfur allowed the polymerization to

proceed up to complete conversion leading to high molar masses linear polymers that were readily soluble in common organic solvents. Considering that the ring-opening step may occur at the two different carbon-sulfur bonds, the formed polymer contained consequently a mixture of two structural units that avoids crystallization. It has to be noticed that cyclic monomers with 8-membered ring can be polymerized to higher conversion than monomers with 7-membered ring counterparts whereas monomer **CAS4** with a 6-membered ring did not polymerize, probably because of a smaller distortion energy of the 6-membered ring.[84] The **CAS3** structure was more deeply studied to better understand the polymerization kinetics and the monomer/polymer transfer side reactions that could limit molar masses at high conversion.[85-86] A chain transfer to monomer constant C_M of 55×10^{-4} was determined. This value was relatively high compared to that of other vinyl monomers (C_M in the range of 0.1 to 1.0×10^{-4} for S, MMA, etc.) but rather low compared to other allylic compounds (C_M in the range of 700 to 1600×10^{-4} for allyl acetate and allyl chloride, respectively). This moderate value was assigned to the poor ability of the propagating sulfur radical to abstract hydrogen atoms compared to that of the carbon-centered radicals.[85] In the same study, the authors also determined the chain transfer constant to the polymer ($C_{\mathbf{PCAS3}} = 0.35$). In the case of chain transfer to polymer, the polymerization mechanism was based on an addition-fragmentation process and thus did not produce branching.

Another interesting feature of CAS monomers is their ability to polymerize with a limited influence of air. Goto and Yamada[87] investigated the photopolymerization of **CAS5** in the absence/presence of oxygen initiated by 2 mol% of lucirin TPO-L. The photopolymerization of **CAS5** was faster than the reference and was insensitive to oxygen, unlike 2-ethylhexyl methacrylate that showed roughly 80 % inhibition when oxygen was present (Figure 35).

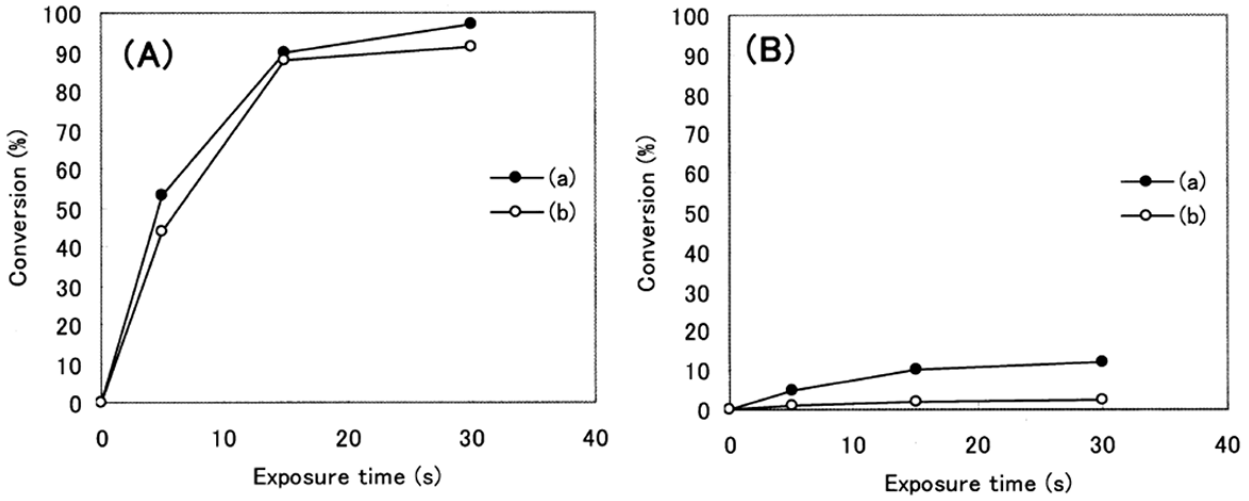


Figure 35. Conversion of monomer versus time plot for (A) **CAS5** and (B) 2-ethylhexyl methacrylate under (a) nitrogen (b) air initiated with 2 mol% of lucirin TPO-L. Reproduced with permission from Ref. [87]. Copyright 2010 The Society of Photopolymer Science and Technology.

The bifunctional cyclic allylic sulfide (**CAS6**, Figure 34) can also be used as a monomer to synthesize cross-linked polymers. Another advantage of polymers obtained from rROP of cyclic allylic sulfide is their high refractive indexes. For instance, **CAS7** that bears a naphtylthio moiety had a refractive index of 1.686 (and presented a volume shrinkage of only 0.02 % when polymerized by rROP) and was successfully used as holographic data storage media (see Section 7.1).[24, 88]

2.7 Monomers with ring-opening driven by aromatization

In addition to the pioneering work of Errede[7] on spiro-di-*o*-xylylene (**AR1**, Figure 3) some other compounds were polymerized *via* a radical ring-opening process using aromatization as the driving force (Figure 36 and Table 7). For example, Bailey and co-workers[68] proved that increasing the temperature and the dilution led to polymerization of **AR2** polymerized through a nearly exclusive ring-opening process. The results were further enhanced by the addition of an aromatic cycle stabilizing the propagating radical (monomer **AR3,** Table 7).

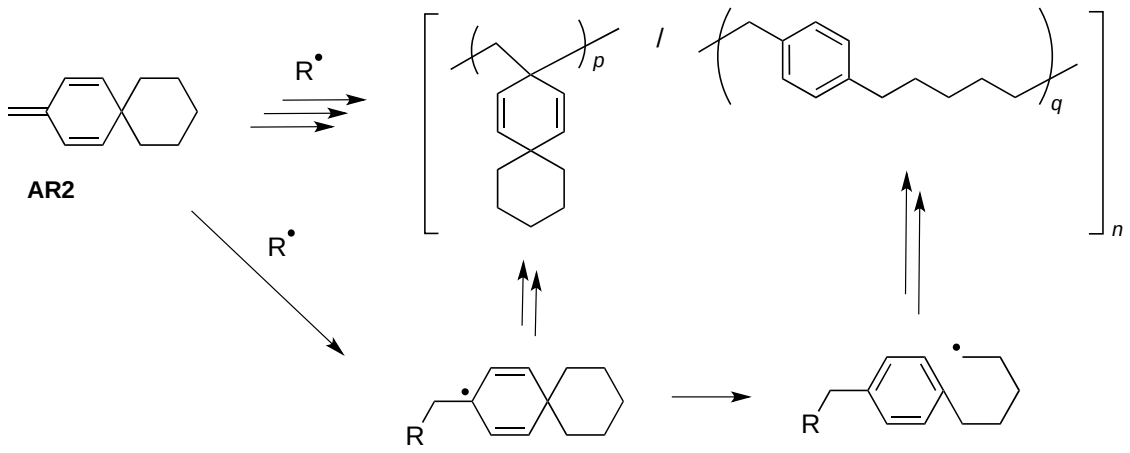
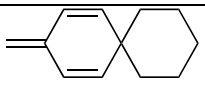
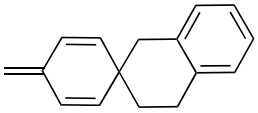


Figure 36. Polymerization mechanism of 3-methylenespiro(5,5)undeca-1,4-diene **AR2**.

Table 7. Polymerization of monomers with aromatization-driven ring-opening mechanism.

Monomer	Initiator, Temperature of polym. (°C)	% of ring-opening
 AR2	BPO, 85	43
	BPO, 100	61-70
	DTBP, 130	79-98
 AR3	BPO, 100	>95

Another particular monomer is **AR4** (Figure 37) that required to be stabilized by triethylenediamine because of its high reactivity. Once in the presence of a radical initiator, reactions of addition followed by rearrangement and cyclopropane ring-opening gave polymers with anthracene moieties in the main chain (Figure 37). The obtained polymers exhibited high thermal stability properties.[74, 89-90]

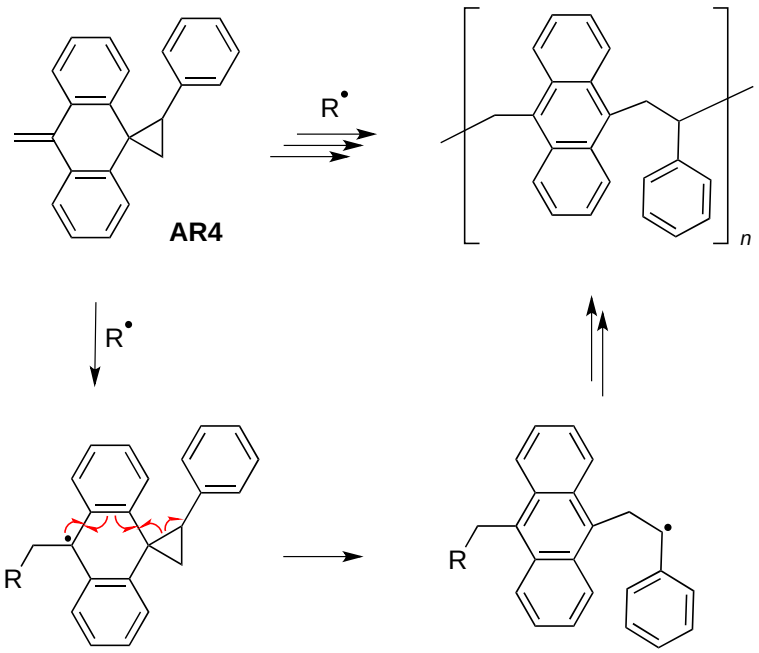


Figure 37. rROP mechanism of cyclopropane with a dihydroantracene moiety (**AR4**).

The same team extended this work to the para bromo and chloro derivatives.[91] After polymerization, optoelectronic groups including diphenylamine, carbazole, and phenothiazine were incorporated on the halostyrene moieties of the polymer by palladium-catalyzed reactions. These polymers presented interesting optoelectronic properties since the UV absorption and

fluorescent spectra of the modified polymers indicated that the characteristic fluorescence resonance energy transfer was present.[91]

Using a similar fragmentation process, the polymerization of the difunctional **AR5** structure at 130 °C with di-*tert*-butylperoxide (DTBP) gave aromatic poly(ketone-ether) after complete aromatization (Figure 38).[68]

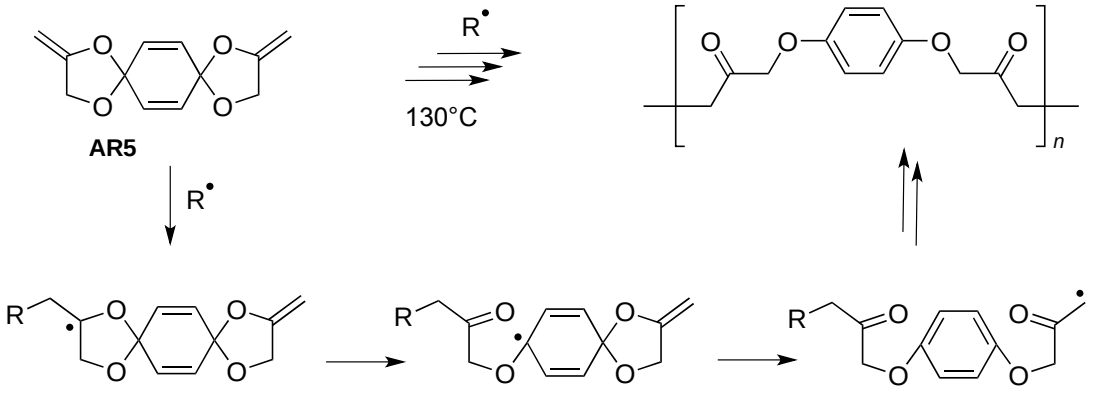


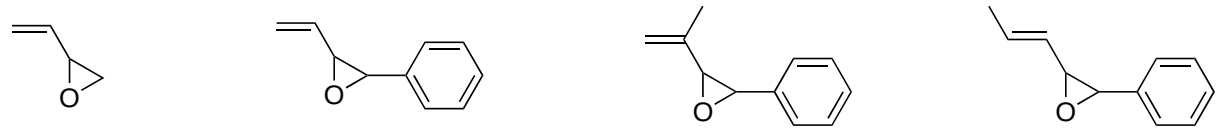
Figure 38. Polymerization mechanism of **AR5**.

2.8 Vinyl oxirane

In 1983, the radical polymerization of vinyl oxiranes was investigated and it was shown that the presence of an aromatic group modified the polymerization mode.[92-93] The radical polymerization of the butadiene monoxide (**VO1**, Figure 39), as a model of vinyl oxirane, involved the opening of the C-O bond followed by the formation of a propagating alkoxyl radical. The high reactivity of this radical prevented high molar masses and high conversion to be obtained. To circumvent this problem, phenylvinyloxiranes **VO2** was prepared and polymerized

via the cleavage of the C-C bond, producing a radical stabilized by the aromatic group and finally gave an unsaturated polyether. At 60 – 75 °C, almost no polymer was obtained whereas at 120 °C, the conversion reached high values. Interestingly, the copolymerization with ethylene was possible at 120 – 155 °C under a pressure of 900 kg/cm^2. The addition of 1 – 3 % of phenyl-vinyloxirane in the polymerization media gave a copolymer with a higher proportion of monomer in the final product. In these conditions, the double bonds on the polymer chains disappeared because of branching/cross-linking reactions.[94] This side and unwanted reaction of cross-linking could nevertheless be avoided by introducing a methyl group on the carbon in α position of the vinyl function (**VO3,** Figure 39) whereas a methyl in β position inhibited the polymerization (**VO4** Figure 39).[95]

a)



VO1 **VO2** **VO3** **VO4**

b)

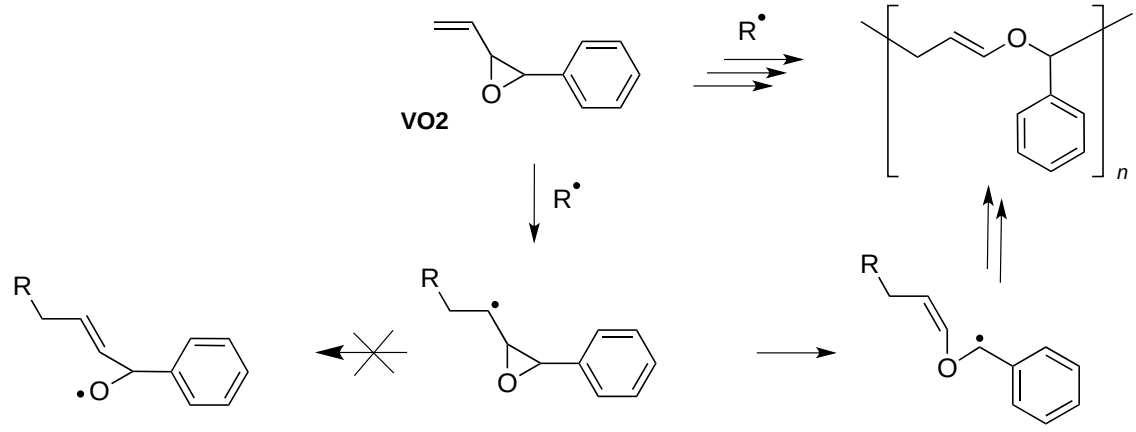


Figure 39. a) Structures of vinyl oxirane monomers. b) Polymerization mechanism of phenyl-vinyloxiranes.

Endo and coworkers[96] studied the influence of different substituents on the aromatic cycle of phenyl-vinyloxiranes derivatives (Figure 40). Whatever the substituent, the polymerization proceeded *via* the same mechanism and, polymers of 1500 – 4000 $g.mol^{-1}$ with a reasonable conversion (30 – 75%) were obtained at 130 °C. Also, **VO5** gave a particular highly cross-linked material.

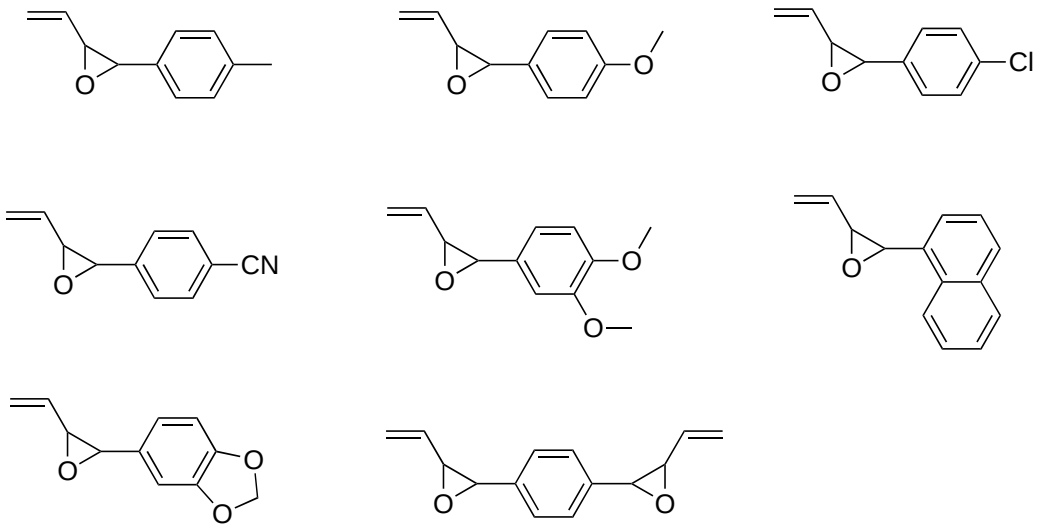


Figure 40. Structure of the main phenyl vinyloxirane monomers studied in the literature.

Endo and coworkers[97] combined vinyl oxirane and cyclohexane moieties to form spirobicyclic **VO6** (Figure 41). After addition of a radical onto the C=C bond, the newly formed radical was transformed into an oxy radical after the ring-opening reaction of the oxirane ring. The successive ring-opening of the six-membered ring was here facilitated by the formation of a benzyl radical.

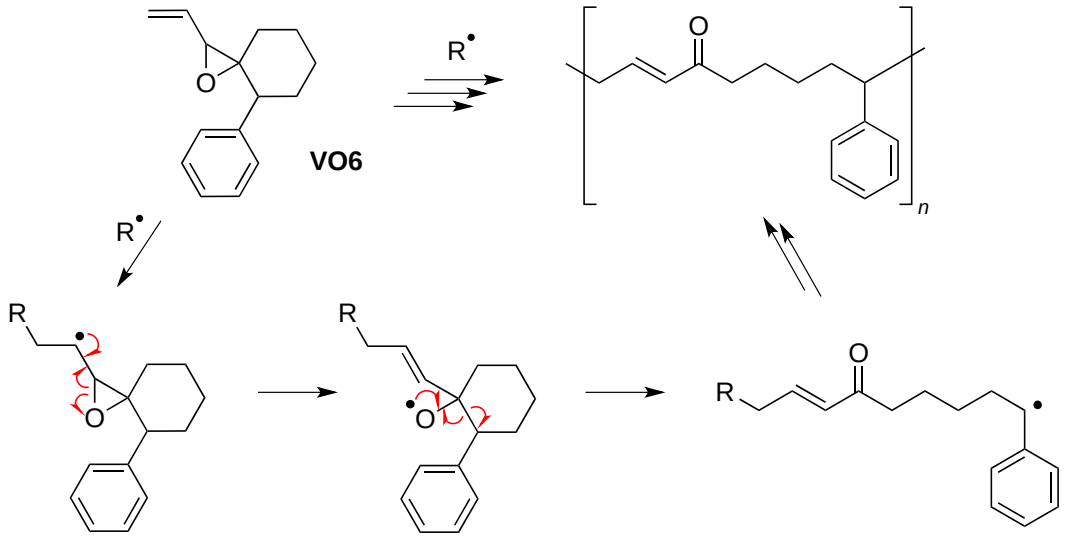


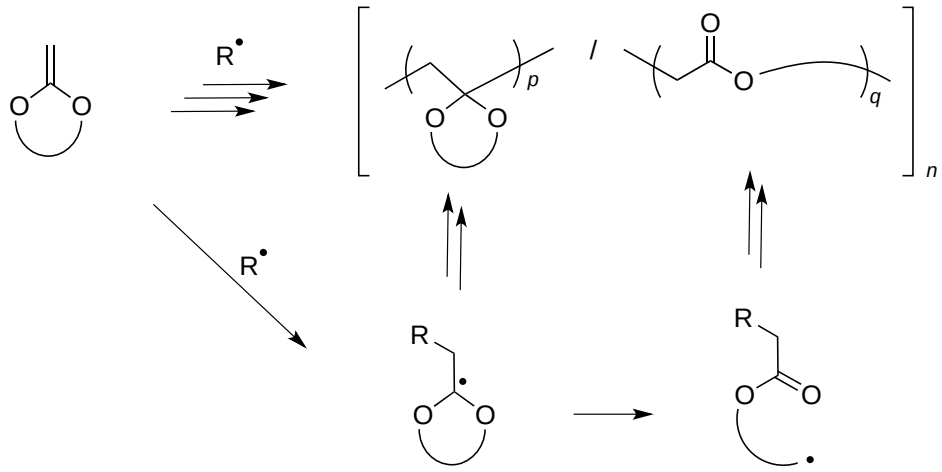
Figure 41. rROP of vinyloxirane with a spirocyclic structure.

2.9 Cyclic Ketene Acetals

Contrary to the majority of monomers described previously, when the polymerization is performed in appropriated conditions, CKAs present the advantage of producing mainly aliphatic polyesters (p = 0, Figure 42), whose structures are similar to those of well-known (bio)degradable polyesters (e.g., PLA, PGA, PCL). The properties of such polyesters and their potential

applications have been already studied and thus the interest to prepare polyester by a radical pathway explained why CKA has been widely studied during the past decades. Secondly, another attractive features of the cyclic ketene acetals is their relatively ease of synthesis compared to other monomers used in radical ring-opening polymerization (see subsection 4.1).

a)



b)

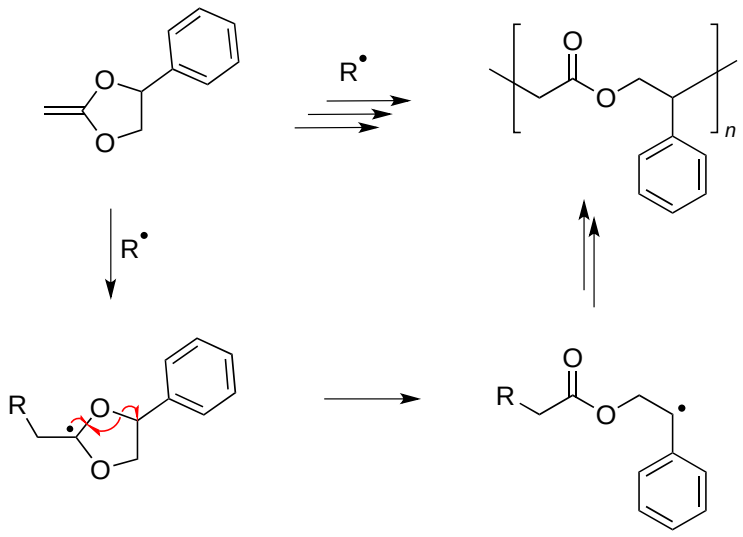


Figure 42. a) rROP mechanism of cyclic ketene acetals (CKA). b) rROP of the MPDO/MPDL **CKA11**.

The development of CKA monomers has been the focus of intensive research (Figure 43), even though their rROP is usually limited in terms of molar masses (M_n typically below 2.0×10^4 $g.mol^{-1}$).[24] The general mechanism of CKA rROP is depicted in Figure 42a. It includes both a ring-opening process and a vinyl polymerization step, even if the first one is usually predominant. In Figure 42b is presented the mechanism involved in the polyester synthesis from a typical CKA monomer, the 2-methylene-4-phenyl-1,3-dioxolane called (MPDO/MPDL **CKA11**). The exo-methylene function plays the role of radical acceptor and the ring-opening reaction is accompanied by the formation of an ester function that is thermodynamically more stable than the original cyclic acetal. The ring-opening reaction is in addition favored by the formation of a radical stabilized by the pendant phenyl group.

The different CKA monomers that have been studied so far and tested in rROP are gathered in Figure 43. The efficiency of the ring-opening process and the competition with the vinyl polymerization of the C=C bond is one the main challenge regarding their use. A lot of studies have been devoted to the study, the synthesis and the polymerization of CKA monomers and the main conclusions are described in the section 4.

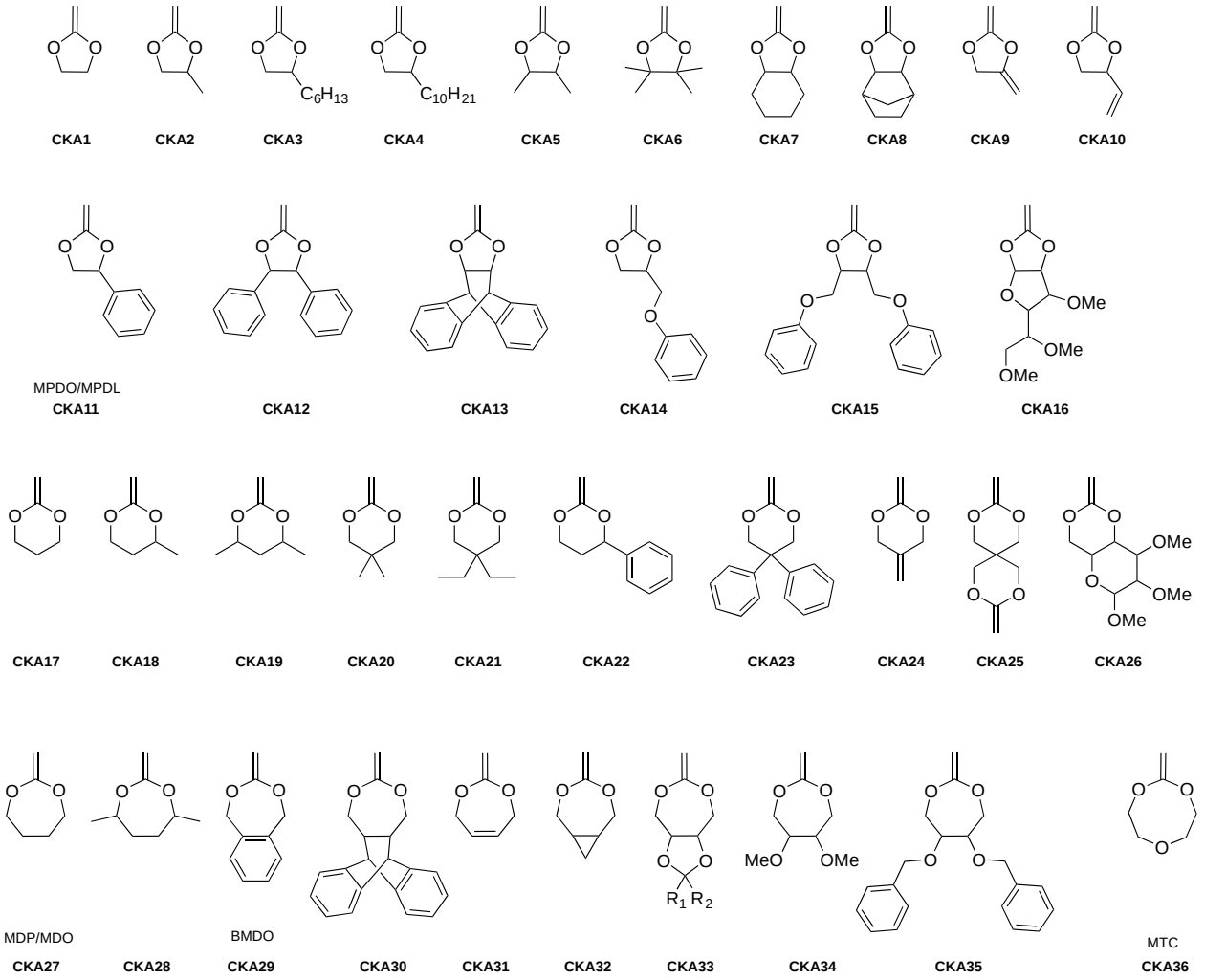


Figure 43. Library of the various CKA monomers.

2.10 Miscellaneous

Among the various structures that have been developed to perform radical ring-opening polymerization, few structures cannot be classified in the various families presented in Figure 5. The benzocyclobutenes **M1** for example do not have formally a double bond but is the precursor

of *o*-quinodimethane intermediate that undergo radical polymerization to produce poly(*o*-xylylene) (Figure 44).[98-99] The driving force of the reaction is the relief of the steric strain of the cyclobutane ring combined with the aromatization of the resulting compound. The influence of various electron donating[99] and withdrawing[100] groups on the cyclobutene ring was investigated. When an hydroxyl group was inserted on the cyclobutene ring, the resulting polymer could be treated with *p*-toluenesulfonic acid (10%) to give pure poly(*o*-phenylenevinylene). The polymerization of the cyano derivative was also performed in the presence of TEMPO to control the polymerization.[101] The authors claimed that diblock copolymers were formed after a re-initiation of the polymerization in presence of styrene.

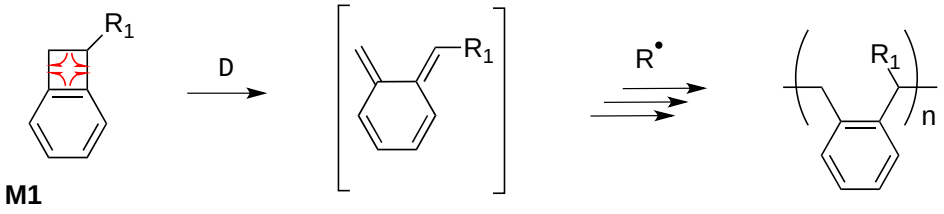


Figure 44. Polymerization of benzocyclobutene derivatives.

The bicyclobutane derivatives **M2** are also other interesting monomers without double bond that could undergo rROP. The ring-opening was due to the high steric strain induced by the presence of the two cumulated cyclopropane rings (Figure 45).[102-105] The obtained polymers had very high T_g due to the presence of rigid cyclobutane rings in the polymer backbone. The copolymerization of these monomers with common vinyl ones was also studied to increase the T_g values of the resulting materials.[106]

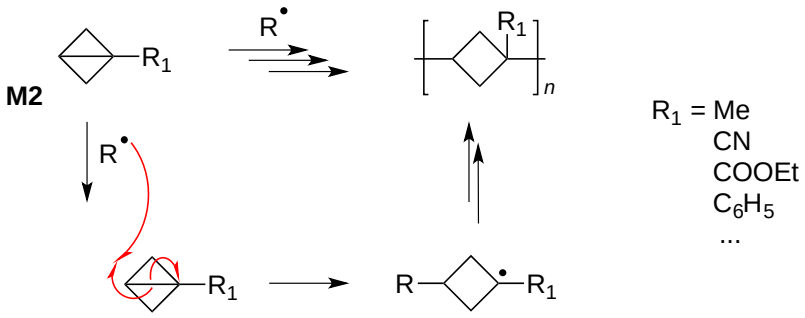


Figure 45. Polymerization of bicyclobutane derivatives.

Hall Jr. and coworkers[107] extended this work to ATRP and thus succeeded to prepare a well-defined polymer with cyclobutane ring units in the chains by controlled/living radical ring-opening polymerization.

β-propiolactone (βPL) is another monomer that could be polymerized by a radical pathway without having a C=C bond.[108] The first polymerizations were performed in 1965 but the radical mechanism[109] was established later. Recently Agarwal and coworkers[110] showed that the bulk copolymerization of styrene and β-propiolactone led to grafted copolymer due to the high difference of reactivity between the vinyl and the cyclic monomers. During the polymerization, polystyrene chains were first formed. The poly(βPL) macroradical that was created in a second time can abstract hydrogen from the PS backbone and thus created a stabilized benzyl macroradical. After recombination with another poly(βPL) macroradical, grafted copolymer was then obtained (Figure 46).

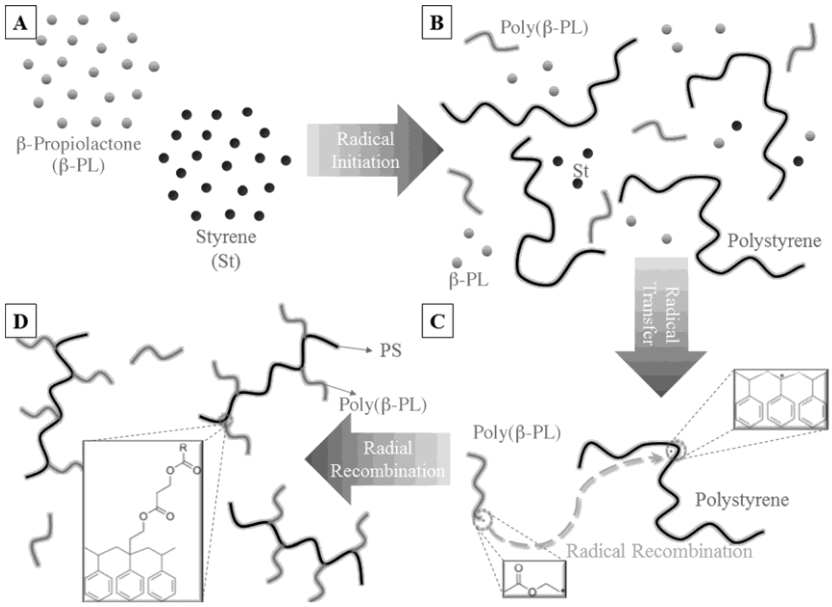


Figure 46. Preparation of polystyrene grafted polyester by copolymerization of styrene and β-propiolactone. Reproduced with permission from Ref. [110] Copyright 2014 John Wiley and Sons.

Calvin and coworkers[111] reported in the 50s the polymerization of cyclic disulfide **M3** under UV irradiation to afford the resulting polysulfide. Many years later, Endo and coworkers[112] tested the polymerization of a new **M3** derivative, the lipoamide **M4** (Figure 47). This compound did not lead to homopolymerization but could be incorporated in copolymerization with common vinyl monomers by a chain transfer mechanism. Using aryl disulfide, Ding and Hay[113] prepared polyphenylene sufides.

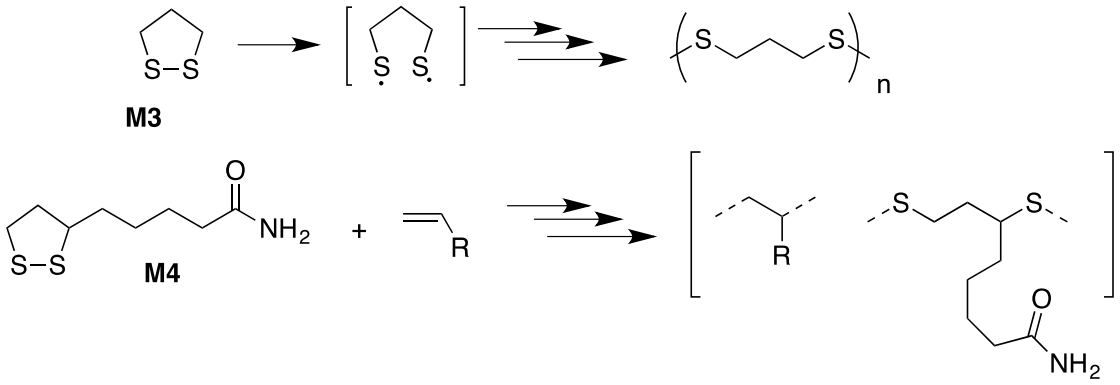


Figure 47. Polymerization of cyclic disulfides **M3** and **M4**.

To conclude, Naka and Chujo[114] reported the copolymerization of a cyclic diarsine compound in the presence of styrene to lead to a copolymer containing arsenic atoms in the backbone. Radical copolymerization with MMA also provided the corresponding copolymer in the presence of AIBN, whereas copolymerization with vinyl acetate yielded no polymeric material. This study was latter extended to the preparation of poly(vinylene-arsine) by the copolymerization of cyclic organoarsenic compounds with acetylenic compounds using AIBN as a radical initiator or irradiation with xenon lamp at room temperature.[115]

3. Vinyl cyclopropane

3.1 General considerations

Vinyl cyclopropanes VCPs have been widely studied in the literature as important synthetic intermediates in organic reactions.[116] They are also found in various natural products such as steroids and anti-inflammatory agent.[117-118] A large number of studies devoted to their synthesis and their reactivity have therefore been reported. Their interest for polymerization has emerged due to the ring opening of the strain cyclopropyl group that is supposed to lead to low shrinkage materials. From the pioneering study[31] in 1949 and the elucidation of the polymer structure in 1965,[8-9] most of the studies were performed in the 90s and have been reviewed in details by Moszner and coworkers.[29] Since then, new compounds have been developed in particular for photo-polymerization purposes.

3.2 Synthesis

Different synthetic routes have to be reported for the preparation of VCPs. The model vinyl cyclopropane **VCP1** is for example prepared by a 6-step procedure with an overall yield of 19%.[119] The main method to prepare VCP derivatives is the reaction of trans-1,4-dihalo-but-2-enes with methylidene functionalized with two electron withdrawing groups such as dimethyl malonate.[120] The reaction required two equivalents of bases (e.g., sodium hydride, sodium ethanolate, etc.) and yielded the desired compounds with 60-90 % yields (Figure 48).

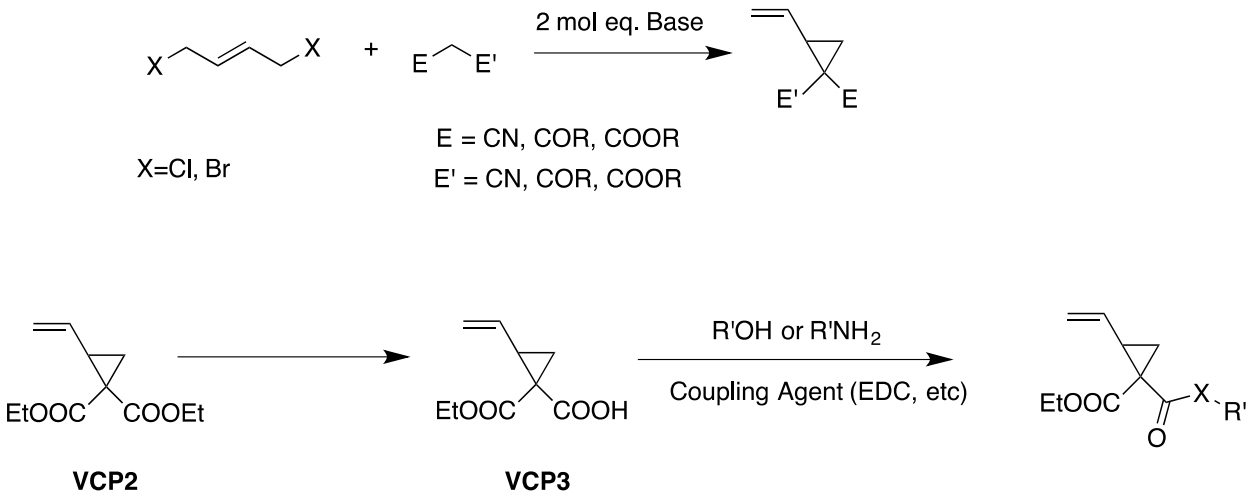


Figure 48. Synthesis of VCP derivatives and example of the synthesis of 1,1diethoxycarbonyl-2-vinyl cyclopropane **VCP2** and its post-functionalization to give 1-ethoxy carbonyl-2-vinyl cyclopropane-1-carboxylic acid **VCP3** as intermediate.

A very interesting feature of VCP is that the vinyl cyclopropane functionality of the 1,1-diethoxycarbonyl-2-vinyl cyclopropane **VCP2** is very stable under both reduction and hydrolysis conditions. This compound was therefore a versatile starting point to prepare a large range of functionalized VCP useful in polymerization (Figure 48 and Table 8 for the various **VCP** structures). Another method consisted in the addition of carbenes onto dienes.[121] Chloroform was often used as carbene precursor to give the 1,1-dichloro-2-vinyl cyclopropane **VCP4**[122] that could be further derivatized into other functionalized VCP monomers (Figure 49).

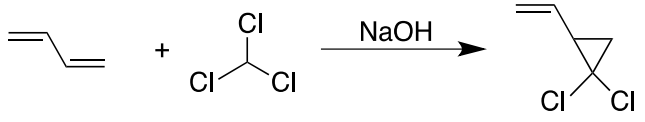


Figure 49. Synthesis of 1,1-dichloro-2-vinyl cyclopropane **VCP4**.

In 2003, 2-cyclopropylacrylates were reported as more efficient VCP derivatives in copolymerization with methacrylates.[123] Such compounds were prepared by a multi-step procedure (Figure 50). The cyclopropanation was performed using the protocol of Shi[124] and the resulting hydroxyl acrylate was oxidized with manganese oxide. The last step consisted in the Wittig reaction yielding the 2-cyclopropylacrylate.

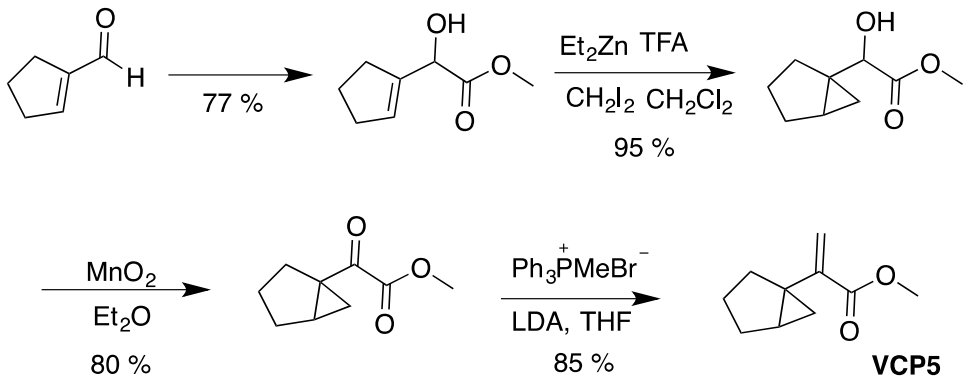


Figure 50. Preparation of Methyl 2-(Bicyclo[3.1.0]hex-1-yl)acrylate **VCP5**.

3.3 Polymerization of VCP derivatives: influence of the structure

The first studies on the polymerization of VCP were performed under UV irradiation in presence of benzoyl peroxide.[31] Nevertheless, cationic polymerization of these derivatives occurring by a 1,2-vinyl addition was mainly reported in the following 20 years.[125] Conversely to

cationic polymerization, the polymerization of **VP1** in the presence of AIBN or di-*tert*-butyl peroxide led to polymers with 1,5 ring-opened units.[8-9]

Electron withdrawing groups linked to the cyclopropane moiety increased both the radical polymerizability and also the ring-opening ability. For instance, the mono-substituted **VPC6** and **VPC7** led to rubber-like high molar mass poly(4-carboxypentenamer)[126] and poly(4-carboxamidopentenamer)[127] respectively. Unlike **VPC6**, the introduction of a phenyl group in position 1, such as 1-phenyl-2-vinylcyclopropane decreased the radical polymerizability[128-129] since only low molar masses were obtained (< 2000 $g.mol^{-1}$) even after 24h at 180 °C.[128] According to the authors,[128] the weak reactivity of 1-phenyl-2-vinylcyclopropane came from side reactions like hydrogen abstraction from the allylic position of the monomer.

Some of the most studied VCPs are the di-substituted derivatives, likely due to their ease of synthesis. 1,1-Dichloro and dibromo vinyl cyclopropane **VPC4** and **8** were then studied at 40, 60 and 120 °C using adapted radical initiators.[130] The first analyses confirmed a complete 1,5 ring-opening polymerization. A few years later, a careful analysis by ^{1}H and ^{13}C NMR results showed that the radical polymerization of 1,1-dichloro vinyl cyclopropane **VP4** yielded a polymer having various repeat units, i.e., ring-opened **A** (60-40%) and **B** (20 %) combined with two cyclobutane units (5-35%) deriving from the intramolecular cyclization of the intermediate radical (Figure 51). The occurrence of cyclization and thus the presence of cyclobutane units increased with increasing temperature.

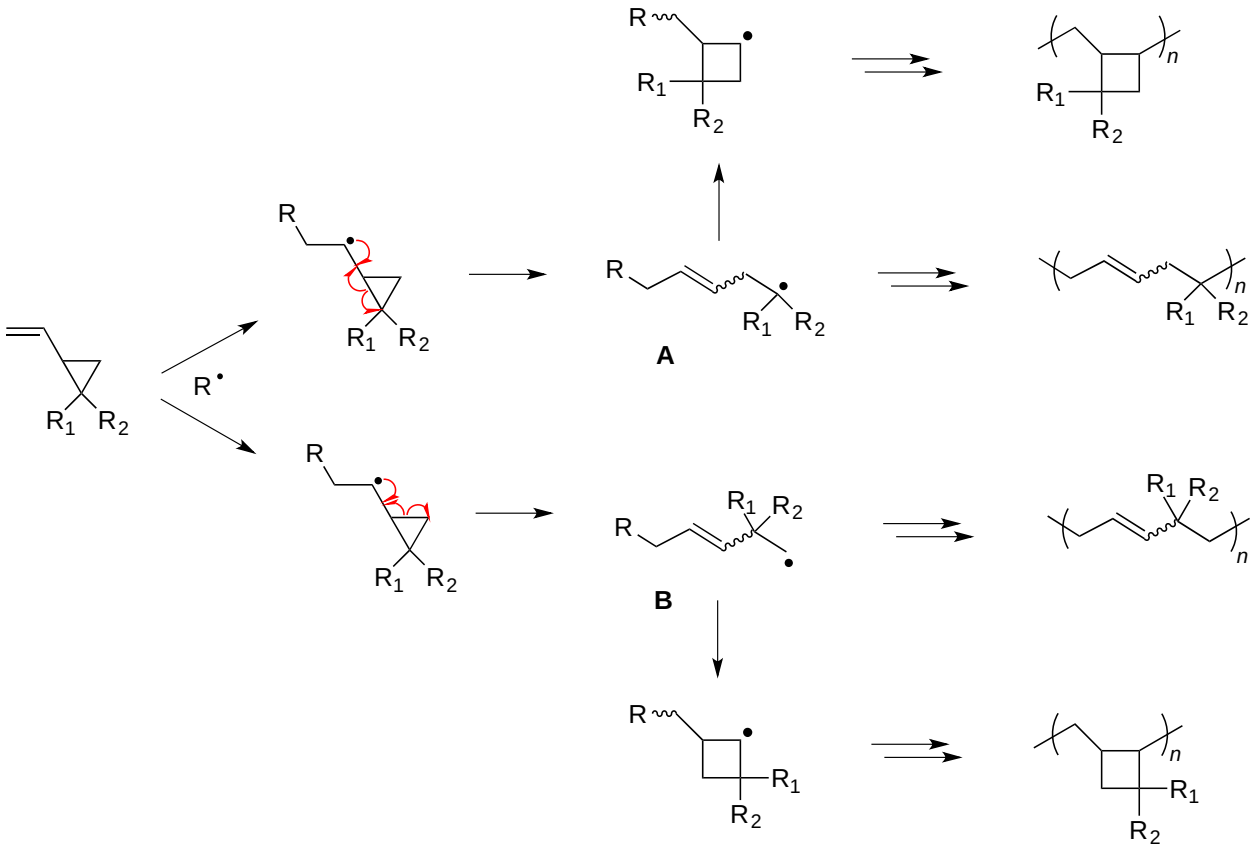


Figure 51. The different polymer repeat units that are formed during the rROP of 1,1disubstitued-2-vinyl cyclopropane.

The most used and studied VCP is the 1,1-diethoxycarbonyl-2-vinyl cyclopropane **VCP2**, due its easy synthesis from the malonate precursor and its possible further functionalization (see Figure 48). Similarly to dihalogeno derivatives, the first studies stated about the complete 1,5 ring-opening but a further characterization of the resulted polymer concluded also to the existence of both 1,5 ring-opened unit and cyclobutane moieties coming from the intramolecular cyclization (Figure 51).[131] Due to the strong radical stabilization brought by the two ester groups, the form B is not present in the case of **VPC2** and the ratio between 1,5 and cyclobutane units is

close to 0.8 for a thermal polymerization at 60 °C. Sato and coworkers[132] studied by ESR the polymerization of **VCP9** at 60 °C in benzene. They observed ESR signals (a doublet (22 G) of 1:2:1 triplets (40 G) further split into doublets (5 G)) that could be attributed to cyclobutyl radicals (Figure 52). The signal of the 1,5 adduct is more difficult to observe since it is hidden in the broad central peak. They observed no change of the spectrum both in shape or in intensity during experiment, showing that an equilibrium was reached in these conditions.

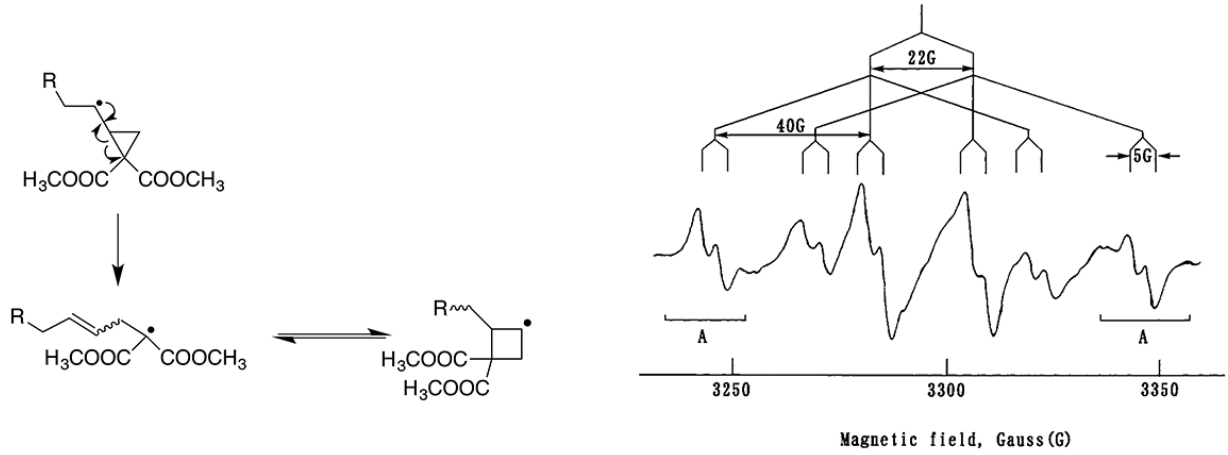


Figure 52. ESR spectrum observed during the polymerization of **VCP9** with MAIB at 60 °C in benzene. [**VPC9**] = 2.33 M; [MAIB] = 0.10 M; the modulation amplitude of 3.2 G was employed. Reproduced with permission from Ref. [132]. Copyright 2001 American Chemical Society.

From these results, a propagation rate constant of 71.0 $L.mol^{-1}.s^{-1}$ and a termination rate constant of 5.8×10^4 $L.mol^{-1}.s^{-1}$ were determined at 60 °C. Even though these values were very low compared to those of conventional vinyl monomers (e.g., S, MMA, etc.), the $k_p/k_t^{1/2}$ value was high thus indicating a good polymerizability.

It was recently found that 1,1 disubstituted-2-vinyl cyclopropane derivatives such as **VCP2** caused a relatively high volume shrinkage for a cyclic monomer that undergoes radical ring opening.[131] This characteristic was assigned to the formation of cyclobutane moieties.[131] To avoid such a drawback, Sugiyama[133-134] prepared **VCP2** derivatives bearing phenoxycarbonyl and adamantyloxycarbonyl instead of ethyl ester that led to quantitative 1,5 adduct units and also to volume expansion. Another approach was explored by Agarwal and coworkers[135] who showed that optimized photo-polymerization conditions (ternary photoinitiator system), led to less than 6% of volume shrinkage. The temperature dependence of such value was thus highlighted (Figure 53). The system was recently improved by preparing VCP derivatives bearing a hydrogen bond forming amide in replacement of one of the ester group of **VCP2**.[136] The supra molecular organization induced by the H-bonding led to an increased rate of photo-polymerization with nearly complete conversion in less than 2 min (see subsection 7.1 for more details).

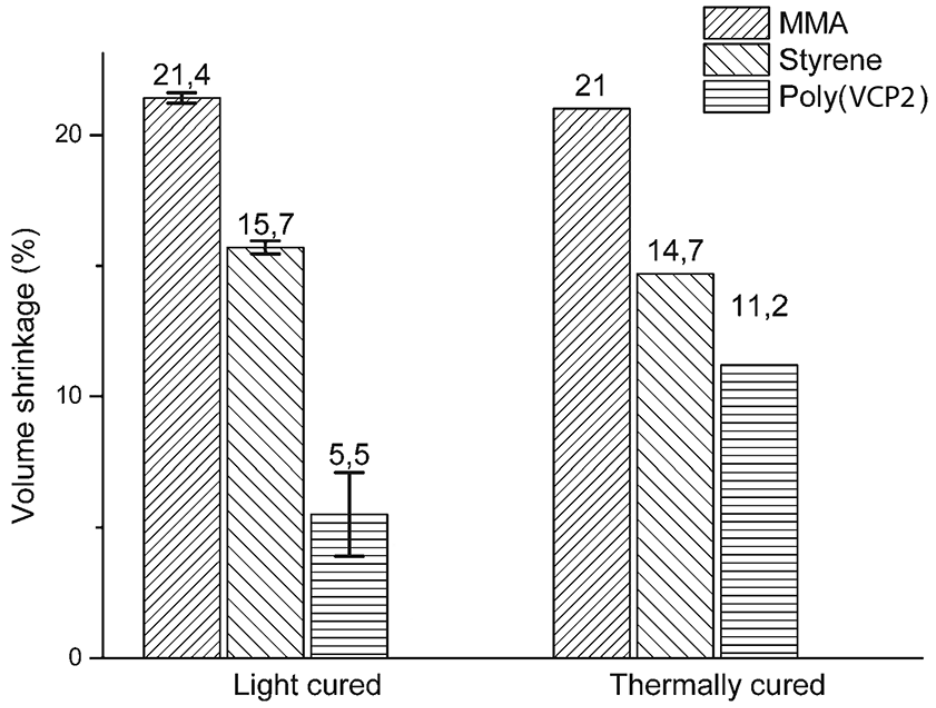


Figure 53. Comparison of volume shrinkages of MMA, styrene and poly(**VCP2**) depending on the polymerization method (light curing at 25 °C with camphorquinone and ethyl-4-dimethylamino-benzoate (EDMAB) as initiators; thermal curing with AIBN at 70 °C). Reproduced with permission from ref. [135]. 2015 Published by the Royal Society of Chemistry.

Compared to methacrylate derivatives, 1,1 diethoxycarbonyl-2-vinyl cyclopropane was less reactive, limiting its application. The introduction of stabilizing groups on vinyl moieties was expected to increase the polymerization rate. By combining styrene and cyclopropane moieties, the monomer **VCP10** showed efficient radical ring-opening.[137] The styrene moiety acted as a radical-acceptor and the formed radical was stabilized by the phenyl group. In particular, the styryl moiety in the monomer trapped immediately the highly reactive radical and suppressed any side termination and/or transfer reactions (Figure 54).

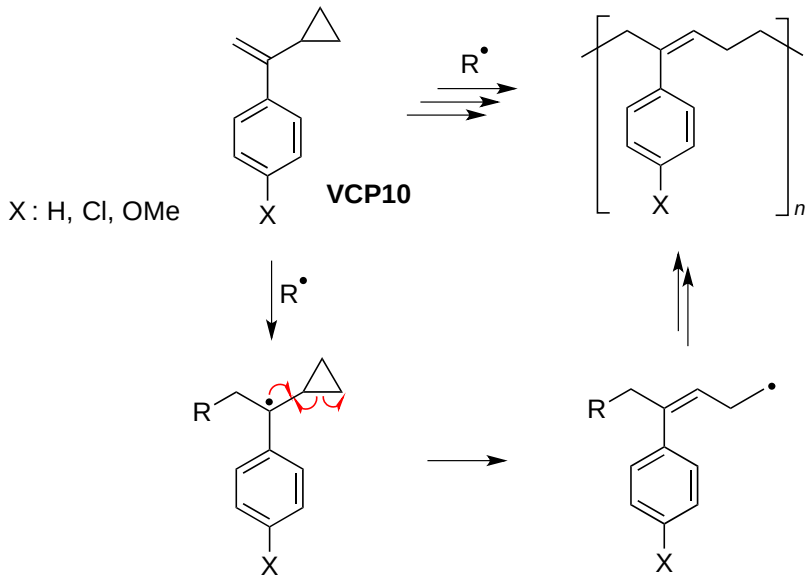
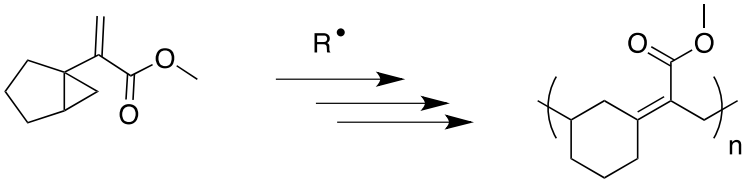


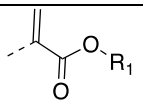
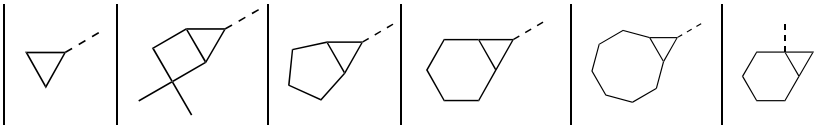
Figure 54. rROP of (1-phenyl)ethenyl-cyclopropane **VCP10**.

The introduction of an ester group instead of the aromatic ring was reported by the group of Moszner.[123, 138-139] through the synthesis of a broad library of structures. Among them, the bicyclic 2-cyclopropylacrylates **VPC5** (methyl 2-(bicyclo[3.1.0]hex-1-yl)acrylate) showed both improved polymerization rate, statistical incorporation with MMA derivatives and high T_g for the resulting polymer (Figure 55). Indeed the formation of an unstrained cyclohexane ring from a highly strained bicyclo[3.1.0] hexane explained both the high reactivity of the monomer and the high T_g of the polymer. T_g above 70 °C is important for the use of such monomers in dental filling composites to prevent the deterioration of the mechanical properties in oral conditions.



a)

b)

Monomer	EtOOC COOEt	 

		R1 =	Me	Et	Me	Me	Et	Me
Conversion (%)[a]	94		71	37	99	98	2	100
x_{VCP}:x_{MMA}[b]	1:15		1:5	-	1:1.4	-	-	1:0.9
T_g (°C)	40		98	46	57	93	-	90

[a] Polymerization of bicyclic cyclopropyl-acrylate (2.0 mol.L^{-1}) initiated with AIBN (2 mol%) in chlorobenzene at 65 °C for 15 h. [b] Composition of copolymers prepared by the copolymerization of VCP (1.0 mol.L^{-1}) and MMA (1.0 mol.L^{-1}) initiated with AIBN (2 mol%) in chlorobenzene at 65 °C for 2 hours.

Figure 55. a) Radical ring-opening polymerization of 2-cyclopropylacrylates derivatives. b) Influence of the monomer structure on the copolymerization results (conversion, monomer incorporation and T_g of the obtained materials) with MMA.

Endo and coworkers[140] prepared various VCP derivatives bearing trimethylsiloxy moieties (Figure 56) for the preparation of poly(silyl enol ether)s. Such polymer chains were reactive since this functionality could be easily hydrolyzed to obtain polyketone or reacted with an electrophile such as benzaldehyde (Figure 56). Similarly, poly(vinyl silane)[141] and poly(allyl silane)[142] from

VP12 and **VPC13** were prepared and were transformed into polymers bearing endo and exo methylene functions, respectively.

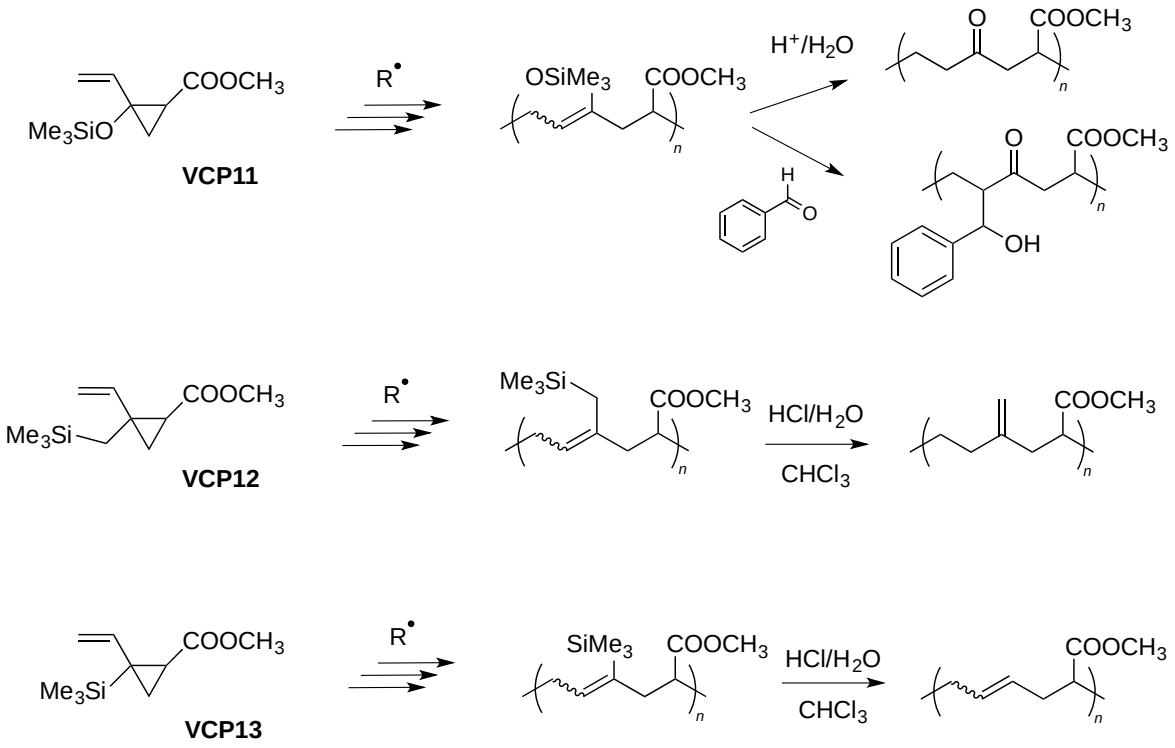


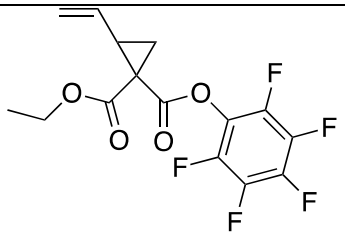
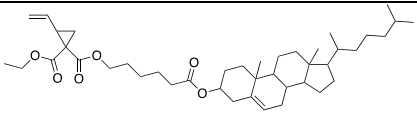
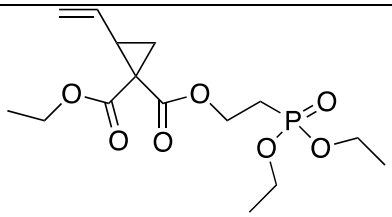
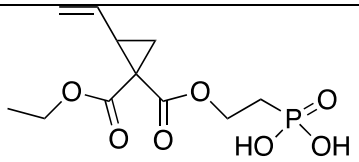
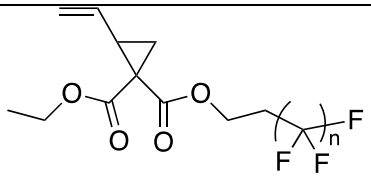
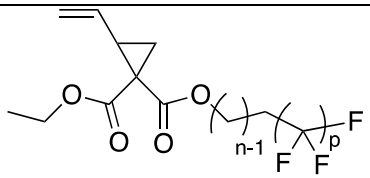
Figure 56. rROP of VCP derivatives bearing silyl moieties.

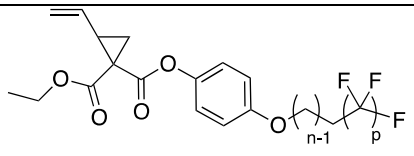
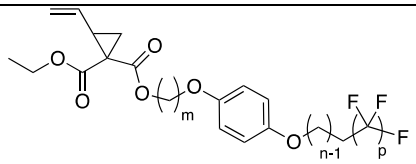
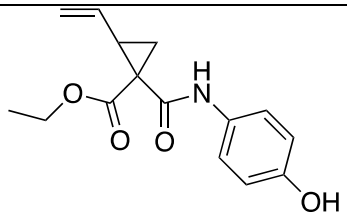
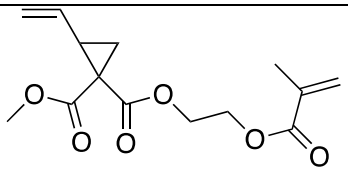
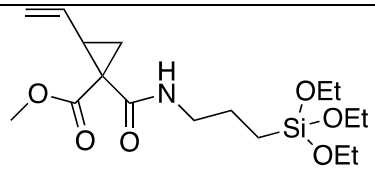
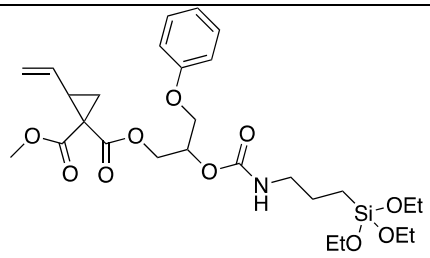
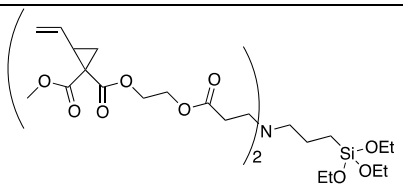
3.4 Polymerization of vinyl cyclopropane derivatives: advanced macromolecular architectures

Considering the ease of synthesis of polymers by rROP of vinyl cyclopropane, this functionality was used to prepare a broad range of advanced macromolecular architectures and cross-linked materials. The main interest of **VCP2** is its ease of preparation from non-expensive

precursors combined with the possibility to prepare the **VCP3** derivative by hydrolysis (the latter compound can be functionalized by numerous compounds bearing either an alcohol or amine function). In Table 8 are gathered all VCP derivatives prepared using this approach.

Table 8. Various functionalized VCP derivatives.

Structure	Reference	Structure	Reference
 **VCP14**	143	 **VCP15**	144
 **VCP16**	145	 **VCP17**	145
 **VCP18**	146 147	 **VCP19**	148

 **VCP20**	148	 **VCP21**	148
 **VCP22**	149	 **VCP23**	150
 **VCP24**	151	 **VCP25**	151
 **VCP26**	151		

Fluorinated VCPs were prepared to obtain liquid crystalline polymers. Such polymers were able to self-organize at the surface of a substrate and to generate low surface energy

products (e.g., low wettability, low adhesion and low friction coefficient).[147-148] The VCP bearing a vinyl phosphonic group was prepared for dental applications to introduce acid groups able to etch dental hard tissue.[145] Theato and coworkers[143] recently combined the VCP polymerization and the pentafluorophenyl ester chemistry (PFP) to prepare a polymer backbone was easily post-functionalized with various aliphatic amines. The resulting polymers exhibited very interesting upper critical solution temperature (UCST) in ethanol and/or water/ethanol mixtures.[143]

An interesting feature of VCP derivatives is their tolerance to water, acid and base, conversely to CKA derivatives for instance. This led Ritter and coworkers[152] to perform the polymerization of VCP in water-based systems. Considering the majority of VCP derivatives were not soluble in water, random methylated β-cyclodextrins (RAMEB) were used as host to solubilize the complex in water, followed by the polymerization at 65 °C using a water-soluble azo initiator. A similar approach was also used to perform the polymerization of macromomers based on poly(*N*-isopropyl acrylamide) end-capped with a VCP functionality (Figure 57).[153]

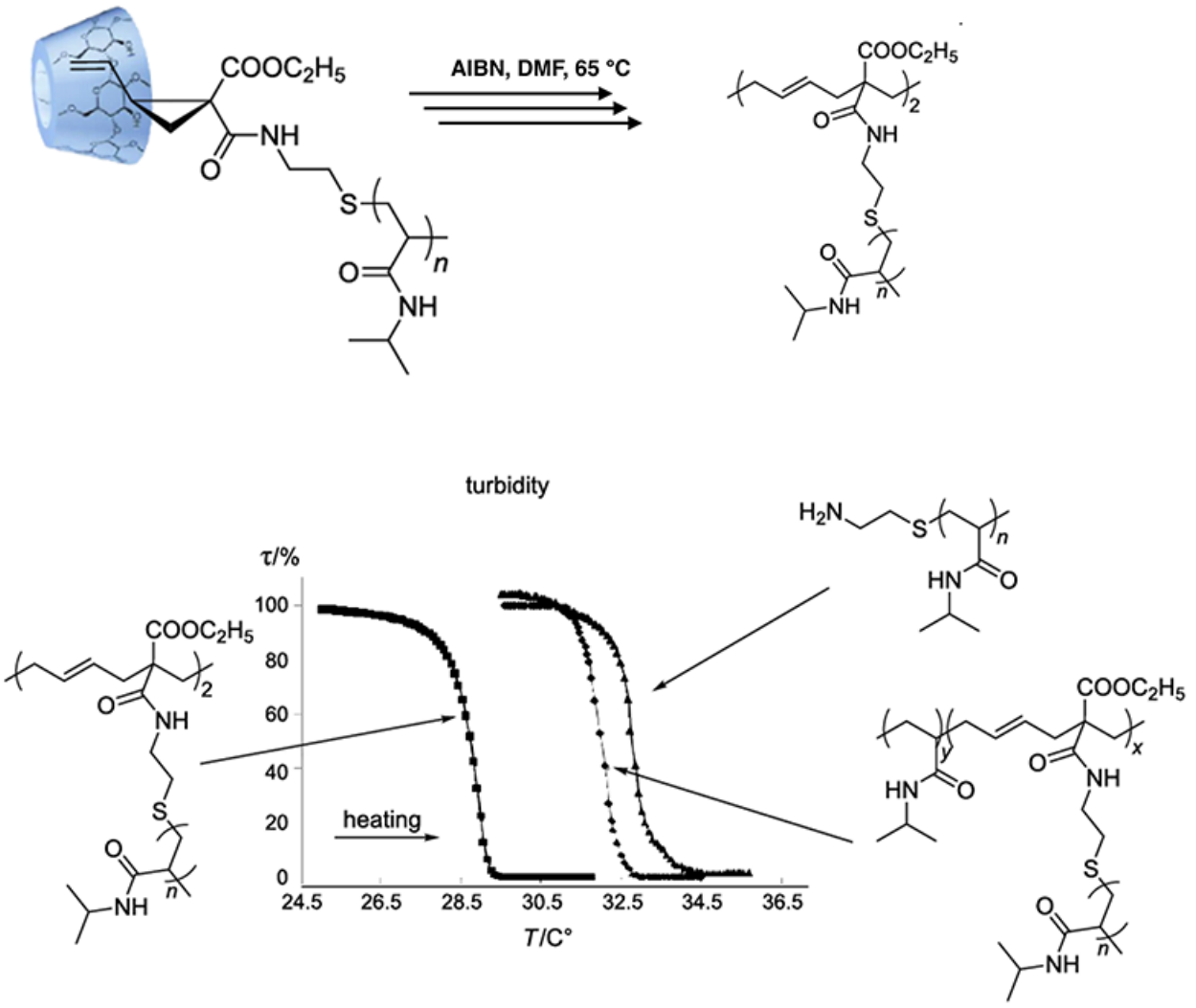


Figure 57. Polymerization of a PNIPAAm-based macromonomer and optical transmittance of aqueous solutions (c = 20 mg/mL) of the resulting polymer as well as PNIPAAm reference during heating, Reproduced with permission from ref. [153] 2012 Published by Beilstein Institute.

Another complex macromolecular architecture has also been prepared using the combination of random methylated β-cyclodextrins (RAMEB) and VCP derivatives. The phenolic function of **VCP22** in a host-guest complex with RAMEB was polymerized in water

using oxido-reductase horseradish peroxidase (HRP) as catalyst.[149] Once the phenylene backbone was prepared, the polymers were cross-linked in THF using AIBN as initiator.

Moszner and coworkers[150] prepared a hybrid VCP derivative linking the 2-vinyl cyclopronane moiety to a methacrylate group (**VCP23** in Table 8). The polymerization of **VPC23** in chlorobenzene at 65 °C in dilute conditions (0.5 $mol.L^{-1}$) led to a polymethacrylate backbone with pendant VCP moieties. After precipitation, the polymer was dissolved again and cross-linked in a second step using AIBN. In bulk the polymerization resulted in transparent solid materials, which were insoluble in common organic solvents, confirming the cross-linking due to the simultaneous polymerization of the two groups.

Conversely to these studies in which cross-linking was performed by two distinct groups, many bi- to tetra-functionalized VCP were synthesized by esterification of 1-methoxy carbonyl-2-vinyl cyclopropane-1-carboxylic acid with diols to tetraols (ethylene glycol, 1,4-cyclohexanediol, resorcinol, 1,1,1-trimethylolpropane, pentaerythritol, etc).[154-155] The advantage of these multi-functional structures was related to an enhanced rate of polymerization, improved mechanical properties and good solvent resistance compared to the mono-functional VCP. All these compounds led in highly transparent solid products, insoluble in common organic solvents. Among the various di-functional structures, the resorcinol-based ones were interesting due to the highest hardness of the resulting materials that came from the presence of a highly rigid monomer structure. Recently Endo and coworkers[156] prepared a di-functional VCP that incorporated the rigid and bulky adamantane moiety **VCP27** and whose mono-functional VCP polymerization presented volume expansion instead of shrinkage (Figure 58a). The network that was then

obtained presented volume expansion and improved thermal stability due to the adamantane moieties. Agarwal and coworkers[136] optimized the structure of bi-functional VCP by reacting 1-methoxy carbonyl-2-vinyl cyclopropane-1-carboxylic acid with a branched bulky amine spacer **VCP28**. This amide functionalized VCP was a mixture of two isomers (Figure 58b) and led to intermolecular H-bonding allowing a pre-organization of the monomer and thus increased the rate of propagation. Another explanation given by the authors on the enhanced reactivity of this monomer was related to an optimized orientation of the singly occupied molecular orbital (SOMO) of radical on the ring-opened structure towards vinyl group of further monomer unit (Figure 58c).

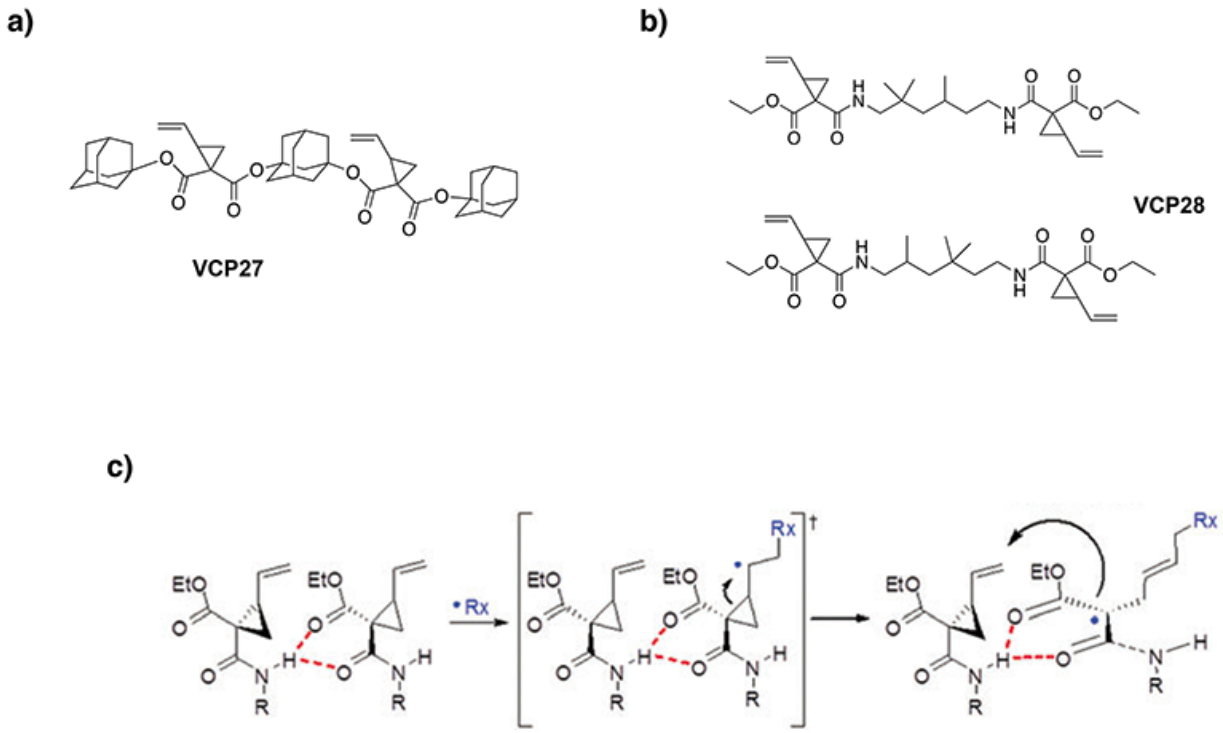


Figure 58. a) Structure of the di-functional VCP that incorporated the rigid and bulky adamantane moiety **VCP27.** b) Structure of the di-functional VCP with a branched bulky amide

spacer. C) Proposed mechanism for amide-based VCP polymerization in which the propagation rate is enhanced because of profitable orbital arrangements. Reproduced with permission from ref. [136]. 2015 published by the Royal Society of Chemistry.

In addition to well-defined multi-functional VCPs, oligomeric VCP were prepared from the 1,1 diethoxycarbonyl-2-vinyl cyclopropane or 2-vinyl cyclopropane-1,1-dicarboxylic acid with diols either by direct polycondensation or by transesterification.[157-158] Oligomers of 2 to 5 units were obtained and showed high reactivity. For instance, films based on these monomers in which photo-initiators were added cured in less than 10 seconds upon exposure to UV light.

In a similar manner, oligomeric poly(vinyl cyclopropanone acetals) were prepared by polycondensation of 1,1-dichloro-2-vinyl cyclopropane with the sodium salts of various diols.[122, 159] Lastly, VCP derivatives (Table 8, **VCP24-26**) bearing trialkoxysilyl groups were prepared and used as precursors of inorganic-organic nanocomposites using the sol-gel process.[151] The polycondensation of the alkyl silane group with tetraethoxysilane TEOS and/or other metal alkoxide (Zr, Ti, Al, etc.) led to silica materials in which the VCP moieties were covalently grafted and could thus be cured under UV (Figure 59).

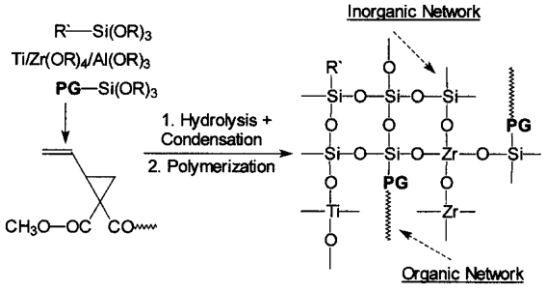


Figure 59. Preparation of organic/inorganic nanocomposite using VCP derivatives functionalized with trialkoxysilyl groups (**VCP24** to **VCP26**). Reproduced with permission of Ref. [29]. Copyright 1999 John Wiley and Sons.

4. Cyclic Ketene Acetals

4.1 Synthesis

The main method for the synthesis of CKA was reported in 1948 by Mc Elvain (Figure 60).[160] It consisted in the ring formation by acid catalyzed (either *p*-toluene sulfonic acid *p*TSA or DOWEX resin) transacetalization from dimethyl chloroacetal and a diol. Considering this step is in equilibrium, the formed methanol has to be removed to shift the equilibrium towards the formation of the cyclic chloromethylacetal. Diethyl chloroacetal can be also used but the secondary condensation product is then ethanol that has a higher boiling point. The second and last step was the formation of the exomethylene function by HCl elimination in presence of a strong base. The mostly used bases were KOH or potassium *tert*-butanolate (*t*-BuOK). To facilitate the deshydrohalogenation reaction, Br derivative was sometimes preferred but the initial product was more expensive than its chlorinated analogue.

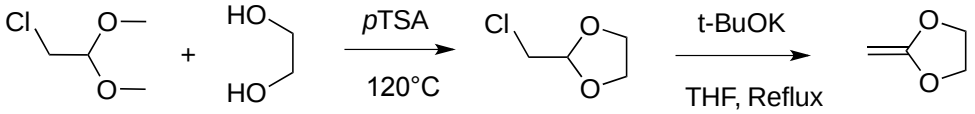


Figure 60. Synthesis of CKA via the transacetalization and dehydrochloration reaction.

The influence of the haloacetaldehyde dimethyl acetal used in this synthetic scheme was studied by Nicolas and coworkers[161] during the synthesis of MDPO/MDPL **CKA11**. The transacetalization yield was not greatly impacted (65 % yield using the chloroacetal versus 80 % with the bromoacetal) but the outcome of the dehydrohalogenation reaction was clearly different. The reaction was performed at 0 ºC for 2 h and the yield of MDPO/MDPL **CKA11** varied from 23 % (chloroacetal) to 81 % for the bromoacetal derivative and even 85 % in 1.5 h for the iodoacetal derivative that was formed in situ by the reaction of the bromoacetal derivative with NaI in acetone. [161]

Because of the high tendency of CKA monomers to polymerize *via* a cationic process, they were exclusively purified by distillation under reduced pressure. This synthesis method enabled the preparation of a large range of CKA by only modifying the diol structure. Other synthesis methods also have been reported in the literature and were based on the pioneering works of Mc Elvain[162] where ketene acetals were prepared from ortho-ester pyrolysis at high temperature (Figure 61a). It was also reported the synthesis of CKA with a hindered exo-methylene function by dealcoholization (Figure 61b).[163] Nevertheless the main drawback of these pathways are generally their low yields (typically ~30%).

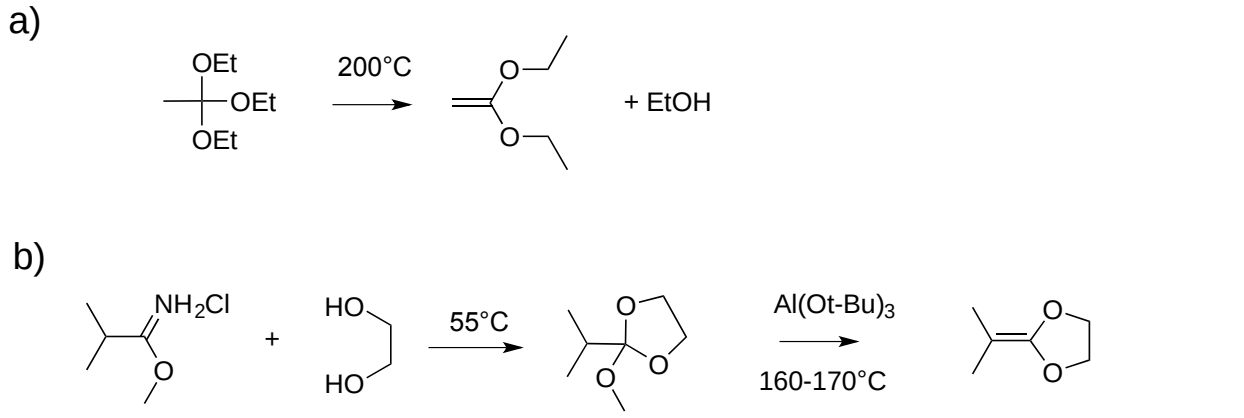


Figure 61. Synthesis of ketene acetals as described by Mc Elvain and co-workers.[162-163]

More recently, a new route for 5-membered CKA was proposed from acetonitrile and ethylene glycol.[164] The reaction took several days to proceed but did not require any intermediate purification step (Figure 62).

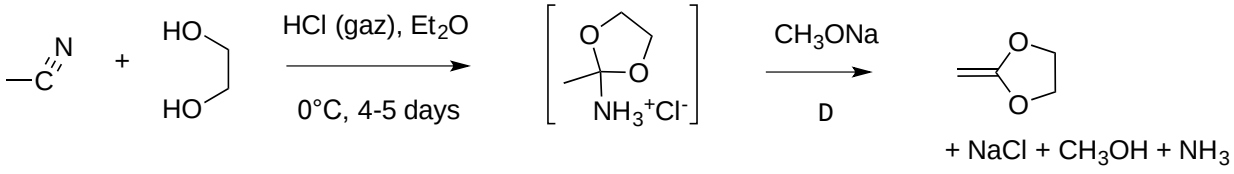


Figure 62. Synthesis of CKA according to Argade and coworkers. [164]

In 1995, Petasis[165] described an enhanced process of Tebbe's olefination[166] and used it to modify several carbonyl functions. He proved for example that by using dimethyltitanocene and cyclic carbonate, it was possible to obtain CKA in small quantity but with very good yields (Figure 63).

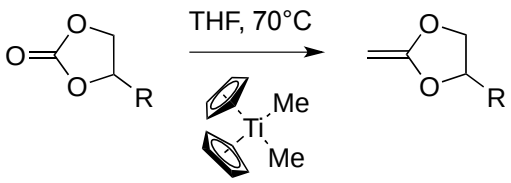


Figure 63. CKA synthesis using the Petasis reagent.

Finally, a recent method for the synthesis of CKA was based on the cyclization from acroleine or methacroleine *via* rearrangement of the double bond, leading to a CKA with a hindered double bond (Figure 64).[167]

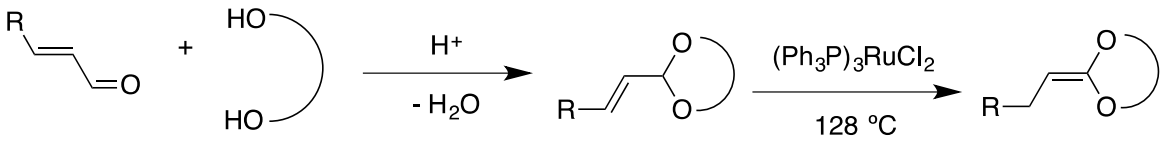


Figure 64. Synthesis of hindered CKA according to Crivello and coworkers.[167]

4.2 Reactivity

The main feature of CKA monomers derives from the acetal functionality. Since the doublet of the two oxygen atoms are delocalized on the C=C double bond, the latter is highly polarized and the β carbon strongly nucleophilic (Figure 65). The nucleophilicity of the CKA double bond explains the instability of these monomers in the presence of protic species. Fukuda[168] proved that the NMR chemical shift of the methylene group changed with the importance of the $\pi - \pi$ conjugation between the oxygen atoms and the C=C double bond.[169] Consequently, CKA

monomers with vinyl hydrogens having low NMR chemical shift corresponded to unsaturation with high electronic density (high degree of conjugation).

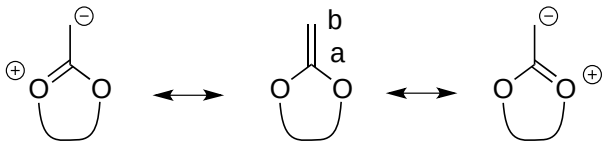


Figure 65. Mesomer forms of CKA.

It also exists a linear relationship between the chemical shift and the rate of methanol addition onto CKA to yield the corresponding ortho-ester (Figure 66). Monomers with large ring (7 or 8-membered ring) are less reactive than small ones and correspond to molecules with the highest chemical shifts. The conclusion was as follows: the C=C double bond from large ring is less anionic/nucleophilic than the one from small ring (because of a weaker $\pi - \pi$ conjugation).

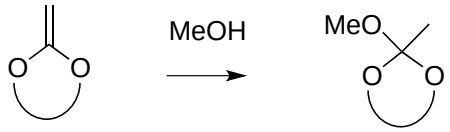


Figure 66. Synthesis of ortho-esters by methanol addition onto CKA.

In the presence of carboxylic acids, Pittman and coworkers[170] observed the formation of an addition product that can rearrange and yield a diester after ring-opening (Figure 67). More recently, Agarwal proved that the intermediate species can be stable and that increasing the temperature facilitated the rearrangement.[171]

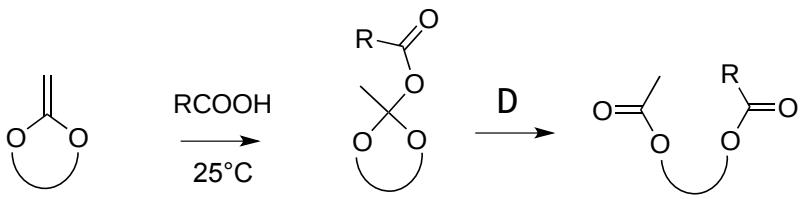


Figure 67. CKA rearrangement in presence of carboxylic acid.

4.3 Cationic polymerization

As discussed previously, CKA derivatives are very sensitive to electrophiles and many papers reported their spontaneous cationic polymerization. Since this undesired polymerization process could compete with the expected radical one, a good understanding of this polymerization mode is mandatory to avoid erroneous conclusions concerning the kinetics and/or the percentage of ring-opening. For instance, the radical polymerization of MPDO/MPDL **CKA11** with and without pyridine to limit the cationic polymerization gave different behaviors.[172]

Many studies were exclusively devoted to the cationic CKA polymerization (Figure 68). The high reactivity of CKA in regards to the cationic process enabled the synthesis of high molar mass polymers (~10^5 g.mol^{-1}) but in many cases exclusively *via* the vinyl polymerization of the C=C double bond, thus giving pure polyacetals (Figure 68).

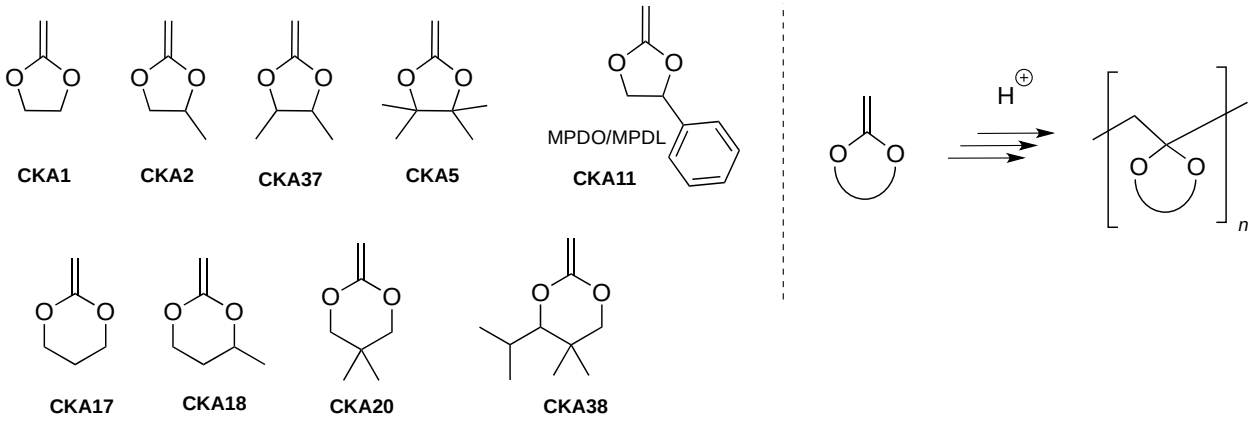


Figure 68. General mechanism of the cationic polymerization of CKA.

Different initiating acidic systems have been tested such as methanesulfonic acid, trifluoromethanesulfonic acid[173] and H_2SO_4 on glass balls[174] or carbon black.[175-178] The polymerizations were performed in a few hours, either at room temperature or at 60 °C. Others cationic initiating systems prepared in solution (e.g., $BF_3.Et_2O$, $NiCl_2$, $ZnCl_2$, $FeCl_3$, $AlCl_3$, ion-exchange resins) usually give unstable polyacetals with unwanted polyketones or other complex side products (which colored in brown-red the reaction medium) (Figure 69).[174]

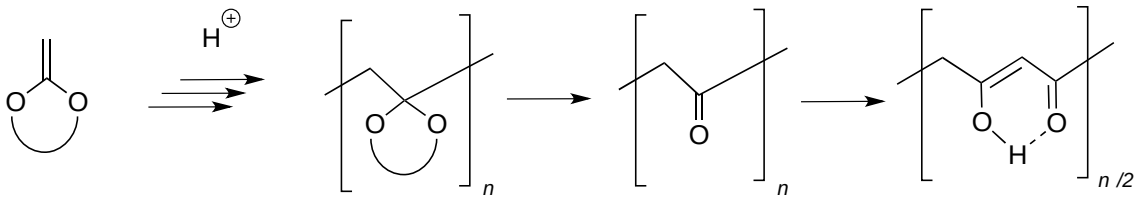


Figure 69. Degradation of polyacetal and formation of polyketones and other complex side products.

The advantage of using glass beads or carbon black rinsed with H_2SO_4 instead of sulfuric acid alone lied in the limited quantity of cation H^+ produced in the reaction medium. The cationic polymerization was then initiated and the polymer degradation limited.[174] Modification of the monomer, the initiator or the polymerization conditions can drastically change the polymerization process and even conduct to the production of polyacetal-polyester copolymers (Figure 70).

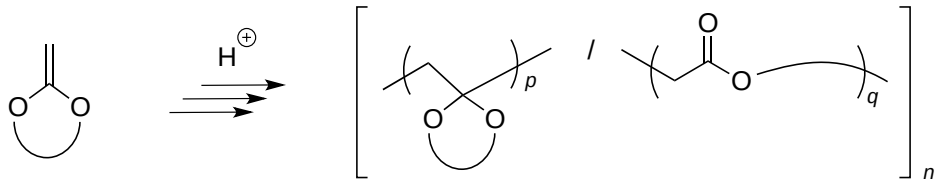


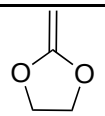
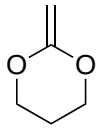
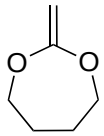
Figure 70. Cationic polymerization of CKA and synthesis of polyacetal-polyester copolymers.

For instance, in the case of monomers **CKA6, CK11** and **CKA38** (Figure 68) an initiation using $BF_3.Et_2O$ (at -20, 25 and 60 °C) gave copolymers deriving from both the direct polymerization of the vinyl function and the ring-opening polymerization, but with no possible quantification of each mechanism.[177]

The temperature plays an important role as well. For instance, with the same initiator $BF_3.Et_2O$, the polymerization of **CKA27** yielded polymers with a higher proportion of ester units when increasing the temperature (60% and 5% of ester units at 150 °C and -5 °C, respectively).[179] The same trend was observed with monomers **CKA1** and **CKA17** in the presence of tris(phenylphosphine)ruthenium (II) chloride (Table 9).[180] After 48h of polymerization, the proportion of ester units was governed by the temperature despite very low molar masses (200

and 1400 g.mol^{-1}). Only the monomer **CKA17**, when polymerized at 138 °C, gave a polymer with a reasonable M_n, close to 10,000 g.mol^{-1} but with only a weak tendency to ring-opening. It was here interesting to notice that the monomers did not present the same ability to ring-open (**CKA1** > **CKA27** > **CKA17**).

Table 9. Cationic polymerization of monomers **CKA1**, **CKA17**, **CKA27** and influence of the temperature on the % of ring-opening.[180]

Monomer	Temperature (°C)	ring-opening (%)
 **CKA1**	133	67
	165	70
	185	72
 **CKA17**	138	18
	160	42
	180	43
 MDP/MDO **CKA27**	20	42
	75	50
	165	58

The cationic ring-opening polymerization of monomers with methyl or ethyl group on the C=C double bond gave interesting results by varying the ratio of vinyl versus ring opening process. Crivello and co-workers[181] reported that an efficient control of the polymerization rate was possible with a photochemical initiating system based on diaryliodonium and triarylsulfonium salts at room temperature (Figure 71).

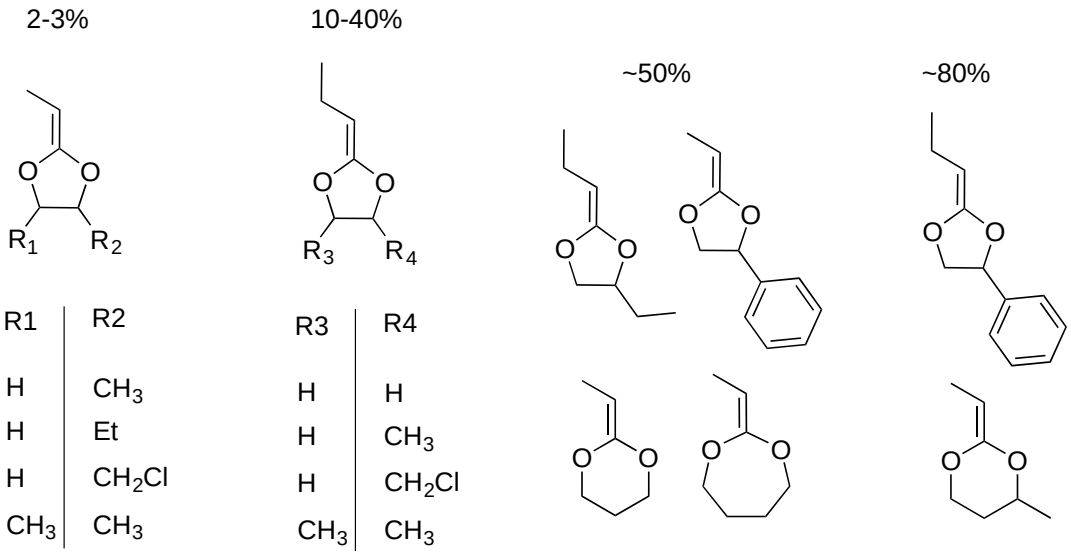


Figure 71. Cationic polymerization of different CKA and corresponding % of ring-opening.[181]

The reactivity of CKA monomers displayed on Figure 71 strongly depends on the monomer structure. Monomers with a 5-membered ring and with a methyl group on the C=C double bond were highly reactive and polymerized in a few minutes giving almost pure polyacetals (~2-3% of ring-opening). On the contrary, the presence of an ethyl substituent on the C=C double bond increased the proportion of ring-opening up to 80%. The molar masses were generally between 5000 and 40,000 g.mol^{-1} except for monomers with a 6 or 7-membered ring where the M_n were lower (500 – 2800 g.mol^{-1}) and the yields weaker (20%). In conclusion and as described in this subsection, even if the cationic polymerization of CKA is facile and can occur at room temperature, the synthesis of pure polyesters by this process is very challenging and has not been deeply investigated.

4.4 Radical polymerization

Contrary to cationic polymerization, the radical polymerization kinetics of CKA is slow and the molar masses of the obtained polymers are usually below to 10^4 g.mol^{-1}. However, in some cases, the radical polymerization of certain CKA could yield pure polyesters thanks to a 100% ring-opening polymerization process (p = 0, Figure 42, subsection 2.9).

With the objectives to prepare pure polyesters, a large library of CKA monomers were reported in the literature (Figure 43, subsection 2.9) to study the influence of different factors on the ring-opening, such as the experimental conditions and structure of the CKA. The most studied monomers are summarized on Figure 72 and the main conclusions of these studies are described thereafter.

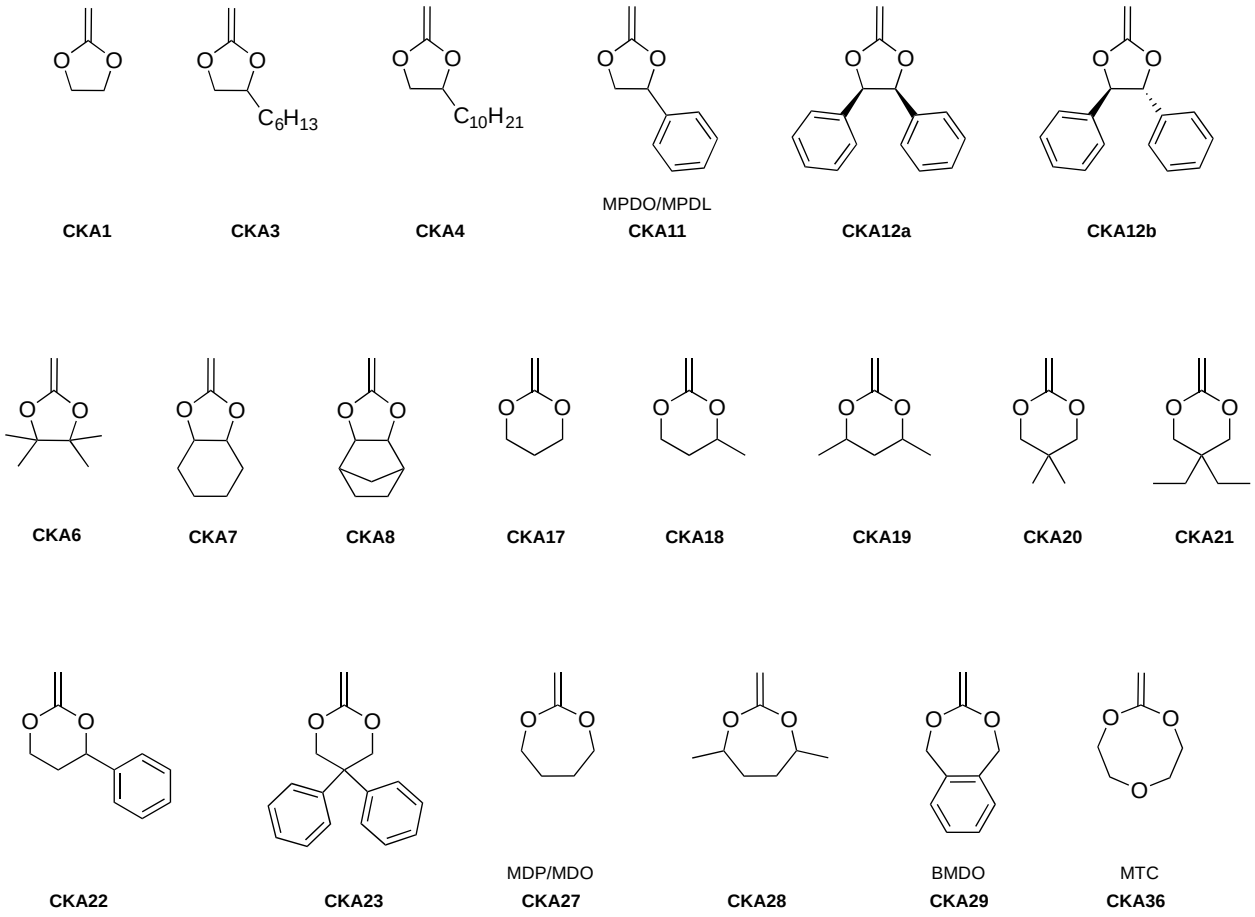


Figure 72. Principal CKA monomers studied in radical ring-opening polymerization.

Because of the radical mechanism, it has to be noted that in certain cases intramolecular and/or intermolecular H-transfer side reactions can occur during the polymerization process (see Figure 108a). The intramolecular mechanism or backbiting led to short chain branches whereas intermolecular H-transfer produced long branches. This phenomenon has been extensively studied for the MDO/MDP **CKA27** monomer that produced the non-stabilized methylene radical after the ring-opening step. Jin and Gonsalves[182] proved the occurrence of 1,7-H-transfer by

NMR and this technique could also be used to determine the branching density by comparing the integrals of CH_3 (0.89 ppm, from a branch) and CH_2 (2.26 ppm, from a linear polyester). The calculated branch density reached 20% for the bulk polymerization of **CKA27** at 50 ºC for 72 h initiated by 2 mol% of AIBN. Even if the repeating unit of P(**CKA27**) was similar to the polycaprolactone (PCL), the occurrence of chain branching avoided any crystallization and no melting peak could be observed by DSC. Interestingly, this feature has been used for different applications (see subsection 7.2 for details).

4.4.1 Influence of the experimental conditions

Several studies, and in particular Bailey's work, proved the importance of the temperature to facilitate the ring-opening process. The polymerization of the 5-membered CKA monomer (**CKA1**, Figure 68) clearly showed that the formation of polyester increased with an increase of the temperature (50% of ring-opening at 60 °C, 83% at 125 °C[10] and 100% at 160 °C).[183] This trend was observed with other CKA monomers.[181]

It has also been shown that addition of a solvent also facilitated the ring-opening, which was explained by favored intramolecular mechanisms (CKA ring-opening in this case), upon dilution.[27] For example, in the presence of *tert*-butyl peroxide at 110 °C, the two monosubstituted 5-membered CKA (**CKA3** and **CKA4**, Figure 72) led to polyester at 73 and 90 % when polymerized in bulk, whereas 100% of ring-opening were observed when the polymerization was performed in 50 wt% benzene.[184] Nevertheless, a decrease of the polymerization yield was

sometimes observed when working in solution.[27] Klemm and Schultze also postulated it was not possible to polymerize CKA in solution because of their too low reactivity.[185]

The photopolymerization of CKA monomers has been less studied. Endo and coworkers[186-187] compared the polymerization of **CKA11** and **CKA27** initiated thermally using either AIBN or DTBP with the photopolymerization either initiated by 2-ethylanthraquinone or isopropoxydeoxybenzoin using a 500 W Xe/Hg lamp (10-12 $mW.cm^{-2}$ at 365 nm). The kinetics were strongly accelerated using UV irradiation since complete conversion was achieved in 3 h at 30 °C instead of 60 h at 70 °C (with 1.5 mol% AIBN). The analyses of the two obtained polymers showed no difference concerning both the structure (100 % of ring-opening) and the molar masses.

4.4.2 Influence of the CKA structure

Impact of the ring-size

The size of the ring is one of the main factors influencing its opening and consequently the polymerization behavior of a CKA. The first work dealing with the influence of the ring-size on the monomer polymerization was based on the polymerization of 5 to 7-membered ring monomers. The 2-methylene-1,3-dioxolane (**CKA1** Figure 72) yielded polymer chains with 83% of ring-opening at 125 °C[10] and 87% at 120 °C.[183] At 50 °C, the percentage of ring-opening decreased to 50 %.[11] A slight lower tendency of ring-opening was observed with the 6-membered

ring monomer: 2-methylene-1,3-dioxane (**CKA17** Figure 72) since 85% of ring-opening were calculated but at 130 °C.[10] If performed at 70 °C, this value decreased to 36%.[188] The 2-methylene-1,3-dioxepane, a 7-membered-ring monomer, termed MDP or MDO (**CKA27**) polymerized exclusively *via* an addition-fragmentation mechanism and this even at 60 °C. Later a study of the 2-methylene-1,3,6-trioxocane (MTC, **CKA36**) proved that this 8-membered ring monomer with an extra oxygen in the ring polymerized *via* a 100% ring-opening process at 70 °C and gave a poly(ester-ether) copolymer (Figure 73).[189]

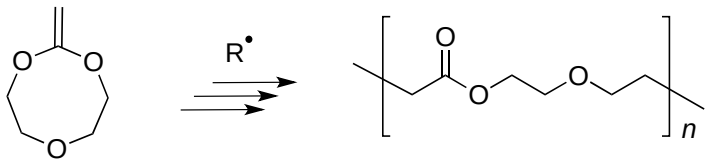


Figure 73. Polymerization of 2-methylene-1,3,6-trioxocane MTC **CKA36**.

Steric hindrance and ring-strain considerations generally explain the differences in terms of ring-opening ability observed between monomers of various ring-size. More details are given below in the case of 6 and 7-membered ring monomers.

6-Membered ring monomers are known to be quite difficult to polymerize *via* a ring-opening process. This is usually explained by the very low ring-strain of monomers analogous to cyclohexane (whose ring-strain was set to zero). Nevertheless, it seemed that some 6-membered ring monomers did not follow this general behavior. Zhende and coworkers[190] studied the polymerization of a selection of 6-membered ring CKA monomers (**CKA18** to **CKA21,** Figure 72) and observed moderate to good ring-opening at 110 °C (78 – 91 % after 18h with polymer yields ranging between 30 and 40 %). The influence of the temperature was also observed since

the percentage of ring-opening for **CKA18** increased from 62 to 89% when the temperature was increased from 50 to 120 °C. In addition, the ring was shown to predominantly open on its more hindered side (73%). The comparison of the percentage of ring-opening of between **CKA17** (85 % at 130 °C), and **CKA20** and **CKA21** (80 and 78 % at 110 °C) showed no influence of the presence of substitutive groups on β position to the oxygen. On the contrary, in the case of **CKA18** and **CKA19**, an increase of the ring-opening ability (89 and 91 % at 110 °C) was observed because of the stabilization effect of methyl or ethyl substituents in α position to the oxygen. Monomer **CKA19** even exhibited a 100% ring-opening polymerization mechanism at 120 °C in diluted benzene. Based on these results, Bailey[46] concluded that the reactivity of 6-membered ring monomers was in between those of 5- and 7–membered ring monomers.

The polymerization of 7–membered ring monomers was less controversial than that of 6-membered ring monomers since all studied 7-membered ring monomers exclusively gave polyesters (i.e., 100% ring-opening). For example, 4,7-dimethyl-2-methylene-1,3-dioxepane **CKA28** and 5,6-benzo-2-methylene-1,3-dioxepane (BMDO, **CKA29**) gave 100% of polyesters when homo-polymerized at 120 °C or copolymerized with MMA at 50 °C.[191]

Stabilization of the radical formed by ring-opening

The most immediate idea to increase the radical ring-opening ability of a CKA was to introduce a substitutive group on the ring that will stabilize the newly-formed radical. For instance, the ring-opening of **CKA3** and **CKA4** (Figure 72) was much easier than for monomer **CKA1** (70-90% at 110 °C and 100% in solution).[184]

In the case of substituted monomers like **CKA3** and **CKA4**, the ring-opening was not symmetrical. The β-scission occurred preferentially on the more hindered side (60-70 %) whatever the temperature (path b on Figure 74). At low temperatures, **CKA4** (C_{10} substituted) presented a more efficient ring-opening than **CKA3** (C_6 substituted) because of its bulkier substitutive group. According to Bailey and co-workers,[184] the long alkyl chain probably decreased the rate of direct propagation.

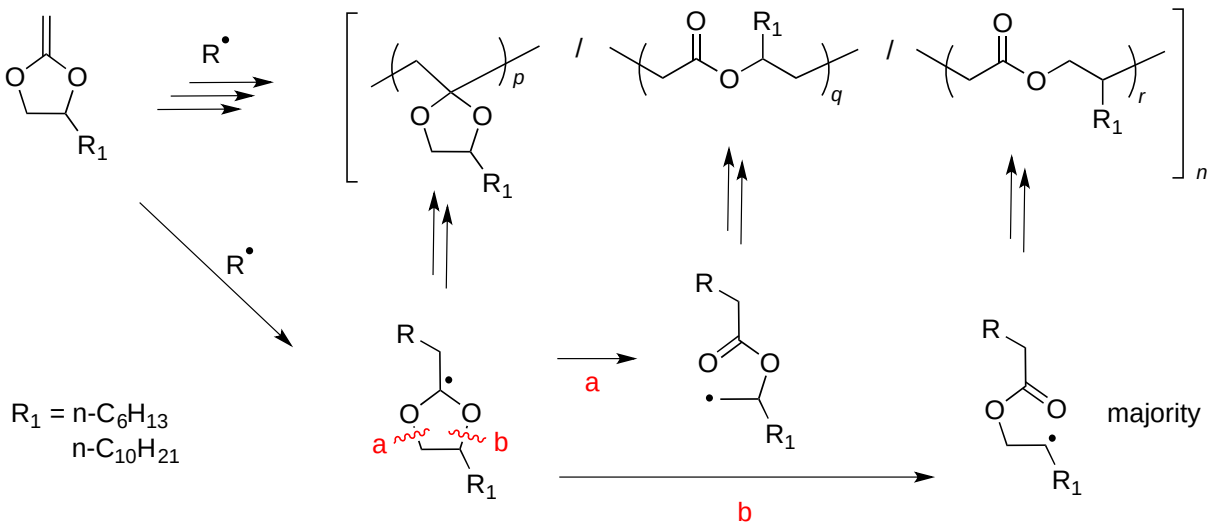


Figure 74. Polymerization mechanism of asymmetrical CKA monomers.

Cho[192] and Bailey[193] reported at the same time the synthesis and the polymerization of **CKA11** also named MPDO or MPDL (Figure 72). Identical results were obtained: with DTBP, at 124 °C or between 60 and 150 °C, the polymerization yielded only polyester chains. This result proved that the presence of a substitutive group stabilizing the propagating radical significantly facilitated the ring-opening which took place only on the more substituted side (path b, Figure 74). Even if **CKA11** was more stable than **CKA1**, it nevertheless polymerized slower at room temperature by a cationic process and gave a polymer that did not belong to the polyester family.

A solution to stabilize this monomer was to use 1-2 % of pyridine to avoid cationic polymerization and to ensure a safe storage.[193]

A few years later, the same ring-opening facility of **CKA11** was however not observed.[194] In particular, the polymerization of this monomer gave polymers with units coming from ring-opening and vinyl polymerization. No use of a base like pyridine, which is crucial to avoid undesirable cationic polymerization, was however mentioned. Endo also reported the presence of about 20 % of polyacetal in the final polymer when polymerizing at 120 °C the pure enantiomer R of **CKA11**.[195]

Importantly, contradictory results were obtained with different 6-membered ring monomers substituted by aromatic groups, usually known to promote ring-opening. The radical polymerization of **CKA22** under UV at 25 – 50 °C or thermal initiation at 80 and 120 °C only gave polyacetals of high molar masses (20,000 – 30,000 $g.mol^{-1}$).[185] That was however in contradiction with Bailey and coworkers' conclusion concerning 6-membered ring monomers. In the case of **CKA23** (Figure 72), the polymer obtained by bulk polymerization was insoluble whereas only oligomers were observed when the reaction was performed in THF or dioxane. Nevertheless, in both cases, the polymer structure did not correspond to a ring-opening mechanism. According to these results, Klemm and Schulze[185] concluded that it was impossible to open 6-membered ring monomers because of their low ring-strength and therefore their low tendency to rearrange. It is however important to mention that in this article was reported the self-initiation of **CKA17** during its distillation (the polymerization seemed initiated by the distillation glassware), showing the difficulty to avoid spontaneous cationic polymerization for 6-membered ring CKAs. Consequently, cautions have to be taken with results from **CKA22** and **CKA23** that could be due to a combination of both radical and cationic processes.

Effects of steric hindrance

Whereas the steric hindrance seemed to promote ring-opening in the case of monosubstituted monomers, the reactivity of disubstituted monomers was apparently more complex and structure/ reactivity relationships were more difficult to establish. For example, the polymerization of **CKA12a** (cis form, Figure 72) gave pure polyester but with very low yields (5% after precipitation) whereas no polymer was obtained with **CKA12b** and **CKA6**. The explanation proposed by Bailey and coworkers[47] was the too high steric hindrance preventing the propagation step to proceed. A copolymerization study of **CKA12a**, **CKA12b** and **CKA6** with MMA showed that the incorporation of **CKA6** was significantly lower, supporting the impact of the steric hindrance over the reactivity of the CKA. Interestingly, this study did not mention the presence of polyacetal for the three monomers as if a high steric hindrance limits or inhibits the vinyl polymerization.

Schulze and coworkers[194, 196] studied more specifically the impact of the steric hindrance for bicyclic monomers. They reported that, whatever the experimental conditions (from 25 to 120 °C, in bulk or in solution), traces of radical initiator (AIBN or Irgacure 651 photoinitiator) are enough to initiate the polymerization of **CKA8**. The polymerization was fast, exothermic and gave a quasi-pure polyacetal insoluble in most organic solvents despite the absence of cross-linking. It was also observed that the polymerization of **CKA7** at 80 °C in bulk gave pure polyacetal with molar masses around 20,000 $g.mol^{-1}$. The authors specified that these monomers were very sensitive to oxygen and that their stability in nitrogen atmosphere did not exceed a few minutes (spontaneous polymerization).

In summary, the radical reactivity (and thus the radical ring-opening ability) of the most common CKA monomers are reported in Figure 75, which only gives a trend since an accurate analysis is very difficult to perform. Indeed, these results have been obtained using various experimental conditions (e.g., temperature, nature of the solvent, nature of the radical initiator, concentration of radical initiator, etc.) and various characterization techniques (e.g., NMR, FTIR, etc.) that could lead to strong variations. From this figure, it is very difficult to extract the key parameters that would favor a complete ring-opening and this explains why the vast majority of studies dealing with CKA monomers and especially those dealing with applications (see Section 7) are based only on **CKA27**, **CKA29** and **CKA36** that are known to undergo complete ring-opening under a broad range of different experimental conditions.

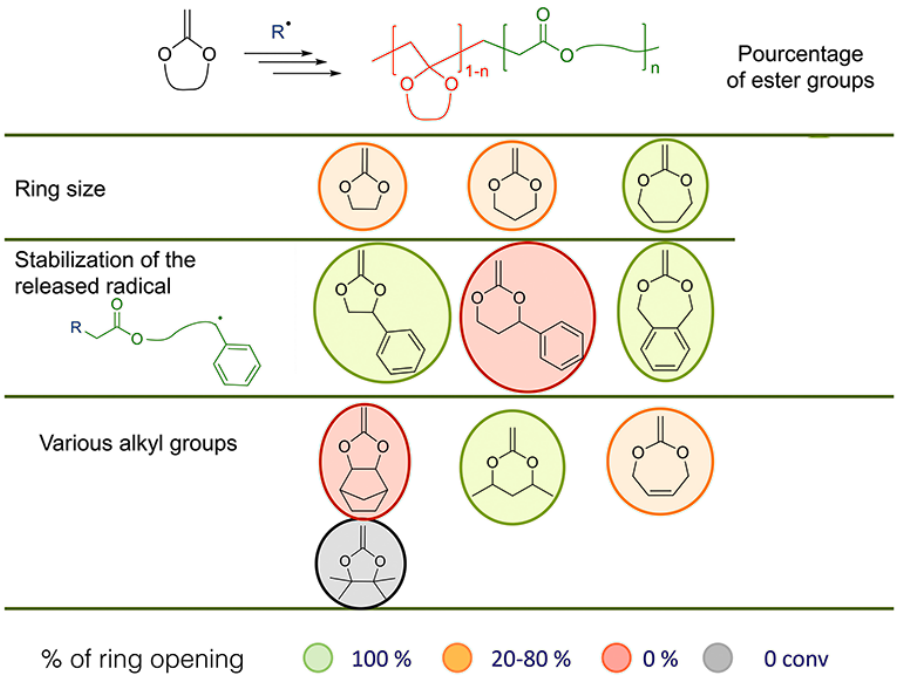


Figure 75. Ring-opening behavior of the most common CKA monomers.

Endo and coworkers[197] attempted to rationalize the reactivity of cyclic monomers and in particular CKAs by quantum calculations (e.g., AM1 and PM3 semi-empirical methods, and DFT calculations). They calculated the internal free energy variation either between the ground state of the initial radical to the activated state ($\Delta E^{\dagger}$) or to the ground state of the opened radical (ΔE). The DFT calculations showed that the monomers with low (<10 kcal.mol^{-1}) and high (>27 kcal.mol^{-1}) $\Delta E^{\dagger}$ could be categorized as selective ring-opening and selective vinyl-type-polymerization monomers respectively. The behavior of partial ring-opening monomers cannot be described properly and no explanation was found to understand these results.

4.5 Functionalized CKA monomers

In addition to traditionnal CKA structures that have been described above, more complex and functionalized CKA have also been synthesized (Figure 76). The photochemical or thermal radical polymerization of **CKA13** gave a mixture of polymers bearing acetal and ester repeating units in proportions difficult to evaluate. In addition, only oligomers were observed probably because of the too strong stabilization of the propagating radical inhibiting the addition on another monomer unit.[196]

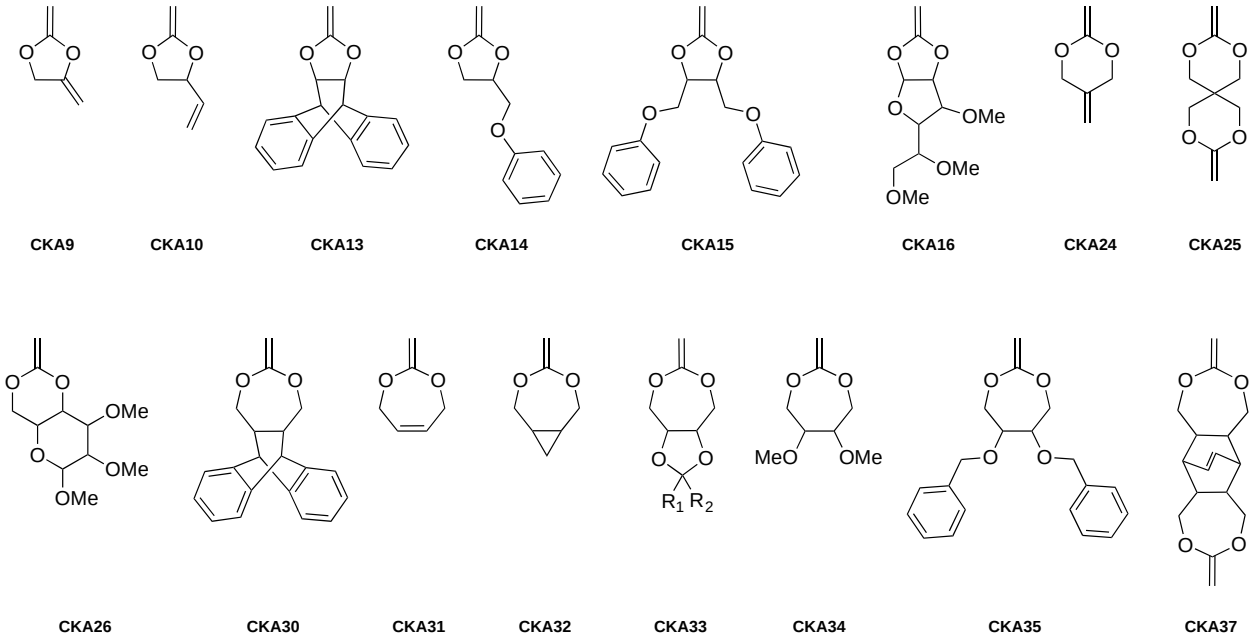


Figure 76. Complex and/or functionalized CKA monomers.

The polymerization mechanism of 2-methylene-4-phenoxymethyl-1,3-dioxolane (**CKA14**) could not be clarified because of numerous rearrangement phenomena not always possible to identify.[194] More recently, Benammar[198] studied the polymerization of cyclic ketene acetal derived from sugar and tartric acid (**CKA15**, **CKA16**, **CKA26**, **CKA34** and **CKA35**) to obtain "green" biodegradable polyesters. Unfortunately only 7-membered ring monomers were polymerized *via* a ring-opening mechanism; the other monomers polymerizing *via* vinyl propagation. This result confirmed the relevance of choosing 7-membered ring CKA monomers to get polyesters *via* radical ring-opening polymerization.

The radical polymerization of **CKA32** initiated by di-*tert*-butyl peroxide at 120 °C gave after 16h an insoluble polymer. IR spectroscopy proved the complete ring-opening of the dioxepane moiety. According to Zeuner and co-workers[199] the cross-linking reactions explaining

the insoluble character of the polymer might imply hydrogen abstraction from tertiary C-H of both the monomer and the polymer (after ring-opening). In addition, after opening of the main ring, the cyclopropane probably underwent a β-scission reaction giving rise to an easily accessible C=C double bond. To prepare low volume-shrinkage monomers, a bicyclic monomers **CKA33** was polymerized to introduce acetal groups in a polyester chain (Figure 77).[200-201] The molar masses of the resulting polymers ranged between 2000 and 6000 g.mol^{-1}. A low volume-shrinkage (-7.5 to -1%) was observed with liquid monomers whereas the polymerization of aromatic crystalline monomers promoted a slight volume expansion (0.5 – 2.9%).

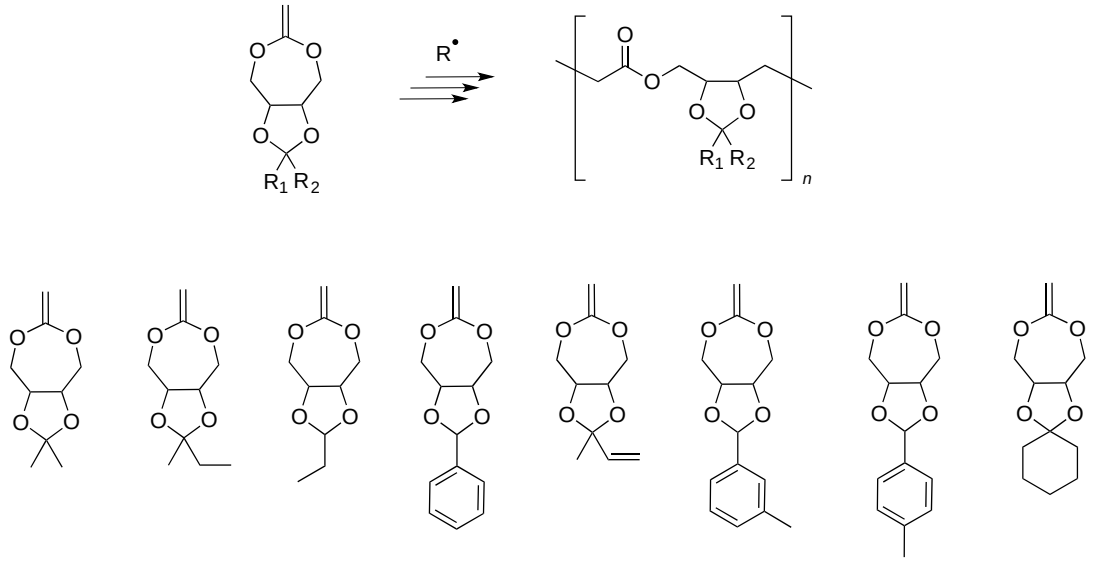


Figure 77. Polymerization of bicyclic 2-methylene-1,3-dioxepane monomers.

Di-functional CKA monomers were also investigated. The polymerization of **CKA10** and **CKA31** at 120 and 115 °C, respectively, was attempted for 30h in benzene with di-*tert*-butyl peroxide as an initiator. The polymerizations gave 100% polyester with specific structures coming from rearrangement reactions (Figure 78a).[46] To explain these unexpected results, Bailey postulated a concerted mechanism instead of a radical addition-fragmentation mechanism. This theory was nevertheless rejected the same year because of a lack of sound evidences.[195]

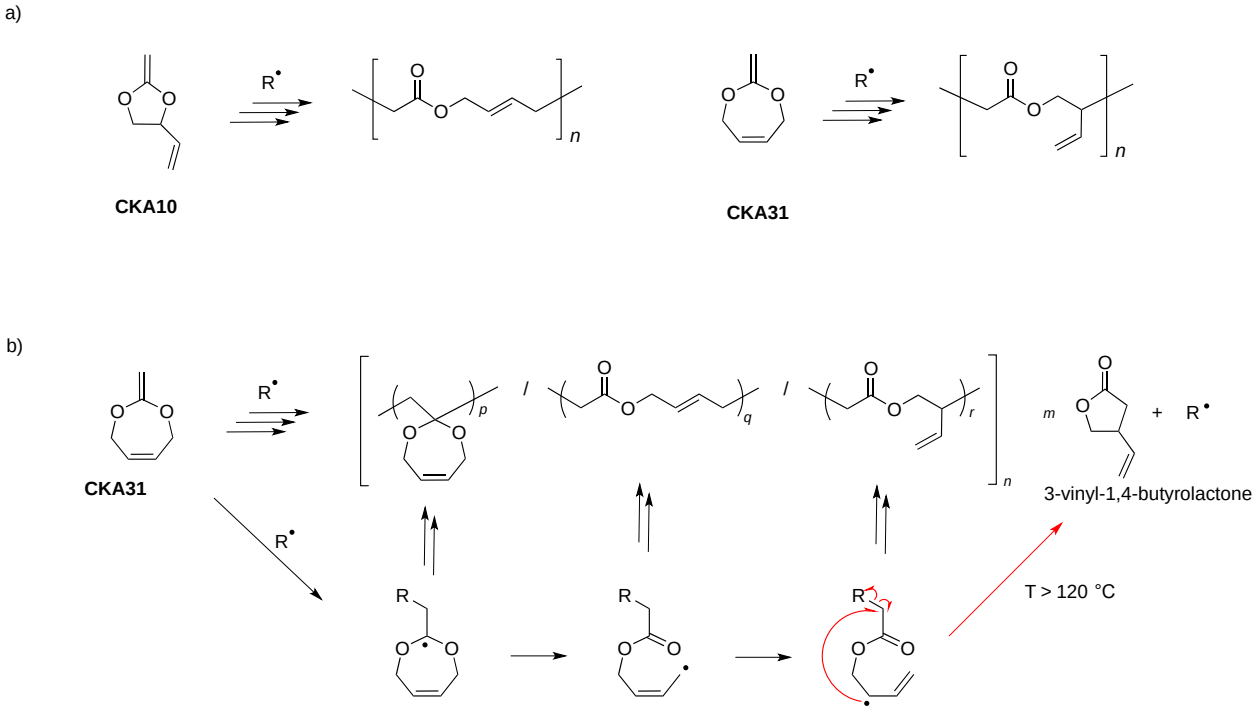


Figure 78. a) Polymerization of di-functional CKA monomers, 2-methylene-4-vinyl-1,3-dioxolane **CKA10** and 2-methylene-1,3-dioxe-5-pene **CKA31**. b) Detailed mechanism of the polymerization of **CKA31** proposed by Albertsson et al.[202]

More recently, Albertsson and coworkers[202] studied in more details the polymerization of 2-methylene-1,3-dioxe-5-pene (**CKA31**). This monomer polymerized partially *via* a ring-opening mechanism at 50 °C to give oligomers (900 $g.mol^{-1}$) with different structures but did not polymerize at high temperatures (> 120 °C) (Figure 77b). The explanation proposed by the authors was that at high temperatures, the monomer fully rearranged into 3-vinyl-1,4-butyrolactone. We can then presume that in the pioneer works of Bailey and coworkers, this cyclic molecule was mixed up with the monomer mixture and thus inserted in the polymer.[46]

According to Endo,[203] the polymerization of **CKA9** (Figure 76) at 60 °C involved concomitant ring-opening and vinyl polymerization mechanisms. Nevertheless, when performed at 120 °C in DMF, its polymerization gave 100 % polyester chains but with low molar masses (1600 $g.mol^{-1}$) and a high branching ratio. Without DMF, the obtained system was a cross-linked polymer network. In the case of a 6-membered ring monomer (2,5-dimethylene-1,3-dioxane, monomer (**CKA24**), Figure 76), the synthesized material was only composed of oligomer chains obtained by a combination of ring-opening and ring-retaining mechanisms, but in undistinguishable proportions. It is here noticeable that according to the different authors studying these difunctional monomers, only the more nucleophilic C=C double bond seemed to be involved in the polymerization mechanism, conversely to the other one, which was only available for cross-linking.

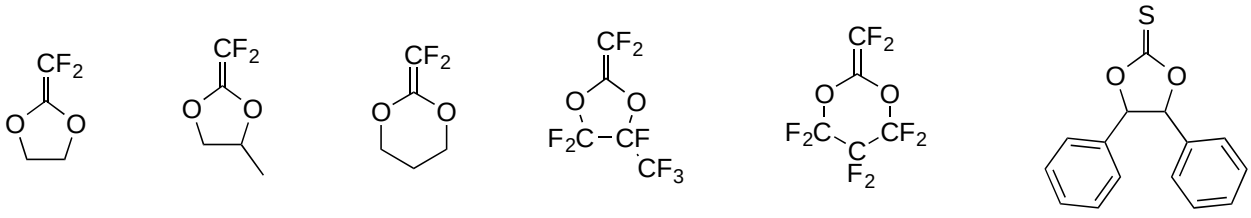
In 1993, Klemm and Schulze[204] revisited the pioneering work of Orth[205] on the synthesis of **CKA25** and its cationic polymerization. By studying the radical photopolymerization of this di-functional monomer, they obtained highly cross-linked and consequently insoluble polymers with a proportion of opened rings difficult to quantify (although presumably weak). A few years later, the same team studied the polymerization of **CKA37** (Figure 76) with the objective of obtaining a higher T_g polymer when copolymerized with other CKAs.[206] Unfortunately, when copolymerizations were performed with **CKA33** (R=Me), only low molar mass copolymers and low yields were obtained and the homopolymerization gave an insoluble polymer but with a high proportion of ring-opened units.

4.6 Analogous CKA monomers

4.6.1 Fluorinated and thionocarbonate monomers

The polymerization of partially or fully fluorinated CKA monomers have also been reported.[207] Compared to non-fluorinated analogous CKA, the ring-opening of these monomers seemed more difficult since the polymerization of **CKA38**, **CKA39** and **CKA40** (Figure 79) at 60 °C with AIBN gave 0, 28 and 22% of ring-opening, respectively. This was explained by the high polarity of the $C=F_2$ double bond leading to a radical adduct which more likely propagated than underwent a β-scission.

The polymerization of **CKA41** and **CKA42** at 60 or 80 °C required a fluorinated initiator and yielded only polyacetal chains. The tentative explanation was that the ether-fluorine bond ($-CF_2-O-$) was too strong to be cleaved during the polymerization. The synthesized polymers were then chemically and thermally stable but soluble exclusively in fluorinated solvents that highly limited their further use.



CKA38 **CKA39** **CKA40** **CKA41** **CKA42** **CK43**

Figure 79. Examples of fluorinated analogous CKA monomers and thionocarbonate monomer.

In 1999, the polymerization of cyclic monomer bearing a C=S double bond instead of a C=C double bond have been investigated.[27, 208-209] They gave radical addition sites similar to those involved in the RAFT process, also called MADIX, where xanthates are used to control the length, composition and architecture of polymer chains.[210-211] The radical homopolymerization of **CKA43** initiated by AIBN at 80 °C or DTBP at 140 °C was however unsuccessful (no polymer was obtained). When it was copolymerized with styrene or MMA, only a small fraction of the thionocarbonate monomer was incorporated in the copolymer, although its proportion and the resulting structure (i.e., ring opened or not) were difficult to evaluate and quantify. Nevertheless, the authors observed that an increase of the thionocarbonate monomer concentration caused a decrease of both the molar masses and the monomer conversion, suggesting termination reactions. In parallel, the loss by hydrolysis of 10,000 $g.mol^{-1}$ from a 50,000 $g.mol^{-1}$ sample could be explained by the presence of thioester units in the final polymer.

4.6.2 O,N-CKA and O,S/S-S CKA monomers

In 1982, Bailey and co-workers[73] reported the synthesis and the polymerization of 3-methyl-2-methyleneoxazolidine (**CKA44**), a 5-membered O,N-CKA monomer that quantitatively gave polyamide (Figure 80), even though no experimental data nor characterization were shown. When **CKA44** was copolymerized with styrene and MMA, the resulting copolymers were claimed to be fragmentable.

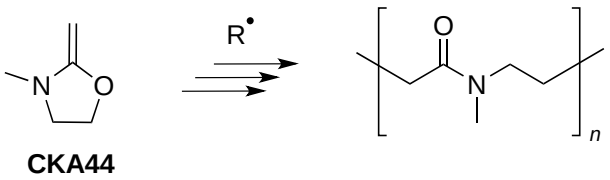


Figure 80. Polymerization of 3-methyl-2-methyleneoxazolidine.

Similar monomers (Figure 81) were synthesized later on but no polymer was obtained when heating at 80 °C in THF.[212] Only a very small fraction of the monomer was consumed to give side reaction products. The analysis of the addition products of BPO onto **CKA47** and **CKA48** confirmed a ring-opening process whereas in the case of **CKA49**, only a 1,2-addition product was observed.

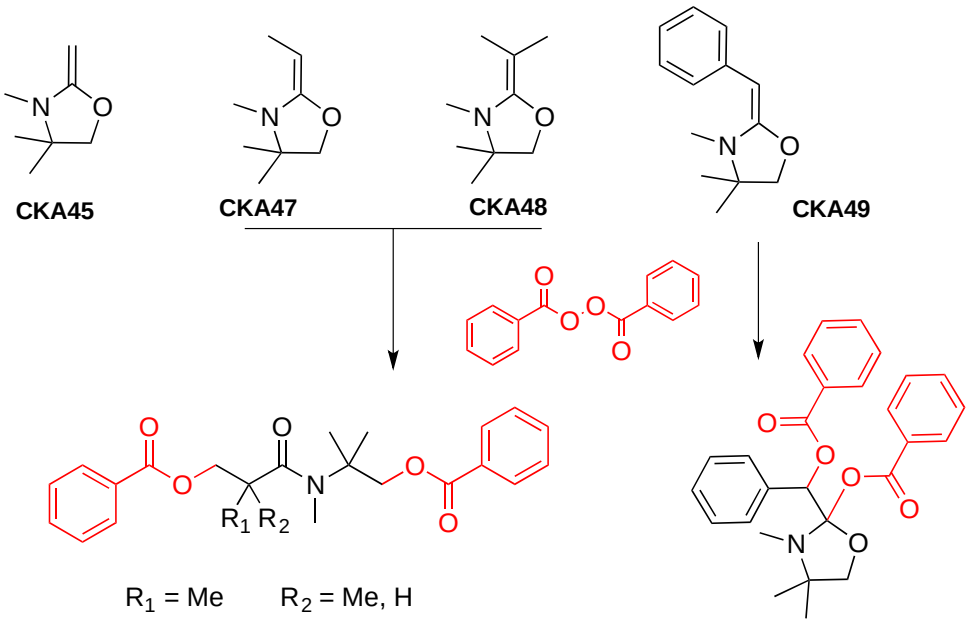
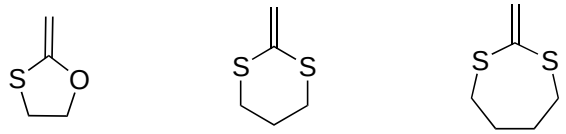


Figure 81. Addition products of benzoyl peroxide onto different O,N-CKA.

These results confirmed that 5-membered O,N-CKA monomers generally undergo 100% ring-opening except for monomer **CKA49** because of the aromatic ring that stabilize the radical formed after addition. The absence of polymerization could be explained by a weak tendency to

propagate in the case of the less reactive monomers, namely the monomers with a substitutive group on the exo-methylene function.

Sulfurated CKAs (O,S/S-S CKA) seemed less reactive than the homologous O,N-CKAs. For instance, polymers containing 15 % and 40 % of ring-opening units (at respectively 120 and 140 °C) were obtained when 2-methyleneoxathiolane (**CKA50**, Figure 82) was polymerized in the presence of di-*tert*-butyl peroxide.[72] Different results were nevertheless found a few years later by Bailey, with 45% of ring-opening at 120 °C.[11] The polymerization of **CKA51** with AIBN at 80 °C in bulk or in solution did not give dithioesters but only low molecular weight (700 – 1500 $g.mol^{-1}$) dithio-acetals by vinyl polymerization.[213] But interestingly, this monomer tend to homopolymerize in the presence of styrene or MMA ($r_{CKA51/Sty}$ = 3.35 & $r_{Sty/CKA51}$ = 0.03 and $r_{CKA51/MMA}$ = 4.12 & $r_{MMA/CKA51}$ = 0.08).[214] The same homopolymerization conditions used for **CKA52** did not give any polymer, likely because of the steric hindrance.[210]



CKA50 **CKA51** **CKA52**

Figure 82. O,S/S-S CKA monomers.

4.7 Hybrid CKA monomers

To find more reactive CKAs, several groups prepared hybrid monomers bearing an acetal ring and a less nucleophilic C=C double bond. For example, the polymerization of a cyclic vinylcetene acetal (Figure 83) with AIBN in benzene has been reported.[215] The polymerization mechanism involved a rearrangement followed by a ring-opening and the presence of high proportions of unsaturated polyester chains has been proved through the synthesis of high molar masses polymers (15,000 – 25,000 g.mol^{-1}) at only 55 °C. At 78 °C, the final product was insoluble likely because of crosslinking reactions. These results were confirmed later on by Fukuda[216] who further indicated that when the monomer was not stabilized by an aromatic ring such as **HA2**, the polymerization was more complex giving rise to polymers with repeat units coming from 1,2 and 1,4 (closed vinyl units) and 1,7 (open ester unit) polymerization.

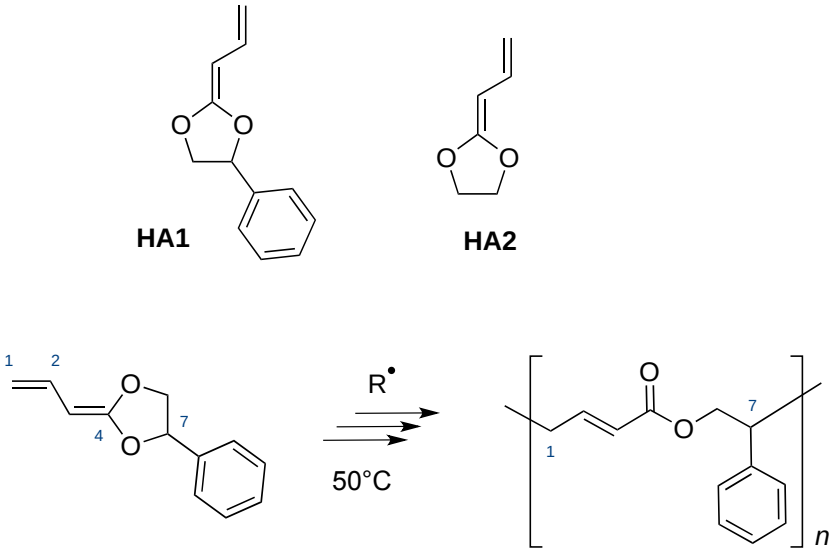


Figure 83. Polymerization of cyclic vinylcetene acetals.

Based on the idea that the formation of an aromatic ring during the polymerization (aromatization) favored the ring-opening, Cho[217] studied the polymerization of 8-methylene-1,4-

dioxaspiro[4.5]deca-6,9-diene **HA3**. This monomer polymerized exclusively by ring-opening and yielded polyether (instead of polyester) (Figure 84).

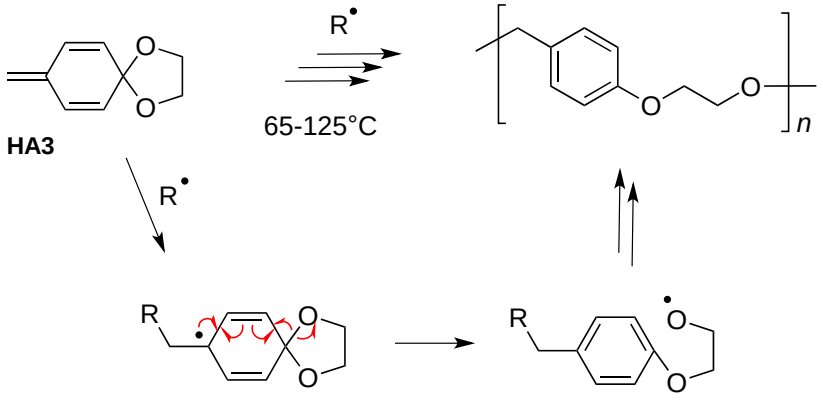


Figure 84. Polymerization mechanism of the 8-methylene-1,4-dioxaspiro[4.5]deca-6,9-diene **HA3**.

In 1993, a new class of monomers have been reported:[218] namely vinylcyclopropane cyclic acetal monomers that enabled the synthesis of polyesters with C=C double bonds along the chain with moderate molar masses (1,000 – 5,000 g.mol^{-1}) (Figure 85). The polymerization mechanism involved a double ring-opening reaction (route iii) often contaminated by the mono ring-opening reaction of the vinyl cyclopropane part (routes i and ii) and, to a lesser extent, by the vinyl polymerization of the C=C carbon double bond.

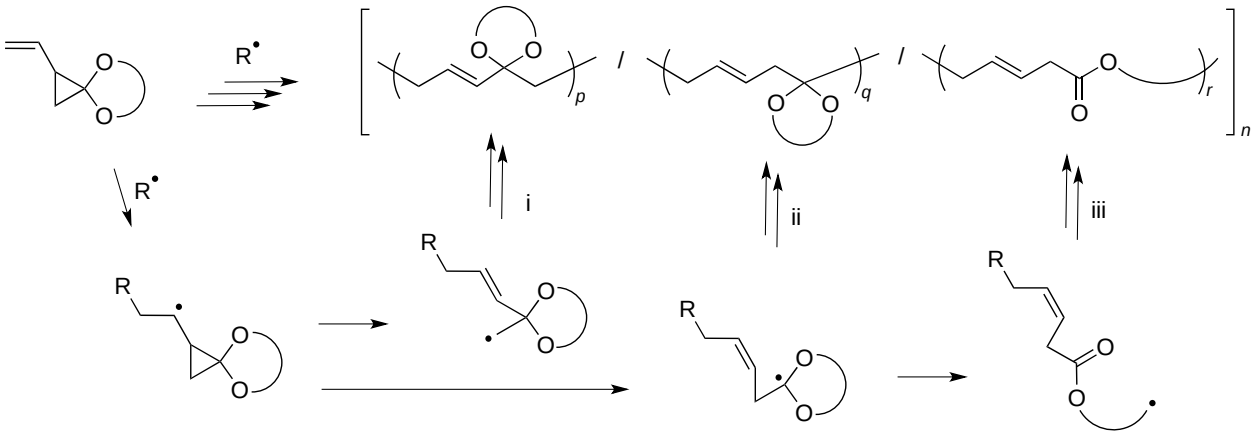
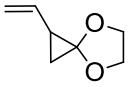
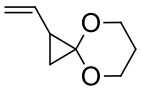
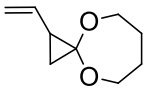
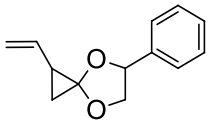
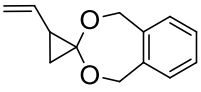
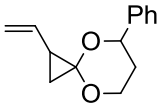
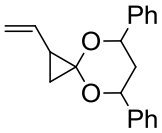
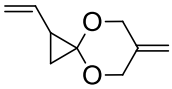
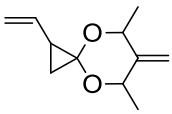
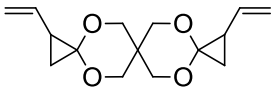


Figure 85. Polymerization mechanism of vinylcyclopropane cyclic acetal monomers.

The size of the ring was here again a crucial parameter that strongly influenced the structure of the obtained polymers. For instance, monomers with a non-substituted dioxolane ring (**HA4** Table 10) or dioxane ring (**HA5**) only polymerized *via* the cyclopropane ring-opening (r = 0% Figure 80) whereas with a dioxepane ring (**HA6**), units coming from a double ring-opening were observed (r > 0%).[219-220] The polymerization mechanism was in addition very complex since several rearrangements were possible giving different repeat units and even different pendant rings (Figure 86).[220]

Table 10. rROP of vinylcyclopropane cyclic acetal monomers

Monomer		Initiator, Temperature (°C)	% of different units in the polymer			Ref
			p + q	***r***	***Other***[a)]	
	**HA4**	AIBN, 60	89	0	11 pathway *a*	[220]
		BPO, 80	64	0	18 pathway *b* 18 pathway *c*	
	**HA5**	AIBN, 60 DTBP, 120	100	0	-	[219]
	**HA6**	AIBN, 60	46	46	8 pathway *a*	[220]
		BPO, 80	25	59	8 pathway *a* 8 pathway	

					b	
	**HA7**	AIBN, 60	74	19	7 pathway *c*	[220]
		BPO, 80	67	21	12 pathway *c*	
		DTBP, 120	26	36	38 pathway *c*	
	**HA8**	BPO, 80	18	46	7 pathway *a* 29 pathway *b*	[220]
	**HA9**	AIBN, 60, bulk DTBP, 120, bulk	-	31-42	-	[221]
	**HA10**	AIBN, 60, DMF DTBP, 120, ClBz	-	32-44	-	[221]
	**HA11**	AIBN, 60, DMF DTBP, 120, bulk	-	55-75	-	[221]
	**HA12**	AIBN, 60, bulk DTBP, 120, bulk	-	25-31	-	[221]
	**HA13**	crosslinked. no opening of dioxanes and around 50% of cyclopropane ring-opening				[222]

[a] See Figure 86, according to ref. [220]

In addition to O,O' cyclic acetal moieties, vinylcyclopropane cyclic S,S' acetal monomers were also prepared.[223] Whatever the thioacetal ring size, the obtained polymers (oligomers with M_n between 600 to 3100 g.mol^{-1}) only presented 1,5 ring opened units due to the cyclopropane β-

scission and kept the thioacetal ring. The unsaturation in the 1,5 repeat unit was poorly observed likely due to the addition of the propagating radical. This phenomenon explained the obtained low molar masses of these polymers.

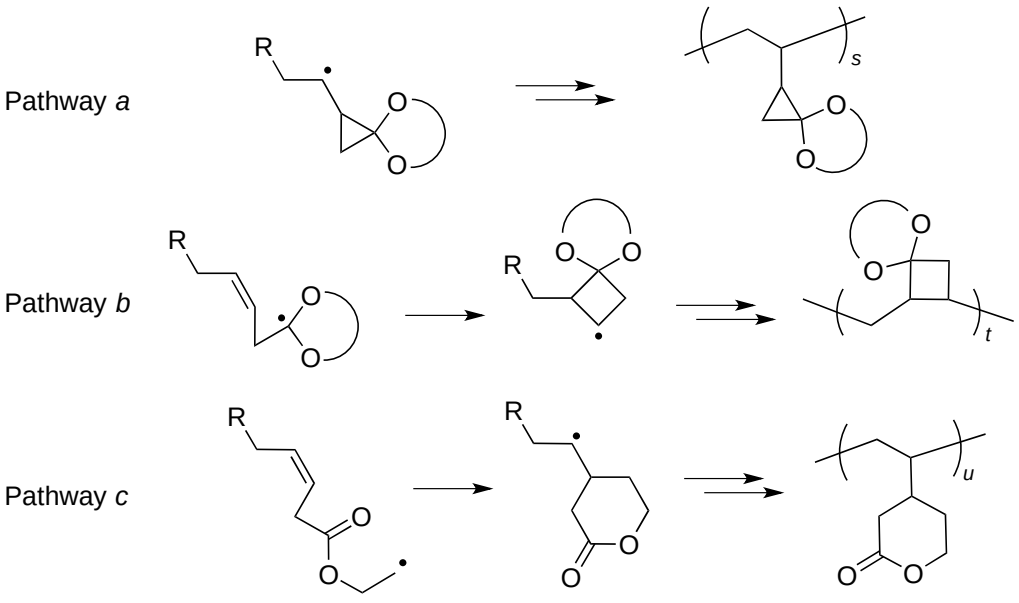


Figure 86. Secondary mechanism of the polymerization of cyclic vinylcyclopropane acetals

5. Radical Copolymerization Approach

5.1 Introduction

The copolymerization of classical vinyl and cyclic monomers was performed to combine the properties of traditional vinyl polymers with the advantages of cyclic monomers (e.g., low shrinkage, insertion of functional groups, etc.). In this section, cyclic monomers bearing heteroatoms are the most used since their copolymerization with vinyl monomers generally aims to elaborate (partially) degradable or fragmentable copolymers (Figure 87). Indeed, the radical ring-opening process of these cyclic monomers gives rise to functional groups (e.g., ester and/or ketone functions, etc.) that are more or less regularly distributed along the copolymer backbone (according to the monomers reactivity ratios). Depending on the type of functional groups deriving from the cyclic monomer after ring-opening, the resulting copolymer will be sensitive to hydrolysis, biodegradation or photoscission. The design of such copolymers represents a very attractive research area since the synthesis of (partially) degradable organic materials is of high concern and one of the main challenges for the future. The main difficulty when targeting degradable copolymers is to get a regular distribution of the hydrolyzable functions along the chain; that is a high incorporation or reactivity of the cyclic monomer versus the vinyl monomer. This is one of the main challenges of such copolymerization systems: to find optimized monomer structures and polymerization conditions to get copolymers as random or alternated as possible, to have enough degradable functions in the chain to ensure significant degradation. The other problem that should be overcome when copolymerizing cyclic and vinyl monomers is to find radical polymerization conditions that only ensure a ring-opening process of the cyclic monomer. Indeed, if the cyclic monomer polymerizes only by polymerization of the C=C carbon double bond without ring-opening (i.e., traditional vinyl polymerization), no degradable function will be inserted in the resulting copolymer backbone.

Another goal when copolymerizing CKA and vinyl monomers is to elaborate functional degradable copolymers. In this case, the copolymerization is performed with an initial large excess of CKA versus the vinylic monomers to ensure that the polymer backbone is mainly constituted of ring-opened units. Not only the copolymer backbone is (bio)degradable, but the vinyl monomer enables the insertion of a broad range of different functionalities in the final material (Figure 87). This will be described in section 5.2.2 entitled "*Synthesis of functional degradable copolymers*".

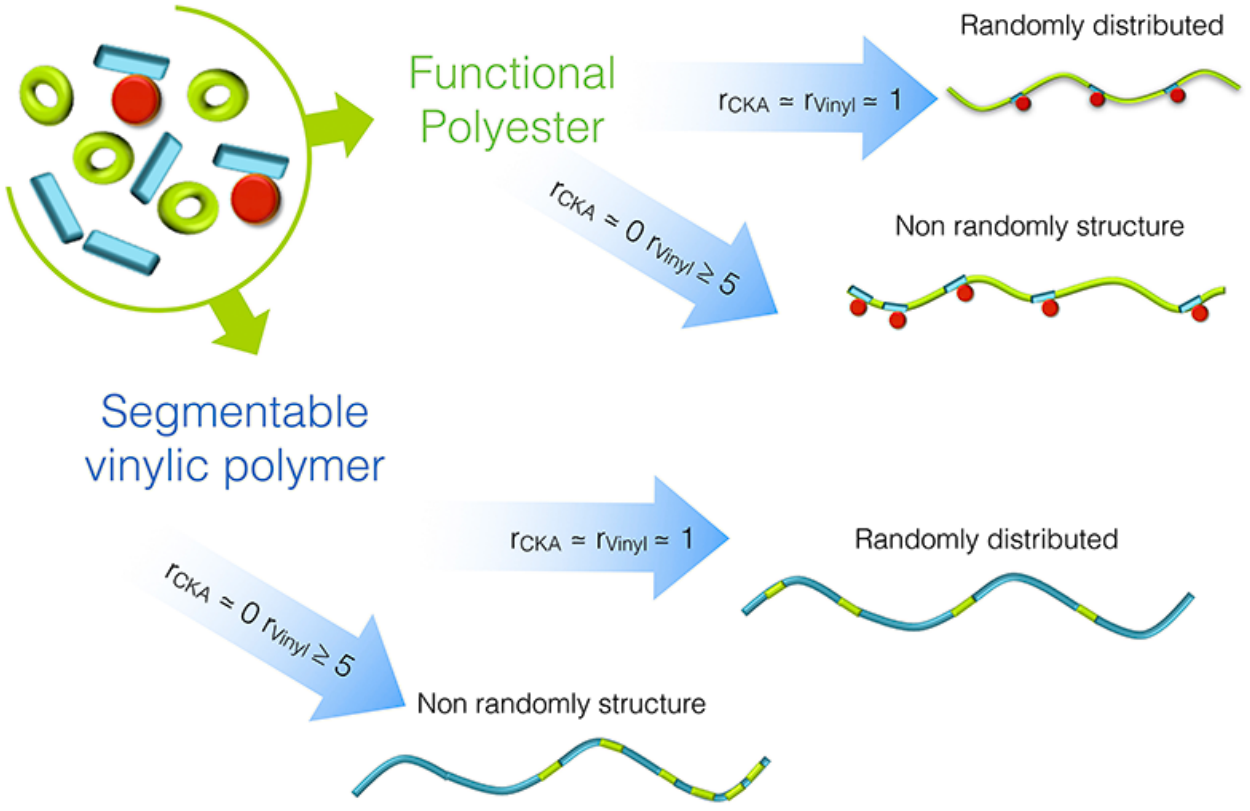


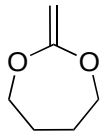
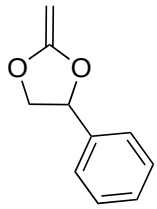
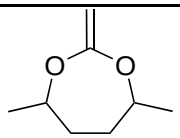
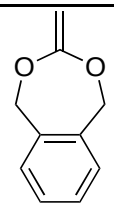
Figure 87. Copolymerization of (functional) vinyl monomer and cyclic monomer to prepare advanced materials.

5.2 Copolymerization of Cyclic Ketene Acetals with vinyl monomers

5.2.1 Monomer incorporation

The main objective when copolymerizing CKA with vinyl monomers is to elaborate copolymers bearing ester functions in their main chain. Different types of vinyl monomers have been copolymerized with 5 to 8-membered cyclic monomers. For instance, the radical copolymerization of 5 to 22% of MDP/MDO (7-membered monomer, **CKA27**) with ethylene at 120 °C enabled the incorporation of 2 to 10% of ester units in the final copolymer.[224-225] Nevertheless, the radical copolymerization of CKA with vinyl monomers is difficult and the first studies reported systems with an initial comonomer composition around 50%. Table 11 summarizes the first copolymerizations performed with CKA and different vinyl monomers. One can notice that the polymerization times were in general very long (24 – 72h). At the end of the polymerization, the vinyl monomer was generally already consumed, leading to P(CKA) chains (in the case of conventional radical copolymerization). In addition, the rate of CKA incorporation in the final copolymer was in general low, except for the copolymerization with vinyl acetate (VAc). A particular attention will be dedicated in this paragraph to the copolymerization of CKA with styrenics, methacrylates, acrylates and acrylamides monomers. The copolymerization with other less common activated and non-activated monomers will also be described.

Table 11. Copolymerizations of CKA with common vinyl monomers.

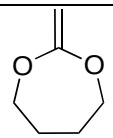
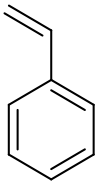
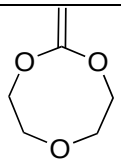
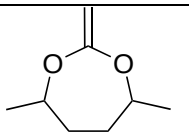
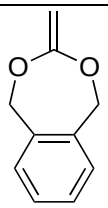
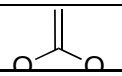
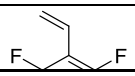
CKA	Vinyl monomer	Polymerization conditions	initial monomer composition (mol%)	mol% of CKA in the copolymer	References
 MDP/MDO **CKA27**	Styrene	DTBP, 120 °C, 36h	50	23	10
	4-vinylanisole	DTBP, 120 °C, 36h	50	19	
	MMA	DTBP, 120 °C, 12h	50	33	
	MMA	AIBN, 50 °C, 48h	50	25	
	VAc	DTBP, 120 °C, 12h	50	49	
	VAc	AIBN, 50 °C, 48h	50	34	
 MPDO/MPDL **CKA11**	Styrene	DTBP, 120 °C, 24h	50	32	193
	4-vinylpyridine	DTBP, 110 °C, 12h	50	34	
	MMA	DTBP, 120 °C, 24h	50	40	
	VAc	DTBP, 120 °C, 24h	50	40	
 **CKA28**	Styrene	DTBP, 120 °C, 72h	50	27	184
	MMA	AIBN, 50 °C, 48h	50	24	
 BMDO **CKA29**	Styrene	DTBP, 120 °C, 42h	50	31	
	4-vinylanisole	DTBP, 120 °C, 42h	50	33	
	MMA	AIBN, 50 °C, 45h	50	13	

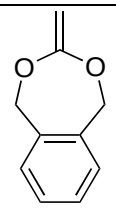
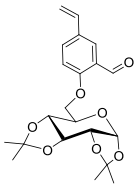
CKA copolymerization with styrenic monomers

The copolymerization of CKA with styrenic monomers is particularly difficult. In particular, an initial molar fraction of 80 mol% of **CKA27** was necessary to obtain a polystyrene with only 10 mol% of CKA units.[226] A further study performed by pulsed laser polymerization was even more

pessimistic since it was concluded that MDO/MDP **CKA27** only acted as spectator (solvent like behavior) during styrene homopolymerization, thus ruling out the possibility to perform **CKA27** /Sty copolymerization.[227] A few studies have nevertheless been reported in the literature on the copolymerization of various CKA and styrenics monomers and an overview is given in Table 12.

Table 12. CKA copolymerization with styrenics monomers.

CKA	Styrenics	Conditions of polymerization	molar composition (% CKA)		References
			comonomer mixture	final copolymer	
 MDP/MDO **CKA27**	Styrene 	120 °C	80	10	226
 MTC **CKA36**		120 °C, 24h	50	24	189
 **CKA28**		ATRP, 110 °C, 24h	50	4,6	228
			70	7,3	
 BMDO **CKA29**		ATRP, 120 °C, 72h	50	19	229
			70	42	
		DTBP, 120 °C,	40	23	230

		18h, C=50-80%	77	46	
 BMDO **CKA29**		RAFT, 130 °C, 48h, anisole	50	15	16
			80	38	231

The copolymerization of styrene with the 8-membered **CKA36** seemed easier than the one with all 7-membered monomers (24% of CKA in the final copolymer versus 4.6 – 19 % for a 50/50 mol% CKA/styrene initial comonomer mixture). In the case of controlled radical copolymerization of BMDO (**CKA29**) with styrene by ATRP, a DSC study revealed the presence of two glass transition temperatures (between the values corresponding of the homopolymers) that were explained by an immiscible blocky random structure of the copolymer. [229] Finally, the copolymerization of MDP/MDO (**CKA27**) with 2,3,4,5,6-pentafluorostyrene also seemed easier. An explanation as proposed by the authors is that the fluorine groups increased the electrophilic character of the pentafluorostyryl radical compared to the styryl radical. The consequence was that copolymerization of the nucleophilic CKA radical was easier with the fluorinated radical than with the non-fluorinated counterpart.

CKA copolymerization with methacrylic esters

Several studies have been devoted to the copolymerization of CKA with methacrylic esters and in particular with MMA (Table 13). If considering **CKA36**, BMDO (**CKA29**) and MDP/MDO (**CKA27**), their copolymerization with methacrylic esters was easier than with styrenics. It was in

particular possible to get copolymers containing up to 35 mol% of CKA units when starting from a comonomer mixture containing 50 mol% of CKA. Surprisingly, Pulsed-Laser Polymerization (PLP) experiments showed that the copolymerization of **CKA27** and MMA was almost impossible.[232] The differences between the results obtained by PLP[232] and classic polymerization[233] could be explained by the difference of experimental conditions. The reaction temperatures were in particular significantly different: 40 °C for the PLP and 120 °C for the classic process. A recent work on the copolymerization of MDP/MDO **CKA27** and MMA by using a PCL macroinitiator[234] also presented a lower incorporation of the CKA than the one calculated in the first studies. Similarly, the copolymerization of MDP/MDO **CKA27** with methacrylate derivatives (e.g., oligo(ethylene glycol) methyl ether methacrylate (OEGMA) and dimethylaminoethyl methacrylate (DMAEMA)) were shown to be relatively difficult since the authors only obtained 15-20% of CKA in the final copolymer for an initial comonomer mixture of 50 mol%.[17-18, 21, 235-238]

The copolymerization of BMDO **CKA29** with methacrylic acid was of particular interest since the carboxylic acid function reacted first with the nucleophilic double bond to form another type of methacrylate. Two types of structure were therefore obtained depending on the initial molar ratio (Figure 88).[171]

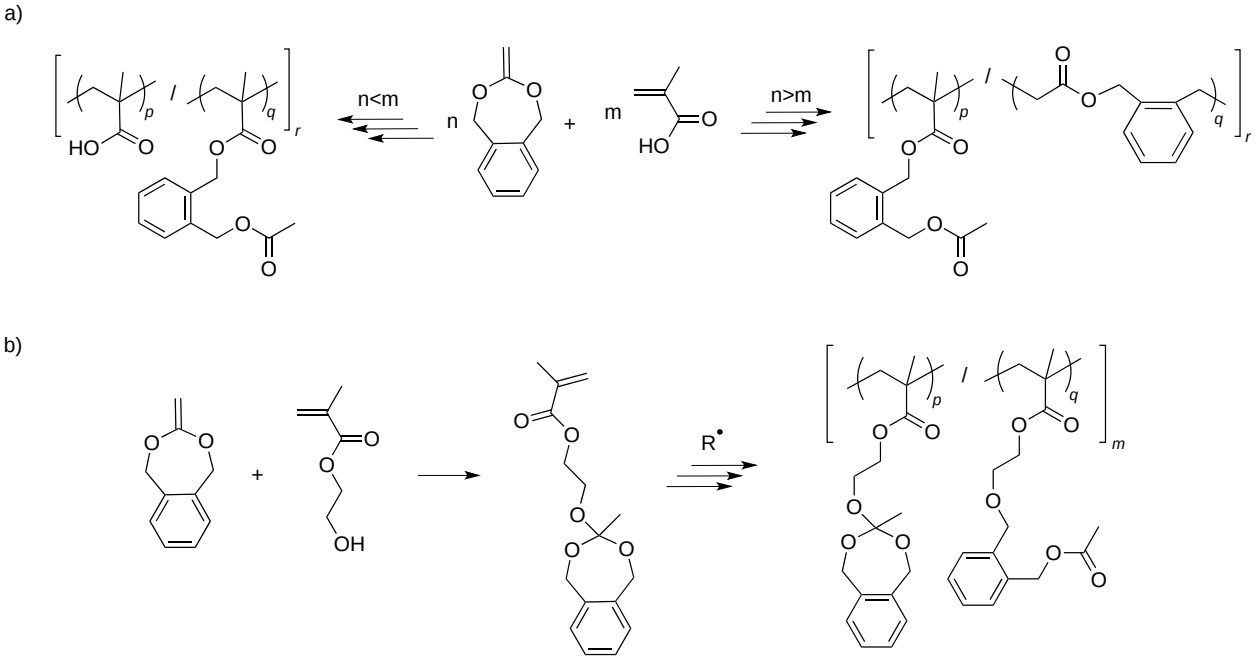
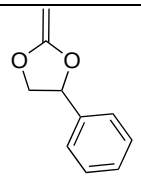
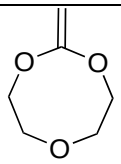
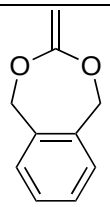
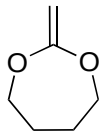
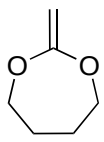
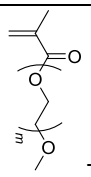
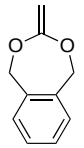
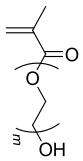
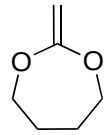
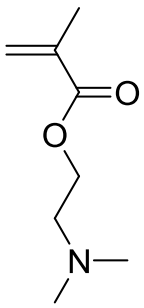
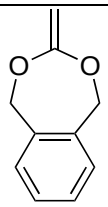
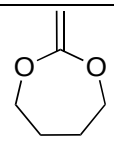
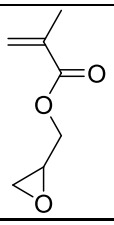


Figure 88. a) Copolymerization of BMDO (**CKA29**) and methacrylic acid. b) Side reaction occurring during the copolymerization of BMDO **CKA29** and 2-hydroxyethyl methacrylate (HEMA).

When copolymerizing CKA monomers such as BMDO (**CKA29**) with hydroxyl containing monomers and in particular with 2-hydroxyethyl methacrylate (HEMA), the occurrence of the undesired proton addition to the double bond led to many different repeat units in the polymer backbone (Figure 87b).[238] To incorporate ester units in the PHEMA backbone, Agarwal and coworkers[238] prepared a TMS-protected HEMA that was efficiently copolymerized with BMDO **CKA29**. The resulting copolymer was then deprotected using KF/TBAF classic procedure.[238]

Table 13. Copolymerization of CKAs with methacrylic esters.

CKA	Methacrylic ester	Polymerization conditions	molar composition (% CKA)		References
			comonomer mixture	final copolymers	
 MPDO/MPDL **CKA11**	MMA	120 °C, 15h, 2h	90	82	186
			50	34	
			10	9	
 MTC **CKA36**		120 °C, 24h	50	38	189
 BMDO **CKA29**		ATRP, 120 °C, 72h, Conv=40-88%	50	34	239
			70	53	
 MDP/MDO **CKA27**		PLP, 40 °C	54	4	232
			76	11	
		120 °C, 2h, Conv≈50%	50	30	233
			78	57	
		Macroinitiator PCL-Azo, 80 °C, 4h, Conv≈60%	50	17	234
			80	31	
 MDP/MDO **CKA27**	 + Methylcoumarin methacrylate		70	45	237

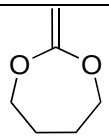
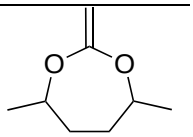
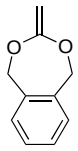
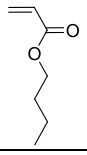
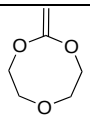
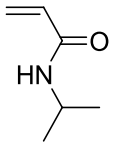
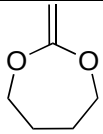
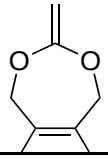
 BMDO **CKA29**		m=2,9	ATRP, 90 °C	20	5-7	17
		m=1 -OTMS	AIBN, 70 °C, 24h, bulk	50	33	238
				75	43	
 MDP/MDO **CKA27**			70 °C, 20h	50	21	235
				70	40	
			PEG-macroinitiator Azo, 70 °C, 24h	50	10-22	236
				90	51-57	
 BMDO **CKA29**			PEG-macroinitiator Azo, 70 °C, 24h	50	16	18
				90	45	
 MDP/MDO **CKA27**			AIBN, 60 °C, 3h	60	24	21
				75	41	
				90	61	

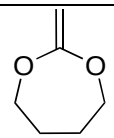
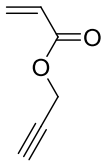
CKA copolymerization with acrylates and acrylamides

The copolymerization of CKA with acrylates is highly influenced by the experimental conditions, such as the reaction temperature and the choice of monomers (see Table 14). The 7-membered dimethyl-substituted **CKA28** presented a surprisingly high rate of incorporation when copolymerized at 110 °C with methyl acrylate (MA).[228] A moderate incorporation was observed when MDP/MDO **CKA27** was copolymerized with propargyl acrylate at 65 °C.[240] Nevertheless one can note that these two examples of high reactivity CKAs were accompanied by a low ratio of ring-opening (only 80% and 30-60% respectively). Conversely to the two previously cited examples, when MDP/MDO **CKA27** was copolymerized with MA at 50 °C, its incorporation in

the final copolymer was very low (only 4 and 18 mol% when starting from a monomer mixture of 50 and 85 mol% of CKA, respectively).[241] Other CKA copolymerizations with in particular *n*-butyl acrylate (nBA) and NIPAAm gave copolymers with higher CKA units contents, in the 20-30 mol% range for an initial monomer mixture of 50 mol%.[20, 242-243]

Table 14. CKA copolymerization with acrylic esters.

CKA	Acrylic ester	Polymerization conditions	molar composition (% CKA)		References
			comonomer mixture	final copolymer	
 MDP/MDO **CKA27**	MA 	50 °C, 24h	50	4	241
			65	11	
			85	18	
 **CKA28**		ATRP, 110 °C, 24h	50	47	228
			70	49	
 BMDO **CKA29**	*n*BA 	ATRP 110 °C, 20h	50	28	242
			70	40	
 MTC **CKA36**	NIPAAm 	AiBN, 60 °C, 24h, benzene	50	17	244
			70	32	
 MDP/MDO **CKA27**		AIBN, 55 °C, 24h	50	29	20
			70	46	
					19
		RAFT, 60 °C, 10h	30	14	14
			10	5	
		ATRP 25 °C, 10h	30	14	

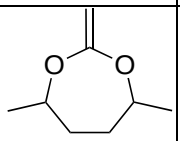
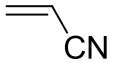
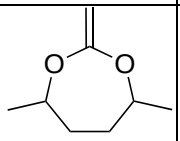
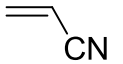
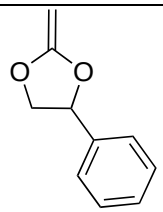
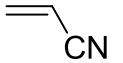
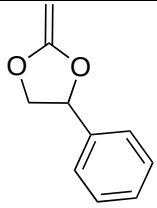
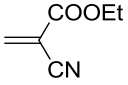
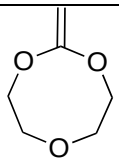
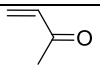
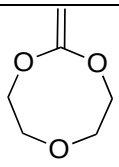
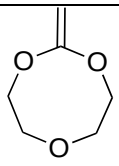
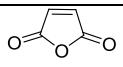
		DTBP, 120 °C , 8h, anisole	20 50 50 70	8 21 10 (10min) 35	243
 MDP/MDO **CKA27**		AIBN 65 °C, 4h	50 80	39 47	240

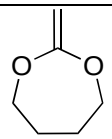
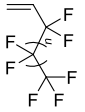
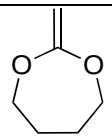
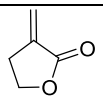
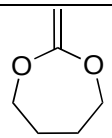
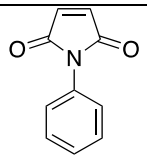
CKA copolymerization with other activated monomers

Other activated monomers have been copolymerized with CKA. The main results from these copolymerizations are summarized in Table 15. The rate of CKA incorporation was here again governed by the copolymerization system and the experimental conditions. The 8-membered ring **CKA36** was copolymerized with methyl vinyl ketone with a reactivity similar to the one of acrylates.[245] According to Yuan and coworkers, the ATRP-based copolymerization of the 7-membered dimethyl-substituted CKA **CKA28** monomer with acrylonitrile afforded a high incorporation rate of CKA in the final copolymer, but with only 70% of ring-opening, likely due to electrophilic-nucleophilic interaction.[228] A similar interaction was already described by Cho and coworkers between **CKA11** and AN also leading to limited ring-opening (7 – 10%).[246]

Table 15. CKA copolymerization with activated monomers.

CKA	**Vinyl monomer**	**Polymerization conditions**	**molar composition (% CKA)**		**% of ring-openin**	**References**
			comonome	**final**		

			r mixture	copolymer	g	
 **CKA28**		ATRP, 110 °C, 24h	50	51	70	[228]
 **CKA28**		ATRP, 110 °C, 24h	70	48	70	[228]
 MPDO/MPDL **CKA11**		AIBN, 60 °C, 12h	50-	26	7	[246]
 MPDO/MPDL **CKA11**		AIBN, 60 °C, 12h	50	70	10	[246]
 MTC **CKA36**		AIBN, 60 °C, benzene, 48h	50	28	100	[245]
 MTC **CKA36**		AIBN, 60 °C, benzene, 48h	70	43	100	[245]
 MTC **CKA36**		AIBN, DTBP, 60-120 °C, chlorobenzene, 24h	50	Alternating	-	[247]

 MDP/MDO **CKA27**	 n=2,3,4	AIBN, 125 °C, bulk, 2h	50	52	100	248
 MDP/MDO **CKA27**		with or without initiator, 70/120 °C, 24h	50	25-35	54-95	249
 MDP/MDO **CKA27**		with or without initiator, 60/120 °C, 2h	50	54	39	250

In the eighties, Endo and coworkers investigated the spontaneous copolymerization of CKA (MDP/MDO **CKA27** and MDPL/MDPO **CKA11**) with various electrophilic compounds (heterocumulenes such as CS_2,[251] cyanoallene,[252] β-propiolactone[253] and vinyl monomers e. g. methyl α-cyanoacrylate,[254-255] MMA,[255] AN,[255] etc.). They reported the preparation of copolymers *via* a pure zwitterionic mechanism. In the case of vinyl monomers, the obtained copolymer was not a pure alternating one since all the reactant was not converted into zwitterions but only partially formed zwitterions that then react with the remaining monomers by ionic reactions.[255] Recently, Agarwal and coworkers[249] reported the spontaneous polymerization of the MDP/MDO **CKA27** with tulipalin A by simply mixing these monomers. According to the authors, the polymerization mechanism was based on a charge transfer complex propagating *via* a radical or an ionic process (Figure 89). The ring-opening ratio decreased down to 54% when the radical mechanism was limited by a radical inhibitor, but reached 95% in the presence of a radical initiator. In addition, the microstructure study proved that the copolymer was not an

alternating one. A similar study with *N*-phenyl maleimide as comonomer was also reported (Table 15). [250] This monomer was chosen since the corresponding materials usually presented interesting mechanical and thermal properties due to the incorporation of rigid structures. When performed at 60 °C, a 1:1 incorporation of the two monomers was observed whatever the feed ratio, which is a characteristic feature of an alternating copolymerization. However MDP/MDO **CKA27** led to pure polyacetals. In order to increase the amount of ring-opened units, the copolymerization was performed at higher temperature (120 °C). In this case, the incorporation of MDP/MDO **CKA27** led to both ring-opened and ring-retained units with a ratio close to 50% when the feed ratio exceeded 1:1 in *N*-phenyl maleimide. Similarly to the copolymerization with Tulipalin A, the polymerization proceeded *via* a charge complex mechanism with a combination of cationic and radical pathways.

The copolymerization of MDP/MDO **CKA27** with various fluorinated alkenes[248] presented the characteristics of an alternating copolymerization (i.e., monomers' conversion higher in copolymerization than in homopolymerization and copolymer composition close to 50 %). However, one can regret that other initial monomer compositions have not been investigated.

Concerning the copolymerization of the 8-membered ring **CKA36** with maleic anhydride, Hiraguri and coworkers[247] reported the synthesis of an alternating structure. Unfortunately, this structure was not clearly demonstrated and could be subjected to discussion since a degradation study revealed a non-complete degradation of the material that was the indirect proof of the presence of non-opened CKA units. Some CKA units have therefore been probably polymerized *via* the traditional vinyl process and not by a ring-opening mechanism.

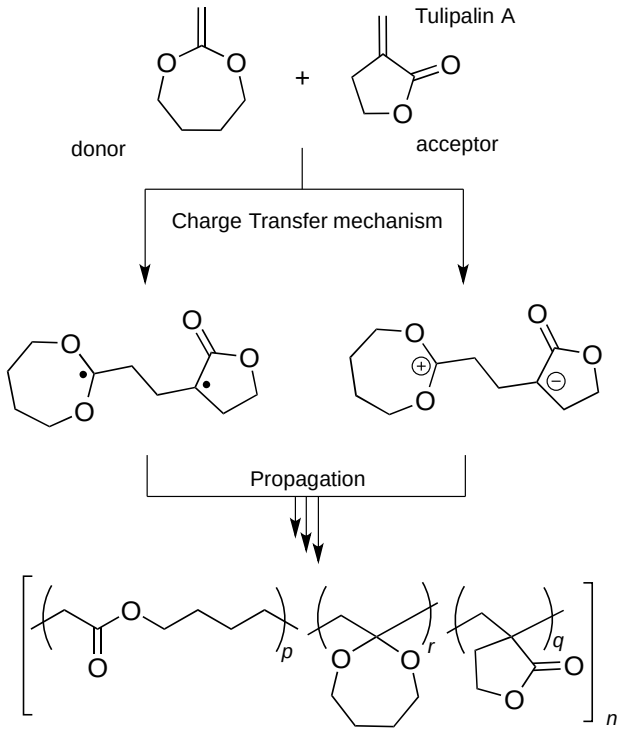


Figure 89. Mechanism of spontaneous copolymerization of **CKA27** with tulipalin A.

CKA copolymerization with non-activated monomers

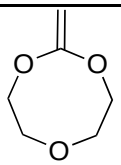
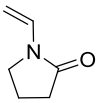
The first copolymerizations of MDP/MDO **CKA27** and MPDL **CKA11** with VAc were reported in 1982 by Bailey and coworkers.[10, 193] Hiraguri and coworkers[189] revisited these experiments a few years later and performed the same kind of copolymerizations but this time with the 8-membered ring **CKA36**. The authors reported a CKA incorporation close to 40 mol% for an initial comonomer mixture containing 50 mol% of CKA. More recently, both Agarwal[256] and Albertsson[257] also studied the copolymerization of MDP/MDO **CKA27** with VAc. They both reported a good incorporation of the CKA monomer in the final copolymer and proved for the

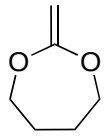
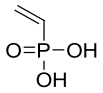
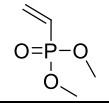
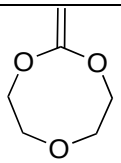
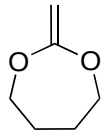
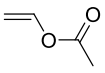
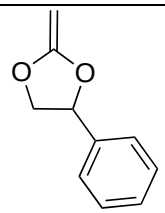
first time the synthesis of random copolymers by means of NMR and investigation of the microstructure.[256-257]

Vinyl dimethylphosphonate and vinyl phosphonic acid both present a resonance stabilized radical but are not highly reactive because of significant steric hindrance.[258-259] The copolymerization of the MDP/MDO **CKA27** with vinyl dimethylphosphonate yielded a copolymer with a good CKA incorporation (36 to 60 mol% of CKA in the copolymer when starting from a comonomer mixture of 50 to 75 mol% of CKA). This was not the case for vinyl phosphonic acid under the same experimental conditions as only 16 to 32 mol% of CKA was inserted in the final copolymer when starting from a comonomer mixture of 50 to 72 mol% of CKA. With the second vinyl monomer, the acid function could initiate a side cationic polymerization that could compete with the radical process. [258]

By comparing two copolymerizations between **CKA36** and *N*-vinylpyrolidone (NVP) performed in different conditions (Table 16), it seemed that the bulk process enabled reaching higher rate of CKA incorporation than when the polymerization was performed in scCO2.[260-261]

Table 16. CKA copolymerization with non-activated vinyl monomers

CKA	Vinyl monomer	Conditions of polymerization	molar composition (% CKA)		References
			comonomer mixture	final copolymer	
 MTC **CKA36**	NVP 	AIBN, 60 °C, 24h, bulk, C=60-80%	50	31	[260]
			70	61	

 MDP/MDO **CKA27**		$scCO_2$, 70 °C, 24h	40 60 80	17 35 38	261
		50 °C, 48h	50 72	16 32	258
			50 75	36 60	
 MTC **CKA36**		120 °C, 24h	50	42	189
 MDP/MDO **CKA27**	VAc 	AIBN, 70 °C 4h, bulk	19 52 52 76	18 47 37 (30min) 73	256
		AIBN, bulk, 60 °C, 2-4h	30 50 70	23 42 66	257
		AIBN, 50 °C, 48h	50	34	10
		DTBP, 120 °C, 12h	50	49	
 MPDO/MPDL **CKA11**		DTBP, 120 °C, 24h	50	40	193

The copolymerization between two CKA monomers have also been attempted. Albertsson and coworkers[262] performed the copolymerization of MDO/MDP **CKA27** and MTC (**CKA36**) and obtained poly(ester-ether) with a certain degree of hydrophilicity and absence of crystallinity. The results seemed to show a random incorporation of the two monomers even if one experiment presented a higher reactivity for **CKA36**. Further studies are therefore necessary to confirm these results.

In conclusion from the literature data presented above, it seemed that both the molar masses and the global conversions decreased when increasing the initial $[CKA]_0/[comonomer]_0$ ratio. In addition, whatever the nature of the comonomer, incorporation of CKA in the final copolymer appeared generally difficult or even limited. Nevertheless, the reported studies were generally performed by using an initial $[CKA]_0/[comonomer]_0$ ratio of 50/50 where one can note a significant difference between samples taken below 10 % conversion and those taken above.[233, 238, 243] To get a more accurate idea of the structure of the synthesized copolymer, evaluation of the reactivity ratio for the couple CKA/comonomer is usually necessary (for given experimental conditions). The values that have been determined so far are listed and discussed in subsection 5.2.3.

5.2.2 Synthesis of functional degradable copolymers

The majority of the studies devoted to the copolymerization of CKAs with common vinyl monomers were performed in order to confer (bio)degradability properties to well-known polymers. This led to many potential applications detailed in section 7.1. Recently, a few authors used this copolymerization approach to introduce functionalities in degradable polyester chains. Contrary to what was presented in section 5.2.1, the objective was here to incorporate only a few percent of functionalized vinyl monomers into a CKA-based degradable backbone to introduce functionalities in a relatively simple manner.

As reported by Albertsson[21, 263] and Agarwal[240, 264], the most frequently studied CKA for such a purpose was MDP/MDO **CKA27** because its radical ring-opening polymerization formed aliphatic polyester chains similar to that of polycaprolactone (PCL). When synthesizing polyester chains by classical ROP or polycondensation, the introduction of functional groups is usually challenging. The radical copolymerization of CKA and in particular of MDP/MDO **CKA27** with vinyl monomers thus offered a very interesting alternative (Table 17). Albertsson and coworkers [21, 263] focused on the radical copolymerization of MDP/MDO **CKA27** and glycidyl methacrylate (GMA) initiated by AIBN in bulk at 60 °C. The reactivity ratios evaluated by the Finemann-Ross method were $r_{\mathbf{CKA27}} = 6.6$ and $r_{GMA} = 26.8$ attesting of the higher reactivity of the methacrylate derivatives. Heparin was then successfully immobilized on the synthesized poly(**CKA27**-*co*-GMA) copolymers. The control of both the introduction of active groups[21] and the degradation rate[263] was achieved by adjusting the feed ratio.

Agarwal and coworkers synthesized poly(**CKA27**-*co*-propargyl acrylate) [240] and poly(**CKA27**-*co*-propargyl acrylate-*co*-DMAEMA)[264] copolymers by radical copolymerization with AIBN as an initiator. It was shown that only 30 to 70 mol% of the **CKA27** inserted in the copolymer were ring opened. The alkyne functions introduced in the (partially) degradable synthetic backbone were then modified by copper(I)-catalyzed azide alkyne cycloaddition (CuAAC) to graft PEG chains. The resulting hydrolytically degradable grafted copolymers revealed low cytotoxicity compared to PEI[240] or PDMAEMA.[264] MDO/MDP **CKA27** and PEG- or PNIPAAm-based macromonomers were also copolymerized and self-assembled into P**CKA27**-*g*-PEG or P**CKA27**-*g*-PNIPAAm amphiphilic copolymers nanoparticles (d = 66 – 350 nm).[265] It was shown that the average diameter of the nanoparticles were controlled by the

grafting ratio of PEG chains and that aggregation of PNIPAAm-based nanoparticles was driven by temperature.

Table 17. Synthesis of degradable functional copolymers based on MDP/MDO **CKA27** and vinyl monomers.

vinyl monomer	conditions of polymerization	molar composition (%**CKA27**)		References
		comonomer mixture	final copolymer	
GMA	AIBN, 60 °C, ,3h, bulk	60 - 90 mol%	24 – 61 mol%	[21, 263]
PA	AIBN, 65 °C, 4 h, THF	20 – 80 mol%	25 – 47 mol%	[240]
PA and DMAEMA	AIBN, 65 °C, 14 h, THF	30 – 70 mol%	30 – 53 mol%	[264]
PEG-MA or PNIPAAm macromonomer	AIBN, 70 °C, 48h, bulk	98 – 99.8 mol% (vs PEG-MA)	98-99 mol% (PMDO-*g*-PEG)	[265]
VDMA	AIBN, 70 °C,	10-90 mol%	2-49 mol%	[266]

	24h, toluene			

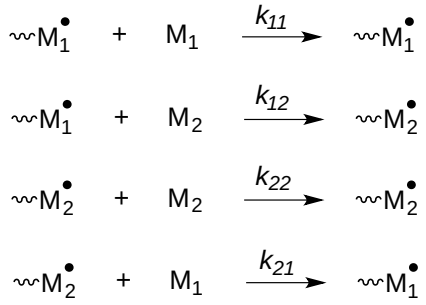
GMA: glycidyl methacrylate; PA : propargyl acrylate; DMAEMA: *N,N*-dimethylaminoethyl methacrylate; PEG-MA: poly(ethylene glycol) methacrylate; NIPAAm: *N,N*-isopropyl acrylamide

Lynn and coworkers performed the copolymerization of MDO/MDP **CKA27** with 2-vinyl-4,4'-dimethylazlactone (VDMA).[266] The azlactone moiety is nowadays widely used in polymer chemistry to introduce pendant functionality since this electrophile group can react efficiently with primary amines to prepare at room temperature and in the absence of a catalyst (or the generation of byproducts) functionalized poly(acrylamide)-type polymers.[267] The incorporation of MDO/MDP **CKA27** was determined to be lower than the initial amount present in the feed (90 mol% of CKA27 in the initial feed led to 49 mol% of ester functions in the polymer backbone). In addition, a non-negligible part of the CKA was inserted into acetal form (ratios between acetal and ester functions equal to 0.33 – 0.66 depending on the initial composition). These two results showed a rather similar reactivity for VDMA and acrylate derivatives[240] (PA).

5.2.3 Reactivity ratio

The copolymerization kinetics involving two monomers (M_1 and M_2) can be described as presented in Figure 90. This approach is based on the terminal model which suppose that the

radicals' reactivity only depends on the last monomer unit and that the propagation reactions are irreversible. The copolymerization of two monomers is then represented by 4 reactions (2 homopropagation reactions (rate constants k_{11} for monomer M_1 and k_{22} for monomer M_2) and 2 cross-propagation reactions (rate constants k_{12} and k_{21}).



$$r_1 = \frac{k_{11}}{k_{12}}$$

$$r_2 = \frac{k_{22}}{k_{21}}$$

Figure 90. Definition of the reactivity ratio r_1 and r_2 for monomers M_1 and M_2, respectively.

The determination of the reactivity ratios of a given couple of monomers is crucial to evaluate the microstructure of the copolymer chains formed during the polymerization. For example, if $r_1 \times r_2 = 1$ the copolymerization is called "ideal" and can form a random copolymer when r_1 and r_2 are not too different whereas when $r_1 \times r_2 = 0$ (with both r_1 and $r_2 < 1$), the copolymer is alternating. The microstructure of copolymers has generally a high influence on the mechanical properties of the material and, in the case of a copolymer comprising degradable monomer units, on its degradation features (Figure 87). Different methods have been proposed to evaluate the reactivity ratios.[259] The methods of Mayo and Lewis (1944, equation 1),[268] and Fineman and Ross (1950, equation 2)[269] are the pioneering ones and consist in a rearrangement of the copolymer composition equation into a linear form. Even if these methods are still used today, their main drawback is that different r_1 and r_2 values are found when changing the subscript 1 or 2 of the monomers. This asymmetrical treatment of the data is due to a too high effect of the high and low

compositions on the equations. A few years later, Kelen and Tudos (1975, equation 3)[270] introduced an arbitrary constant α in the linearization equation of Fineman and Ross to give an equal weight to all the data. Nevertheless, the three above-mentioned methods use the differential form of the copolymerization equation that assumes that the feed composition is not modified during the reaction (i.e., the overall molar conversion remains very low; typically <5 %). To investigate the copolymerization over a larger range of conversion values, it is then recommended to use calculation methods based on the integrated form of the copolymerization equation, such as the one proposed by Meyer and Lowry[271-272] in 1965 (equation 4) that requires computational procedures (e.g., non-linear least square method NLLS).

$$r_2 = \frac{[M_1]}{[M_2]}\left(\frac{d[M_2]}{d[M_1]}\left(1+\frac{r_1[M_1]}{[M_2]}\right)-1\right) \quad (1)$$

$$\frac{f_1}{f_2}\left(1-\frac{F_2}{F_1}\right) = r_1\left(\frac{f_1}{f_2}\right)^2\frac{F_2}{F_1} - r_2 \quad (2)$$

$$\eta = \left(r_1 - \frac{r_2}{\alpha}\right)\xi - \frac{r_2}{\alpha} \quad (3)$$

with :

$$\eta = \frac{\left(\frac{f_1}{f_2}\right)\left(\frac{F_1}{F_2}-1\right)\left(\frac{F_2}{F_1}\right)}{\alpha+\left(\frac{f_1}{f_2}\right)\left(\frac{F_1}{F_2}-1\right)\left(\frac{F_2}{F_1}\right)} \qquad \xi = \frac{\left(\frac{f_1}{f_2}\right)^2\left(\frac{F_2}{F_1}\right)}{\alpha+\left(\frac{f_1}{f_2}\right)^2\left(\frac{F_2}{F_1}\right)} \qquad \alpha = \sqrt{\left[\left(\frac{f_1}{f_2}\right)^2\left(\frac{F_2}{F_1}\right)\right]_{max}\left[\left(\frac{f_1}{f_2}\right)^2\left(\frac{F_2}{F_1}\right)\right]_{min}}$$

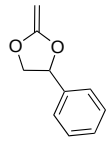
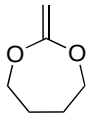
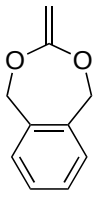
$$1-\frac{M}{M_0} = 1-\left[\frac{f_1}{(f_1)_0}\right]^{\alpha}\left[\frac{f_2}{(f_2)_0}\right]^{\beta}\left[\frac{(f_1)_0-\delta}{f_1-\delta}\right]^{\gamma} \quad (4)$$

with :

$$\alpha = \frac{r_2}{1-r_2} \qquad \beta = \frac{r_1}{1-r_1} \qquad \gamma = \frac{1-r_1r_2}{(1-r_1)(1-r_2)} \qquad \delta = \frac{1-r_2}{2-r_1-r_2}$$

To the best of our knowledge, reactivity ratios for CKA/vinyl monomer pairs published so far are listed in Table 18.

Table 18. Reactivity ratio of CKA (MDPO/MPDL **CKA11**, MDP/MDO **CKA27** and BMDO **CKA29**) with various vinyl monomers.

CKA	vinyl comonomer	r_{CKA}	r_{vinyl}	Method[b]	Polymerization conditions	Reference/ year
 MPDO/MPDL **CKA11**	MMA	0.01	4	NLLS	NMP, 90°C 50 w% toluene	[161] 2016
	MeOEGMA	0	6.95	NLLS	NMP, 90°C 50 w% toluene	[273] 2015
 MDP/MDO **CKA27**	St	0,021	22,6	-	DTBP 120 °C	[226] 1984
	MMA	0,04 0,057	3,5 34,12	KT NLLS	DTBP, 120 °C, bulk PLP, 40 °C, bulk	[233] 2007 [232] 1999
	MA	0,023	26,53	LW	AIBN, 50 ou112 °C, benzene or C_6H_5Cl	[241] 2003
	GMA	6.6	26.8	FR	AIBN, 60 °C, bulk	[21, 263] 2013
	NVP	0,014 0,081	6,31 9,25	NLLS NLLS	AIBN, 60 °C, sCO_2 300bar AIBN, 70 °C, sCO_2 300bar	[261] 2006
	VAc	0,93 0,47 0.14	1,71 1,53 1.89	FR KT KT	AIBN, 60 °C, bulk AIBN, 70 °C, bulk PhotoCMRP, 30°C, bulk	[257] 2012 [256] 2009 [274] 2016
 BMDO **CKA29**	St	1,08	8,53	KT	ATRP, 120 °C, bulk	[229] 2003
	PFS	0,35	9,9	KT	DTBP, 120 °C, bulk	[230] 2006
	MMA	0,53	1,96	KT	ATRP, 120 °C, bulk	[239] 2003
	DMAEMA	0,14	6,96	KT	DTBP 70 °C, bulk	[275] 2010
	HEMA-TMS	1,2	7,6	KT	AIBN, 70 °C, bulk	[238] 2012
	*n*BA	0,08	3,7	KT	ATRP, 110 °C, bulk	[242] 2005

	NIPAAm	0,11	7,31	KT	DTBP, 120 °C, anisole	[243] 2007

[a] St : Styrene, MMA : methyl methacrylate, OEGMA : oligo(ethylene glycol) methacrylate, MA : methyl acrylate, NVP : *N*-vinylpyrolidone, VAc : vinyl acetate, PFS : 2,3,4,4,6-pentafluorostyrene, DMAEMA : *N,N*-dimethylaminoethyl methacrylate, HEMA-TMS : trimethylsilyl hydroxyethylmethacrylate, *n*BA : *n*-butyl acrylate, NIPAAm : *N*-isopropylacrylamide ; [b] FR : Fineman-Ross, KT : Kelen-Tüdos, LW : Lewis and Mayo, NLLS: non-linear least square method

Even though the conversions used in the case of the linearization methods (ML, FR and KT) were generally higher than 5% (i.e., too high to use the differential form of the copolymerization equation), the main trend is a low reactivity of the CKA monomer in the presence of vinyl monomers excepted for VAc. These results were in good agreement with those already observed and previously reported in the "*monomer incorporation*" part (see section 5.2.1). It has to be noted that the reactivity of the CKA double bond was thus comparable to that of VAc and its copolymerization behavior was poorly compatible with styrenics, acrylates and methacrylates. This feature was rather surprising since one could expect that CKA monomers are strong nucleophilic olefins due to the presence of the two oxygens of the acetal moiety and thus could lead to good copolymerization behavior with electrophilic monomers such as methacrylic esters. It has to be noted that the reactivity ratio for the **CKA27**/VAc system is strongly dependent on the temperature (Table 18) compared to common reactivity ratios, highlighting the inherent difference of reactivity between CKA and classic vinyl monomers.

5.2.4 Q –e approach of the copolymerization between cyclic and vinyl monomers

During the 50s, Alfrey and Price[276] developed an empirical model called the Q-e scheme for predicting the reactivity of vinyl monomers in radical copolymerization. According to this model,

each reactant, monomer or free radical has a first parameter (Q for the monomer and P for the free radical) that represents its "general reactivity" in terms of resonance and a second parameter, e for both the monomer and the free radical, describing its "polar properties". Using the terminal model, the authors described the four propagation rate constants using the couple of P-Q-e parameters. The P parameter for the radical species could be eliminated by establishing the two following equations for the reactivity ratios that depend only on the monomers:

$$r_{12} = \frac{Q_1}{Q_2} e^{-(e_1(e_1-e_2))} \quad (5)$$

$$r_{21} = \frac{Q_2}{Q_1} e^{-(e_2(e_2-e_1))} \quad (6)$$

In practice, the Q-e scheme requires a reference monomer to which all other monomers can be classified. Styrene is usually taken as the reference monomer with Q = 1.0 and e = -0.8.[277] The Q and e values of any other monomer can be determined by using eq 5 or 6, using the experimental reactivity ratios and the Q and e values of the reference monomer. A large number of reviews on the Q-e scheme has been published,[278-280] giving Q – e databases for many vinyl monomers.

Concerning cyclic monomers only a few studies have been performed to experimentally determine Q-e values. Agarwal and coworkers[256] for example determined the value for the MDO/MDP **CKA27** monomer (Q = 0.01 and e = -0.3363) by copolymerizing this monomer with VAc. The obtained values are in agreement with a lower reactivity compared to styrene (Q =1) or methacrylate derivatives (Q = 0.76) and a high nucleophilic character (e = 1.23 for methacrylonitrile and 0.85 for butyl acrylate).[278] The value obtained for the CKA monomer

confirmed its difficulty to copolymerize with common vinyl monomers and such results were also confirmed by Mori et al.[281] using **AR4** as cyclic monomer.

The Q-e scheme is nevertheless only empirical and Price already said in the seminal article[276] that: "*to a reasonable approximation, the Q-e scheme permits the codification of copolymerization results*". One of the main drawbacks of the Q-e scheme is related to the approximation that the polarity of the monomer and the radical are similar. In the case of cyclic monomers, the addition-fragmentation process led to drastic changes in the structure of the radical compared to the monomer and such approximation is far less plausible.

5.3 Copolymerization of others cyclic monomers with vinyl monomers

5.3.1 Vinyl cyclopropane derivatives

The main interest of vinyl cyclopropane derivatives is to produce materials with low shrinkage (for instance for dental applications). Nevertheless the cost and the mechanical properties of the obtained materials make this option hardly relevant. To combine the low shrinkage feature and the properties of the matrix, VCP derivatives were copolymerized with traditional vinyl monomers. In particular, copolymerization of 1,1-dichloro-2-vinyl cyclopropane **VCP4** with maleic anhydride, Sty, MA and MMA was studied using BPO as an initiator.[282] The obtained polymers did not show substantial amounts of unsaturated double bond deriving from the 1,5 polymer units as expected if the VCP monomer was inserted after ring opening. Similar results

were also obtained when **VPC2** was used.[283] It was later shown that rings were formed by intramolecular cyclization of the growing radical on the unsaturated double bond (Figure 91) because of the relatively slow addition of the growing radical compared to the formation of a much favored 5- or 6-membered ring.[283]

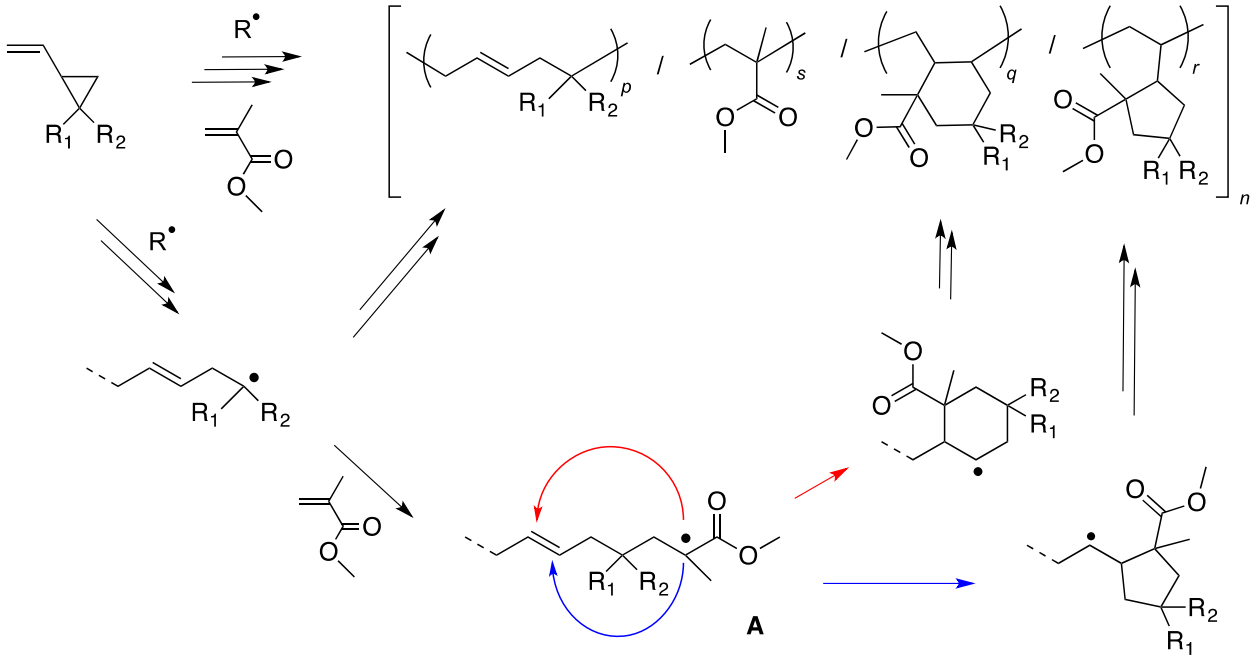
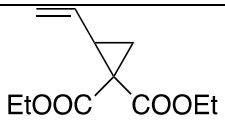
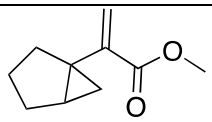
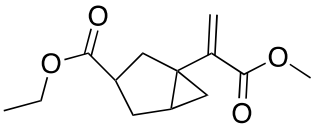


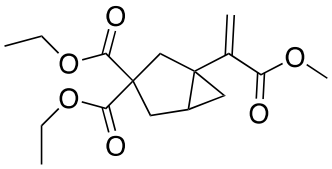
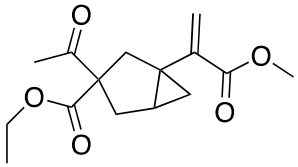
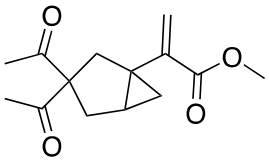
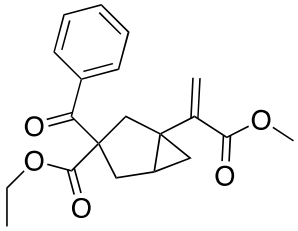
Figure 91. Intramolecular cyclization that could occur during the radical ring-opening polymerization of VCP derivatives with MMA.

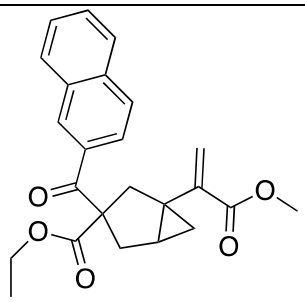
Whatever the VPC derivatives, the reactivity ratios were poorly compatible ($r_{MMA/\mathbf{VPC4}}$ =11 and $r_{MMA/\mathbf{VPC2}}$ = 26 compared to $r_{\mathbf{VPC4}/MMA}$ = 0.07 and $r_{\mathbf{VPC2}/MMA}$ = 0.03). Galli and coworkers[284] confirmed these results using a perfluoro vinyl cyclopropane derivative copolymerized with MMA. The reactivity ratios led to 5 – 8 % of **VCP2** when copolymerized with MMA from a 50 % feed ratio. In order to increase the reactivity of VCP derivatives, 2-cyclopropyl acrylate monomers and in particular **VCP5** (Figure 50, Table 19) were developed and led to quantitative and random incorporations of VCP and MMA in the copolymer backbone.[123, 138] To even further

increase the reactivity of VCP derivatives, substituted methyl 2-(Bicyclo[3.1.0]hex-1-yl)acrylates were prepared.[139] The introduction of keto or ester moieties (**VCP30 -VCP32)** further increased the reactivity of the VCP derivatives towards MMA leading to an incorporation of 60 % of VCP unit into the copolymer backbone and high molar mass copolymers (Table 19).

Table 19. Copolymerization of substituted methyl 2-(Bicyclo[3.1.0]hex-1-yl)acrylates with MMA ($[MMA]_0$ = 2.0 mol.L^{-1}, $[VCP] =_0$ = 2.0 mol.L^{-1}, AIBN (2 mol%), 65 °C, 15 h). [139]

Monomer	Conversion (%)	M_n (kg.mol^{-1})	$Đ$	Tg (°C)
 **VCP2**	94.7	67.5	1.87	22
 **VCP5**	100	120.2	2.48	90
 **VCP29**	100	66.0	1.93	77

 **VCP30**	91.1	143.4	2.27	83
 **VCP31**	94.8	434.4	2.17	97
 **VCP32**	94.3	142.1	2.47	121
 **VCP33**	80.4	66.0	1.82	107

 **VCP34**	14.9	13.0	1.47	96

Since the propagating radical of VCP derivatives is non-activated, Rimmer and coworkers[285] performed the copolymerization of **VCP2** with allylic carbonate monomers that are also non-activated monomers. These molecules were previously tested in copolymerization with VAc and allowed for the preparation of highly branched polymer structures.[286] The non-activated radicals could abstract hydrogen onto the isopropyl group leading to brush structures (Figure 92). The polymerization was performed for 10 hrs at 150 °C in chlorobenzene in the presence of AIBN and led to low molar masses highly branched structures.

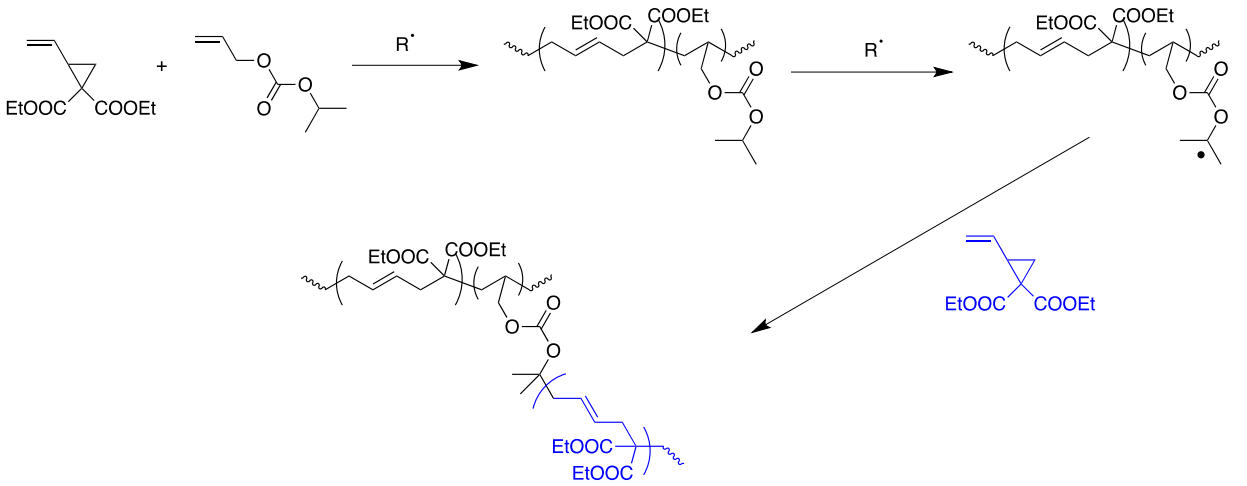


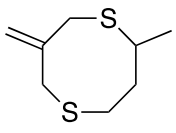
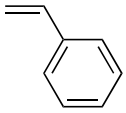
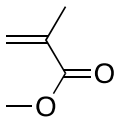
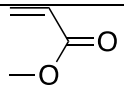
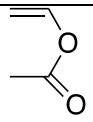
Figure 92. Copolymerization of VCP2 with allylic carbonate monomers.

This study was later extended to allylic carbomate macromonomers bearing a polysiloxane chain.[287] Such macromonomers was prepared by anionic polymerization of hexamethylcyclotrisiloxane initiated with lithium isopropoxide and end capped with allyl chloroformate. The polymerization was performed for 20 hrs at 60 °C in chlorobenzene in the presence of AIBN (2 mol%). In that case, there was no evidence of H-transfer to the isopropoxy silyl ether group giving rise to only grafted copolymers with no highly branched structures. The obtained grafted copolymer was characterized using gradient polymer elution chromatography (GPEC) that confirmed the grafted structure since no or only a negligible amount of unwanted homopolymer chains was detected.

5.3.2 Sulfur containing monomers

A common drawback of usual cyclic monomers is their low propensity to copolymerize with vinyl monomers. The main advantage of cyclic allylic sulfide (CAS) monomers is their ability to form copolymers with traditional acrylic and vinyl monomers such as MMA and Sty. Harrisson and coworkers[288] determined reactivity ratios between **CAS3** with several vinyl monomers (Table 20).

Table 20. Apparent reactivity ratios of monomers during the copolymerization with **CAS3** at different temperatures.

Monomer 1	Monomer 2	T (°C)	r_1	r_2	$r_1.r_2$
		25	0.26	8.6	2.2
		60	0.52	6.3	3.3
		80	2.8	13	36
		60	0.59	3.1	1.8
		80	2.5	4.8	12
		60	2.8	0.41	1.1
		60	140	0.08	11

For every studied copolymerization, the product of the two reactivity ratios, r_1r_2, was greater than one, thus showing a tendency to form blocks of homopolymer. This feature was ascribed to the occurrence of a reverse cross-propagation reaction (Figure 93). This resulted in a higher apparent reactivity ratio for the cyclic monomer and thus this led to high proportion of sulfide monomer in the final copolymer incorporated as blocks, even at low conversion.[288] The reversible cross-propagation model was supported by the variation of the copolymer composition with the

monomer concentration, the temperature and the observed sequence distributions, as well as the ability of allylic sulfides to act as chain transfer agents.

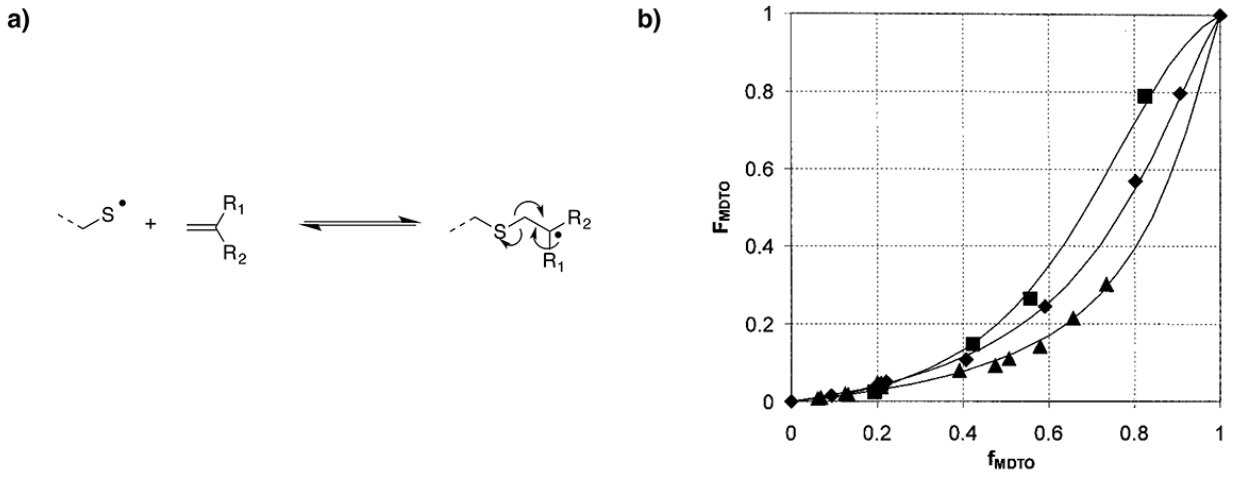


Figure 93. a) Reversible cross-propagation occurring during the copolymerization of **CAS3** (MDTO) with common vinyl monomers. b) Copolymer composition plot showing the effect of temperature on the copolymer compositions for the copolymerization system Styrene-**CAS3**. Triangles, 25 °C; diamonds, 60 °C; squares, 80 °C. Solid lines show the values predicted by the reversible cross-propagation model. Reproduced with permission from Ref. [288]. Copyright 2001 American Chemical Society.

It has to be noted that Hawker and coworkers[82] performed the copolymerization of sulfur containing monomers **SCM5** to **SCM7** (Figure 33) with methacrylate derivatives (e.g., MMA, HEMA, DMAEMA) to confer degradability to the resulting copolymer (see subsection 7.2 for more details). Although there was only a few data on the copolymerization behavior, the amount of cyclic monomer in the feed and in the copolymer seemed identical.

6. Living/Controlled Radical Ring-opening Polymerization

6.1 Homopolymerization

6.1.1 Cyclic Ketene Acetals

The advent of controlled/living radical polymerization (CLRP) in the last past 20 years led to the development of well-defined complex macromolecular architectures containing block of various chemical structures.[22] Early attempts have thus been reported to combine the possibility to prepare well-controlled polymers and/or block copolymers comprising degradable blocks/segments by using CKA monomers.

Among the various system, Wei and coworkers reported in 1996 the nitroxide-mediated radical ROP (NMrROP) of MDO/MDP **CKA27**.[289] With a bicomponent system based on di-*tert*-butyl peroxide (DTBP) and TEMPO as a nitroxide, they could obtain after 48h at 125 °C a polymer of M_n = 7900 g.mol^{-1} with $Đ$ = 1.3. The living character of the system was proven by successful chain-extension of P(**CKA27**) chains from the same monomer.[290] These pioneering results should however be taken with great caution since the half-life time of DTBP at 125 °C is 10h. A rapid and quantitative initiation, and thus a control of the polymerization, can therefore not be envisioned on a 48h period. In addition, a degenerative transfer mechanism was suggested that normally does not occur by NMP. The amounts of TEMPO used to achieve a controlled system were also questioning. The authors used a $[TEMPO]_0/[DTBP]_0$ ratio of 1.6 that usually does not enable exceeding M_n of 1000 g.mol^{-1}. Finally, the main criticism concerned the claimed control

of the polymerization. Indeed, the propagating radical created from the ring-opening reaction of the MDO/MDP **CKA27** was not stabilized. Consequently, the C-O bond formed between the TEMPO and this radical should be too strong,[291] even at 125 °C, to allow the establishment of the NMP equilibrium. The long induction time observed was then probably more consistent with a polymerization inhibited by the TEMPO nitroxide than with a true controlled system.

Later on, the controlled/living radical ring-opening polymerization (CLRrOP) of MPDO/MPDL **CKA11** by ATRP was reported,[292] using the ethyl α-bromobutyrate/CuBr/bipyridine system. This study showed a linear evolution of $\ln([M]_0/[M])$ with conversion and the obtained polymers presented low molar masses (7000 $g.mol^{-1}$) and low $Đ$ (1.2) for a conversion of 72%. However, one can note that M_n values were calculated by NMR on the purified product and not by SEC on the crude sample, and that no investigation of the livingness was performed. Also, it was mentioned that, contrary to conventional radical ROP, the obtained polymers presented an important quantity of acetal units coming from the vinyl polymerization of the C=C carbon double bond (between 30 and 60%). Those issues were further tackled by using 5,6-benzo-2-methylene-1,3-dioxepane (BMDO **CKA29**) instead.[293] Well-defined polymer chains with a good control (linear increase of molecular weights with conversion and narrow molecular weights distribution) were obtained. By ATRP, greater chain lengths and monomer conversions were observed than for a free-radical mechanism. The RAFT technique was also employed to control the rROP of the same monomer.[294] By using 1-(ethoxycarbonyl)prop-1-yldithiobenzoate (EPDTB)/dicumyl peroxide (DCP), a good control of the polymerization ($Đ$ = 1.27), with M_n values evaluated by SEC was shown. The only drawback of this method is the necessity to work in solution to avoid a significant increase of the $Đ$ values.

More recently, Tardy and coworkers[172] studied the NMrROP of BMDO **CKA29** and MPDO/MPDL **CKA11** initiated by the BlocBuilder MA alkoxyamine as initiating/controlling system. With BMDO in bulk at 140 °C, it was possible to obtain a good control of the polymerization (i.e., regular shift of the molar mass distribution with conversion and $Đ$ values < 1.5) when low molar masses and moderate conversions were targeted (i.e., M_n < 10,000 g.mol^{-1} and <50% conversion). Above this threshold values, a loss of control was obtained. The resulting polymers were then analyzed by ^{31}P NMR and ESI-MS and analyses showed that different chain-end groups were present.[295] Considering the alpha chain-end, in addition to the expected initiating moiety, the diethyl phosphonyl group was also found to initiate extra chains. Considering the omega chain-end, both SG1 and hydrogen moieties were found. A complex mechanism was postulated to explain such results (Figure 94).[172] The key point was related to the irreversible trapping of the SG1 nitroxide by ketal-based radicals followed by the CO–N bond dissociation of the corresponding macroalkoxyamine. The aminyl radical easily degraded into the diethyl phosphonyl radical that initiated extra chains. This mechanism was supported by both DFT calculations of the bond dissociation energy of C-O and N-O bonds of alkoxyamines and PREDICI kinetic modellings (Figure 94b and 94c).[172]

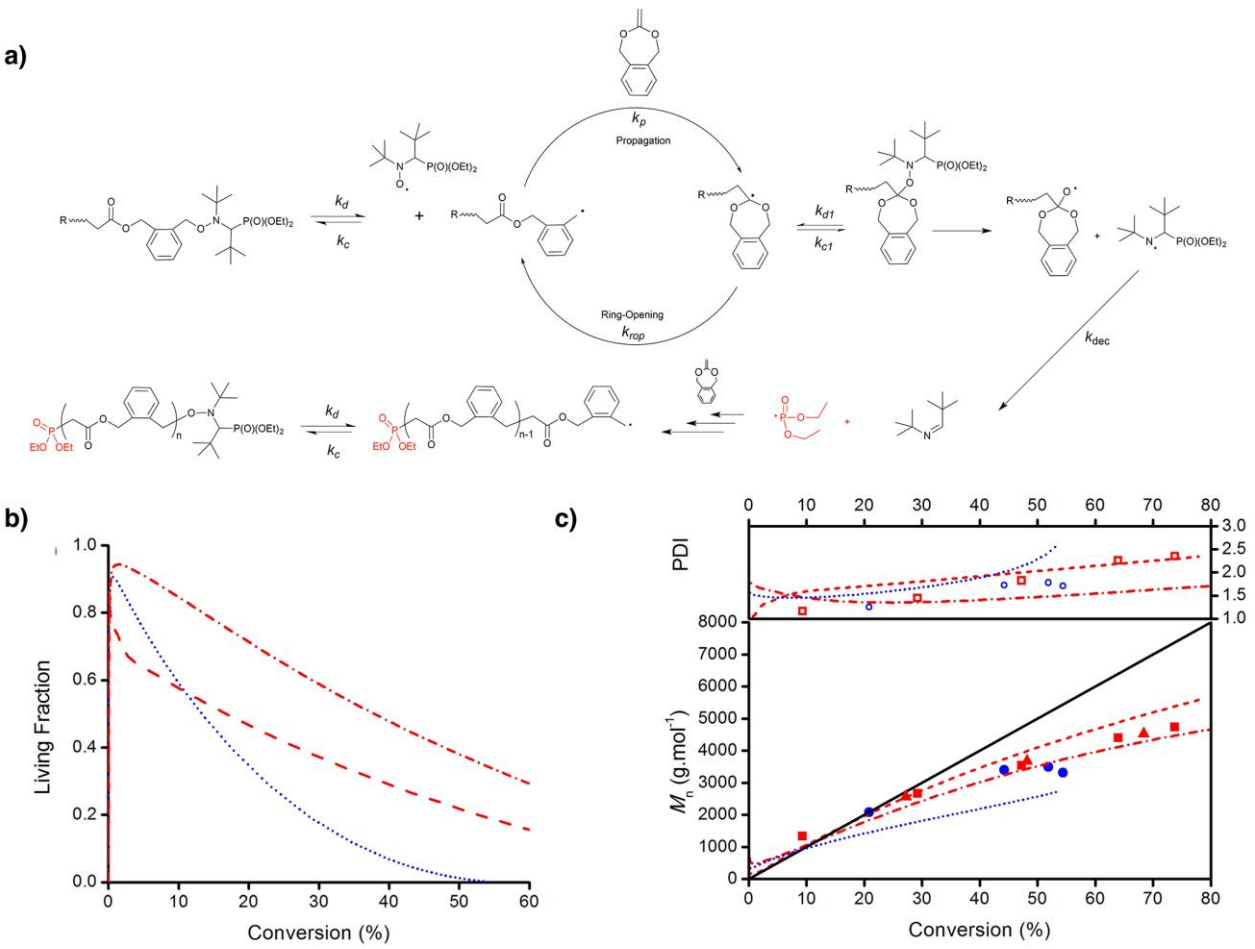
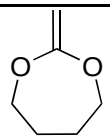
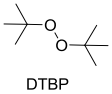
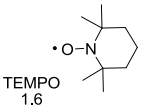
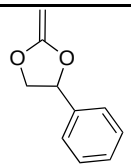
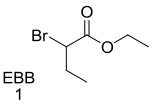
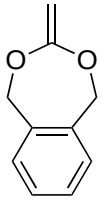
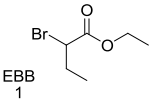


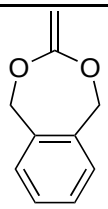
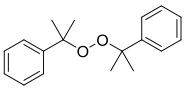
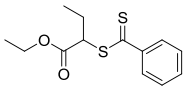
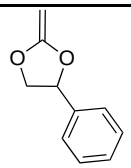
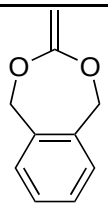
Figure 94. a) Proposed mechanism of the BMDO **CKA29** NMP taking into account the trapping of the ketal-based macroradical. b) Evolution of the living fraction obtained using PREDICI versus conversion (short dotted blue line) MPDL **CKA11**; (short dashed red line) BMDO **CKA29** initiated by BlocBuilder MA; (short dashed dotted red line) BMDO **CKA29** initiated by MONAMS. c) Evolution of number-average molar mass (M_n full symbols) and polydispersity index (Đ empty symbols) vs. conversion for the bulk BMDO **CKA29** or MPDL **CKA11** polymerization ($[CKA]_0$: $[alkoxyamine]_0$ = 62 : 1). The solid line corresponds to the theoretical M_n. (■) BMDO **CKA29** initiated by BlocBuilder MA; (▲) BMDO **CKA29** initiated with MONAMS; (●) MPDL **CKA11** + 3 wt% pyridine initiated with MONAMS; The lines

corresponds to the PREDICI modellings. Reproduced with permission from ref. [172]. 2013. Published by the Royal Society of Chemistry .

The MPDO/MPDL **CKA11** polymerization, initiated by the MONAMS alkoxyamine was however less successful since this monomer presented the same behavior for the evolution of the molar mass distribution but presented also a plateauing of the conversion at 40%.[172]

Table 21. Controlled radical ring-opening homopolymerization of various CKA monomers.

Monomer	**Initiator**	**control system**	**Condit.**	**Conv.**	M_n **(g/mol)**	**Đ**	**Ref**
 MDP/MDO **CKA27**	 DTBP 1	 TEMPO 1.6	125 °C 48h	41%	7400	1.2	290
 MPDO/MPDL **CKA11**	 EBB 1	CuBr +ffdf bpy 1 3	120 °C 32h	72%	8100	1.21	292
 BMDO **CKA29**	 EBB 1	CuBr +ffdf bpy 1 3	120 °C 48h	73%	7600	1.23	293

 BMDO **CKA29**	 DCP 1	 EPDTB 10	120 °C 52h	66%	7000	1.27	[294]
 MPDO/MPDL **CKA11**	MONAMS 1		140 °C 5h	31%	2600	1.5	[172]
 BMDO **CKA29**	BlocBuilder 1		140 °C 6h	47%	2900	1.77	[172]

6.1.2 Other monomers

The NMP, ATRP and RAFT techniques have been used to control the rROP of vinyl cyclopropane and spiro-ortho-ester monomers. The main results of these works are summarized in Table 22. Mori and coworkers[90] reported the RAFT polymerization of cyclic monomers allowing the synthesis of polymers containing anthracene moieties in the main chain. Different

polymerization conditions were tested, by varying the $[monomer]_0/[CTA]_0/[AIBN]_0$ initial ratio, the polymerization temperature (60 or 80 °C) and the nature of the RAFT agent (CTA_1 = benzyl dithiobenzoate or CTA_2 = benzyl 1-pyrrolecarbodithioate). As expected for the RAFT process, an increase of the $[CTA\ 1]_0/[AIBN]_0$ from 2 to 5 enabled a decrease of the dispersity from 1.53 to 1.14 (at 60% conversion). The decrease of the temperature from 80 to 60 °C for $[monomer]_0/[CTA\ 1]_0/[AIBN]_0$ = 100/2/1 helped to decrease the dispersity of the polymer but led to lower yields (15 and 80 % conversion at respectively 60 and 80 °C after 20h of polymerization). Compared to CTA_1 under the same polymerization conditions (i.e., $[monomer]_0/[CTA]_0/[AIBN]_0$ = 100/2/1, 80 °C, 20h), CTA_2 gave homopolymers with lower yields (59 % instead of 80%) for similar M_n (5600 – 5900 $g.mol^{-1}$) and $Đ$ values (1.43 and 1.53).

The conventional rROP and the ATRP-controlled rROP of 1,1-bis(ethoxycarbonyl)-2-vinylcyclopropane **VCP2** were compared (Figure 7).[296] AIBN was used to initiate the conventional rROP whereas the catalytic system for ATRP was composed of ethyl 2-bromoisobutyrate (EBiB) or phenylethyl bromide (PEBr) in combination with the CuBr/PMDETA complex. The authors proved by NMR that in the case of ATRP, only 1,5 ring-opening units were identified (1.2 - 1.3 % of cyclobutane structures were only detected) unlike the conventional rROP where around 20 % of cyclobutane units due to intramolecular cyclizations) were commonly obtained (see subsection 3.3). The difference in reactivity was ascribed to the equilibrium implying the dormant species that decreased first the instantaneous concentration of growing radicals and thus the number of undesired intramolecular cyclization reactions (Figure 95). The better defined polymer structures can also be observed by comparing the T_g of the polymers prepared by ATRP and by conventional radical polymerization (-1 and 24

ºC respectively) where the presence of rigid cyclobutane structures is indeed known to increase the glass transition temperature.

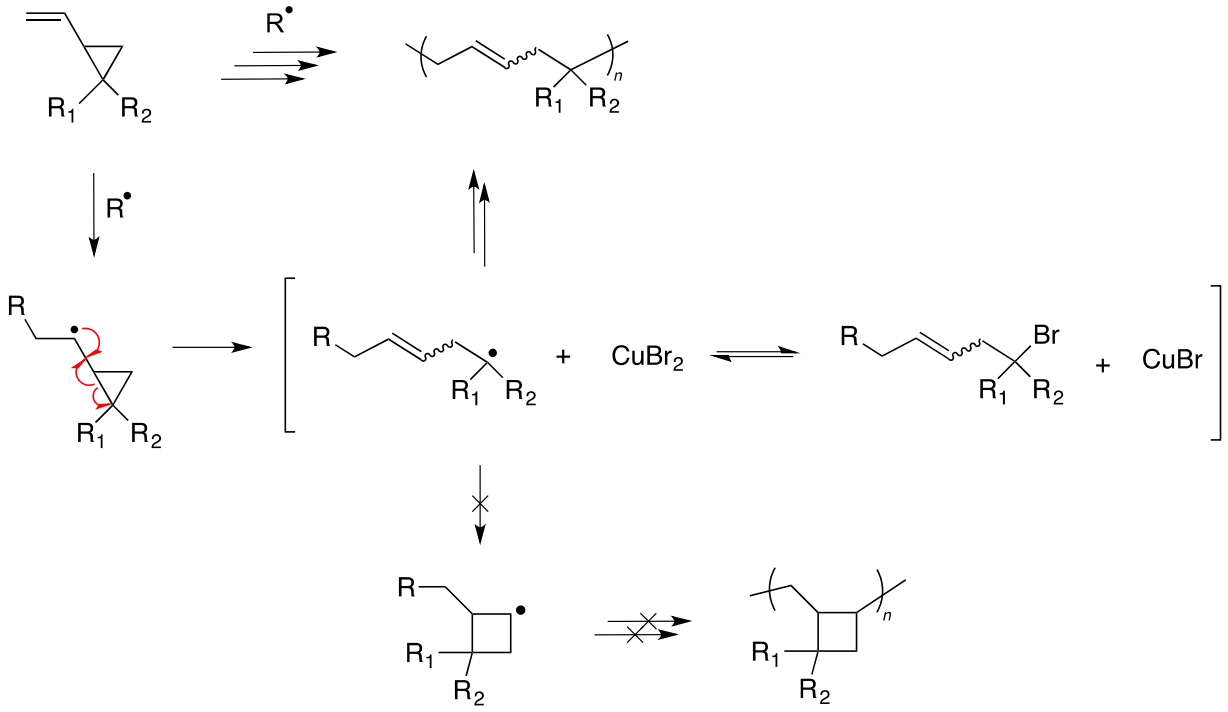


Figure 95. Atom transfer radical polymerization of 1,1-disubstituted-2-vinyl cyclopropane.

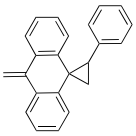
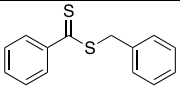
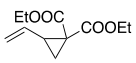
A more efficient catalytic system (i.e., CuBr/Me_6-TREN) for ATRP was used later on to control the polymerization of 1,1-bis (ethoxy carbonyl)-2-vinylcyclopropane **VCP2**.[297] Faster polymerization rates were obtained with Me_6-TREN than with PMDETA.

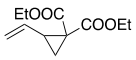
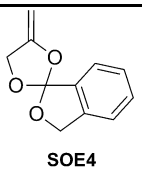
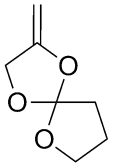
Endo and coworkers[298] tried to control the polymerization of 1-phenyl-2-vinylcyclopropane by using BPO as initiator and TEMPO as a nitroxide. However, only oligomers were obtained (M_n < 1000 g.mol^{-1}). Such results were in fact predictable since this monomer presents a very low radical polymerizability (see section 3.3). Besides, the benzoxy radical/TEMPO adduct on the monomer could not be obtained. In such conditions, it was thus

very difficult to envision obtaining a controlled radical polymerization of 1-phenyl-2-vinylcyclopropane.

Wei and coworkers studied the controlled rROP of spiro-ortho-ester monomers (BMTN: 8,9-benzo-2-methylene-1,4,6-trioxaspiro[4,4]nonane (**SOE4**, Figure 14)[299] and MTN: 2-methylene-1,4,6-trioxaspiro[4,4]nonane (**SOE1**, Figure 13)[300]) by using TEMPO-mediated NMP. At 125 °C and by using a high [TEMPO]/[initiator] ratio (1.8 - 2), a linear increase of the molar masses with conversion was obtained. Nevertheless, it was difficult to assess the livingness of the system since very low DP were targeted (typically 10)[299] and P(**SOE1**) oligomers were mainly obtained.[300] In the case of **SOE1**,[300] the results were rather surprising since the propagating radicals were not stabilized and the corresponding macroalkoxyamine was not supposed to cleave at the polymerization temperature.

Table 22. Controlled radical ring-opening homopolymerization of other cyclic monomers.

Monomer	**Initiator n equiv.**	**control system n equiv.**	**Condit.**	**Conv.**	**M_n (g/mol)**	**Đ**	**Ref**
 **AR4**	AIBN 1	 5	80 °C 20h	60%	2700	1.14	[90]
 **VCP2**	EBiB 1	CuBr/PMDETA 0.51/0.87	90 °C	33%	3000	1.16	[296]
	EBiB	CuBr/Me_6TR	105 °C	37%	6100	1.11	[297]

 **VCP2**	1	EN 1.5/2.5	22h				
 SOE4	Tert-butyl perbenzoate 1	TEMPO 1.6	125 °C 16-72 h	40%	3500	1.8	[299]
 SOE1	Tert-butyl perbenzoate 1	TEMPO 1.2	125 °C 16-72 h	20-25 %	3500	1.4	[300]

6.2 Copolymerization with vinyl monomers

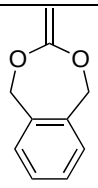
The large majority of block copolymers used today are synthesized *via* a radical process and present the advantage of being easy to synthesize even at a large scale. One of their main drawbacks, if one considers biomedical applications or environmental health, is nevertheless their non-readily degradable C-C backbone. Even though a first solution is to introduce labile functionalities by rROP in the copolymer backbone, partial degradation can be achieved by combining different polymerization techniques (e.g., radical polymerization and ROP) or by using alternatives to rROP that are described in section 8. The former method usually leads to diblock copolymers comprising one degradable block.

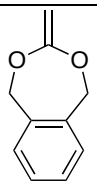
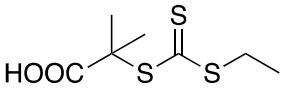
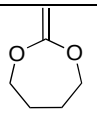
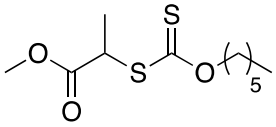
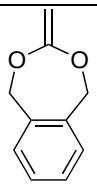
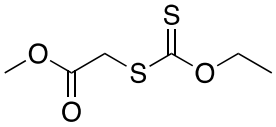
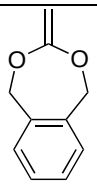
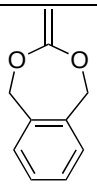
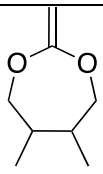
Consequently, the controlled radical copolymerization of vinyl and CKA monomers then represent the method of choice since it is possible *via* the same radical process to introduce ester bonds, that represent the more studied cleavable bonds, distributed more or less regularly all along the copolymer chains. Contrary to a free radical process, a controlled polymerization

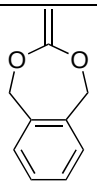
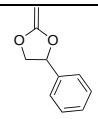
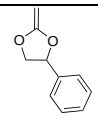
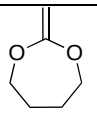
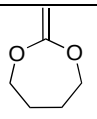
allows for the precise control of the length, the structure and the composition of the copolymer chains. These considerations explain why until now the most studied controlled radical copolymerizations between cyclic and vinyl monomers are those based on CKA as cyclic monomers that lead to the production of well defined degradable polymers useful for biomedical applications or environmental concerns.

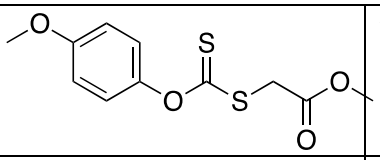
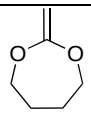
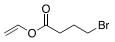
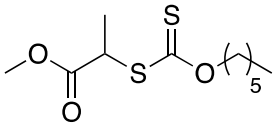
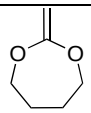
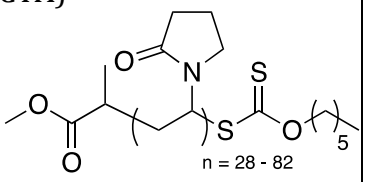
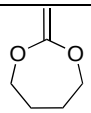
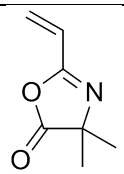
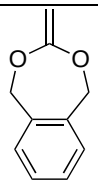
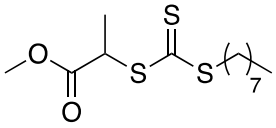
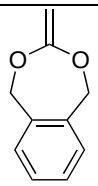
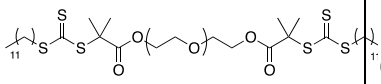
Table 23 gives an overview of the studies dealing with the CLRP by ATRP, PhotoCMRP, NMP or RAFT of CKA and other cyclic monomers with different vinyl monomers (e.g., Sty, MMA, VAc, MA, etc.). A particular attention will be focused on the controlled/living character of the copolymerizations.

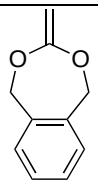
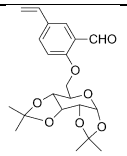
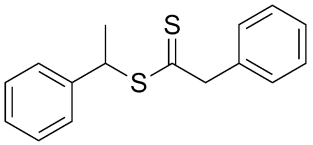
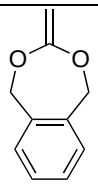
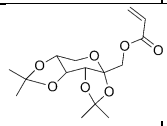
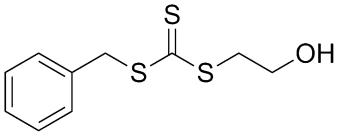
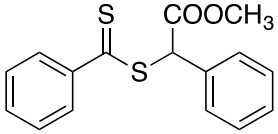
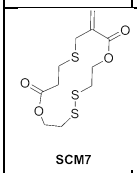
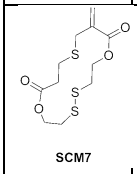
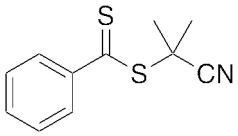
Table 23. Controlled radical ring-opening copolymerization of cyclic and vinyl monomers.

Cyclic monomers	vinyl monomers	CRP technique	conditions : solvant, T°C, time, initial mol% of CKA	copolymer M_n (g.mol^{-1}) ; Đ	structure & mol% CKA in the copolymer	ref
 BMDO **CKA29**	NIPAAm	ATRP (CuCl/Me_6TREN)	solution (DMF or 2-propanol), 25 - 35 °C, 10h, 5 – 30 mol% BMDO	10,000 - 50,000 ; 1.19 - 1.39	random, 5 – 14 mol%	[14]

 BMDO **CKA29**	NIPAAm	RAFT 	solution (DMF or toluene), 60 °C, 10h, 5 – 30 mol% BMDO	9900 - 35000 ; 1.08 - 1.31	random, 2 – 14 mol%	[14]
 MDP/MDO **CKA27**	VAc	RAFT/MADIX 	bulk, 60 °C, 16h, 30 - 70 mol% MDP	2000 – 8000 ; 1.2 – 1.6	NA, 10 – 61 mol%	[301]
 BMDO **CKA29**	VAc	RAFT/MADIX 	toluene, 80 °C, 24, 0 - 30 mol% **CKA29**	1300 – 3000 ; 1.2 – 1.3	NA, 5 – 24 mol%	[302]
 BMDO **CKA29**	MEO_2MA and OEGMA	ATRP (CuCl/bpy)	bulk, 90 °C, 5h, 20 mol% BMDO	12,000 – 15,000 ; 1.32 – 1.65	NA, 5 – 7 mol%	[17]
 BMDO **CKA29**	St, MMA or MA	ATRP (CuBr/bpy)	2 steps in solution in chlorobenzene, 120 °C for the PBMDO block	7,000 – 24,000 ; 1.17 – 1.59	diblock (PS-*b*-PBMDO ; PMMA-*b*-PMDO ; PMA-*b*-PMDO)	[303]
	S, AN or MA	ATRP (CuBr/bpy)	110 °C, 24-48h, 30 – 70 mol% CKA	7,000 – 22,000 ; 1.14 – 1.90	alternate (with AN), 3-7mol% with Styrene ; 50	[228]

					mol% with AN and 50% with MA	
 BMDO **CKA29**	nBA	ATRP (CuBr/PMDETA)	110 °C, 20h, 20-80 mol% BMDO	5000 – 20,000 ; 1.54-1.84	random , 11 – 48 mol% BMDO	[242]
CKA27 CKA11 CKA29	MeOEGMA (+ S or AN)	NMP (BlocBuilder)	bulk or in toluene, 90 °C, 1 – 30h, 20-70 mol% CKA,	4000 – 13000 ; 1.26 – 1.85	NA, 6-20 mol% CKA	[304]
 MPDO/MPDL **CKA11**	MeOEGMA	NMP (BlocBuilder)	solution (toluene), 90 °C, 20-70 mol% MPDL	14,000 – 25,000 ; 1.30 – 1.55	NA, 4 – 25 mol% of MPDL	[273]
 MPDO/MPDL **CKA11**	MMA	NMP (BlocBuilder)	solution (toluene), 90 °C, 20-70 mol% MPDL	8,000 – 28,000 ; 1.23 – 1.42	NA, 4 – 29 mol% of MPDL	[161]
 MDP/MDO **CKA27**	VAc	Photo CMRP	30 °C (TPO/Co(acac)$_2$, UV (450 μW.cm^{-2} at 365 nm)	24,500, 1.2-1.4	NA, 26 mol%	[274]
 MDP/MDO **CKA27**	VAc	RAFT	solution (C_6D_6), 90 °C, 10 – 70	6000 – 8000 ; 1.32 – 1.43	NA, 7 – 54 mol% MDP	[305]

			mol% MDP			
 MDP/MDO **CKA27**	VBr 	RAFT 	solution (benzene), 60 °C, 10 – 50 mol% MDP	5000 – 6500, 1.50 – 1.57	random, 9 – 34 mol%	306
 MDP/MDO **CKA27**	VAc or VBr	RAFT (poly(NVP) macro-CTA) 	solution (benzene), 60 °C	4000 – 20,000 ; 1.34 – 1.90	diblock PNVP-b-P(MDP-co-VAc/VBr)	307
 MDP/MDO **CKA27**		RAFT PS macroinitiator	solution (toluene), 70 °C, 50 mol% BMDO	33,800	1.57	266
 BMDO **CKA29**	MMA	RAFT 	solution (anisole), 110 °C, 50 mol% BMDO	1800 – 6000 ; < 1.5	random (linear and 4 star copolymer) ; 20 mol% BMDO	308
 BMDO **CKA29**	NIPAAm	RAFT 	solution (1,2-dichlorobenzene), 90 °C, 24h, 10 mol% BMDO	35,000 – 47,000 ; 1.46 – 1.83	triblock copolymers P(NIPAAm-*co*-**CKA29**)-b-PEG-b-P(NIPA	309

					Am-co-**CKA29**), 1.5 – 4 mol% BMDO	
 BMDO **CKA29**		RAFT 	Solution (anisole), 130 °C, 30-80 mol% cyclic monomer	6,000-18,000	NA, 1.29-1.35	231
 BMDO **CKA29**		RAFT 	Solution (anisole), 90°C, 20-35 mol% cyclic monomer	6800-10300	NA, 1.14-1.35	310
	MMA, DMAEMA or HEMA	RAFT 	solution (DMF or chlorobenzene), 70 °C, < 5 mol% cyclic monomer	around 30,000 ; 1.35 – 1.80	NA ; 1.28 – 1.70	82
 SCM7	HPMA	RAFT PGMA-RAFT	Solution (water), 70 °C, < 2 mol% cyclic monomer	26,000	NA, 1.52	311
 SCM7	DMAEMA TEGDA	RAFT 	Solution (toluene), 70 °C, < 5 mol%	10,000	NA, 2.5	312

			cyclic monomer			

NA : not available ; MEO_2MA : 2-(2-methoxyethoxy)ethyl methacrylate ; OEGMA : oligo(ethylene glycol) methacrylate ; bipy : 2-2' bipyridyl ; Me_6TREN : tris[2-(dimethylamino)ethyl]amine ; MA : methyl acrylate ; AN : acrylonitrile, MMA : methyl methacrylate ; S : styrene ; MeOEGMA : oligo(ethylene glycol) methyl ether methacrylate ; VBr : vinyl bromobutanoate ; HEMA :2-hydroxyethyl methacrylate ; DMAEMA : *N*,*N*-dimethylaminoethyl methacrylate ; HPMA :2-hydroxypropyl methacrylate ; TEGDA : Triethylene glycol diacrylate ; PGMA-RAFT : poly(glycerol methacrylate) end capped with a dithiobenzoate RAFT agent ;

Siegwart and coworkers compared the ATRP and the RAFT polymerization of BMDO **CKA29** and *N*-isopropyl acrylamide (NIPAAm).[14] The two techniques yielded copolymers with low dispersites ($Đ < 1.39$) and a random structure (according to the reactivity ratios reported in the literature). Regarding their copolymerization results, the authors concluded that ATRP enabled reaching higher molar masses whereas RAFT yielded copolymers of lower *Đ* values. No further study of the controlled/living character of the copolymerization was nevertheless given in this work.

When the RAFT copolymerization between MDO/MDP **CKA27** and VAc was performed, it gave living poly(**CKA27**-*co*-VAc) chains, that were further chain-extended by a new addition of VAc.[301] By changing the initial comonomer ratio, poly(**CKA27**-*co*-VAc) copolymers with different degradation properties were obtained. The authors completed this work by optimizing the structure of the CTA.[305] When using a *p*-methoxyphenyl xanthate, they obtained a better control of the copolymerization with lower dispersities and higher chain-end retentions. They also reported the RAFT copolymerization of MDO/MDP **CKA27** with vinyl bromobutanoate.[306] The novelty/advantage of the synthesized copolymer was its easy post-modification, opening the way to functional degradable polymers prepared *via* a versatile radical process. Whatever the

initial monomer composition, the copolymerizations presented a controlled character (i.e., low dispersity and good agreement between experimental and theoretical M_n).

Chain growth experiments performed with VAc from poly(**CKA27**-*co*-VBr) macroinitiators confirmed the living character of the system as well as the good retention of the CTA end-groups. The synthesis of well-defined PNVP-*b*-P(**CKA27**-*co*-VAc/VBr) diblock copolymers by RAFT from MDO/MDP **CKA27** and VAc or VBr initiated by a PNVP-macro RAFT agent was also reported.[307] The SEC analysis showed a clear shift of PNVP macro-CTA trace towards higher molar masses together with a monomodal molar mass distribution together with low dispersity values and a good agreement between theoretical and experimental M_n. All these characteristics demonstrated the controlled nature of the polymerization and the synthesized diblock copolymers were further self-assembled into nanoparticles.

The copolymerization between MDO/MDP **CKA27** and VAc was also performed using the photo-induced CMRP method (TPO:$Co(acac)_2$ = 1:0.6-0.8).[274] This process performed at room temperature led to poly(**CKA27**-*co*-VAc) chains whose livingness was assessed by MALDI-TOF and where the polymer was chain extended by another batch of VAc. The low temperature of the polymerization induced a more difficult incorporation of the **CKA27** units in the backbone (see section 5.2.3 *reactivity ratio*) and a non-negligible amount of closed unit was detected (21 %).

Lutz and coworkers[17] reported the ATRP synthesis of a thermoresponsive, biocompatible and partially degradable PEG-based terpolymer for potential biomedical applications. Non-linear PEG analogues (copolymerization of 2-(2-methoxyethoxy)ethyl methacrylate MEO_2MA and oligo(ethylene glycol) methacrylate OEMA) ensured the thermoresponsive character (LCST between 30 and 70 ºC depending of the feed ratio) whereas insertion of BMDO **CKA29** allowed for partial degradation of the resulting terpolymer into short oligomers.

Even if no kinetic study was here available, the synthesis of well-defined terpolymers with rather low *Đ* values was described. Other diblock copolymers from MDO/MDP **CKA27** and BMDO **CKA29** were synthesized, such as PS-*b*-P(**CKA29**), PMMA-*b*-P(**CKA27**) and PMA-*b*-P(**CKA27**).[303] These copolymers were prepared following a two-step ATRP method from a living PS, PMMA or PMA macroinitiators, respectively. The SEC analysis showed a clear shift of the SEC trace of the macroinitiator towards higher M_n and a monomodal distribution, confirming the synthesis of diblock copolymers. The same authors studied the copolymerization by ATRP of the 4,7-dimethyl-2-methylene-1,3-dioxepane **CKA28** with Sty, AN and MA.[228] They proved the living nature of the copolymerization between CKA and AN (but not with Sty and MA). The controlled character of the copolymerizations was studied for the three vinyl monomers by comparing the theoretical and experimental M_n values obtained by SEC and also by measuring the *Đ* value of the copolymers. In all cases, the experimental and theoretical M_n values were in good agreement and the *Đ* values generally < 1.6 (except for the copolymerization with AN). The SEC curves were in addition monomodal, ruling out the hypothesis of the synthesis of two distinct homopolymers. Nevertheless, in the case of the copolymerization with Sty, only less than 7 mol% of CKA were incorporated in the final copolymer (due to the high styrene reactivity) whereas the content of CKA reached higher values around 50 mol% in the case of AN and MA. The structure of the poly(CKA-*co*-AN) copolymer seemed to be alternating because of the supposed formation of a charge-transfer complex between the electron-donor CKA and the electron-acceptor AN.

The ATRP copolymerization of BMDO **CKA29** and *n*BA reported by Huang and coworkers[242] did not present the characteristics of a controlled process. The experimental and theoretical M_n values were not in good agreement and dispersity values were above 1.55. The livingness was not investigated.

Partially degradable triblock copolymers can also be synthesized. For instance, the RAFT polymerization of NIPAAm and BMDO **CKA29** by divergent chain growth from a trithiocarbonate-based difunctional PEG-macroRAFT agent yielded a P(NIPAAm-*co*-**CKA29**)-*b*-PEG-P(NIPAAm-*co*-**CKA29**) triblock copolymer (Table 23).[309] According to the results, the controlled nature of the copolymerization was not demonstrated because of rather high dispersity values (1.46 – 1.83) and bimodal molar mass distributions. In addition, the fraction of **CKA29** in the final copolymer did not exceed 4 mol%. We can nevertheless mention that the thermo-sensitive and degradable properties of the triblock copolymers were the main objective of this work.

Nicolas and coworkers[304] recently took benefit of both the simplicity and innocuousness of the NMP process and reported the nitroxide-mediated radical copolymerization of oligo(ethylene glycol) methyl ether methacrylate (MeOEGMA) with either BMDO **CKA29**, MDO/MDP **CKA27** or MPDO/MPDL **CKA11**, in the presence of a small amount of Sty or AN (used as a controlling comonomer in the case SG1-mediated radical polymerization of methacrylic esters).[313] A detailed analysis of the controlled/living character of the copolymerizations was presented together with kinetic considerations explaining the significant difference in behaviour between the different CKAs. Among the three CKAs, only MPDO/MPDL **CKA11** enabled high conversions to be reached and significant insertion in the copolymer (up to 29 mol.%) whereas BMDO **CKA29** and MDO/MDP **CKA27** resulted in a conversion plateauing for initial molar fractions above 20 mol.%. This result was assigned to the styrene-like open radical structure of MPDL which favoured cleavage of the MPDL-SG1 macroalkoxyamine conversely to primary radical structures deriving from the two other CKAs which trapped the nitroxide under the experimental conditions tested. The best experimental conditions (linear increase of M_n with conversion, low Đ values and linear evolution of ln(1/(1-

conv)) with time) were established in 50 wt% toluene at 90 °C (Figure 96). A successful chain extension experiment was performed from P(MeOEGMA-*co*-AN-*co*-**CKA11**)-SG1 macroinitiator using Sty to form P(MeOEGMA-*co*-AN-*co*-**CKA11**)-*b*-PS diblock copolymers, thus proving the livingness of the system.

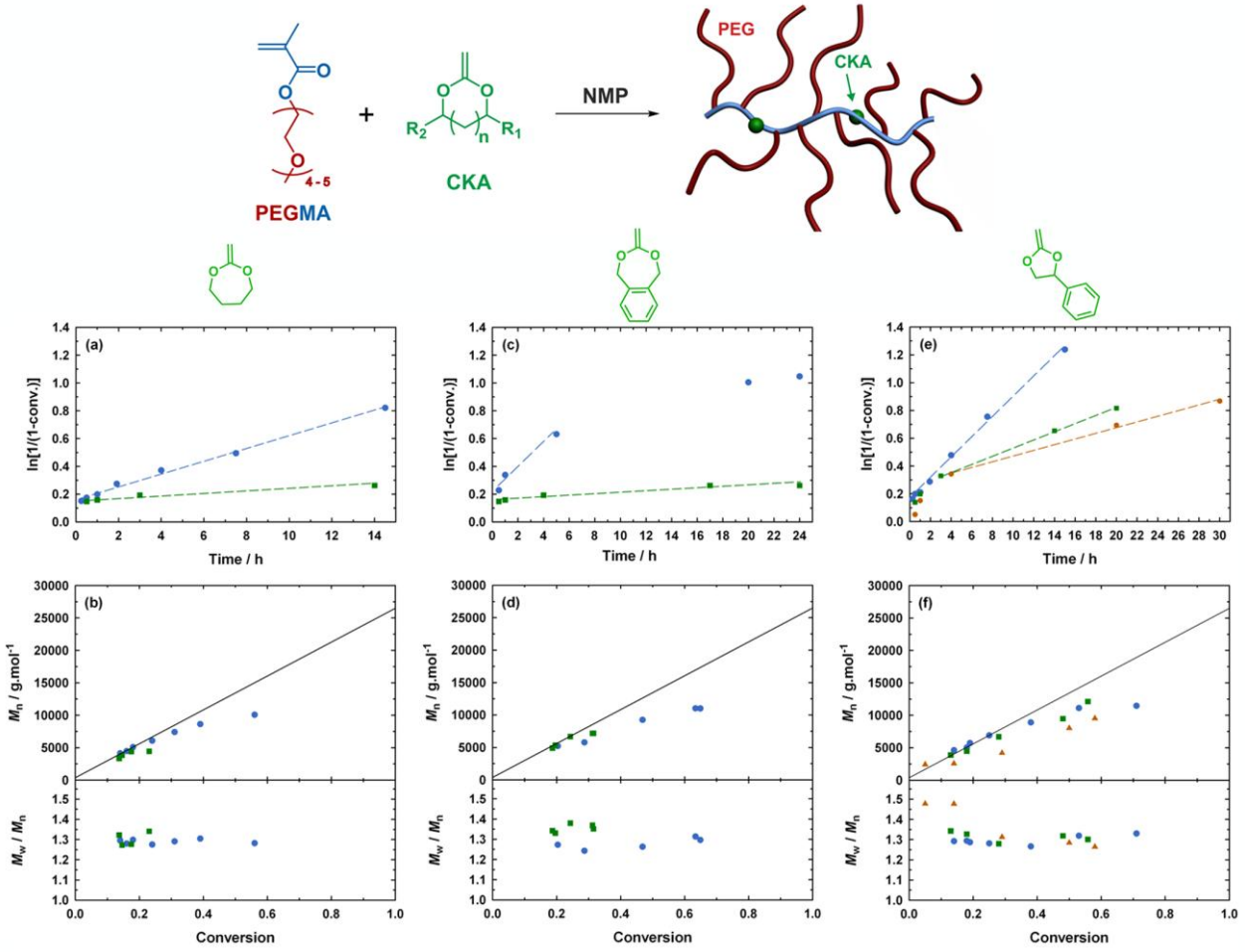


Figure 96. Solution NMP of poly(ethylene glycol) methyl ether methacrylate (MeOEGMA), acrolynitrile (AN), and CKAs, in 50 wt % toluene, initiated by the BlocBuilder alkoxyamine at 90 °C, as a function of the CKA and its initial amount in the feed. BMDO **CKA29** (a) and (b): ●, $f_{\mathbf{CKA29},0}$ = 0.2; ■, $f_{\mathbf{CKA29},0}$ = 0.4. MDO/MDP **CKA27** (c) and (d): ●,$f_{\mathbf{CKA27},0}$ = 0.2; ■, $f_{\mathbf{CKA27},0}$ = 0.4. MDPO/MPDL **CKA11** (e) and (f): ●, $f_{\mathbf{CKA11},0}$ = 0.2; ■,$f_{\mathbf{CKA11},0}$ = 0.4; and ▲, $f_{\mathbf{CKA11},0}$ =

0.7. For each set of experiments: Ln[1/(1 − conv)] vs time (conv =MeOEGMA conversion) and number-average molar mass, M_n, and dispersity, M_w/M_n, vs conversion. The full line represents the theoretical M_n and the dashed ones represent the best fit of the linear domains. Adapted with permission from Ref. [304]. Copyright 2013 American Chemical Society.

An in-depth analysis of the copolymer chain-end was then performed by ^{31}P NMR (which has been shown to be an accurate method to qualitatively and quantitatively determine the chain-end structure of SG1-terminated polymers).[314] ^{31}P NMR analyses first showed that the conversion plateauing during the copolymerization of methacrylate derivatives with MDO/MDP **CKA27** was explained by the irreversible coupling of the open form of **CKA27** macroradicals with SG1 (Figure 97). When performing the terpolymerizations of MPDO/MPDL **CKA11** (by increasing the initial molar fraction from 20 to 70 mol.%) with methacrylate derivatives in the presence of AN, the ^{31}P NMR signal, shifted progressively from a CKA-free P(OEGMA-*co*-AN) copolymer to a signal resembling that of a PS-SG1 homopolymer (which should be similar to a P(**CKA11**)-SG1 structure), proving that MPDL replaced AN as the last monomer unit. The greater lability of the P(**CKA11**)-SG1 structure due to the presence of a stabilized secondary alkyl moiety explained the successful terpolymerization of methacrylate derivatives with **CKA11**.

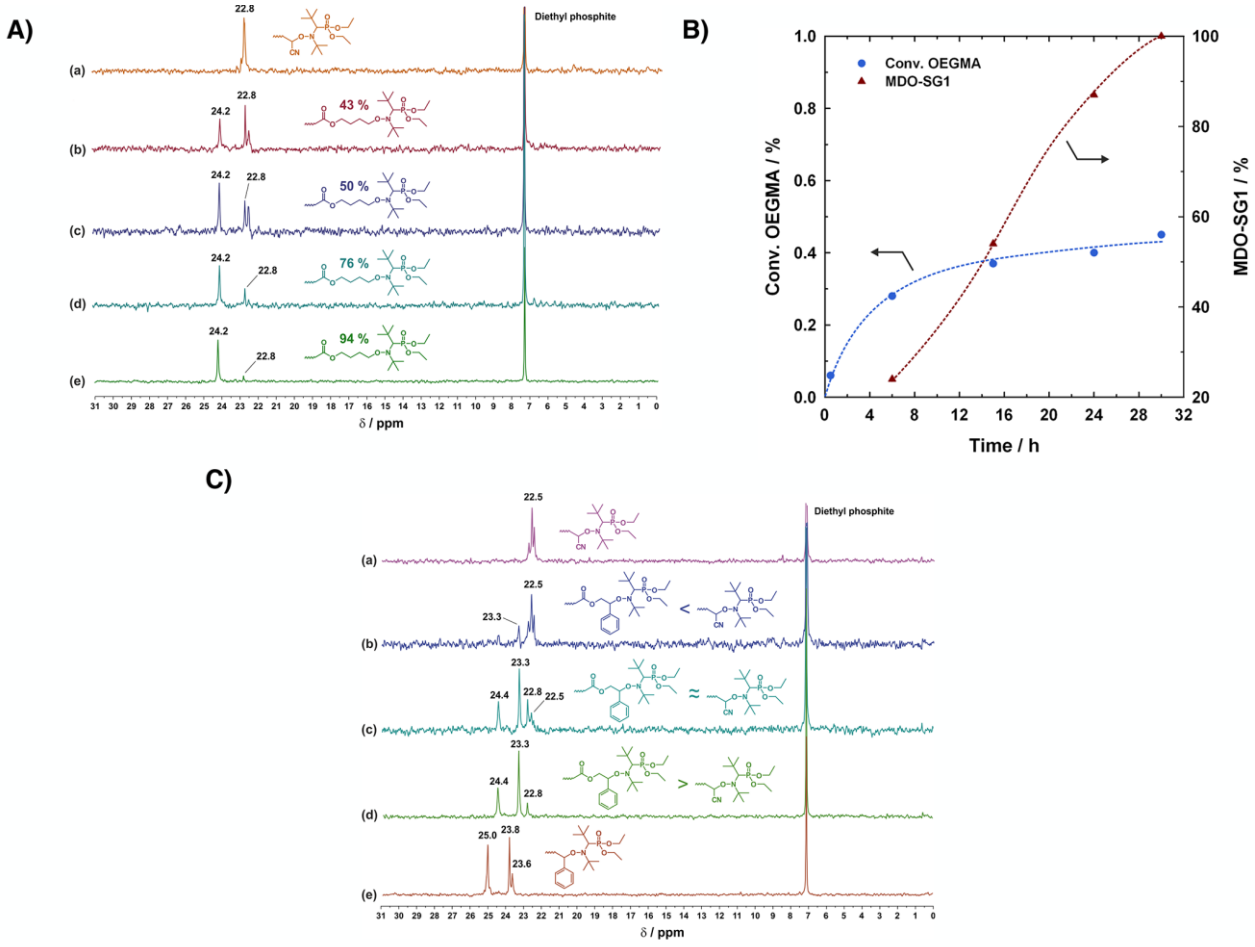


Figure 97. A) ^{31}P NMR spectra in $CDCl_3$ of (a) P(MMA-*co*-AN)-SG1 after 15 h and P(MMA-co-AN-*co*-MDO)-SG1 for $f_{\mathbf{CKA27}}$ = 0.2 at different time intervals: (b) 6 h (c) 15 h; (d) 24 and (e) 30 h. B) Evolution of the OEGMA conversion followed by ^{1}H NMR and the relative proportion of MDO/MDP **CKA27**-SG1 terminal sequences compared to AN-SG1 sequences followed by ^{31}P NMR during the copolymerization of OEGMA, AN and MDO/MDP **CKA27** initiated with the BlocBuilder MA alkoxyamine at 90 °C. C) ^{31}P NMR spectra in $CDCl_3$ of: a) P(OEGMA-*co*-AN)-SG1; b) P(OEGMA-*co*-AN-*co*–**CKA11**)-SG1 ($f_{\mathbf{CKA11},0}$ = 0.2); c) P(OEGMA-*co*-AN-*co*–**CKA11**)-SG1 ($f_{\mathbf{CKA11},0}$ = 0.4); d) P(OEGMA-*co*-AN-*co*–**CKA11**)-SG1 ($f_{\mathbf{CKA11},0}$ = 0.7) and e) PS-SG1. Adapted with permission from ref. [314]. Copyright 2014 John Wiley and Sons.

Considering the structural similarly between the open radical structure of Sty and MPDL, and considering the results from the different terpolymerizations, the SG1-mediated copolymerization between MPDO/MPDL **CKA11** and MeOEGMA was then successfully performed without any addition of AN or Sty, leading to controlled copolymers providing the initial amount of MPDL was high enough (typically > 20 mol.) to act as the sole controlling comonomer.[273] In addition, the obtained copolymer were degraded under accelerated hydrolytic conditions and exhibited no obvious cytotoxicity (Figure 100, subsection 7.2). This copolymerization system was also extended to MMA with similar success.[161]

In addition to CKA monomers, a few studies were devoted to the CLRP of other cyclic monomers. Smith and coworkers[315] performed the copolymerization of 5-methylene-2-phenyl-1,3-dioxolan-4-one **CαOA1** with Sty and MMA using ATRP. The obtained copolymers[315] were not reported in Table 23 because even if the ATRP-controlled rROP of **CαOA1** with MMA or Sty seemed consistent with a controlled system, the authors showed that the **CαOA1** did not polymerize *via* a ring-opening process but only *via* a vinyl pathway, i.e. without formation of keto ester bonds in the final copolymer. In 2009, Paulusse and coworkers[82] published an interesting work on the RAFT copolymerization of sulphur-containing cyclic monomers and different methacrylates (MMA, *N*,*N*-dimethylaminoethyl methacrylate or 2-hydroxyethyl methacrylate). For a low initial cyclic monomer/vinyl monomer ratio, the experimental M_n values of the synthesized copolymers were in agreement with the expected values. No kinetic studies were however reported and the living/controlled character of the copolymerizations was not fully described. Nevertheless, the synthesized copolymers presented the advantages of having different kinds of cleavable functional groups in their main chain (e.g., esters, thioesters or disulfides), leading to a larger range of hydrolysable functions (see subsection 7.2).

7. Applications

7.1 Low shrinkage materials

As already discussed in the introduction, one of the main applications of cyclic monomers is related to the preparation of low shrinkage materials.[316-317] For example, MMA leads to -25 % shrinkage after polymerization and some strategies such as the use of inorganic fillers were then developed to lower this shrinkage in particular for dental applications. Nevertheless the best way to decrease the shrinkage is to design new monomers. Indeed the shrinkage induced by modification of the Van der Waals distances in the monomer further converted into a covalent bond upon polymerization could be partially or entirely counterbalanced by the opening of a cyclic monomer. This can result in no change in volume and possibly even to a slight volume expansion. In addition, the molecular weight of the monomer is also known to have an impact on the volume shrinkage since the higher the molecular weight, the less important is the ratio of double bonds per volume (Figure 98).

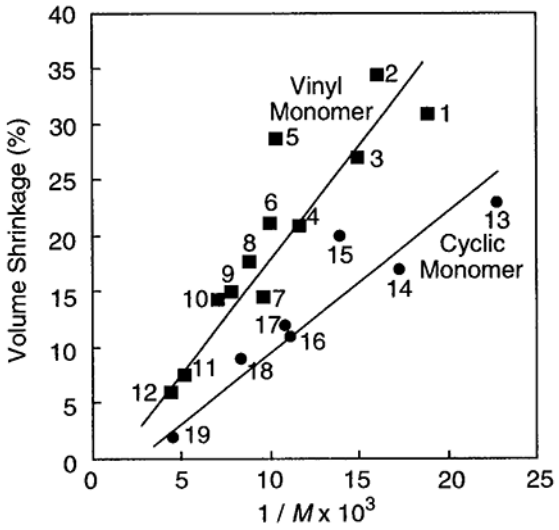


Figure 98. Relationship between the volume shrinkage and the reciprocal of the molecular weight (M): 1, acrylonitrile; 2, vinyl chloride; 3, methacrylonitrile; 4, vinyl acetate; 5, vinylidene chloride; 6, methyl methacrylate; 7, styrene; 8, ethyl methacrylate; 9, n-propyl methacrylate; 10, n-butyl methacrylate; 11, N-vinyl carbazole; 12, 1-vinyl pyrene; 13, ethylene oxide; 14, propylene oxide; 15, 2,2-dimethylethylene oxide; 16, 1,3,5-trioxane; 17, epichlorohydrin; 18, styrene oxide; and 19, hexamethylcyclotrisiloxane. Reprint with permission from Ref. [26]. Copyright 2001 John Wiley and Sons.

The first publication on cyclic monomers that undergo radical ring-opening polymerization as new low shrinkage monomers was reported by Baily in 1979.[318] The rROP of spiro-ortho-carbonates **SOC1** was described. When the polymerization was stopped below 30 % conversion, a slight 4-7 % volume expansion was observed depending on the temperature. The use of such monomer in dental application was not really successful due to stability issue upon storage, solubilization in the filling mixture and incorporation in MMA-based formulations.[318-319] A more

detailed examination of SOC-based polymers showed that radical polymerization mechanism was more complex than expected and this monomer family was discarded from further consideration for this application.

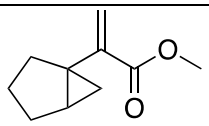
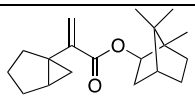
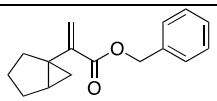
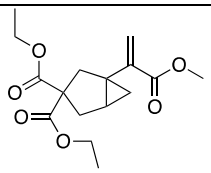
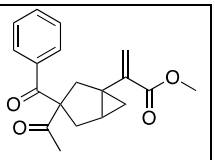
VCPs were then preferred since they had the advantage to be stable in the presence of humidity, acidic and basic impurities and inorganic fillers such as silica. As already discussed in subsection 3.3, the most used and studied VCP derivative is 1,1-diethoxycarbonyl-2-vinyl cyclopropane **VCP2**. Upon thermal radical polymerization, the polymer consisted in 90 % of the ring-opened unit and 10 % of the cyclobutane unit, and thus led to volume shrinkage of 11 %.[131] Under similar conditions, Agarwal and coworkers obtained 60 % ring-opened unit.[135] It has to be noted that recently Agarwal et al. compared the proportion of cyclobutane/1,5 unit using a thermal and photochemical process. They showed that UV irradiation led to a decrease of cyclobutane unit and consequently to a lower shrinkage (-5.5 instead of -11.2 % for **VCP2,** Figure 52).[135] In order to decrease the shrinkage, the methyl ester group of VCP2 was substituted by various substituents. The introduction of strong electron withdrawing groups or the variation of the alkyl group did not lead to a strong decrease of the shrinkage. Only very bulky and heavy substituents (e.g., adamantyloxycarbonyl) led to volume expansion of 4-6 %.[133]

Since VCP monomers were dedicated to adhesives and/or composites, multi-functional monomers were usually prepared to get higher polymerization rates, better mechanical properties and greater solvent resistance (see subsection 3.4). Compared to **VCP2**, these structures enabled a slight decrease of the shrinkage.[154] Similar work also combined multi-functional VCP derivatives bearing bulky and liquid crystalline cholesteryl groups.[320] The preparation of crystalline monomers was suggested to lower the volume shrinkage by transition from denser monomer structures to less compact amorphous polymer matrices. For example, the volume

change of the polymer derived from the crystalline 1,1-bis(phenoxycarbonyl)-2-vinyl cyclopropane was estimated to +6.8%.[134] Moszner et al.[321] revisited this structure and confirmed the importance of the crystalline structure by preparing a liquid VCP analog that had a higher shrinkage (-3.9%). Endo and coworkers[156] prepared a high molecular weight difunctional VCP derivative combining three bulky adamantyl moieties **VCP27** (Figure 58) and showed a volume expansion of 6.1%.

One of the reasons of the poor industrial application of such monomers is their low reactivity with MMA that is the main component of the filling mixture. Indeed, a starting **VCP2**/MMA equimolar ratio led to only 10% of incorporation of both cyclic and 1,5 linear unit in the copolymer backbone. In order to increase the reactivity, a bicyclic 2-cyclopropyl acrylate monomer family that allowed for statistical incorporation of VCP derivatives with MMA was developed (see subsection 3.3 and Figure 55).[123] Many derivatives were then prepared and their shrinkage behavior evaluated (Table 24).[139, 322] The substitution of the methyl ester by a substituent increasing the molecular weight decreased the shrinkage (-10.6 to -5.5 and -4.7 %) but the bridgehead substitution had a higher impact with a shrinkage value with up to -3% shrinkage combined with a T_g value of 107 ºC.

Table 24. Volume change in the radical polymerization of bicyclic cyclopropyl acrylate monomers and Tg of the formed polymers.[139, 322]

	 **VCP5**				
Shrinkage (vol%)	-10.6	-5.5	-4.7	-5.1	-3.0
Tg (ºC)	90	143	52	97	107

An interesting feature of the bicyclic 2-cyclopropylacrylate monomer family is related to its behavior once used in dental curing composite. This mono-functional monomer could efficiently replace the dimethacrylate diluent and thus produced materials with similar flexural modulus of elasticity.[139] This modulus usually decreased with decreasing the cross-linking density, which was the case with the monofunctional 2-cyclopropylacrylate. The authors suggested that the double bond formed by the radical ring-opening process could be involved in cross-linking reactions.[139]

Recently a breakthrough in this field has been presented by Agarwal and coworkers.[136] They prepared a new di-functional VCP derivatives (**VCP28**, Figure 58) based on a branched bulky amine spacer. This new resin had a low viscosity and a very high reactivity in photo-polymerization (80 % monomer conversion in 30 s) with no sensitivity towards oxygen (Figure 99a). The obtained material had low shrinkage (-4.9%) and good mechanical properties. The difference of reactivity with other difunctional VCP derivatives was related to the intermolecular

hydrogen bonding *via* amide units, which led to a pre-organization of the monomer (see subsection 3.3 and Figure 58 for details). Another clear advantage compared to classical urethane dimethacrylate (UDMA) matrix was the relatively low viscosity of the monomer that allowed its use without diluent (Figure 99b).

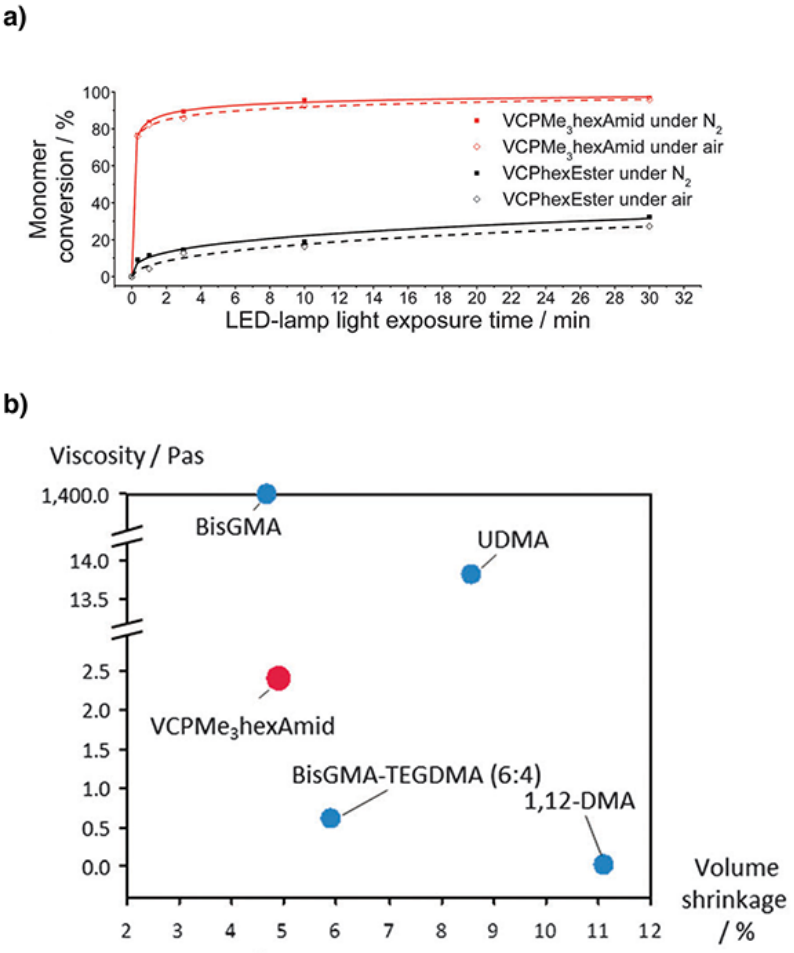


Figure 99. a) Photo-polymerization of **VCP28** and the VCP analog with ester spacer instead of amide (1mol% photo-initiator CQ:EDMAB in a molar ratio of 1 : 2) under a controlled

atmosphere of nitrogen and air using a commercial blue-light LED source (2.013 mW cm^{-2} for 465 nm). b) Ashby plot of specific monomer viscosities as a function of the volume shrinkage. BisGMA for bisphenol-A-glycidyl methacrylate, UDMA for urethane dimethacrylate, 1,12-DMA for dodecanediol-dimethacrylate, TEGDMA for triethylene-glycol-dimethacrylate. Reproduced with permission from Ref. [136]. 2015 Published by the Royal Society of Chemistry.

The same methodology (amide linkage) was further extended to other VCP derivatives, with either a poly(propylene oxide) PPO core or two rigid aromatic compounds and showed enhanced reactivity compared to classical VCP derivatives,[323] in good agreement with the results previously obtained with **VCP28** because of the intermolecular H-bonding effect. The nature of the spacer did not influence the kinetics but only the mechanical properties of the obtained materials. Interestingly, the E-modulus of the materials could be sharply tuned by copolymerizing two VCP derivatives presenting a soft and a rigid core (Figure 100). This system could thus be seen as a low shrinking modular construction kit to prepare on demand materials.

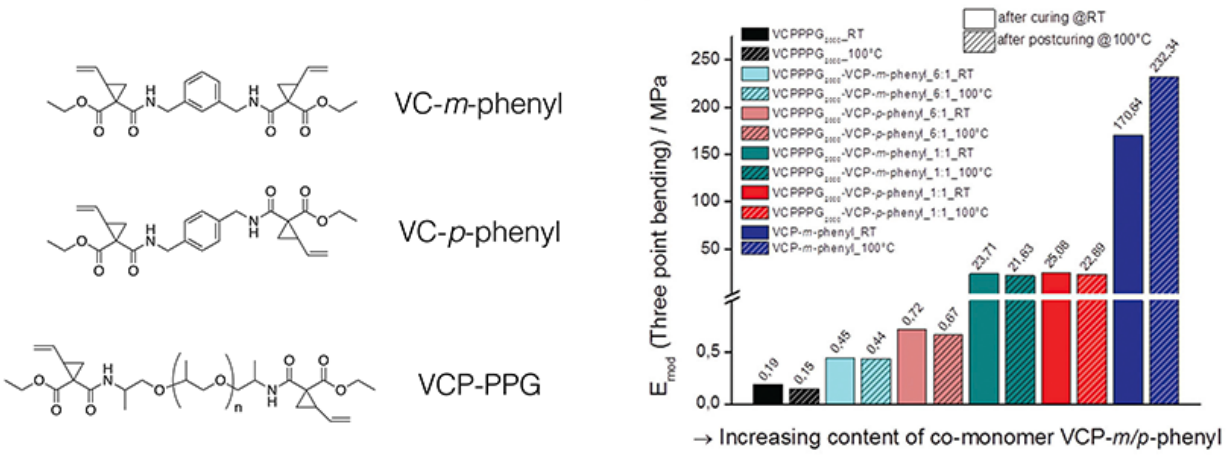


Figure 100. Determined E-moduli of cured VCP-PPG and VCP-*m*-phenyl specimens, as well as by co-networks in ratios of 6:1 and 1:1 of VCP-PPG, VCP-*m*-phenyl and VCP-*p*-phenyl. With

increasing content of the co-monomer VCP-*m/p*-phenyl, the moduli could be raised up to 1200 times to higher values. Reproduced with permission from Ref. [323]. 2016 Published by the Royal Society of Chemistry.

In a similar manner than VCP, cyclic allyl sulfide (CAS) monomers are also stable in the presence of water and/or impurities, and are thus interesting for low shrinkage materials. Evans and Rizzardo[84] reported the preparation of **CAS3** and **CAS8** (Figure 34) and studied the shrinkage behavior of the resulting polymers. The shrinkage was measured to -1.5 and -2.4 %, respectively, which corresponded to one of the lowest values for a liquid (and thus non-crystalline) compound. The effect of substituent on 7-membered CAS monomers was also investigated.[83] Among the various structures synthesized, the liquid **CAS5** monomer gave polymers with shrinkage value of -1.4 %. For dental composites, the main disadvantage of these monomers was the low T_g of the obtained polymer. Despite being clear, elastic and soft rubbery materials, the polymers did not have sufficiently interesting mechanical properties.

The low shrinkage property of CAS monomers has been used for holographic data storage media. Indeed, this new mode of data storage has recently received great attention by its ability to store multiplexed data in the entire volume of the media and could reach one terabyte per disc.[324-326] One of the main barriers of the development of this technique is the polymerization-shrinkage-induced distorsion that strongly affects the reachable thickness and resolution. Evans and coworkers[327] uses **CAS3** in a classical recipe and use 4-bromo-styrene as reference monomer. Whereas 4-bromo-styrene led to significant distortion of the grating (associated with a shrinkage of 0.1±0.05 of the whole material), the use of **CAS3** led to perfect agreement between theoretical

and experimental diffraction efficiency (shrinkage of the whole materials was 0.02±0.008%). The system was further optimized by using **CAS7** that gave a similar shrinkage value but with an enhanced reactivity due to the higher refracting index contrast from the naphthalene moiety (1.5672 for **CAS3** and 1.686 for **CAS7**). Figure 101 showed the interest of this approach by recording and reading a single data page on the sample prepared using **CAS3**. The peak signal-to-noise ratio was calculated to be 44 dB, which is compatible with data storage applications.

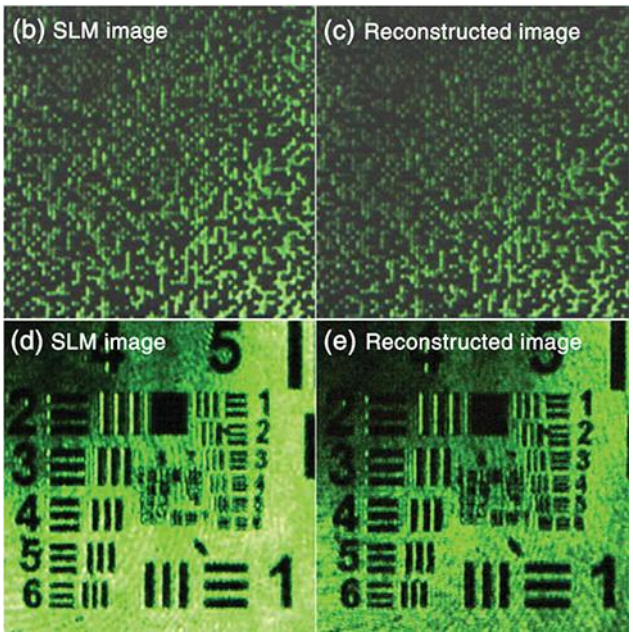


Figure 101. Digital data page recordings. b,d) Imput data and image pages loaded on an amplitude-type spatial light modulator (SLM). c,e) reconstructed images from the recorded holograms on **CAS3** sample. Reproduced with permission from Ref. [327]. Copyright 2009 John Wiley and Sons.

To conclude with low shrinkage materials, Bowman and coworkers[328] used allyl sulfide functional groups to reduce the stress produced during the cross-linking of multi-functional methacrylates. The addition-fragmentation chain transfer (AFTC) mechanism was used to enable non-degradative radical mediated breaking and re-formation of polymer network during the polymerization. Among various allyl sulfide containing structures, the use of **CAS9** (Figure 34) in combination with a thiol-norbornene resin demonstrated a stress decreased by one order of magnitude compared to conventional dimethacrylates, but with similar mechanical properties.

7.2 Degradable materials

The degradability of copolymers prepared by rROP has been extensively studied. The copolymers, generally based on CKA monomers, can be degraded *via* a hydrolytic (i.e., acidic, alkaline or nearly neutral conditions) or an enzymatic process (e.g., lipase, proteinase K, etc.). A limited number of articles also reported a possible degradation by combining different approaches (e.g., enzymatic and hydrolytic or enzymatic and photolysis). We attempted here to summarize the main results on the degradation of copolymers prepared by radical ring-opening copolymerization as follows: materials degraded *via* a hydrolytic mechanism, materials degraded *via* an enzymatic process and materials degraded by a combination of methods.

7.2.1 Hydrolytic degradation

Hydrolytically degradable (co)polymers were generally designed for biomedical applications (e.g., tissue engineering, nanoparticles for drug delivery, etc.) and others such those connected to environmental issues.

Degradable copolymers designed for biomedical applications

Cyclic monomers used for biomedical applications were generally CKA monomers and especially MDO/MDP **CKA27** and BMDO **CKA29**. They have been copolymerized with different vinyl monomers including glycidyl methacrylate (GMA),[21, 263] vinyl acetate (VAc),[256-257] poly(ethylene glycol) methyl ether methacrylate (MeOEGMA),[273, 304] *N*,*N*-isopropylacrylamide (NIPAAm)[243, 309] and poly(ethylene glycol) methacrylate (PEGMA).[329]

Two poly(**CKA27**-*co*-GMA) copolymers with different monomers ratio were synthesized by free radical copolymerization initiated by AIBN.[263] The hydrolysis study performed in PBS at pH 7.4 and in deionized water at 37 °C proved that the amount of ester units in the backbone and the amorphous nature of the copolymer had a significant influence on the degradation rate. In addition, no fast release of degradation products was observed, which may limit inflammatory response at the implantation site if in vivo experiments are envisioned.

Albertsson and Agarwal synthesized poly(**CKA27**-*co*-VAc) copolymers by free radical copolymerization initiated by AIBN.[256-257] Their hydrolysis under both accelerated hydrolytic conditions (i.e., KOH) and in the presence of enzymes (Candida rugosa) was achieved and the alkaline hydrolysis was faster that the enzymatic one.[257] Secondly, both the polymer and the degradation product were shown to be not cytotroxic.[256] Note that in these studies, both MDO/MDP **CKA27** and VAc were involved in the degradation mechanism since the acetate groups of VAc units were also hydrolysed and transformed into alcohol group giving the corresponding poly(vinyl alcohol) PVOH.

Nicolas and coworkers[273, 304] reported the nitroxide-mediated controlled radical ring-opening copolymerization of MPDO/MPDL **CKA11** with OEGMA. The SG1-based controlled process enabled the elaboration of copolymers with adjustable amounts of ester groups in the backbone. The hydrolysis study proved that under accelerated hydrolytic conditions, the copolymers were nearly fully degraded without any toxicity towards three representative cell lines (fibroblasts, endothelial cells and macrophages) (Figure 102). The absence of cytoxicity from both the copolymer and the degradation products highlighted the great potential of such copolymers as biomaterial building blocks.

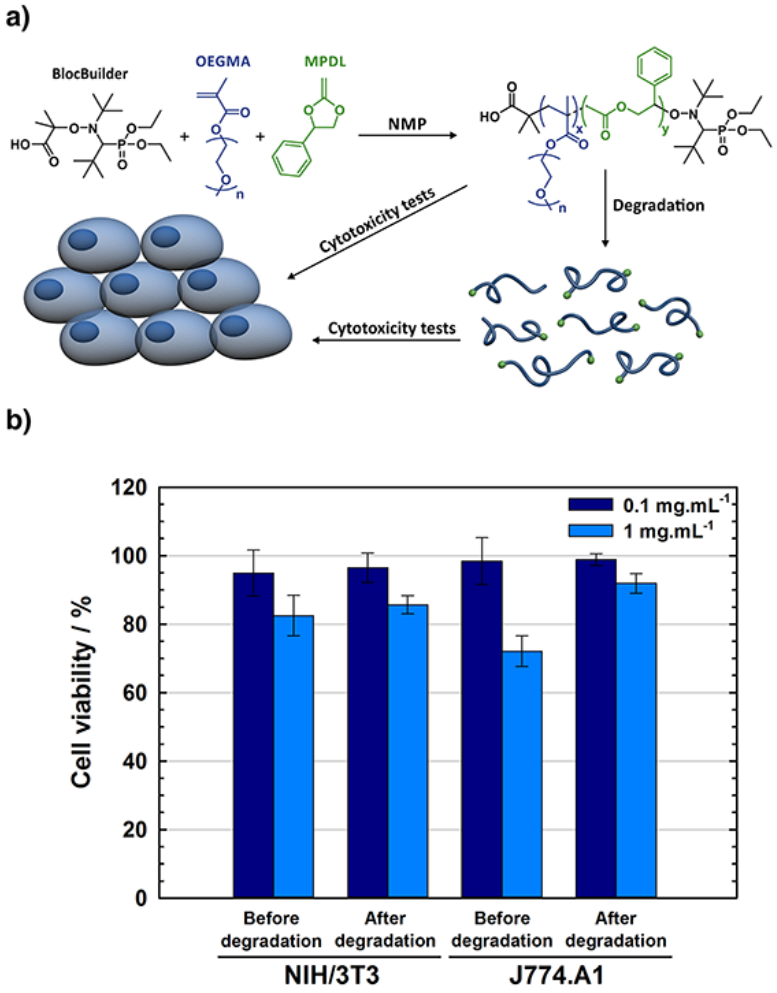


Figure 102. a) Synthesis, degradation and cytotoxicity of P(MeOEGMA-*co*-**CKA11**) prepared by NMP, b) cell viability (MTT assays) after incubation of NIH/3T3 cells and J774.A1 cells with P(MeOEGMA-*co*-**CKA11**) (F_{CKA11} = 0.113) at 0.1 and 1 mg.mL^{-1} (results expressed as percentages of absorption of treated cells in comparison to that of untreated ones as a control). Reproduced with permission from ref. [273.] 2015 published by the Royal Society of Chemistry.

P(NIPAAm-*co*-**CKA29**)-*b*-PEG-*b*-P(NIPAAm-*co*-**CKA29**) triblock copolymers were prepared by a RAFT-controlled radical ring-opening copolymerization of NIPAAm and **CKA29** from a PEG-based difunctional macroRAFT agent.[309] The copolymers were fully hydrolysed within 24h

in KOH solution at room temperature as proven by the low molecular weights monitored by SEC after degradation. The hydrolytic degradation of the triblock copolymer was observed also in PBS, pH 7.4 at 37 °C with even the loss of the thermogelation ability of the degradation products up to 60 °C in less than 24 days. Riachi and coworkers[329] described an elegant method to elaborate functional and degradable coatings. More precisely, the authors copolymerized BMDO **CKA29** and PEGMA by a surface-initiated ATRP method to form hydrolytically degradable brushes. If the brushes were relatively stable under neutral and mild-basic conditions (pH 9), the degradation rate was enhanced at pH 3-5 and increased with the BMDO **CKA29** content (Figure 103).

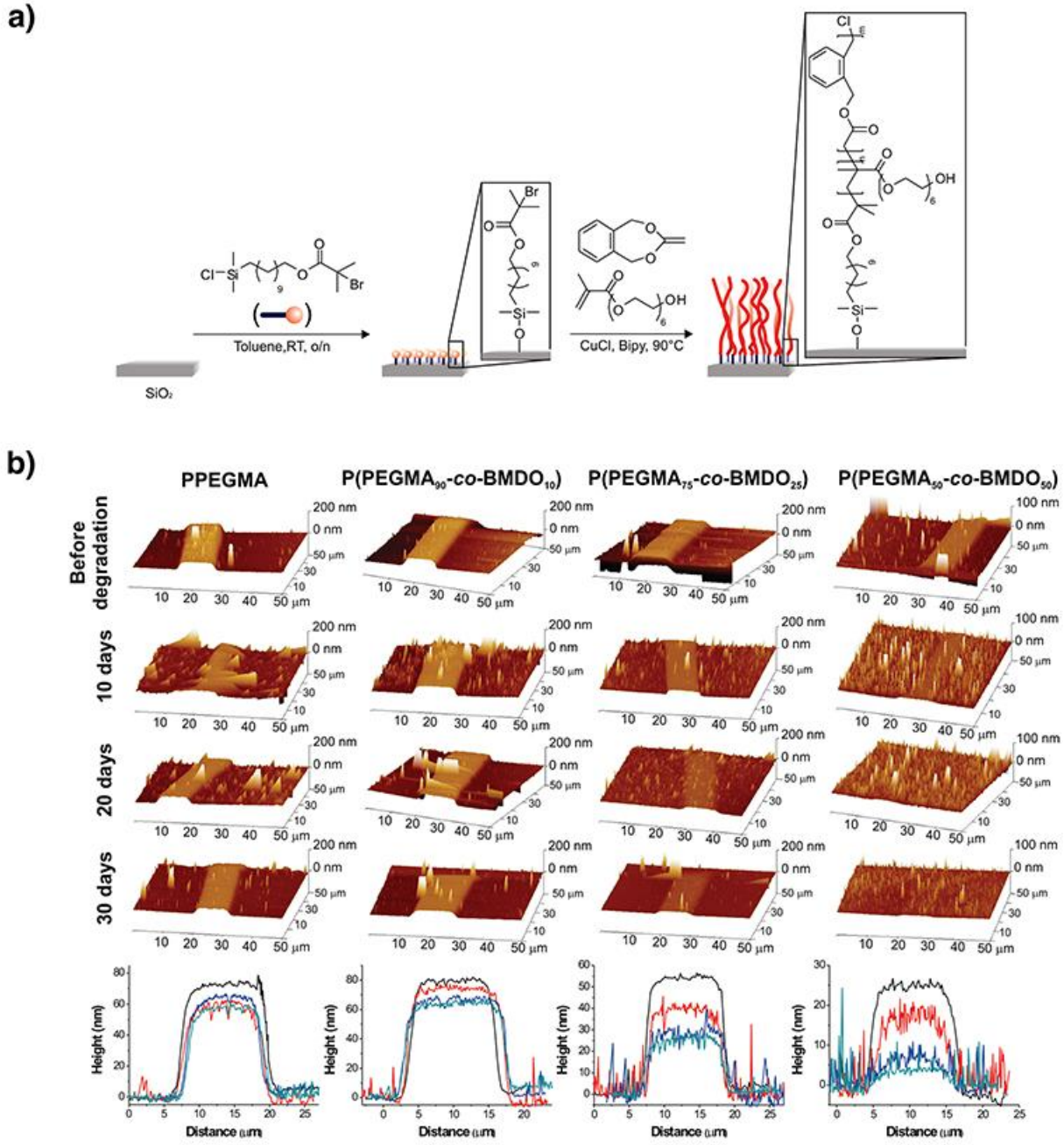


Figure 103. Up: grafting of P(PEGMA-*co*-**CKA29**) chains on silicon wafer by the Surface-initiated ATRP technique (Si-ATRP); down: AFM images and 2D cross-sectional profiles of different P(PEGMA$_x$-*co*-**CKA27**$_y$) brushes taken at different time intervals upon exposure to a pH 3 solution at 25 °C. Cross-sectional profiles: black lines, before degradation; red lines, after

10 days; blue lines, after 20 days; green lines, after 30 days. Reproduced with permission from ref. [329]. Copyright 2009 American Chemical Society.

Lynn and coworkers[266] prepared reactive and degradable cross-linked multilayer microcapsules using P(VDMA-*co*-**CKA27**). The preparation of multi-layered assembly from PVDMA polymers and others polymers bearing primary amine (PEI, etc.) has already been reported but these materials have the disadvantage to be very stable and thus to do not release the entrapped molecules over time. Microcapsules were then prepared using PEI/ P(VDMA-*co*-**CKA27**) with a feed ratio of 70 % in **CKA27**. The corona was also tagged with tetramethylrhodamine cadaverine. Once loaded with FITC-dextran in the core, the degradation of the capsules dispersed in PBS buffer was monitored by fluorescence microscopy before and after addition of 1 M KOH at 50 °C. The image revealed a clear degradation of the capsules with the release of the FITC-dextran in the medium. Reference capsules with only PVDMA/PEI corona remained intact in similar conditions demonstrating the interest of such approach to prepare capsules with tailored degradation and release rates.

The same polymer was also used to prepare covalently cross-linked degradable gels using multifunctional amines.[266] For example, P(VDMA-*co*-**CKA27**) could react with tris(2-aminoethyl)amine (TREN) in THF to yield a non-flowing gel, that can degrade upon incubation in PBS buffer overnight.

Degradable nanoparticles

Nanoparticles of P(**CKA27**)-*g*-PEG and P(**CKA27**)-*g*-PNIPAAm have been synthesized by free radical copolymerization of MDO/MDP **CKA27** with either PEG methacrylate or PNIPAAm in the presence of AIBN.[330] The nanoparticles were formed in THF/H_2O (diameter 60-300 nm

depending on the conditions). The authors observed a good colloidal dispersion and chemical stability of the nanoparticles when incubated in PBS at 37°C for 8 days. The alkaline hydrolysis of the nanoparticles was studied and showed the degradation of the polyester backbone. Nevertheless they maintained their colloidal stability during the degradation process due to a reorganization of the released PEG chains (Figure 104). As expected, the P(**CKA27**)-*g*-PNIPAAm nanoparticles presented an thermo-sensitive aggregation and may be interesting candidates for drug-delivery purposes.

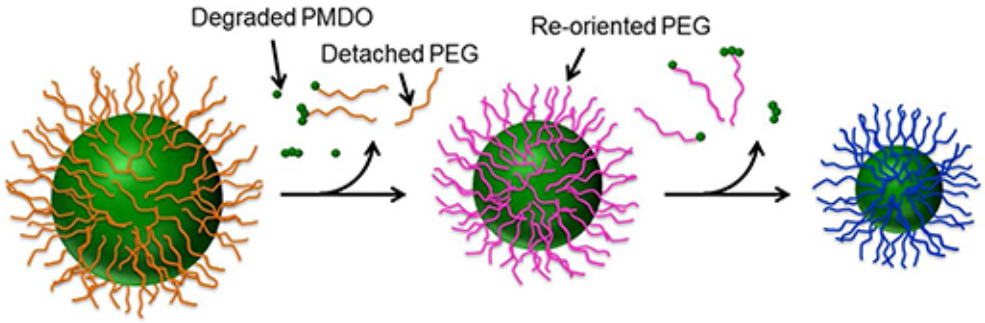


Figure 104. Proposed mechanism of nanoparticles degradation with reorganization of PEG chains during hydrolysis. Reproduced with permission from ref. [330]. Copyright 2015 American Chemical Society.

Agarwal and coworkers[238] used a protection-deprotection chemical method to synthesize P(HEMA-*co*-**CKA29**) copolymers by free radical copolymerization. The chemical protection of the OH functions of the HEMA was indeed necessary to ensure the ring-opening of the BMDO **CKA29** and the formation of ester functions in the main copolymer chain. The synthesized copolymers successfully degraded in alkaline conditions, and surface and bulk erosion was observed in the presence of macrophages (J774A cells). Finally, when loaded with coumarin, the

P(HEMA-*co*-**CKA29**) nanoparticles presented no burst release but rather a retarded release that was complete after 24h.

Hydrolysable (co)polymers used for various applications

Marine antibiolouling coatings require the preparation of surface with a self-polishing ability and that could release biocides. Silyl acrylate polymers are promising materials for such an application but require optimization in terms erosion and release properties. To tackle these problems, P(**CKA27**-*co*-tributylsilyl methacrylate-*co*-MMA) (PMSM) copolymers were synthesized by free radical copolymerization in the presence of AIBN.[331] Hydrolysis experiments performed in artificial seawater showed that this system can be used to inhibit marine biofouling by the controlled release of organic antifoulants like 4,5-dichloro-2-octyl-isothiazolone (DCOIT). More than 20 wt% of MDO/MDP **CKA27** in the copolymer were nevertheless required to get a modified silyl acrylate copolymer-based coating that efficiently prevented the growth of marine organisms for four months (Figure 105).

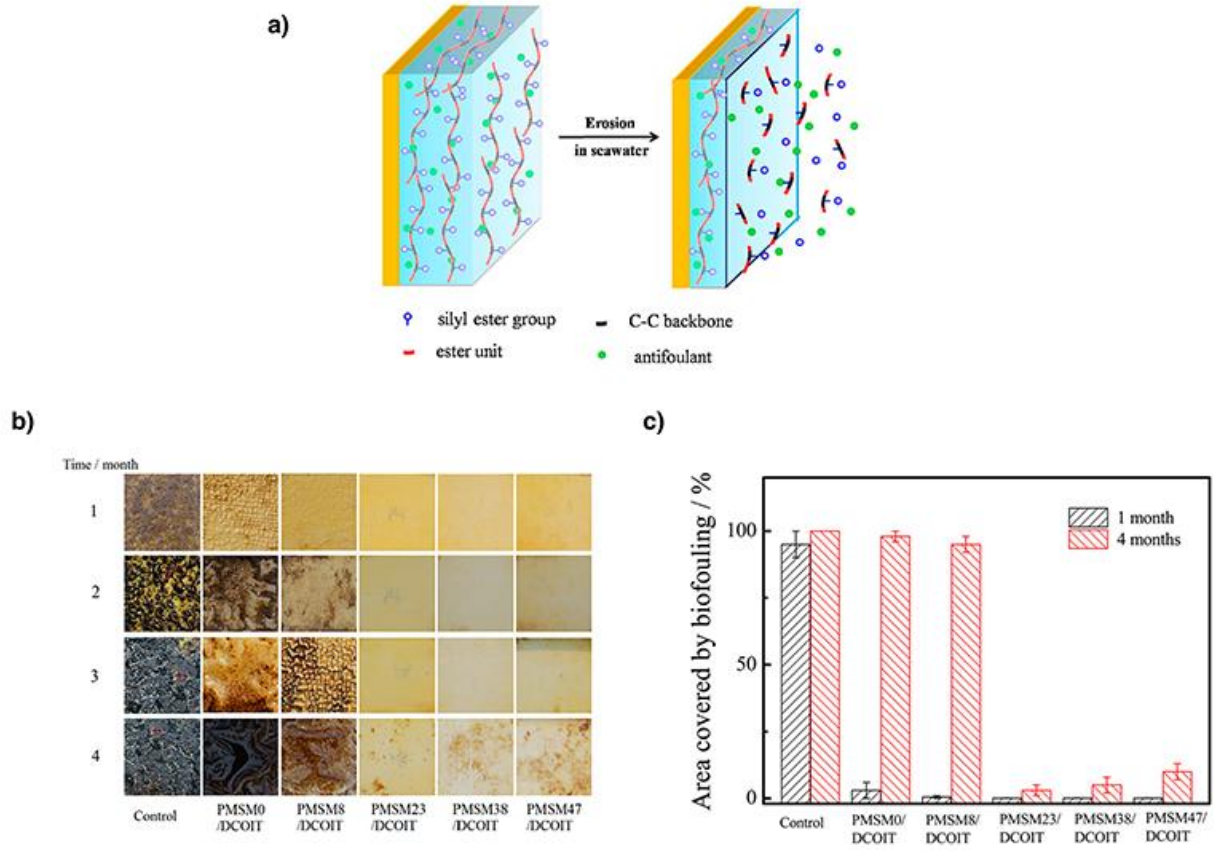


Figure 105. Left: Mechanism of degradation and release of antifouling molecules, right: a) typical images of panels coated with PMSM copolymer loaded with 10 wt% of DCOIT; b) quantitative analysis of biofouling estimated from the area covered by foulants. Reproduced with permission from Ref. [331]. Copyright 2015 American Chemical Society.

Another general goal when incorporating CKA monomers like MDO/MDP **CKA27** into vinyl (co)polymer chains is to impart new degradability properties to the initial material. For instance, Borkar and coworkers[248] synthesized P(**CKA27**-*alt*-fluoroalkene) alternating copolymers by free radical copolymerization to form hydrophobic films. The presence of ester functions in the

backbone enabled the hydrolysis of the copolymers in trifluoroacetic acid solutions heated at 60 °C for 24h.

Wu and Lenz[225] incorporated MDO/MDP **CKA27** into PE and PS chains by free radical copolymerization with AIBN or di-*tert*-butyl peroxide as initiators. P(**CKA27**-*co*-E) and P(**CKA27**-*co*-S) were further degraded by methanolysis (HCl/MeOH). Concerning P(**CKA27**-*co*-E) copolymers, the M_n of the oligomers formed by hydrolysis was dependant on the fraction of MDO/MDP **CKA27** units incorporated in the copolymer. On the contrary, the oligomers obtained from the degradation of P(**CKA27**-*co*-S) copolymers presented a broader molecular weight distribution that the initial material. This phenomenon could be assigned to the high difference in reactivity of the two monomers implying a non-regular distribution of the ester functions along the copolymer chains. The copolymers with ethylene having 6-15% of ester units on the backbone led to oligomers that were consumed by microorganisms.

Agarwal and coworkers[234] described the elaboration of degradable, transparent and elastomeric materials based on polycaprolactone. A PCL-macroinitiator formed by condensation of ACPC (azobis(cyanopentanoic acid chloride)) with PCL-diol was used to copolymerize MDO/MDP **CKA27** and MMA. The obtained P(MMA-*co*-**CKA27**)-*b*-PCL-*b*-P(MMA-*co*-**CKA27**) multiblock copolymers showed interesting mechanical properties (e.g., low modulus, high elongation at break) that depended on the composition of the P(MMA-*co*-**CKA27**) block. The copolymers were also partially hydrolysed in alkaline conditions and resulted in a fraction of stable molecular weight (600 to 5500 $g.mol^{-1}$) depending on the copolymer composition and block lengths.

Nicolas and coworkers[161] extended their works previously focused on the NMP copolymerization of MeOEGMA[273] and MDPO/MDPL **CKA11** to MMA. With a **CKA11** initial fraction above 20 mol%, well-defined copolymers were readily obtained that in addition

presented interesting features. The degradation studies in accelerated hydrolytic conditions (5 % KOH in MeOH/THF) showed extremely rapid kinetics (up to 5 min, Figure 106a) and significant molar masses decreases (from -60 % M_n to complete degradations). Moreover the incorporation of **CKA11** units in the copolymer backbone up to 14 % affected only moderately the T_g of the materials (97 instead of 106 ºC, Figure 106b). The NMP copolymerization of methacrylate derivatives opens up a new process to prepare well-defined degradable materials.

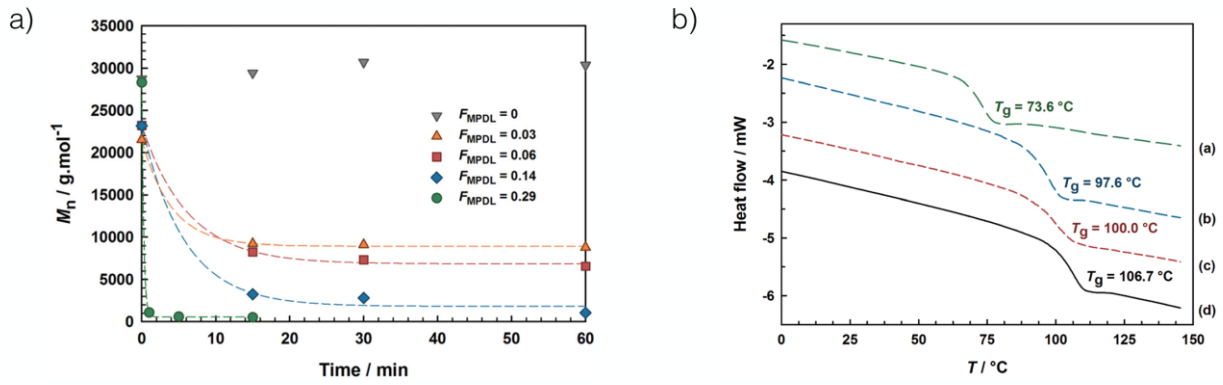


Figure 106. a) Hydrolytic degradation in THF with 5% KOH in methanol of P(MMA-*co*-MPDL) as a function of the MPDL **CKA11** fraction: ▼, (P(MMA-*co*-S), F_{MPDL} = 0); ▲, (F_{MPDL} = 0.03); ■, (F_{MPDL} = 0.06); ◆, (F_{MPDL} = 0.14); ●, (F_{MPDL} = 0.29). Evolution of the number-average molar mass, M_n, with time. Dashed lines represent the exponential fit, equation plot: $Mn(t) = Mn_{,\infty} + a \times \exp(-t/\tau)$. b) DSC curves of the purified P(MMA-*co*-MPDL) and P(MMA-*co*-S) obtained by NMP of MMA and MPDL (or S) in toluene initiated by the BlocBuilder at 90 °C, as a function of the molar fraction of MPDL in the copolymer: (a) (F_{MPDL} = 0.29); (b) (F_{MPDL} = 0.14); (c) (F_{MPDL} = 0.06); (d) (P(MMA-*co*-S), F_{MPDL} = 0).

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7.2.2 Enzymatic degradation

In addition to hydrolytic degradation, enzymatic degradation (e.g., lipases, proteinases) has been investigated to degrade CKA-containing copolymers. In this part, hydrogels and co-networks are presented separately from non-cross-linked compostable or bio-assimilable copolymers.

Enzymatic degradation of co-networks or hydrogels

According to a review of Erdodi and Kennedy,[332] amphiphilic co-networks (APCN) can be defined as "*two-component networks of covalently interconnected hydrophilic/hydrophobic phases of co-continuous morphology; as such they swell both in water and hydrocarbons, and respond to changes in the medium by morphological isomerization*". APCN could then be qualified as hydrogels that swell in hydrocarbons. Agarwal and coworkers[333] prepared enzymatically degradable APCN by radical copolymerization. 1,1 diethoxycarbonyl-2-vinyl cyclopropane (**VCP2**) and MPDO/MPDL **CKA11** were copolymerized by radical ring-opening copolymerization in the presence of di-*tert*-butyl peroxide to form the hydrophobic parts of the APCN. The ring-opening of VCP introduced cross-linkable C=C double bonds in the P(**VCP2**-*co*-**CKA11**) copolymer chains. According to the reactivity ratio (r_{VCP} = 0.23 and r_{MPDL} = 0.18), the distribution of the insaturations along the copolymer backbone can be considered as random and regular. Consequently, the synthesized P(**VCP2**-*co*-**CKA11**) hydrophobic chains were then successfully cross-linked with hydrophilic OEGMA macromonomer (M_n = 500 g.mol^{-1}) to form an amphiphilic co-network. The enzymatic degradability of APCN with different [**VCP2**]/[**CKA11**] ratio was determined in PBS, pH 7 at 37 °C in the presence of lipases. The authors observed a regular weight loss of the different APCN with time and the highest

degradation rate was obtained with the copolymer of higher **CKA11** content (35 days for APCN with P(**VCP2**$_{45\%}$-co-**CKA11**$_{55\%}$). As expected, the higher the content of ester functions, the faster the degradation of the copolymer (Figure 107).

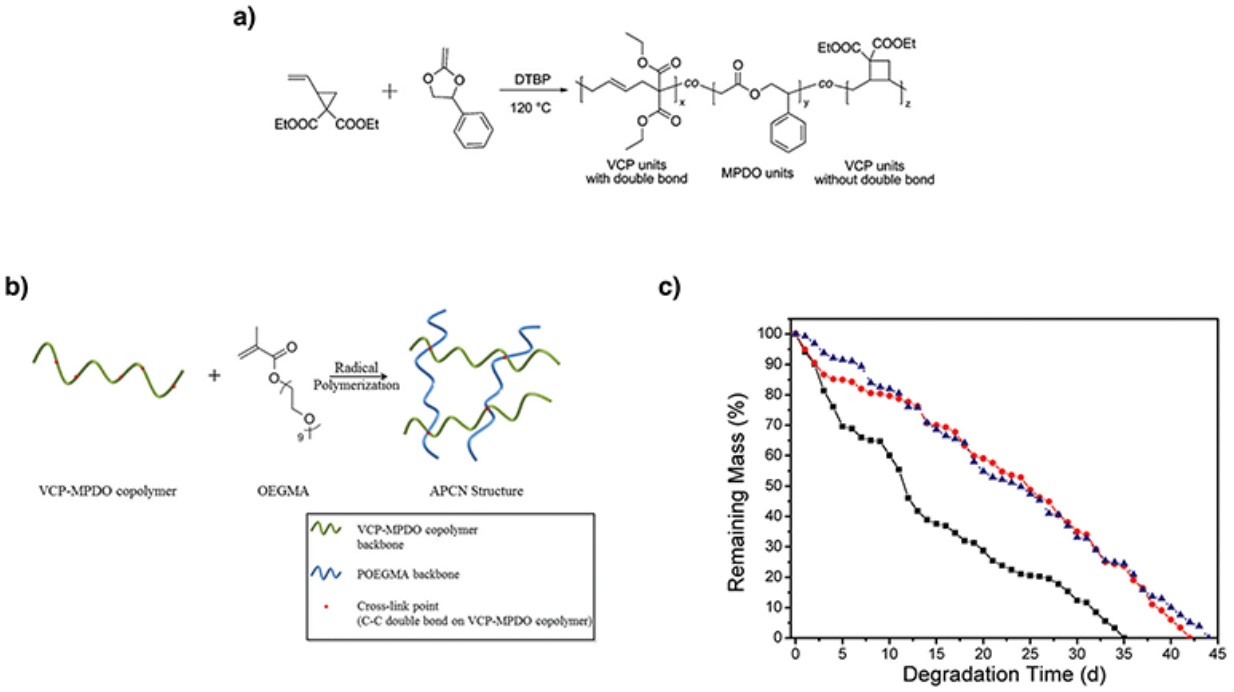


Figure 107. a) Preparation of biodegradable amphiphilic APCN based on P(**VCP2**-*co*-**CKA11**) copolymer chains cross-linked with OEGMA. b) Mass loss of APCN against enzyme in pH 7 for P(**VCP2**-*co*-**CKA11**) with 55 mol% **CKA11** (black square); 41 mol% **CKA11** (red circle) and 36 mol% **CKA11** (blue triangle). Reproduced with permission from Ref. [333]. 2015 published by the Royal Society of Chemistry.

Sun and coworkers[20] reported the elaboration of thermoresponsive and biodegradable P(*N*-isopropylacrylamide-*co*-**CKA27**) hydrogels (P(NIPAAm-*co*-**CKA27**)) designed for biomedical applications. Linear P(NIPAAm-*co*-**CKA27**) copolymers were synthesized by radical ring-

opening copolymerization of NIPAAm and **CKA27** with AIBN. *N,N'*-Methylene-bis-acrylamide was then used as cross-linking agent to form the corresponding hydrogel. The degradation study performed with proteinase K in Tris-HCl, pH 8.6 showed that the enzymatic degradation rate was faster at 22 °C than at 37 °C. This phenomenon was assigned to a higher swelling ratio and consequently to a higher porosity at 22 °C that facilitated the accessibility of enzymes to the material.

Bio-assimilable materials

If polymers like PS, PMMA or PVAc are extensively used today in a broad range of different areas, one of the main limitations of commodity polymers is their lack of degradability. A solution consisted in the incorporation of monomer units sensitive to enzyme degradation. The resulting copolymers can then be (partially) bio-assimilated or compostable.

The copolymerization of MPDO/MPDL **CKA11**, MTC **CKA36** or MDO/MDP **CKA27** with different vinyl monomers has proven to be an efficient method to confer new biodegradability properties to common vinyl polymers. Contrary to P(**CKA36**-*co*-MMA), P(**CKA36**-*co*-S) and P(**CKA36**-*co*-VAc) could be degraded by lipases in PBS, pH 7 after 16h at 30 °C.[189] The biodegradability of P(**CKA36)** and P(**CKA27**) was also compared in the presence of lipases in PBS (pH 7, 24h, 30 °C) and it was shown that P(**CKA36)** was more degradable certainly because of its higher hydrophilicity.[334] The biodegradability of P(NIPAAm-*co*-**CKA36**) copolymers was also studied and it was concluded that 10 mol% of **CKA36** in the copolymer were enough to observe a biodegradation by lipases at 30 °C.[240] Nevertheless, the authors did not perform a monitoring of the mass loss but only measured the decrease of the height of the SEC peak. Sun and coworkers[241] confirmed that poly(methyl acrylate) (PMA) polymer chains become

biodegradable by incorporation of MDO/MDP **CKA27** units and that the higher the inserted **CKA27** fraction, the faster the degradation.

In 2010, Agarwal and coworkers[335] proved that the compostability of a semi-crystalline PCL synthesized by ROP can be enhanced by incorporating low percentage of amorphous P(**CKA27**) chains (Figure 108). P(**CKA27**) synthesized by rROP can be indeed considered as analogous to PCL but with a higher branching ratio. The PCL synthesized by rROP was consequently an amorphous polyester. Blends of semi-crystalline and amorphous PCL also presented interesting properties such as an increase of the PCL transparency when increasing the amount of amorphous component and changes of the spherulite size with the initial polymers' ratio (Figure 108).

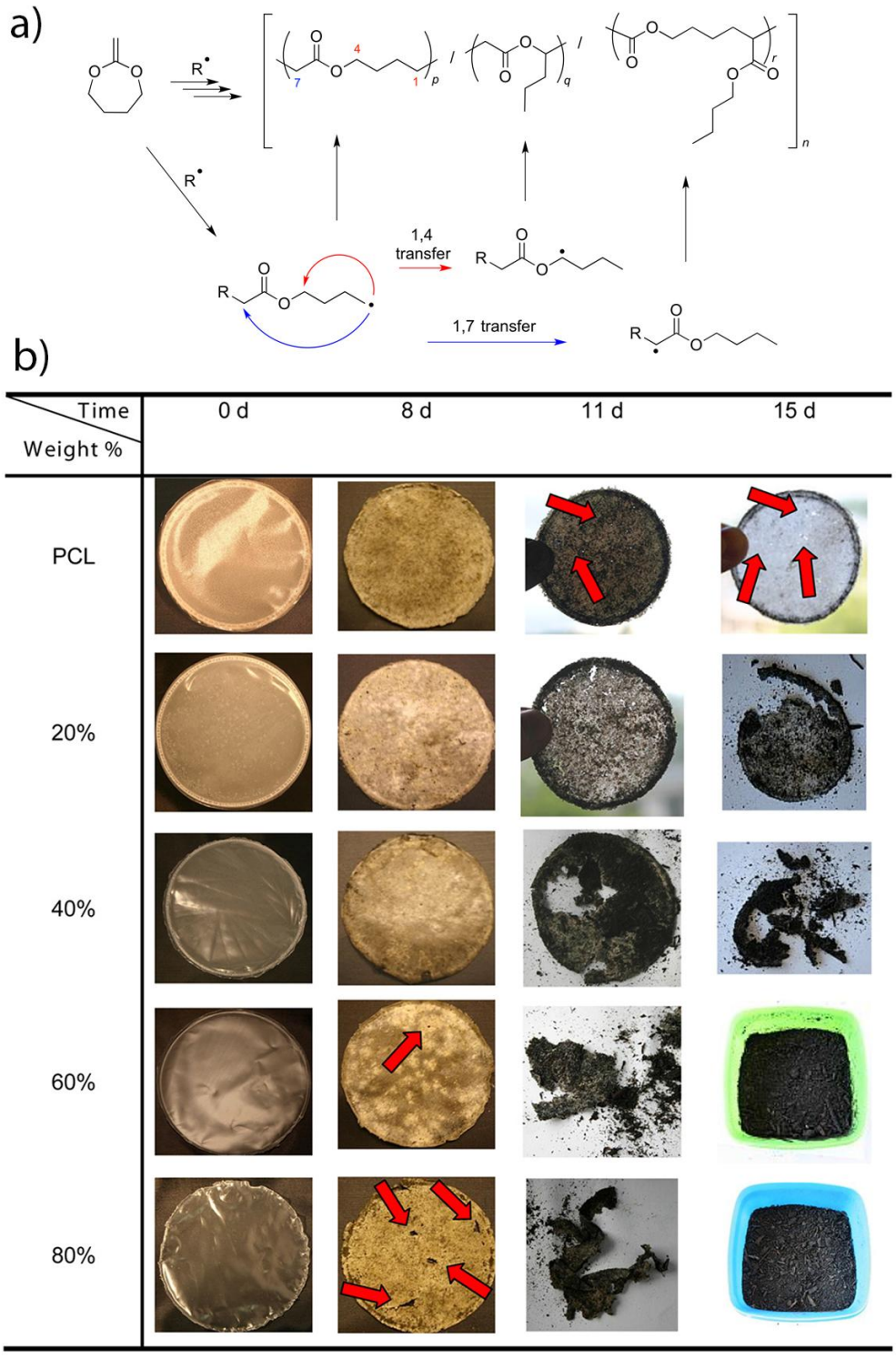


Figure 108. a) Mechanism of the intramolecular (backbiting) reaction that occurs during the rROP of MDO/MDP **CKA27**. b) Compostability study performed on blend films (% of

amorphous PCL/P(**CKA27**) and compared to semi crystalline PCL. Films of 5.9 cm of diameter and 80 μm of thickness. Compost at 45 °C. Reproduced with permission from Ref. [335]. Copyright 2010 Elsevier.

7.2.3 Materials that combine different methods of degradation

In addition to hydrolytic and enzymatic degradations, a smart and efficient method to elaborate degradable copolymers consisted in the synthesis of materials with different degradation pathways. This concept was introduced by Hiraguri and coworkers[245] with the elaboration of P(**CKA36**-*co*-methyl vinyl ketone) that could degrade with lipases or by photolysis. More recently, Hawker and coworkers[82] copolymerized sulphur containing monomers containing orthogonal functionalities (**SCM5**-**7**, Figure 33) with vinyl monomers (e.g., MMA, DMAEMA or HEMA) by RAFT-mediated rROP. This strategy presented the advantage of an easy incorporation of different cleavable groups (e.g., ester, thioester, disulphide) into a vinyl-based polymer backbone by either copolymerizing different cyclic monomers or by the copolymerization of cyclic monomers bearing different cleavable functionalities. The degradation profile of the synthesized copolymers was thus finely tuned (Figure 109).

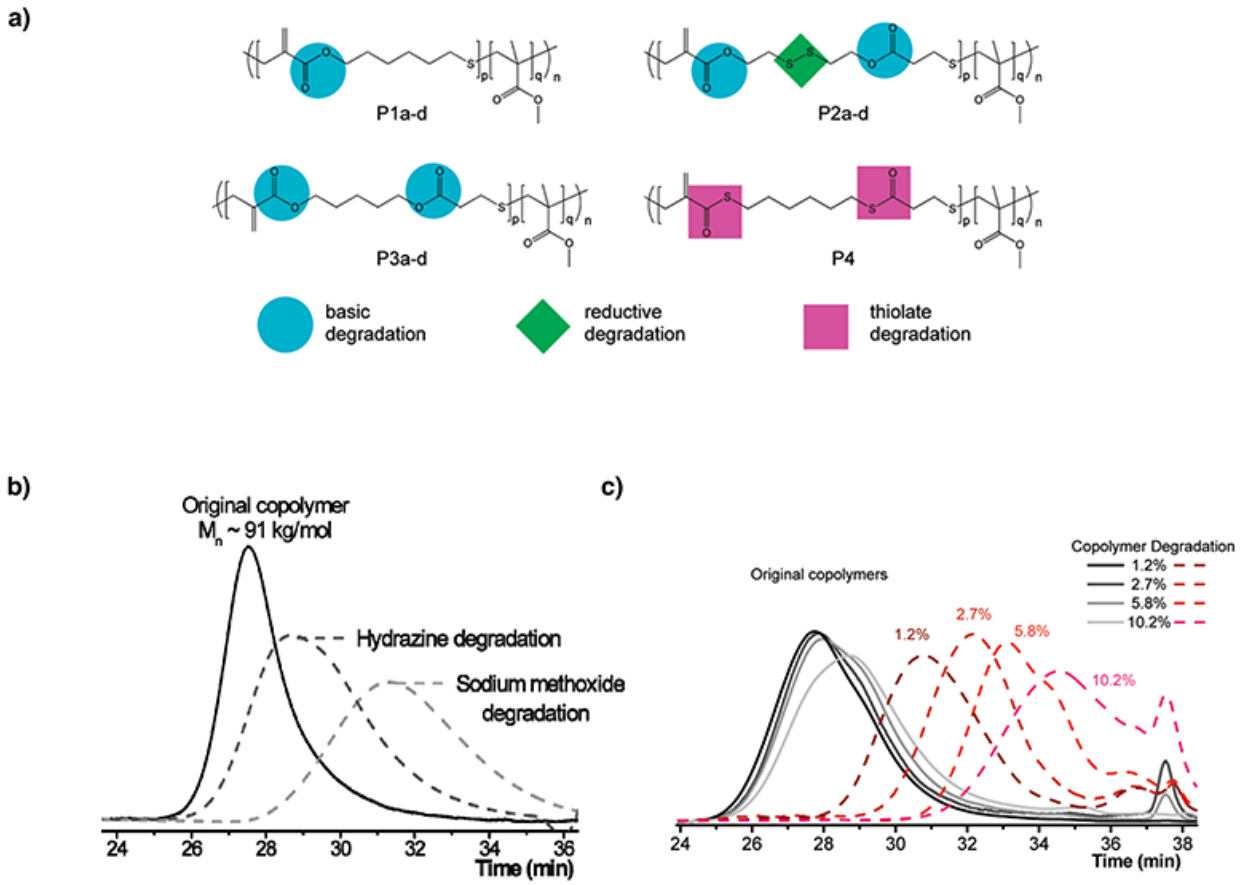


Figure 109. a) Copolymers of MMA and sulphur containing monomers (**SCM5-7**) and their degradation conditions, b) SEC traces of copolymer obtained by terpolymerization of MMA, **SCM5** and **SCM6** and its stepwise degradation using first hydrazine and secondly sodium methoxide, c) SEC traces of copolymers P(MMA-*co*-**SCM5**) (% values indicate the mol% of sulphur containing monomer in the copolymer). Reproduced with permission from Ref. [82]. Copyright 2009 American Chemical Society.

7.3 Biomedical applications

7.3.1 (Co)polymers used for anticancer drug delivery

CKA27-based copolymers (P(**CKA27**-*co*-PEGMA-*co*-CMA),[237] P(**CKA27**-*co*-PEGMA-*co*-PDSMA)[336-337] with CMA for 7-(2-methacryloyloxyethoxy)-4-methylcouparin methacrylate and PDSMA for pyridyldisulfide ethylmethacrylate) were used as potential drug delivery carriers. The copolymers were synthesized by free radical copolymerization in the presence of AIBN and further self-assembled into degradable and biocompatible micelles. More precisely, micelles of amphiphilic P(**CKA27**-*co*-PEGMA-*co*-CMA) copolymers were formed by self-assembly in water and then cross-linked upon UV irradiation (λ = 365 nm) using the dimerization of the coumarin moieties in the micelle core. The drug (doxorubicin, DOX) was loaded into the micelles during the self-assembly process (Figure 110).[237] In the case of P(**CKA27**-*co*-PEGMA-*co*-PDSMA) micelles, DOX was either covalently linked to the micelles (polymeric prodrug)[336] or loaded into the core of the micelles.[337] The degradable polymeric prodrug nanocarriers were prepared by thiol-ene 'click chemistry' between PDSMA and a maleimide derivative of doxorubicin (Mal-DOX) that contained a pH-sensitive hydrazone bond (Figure 111). The advantage of polymeric prodrug compared to encapsulated drug is that this drug-delivery vehicle is more stable during the transport and circulation in the body. In this work, the pH-sensitive hydrazone bonds presented the advantage of being cleavable at lysosymal pH (5.5). Flow cytometry and fluorescence microscopy proved that these pH-sensitive prodrug micelles were efficiently internalized by A549 cancer cells and MTT assays showed that the DOX conjugated prodrug micelles were able to inhibit the proliferation of cancer cells.

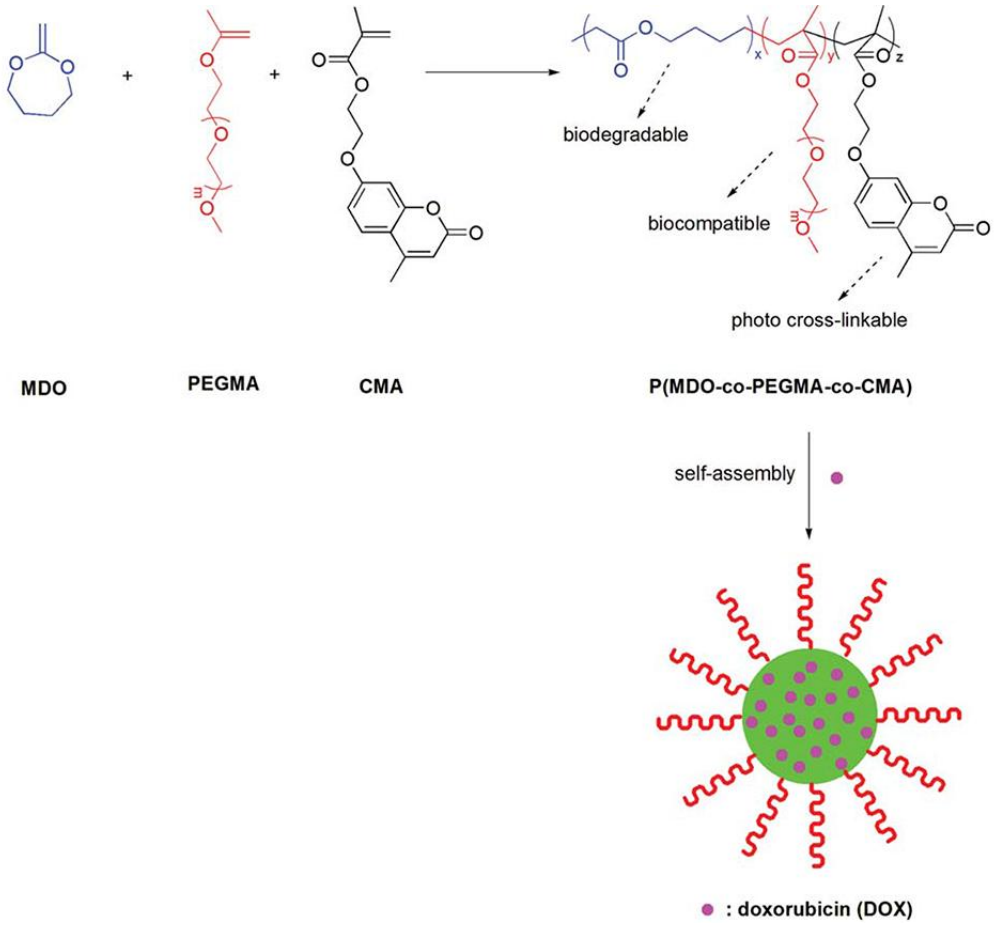


Figure 110. Doxorubicin (DOX) loading in P(**CKA27**-*co*-PEGMA-*co*-CMA)-based micelles and % of cumulative DOX release from micelles of copolymer P3 before and after cross-linking in PBS, pH 7.4, 37 °C. Reproduced with permission from Ref. [237.] Copyright 2012 the Royal Society of Chemistry.

The same P(**CKA27**-*co*-PEGMA-*co*-PDSMA) copolymers were also used to form reduction-sensitive biodegradable DOX-loaded micelles.[337] The copolymer chains contained disulphide bonds that could be cleaved under reductive environment (1.10^{-4} $mol.L^{-1}$ gluthanione (GSH)). The disassembly of the micelles resulted in the anticancer drug release and MTT assays proved that the DOX-loaded micelles inhibited the proliferation of cancer cells (A549 cells) and that the

blank micelles did not present any toxicity to human umbilical vein endothelial cells (HUVEC) and A549 cells (Figure 112).

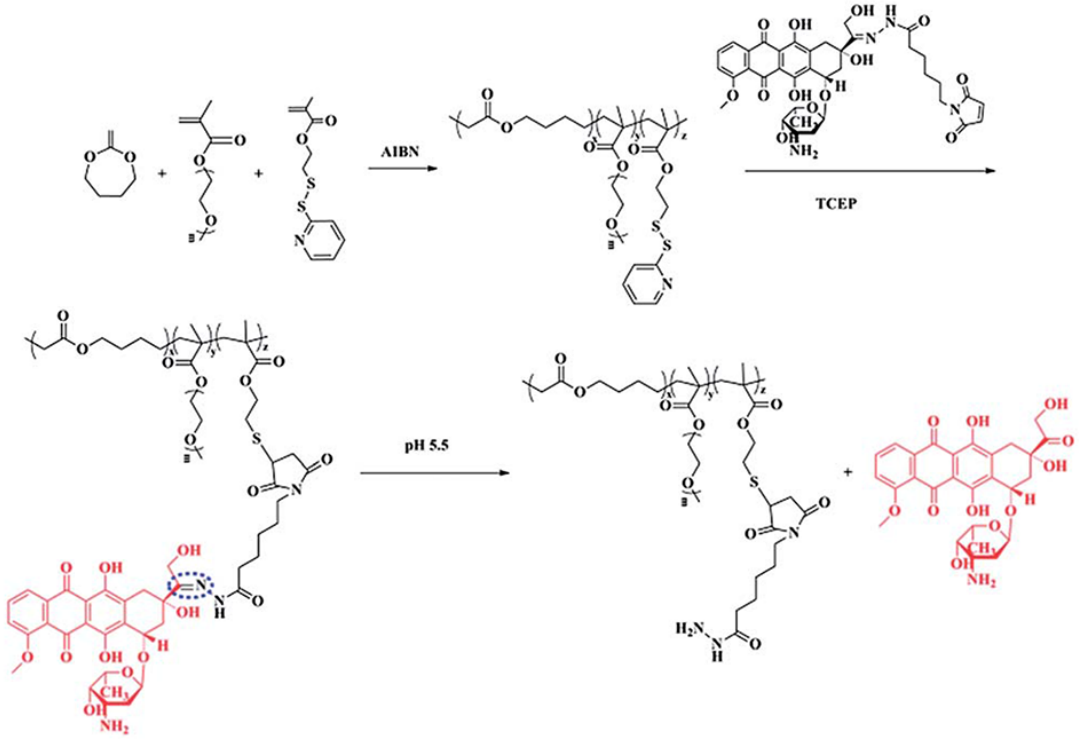


Figure 111. Synthesis of DOX-conjugated P(**CKA27**-*co*-PEGMA-*co*-PDSMA) copolymers. Reproduced with permission from Ref. [336]. 2014 published by the Royal Society of Chemistry

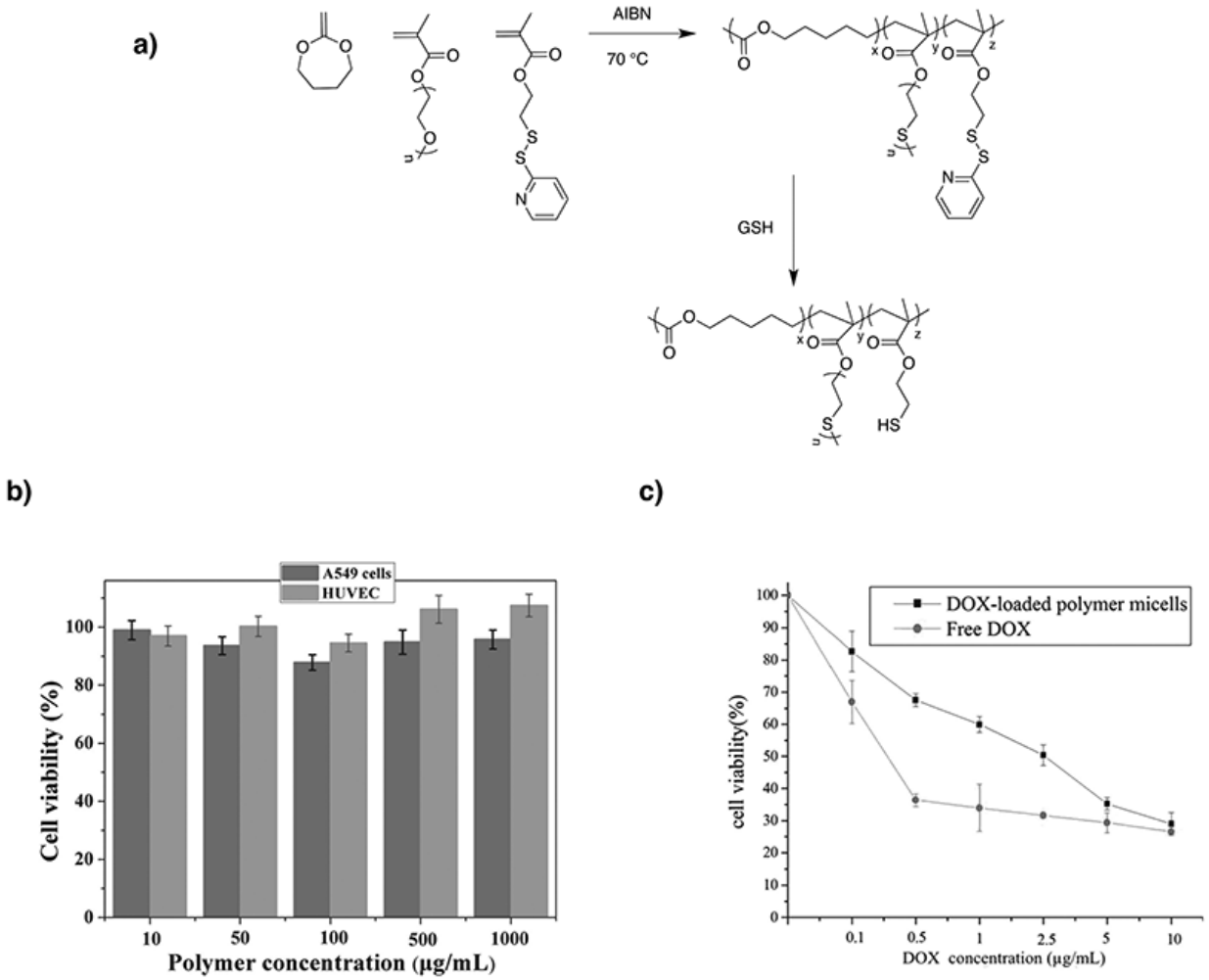


Figure 112. a) Synthesis and GSH responsiveness of P(MDP-*co*-PEGMA-*co*-PDSMA) copolymers. b) cell viability of HUVEC cells and A549 cells incubated with different concentrations of micelles; c) cell viability of A549 cells incubated with various concentrations of DOX-loaded micelles. Reproduced with permission from Ref. [337]. Copyright 2014 John Wiley and Sons.

Lu and coworkers prepared another Dox delivery system based on micelles bearing a glycopolymer corona with drugs conjugated to the cargo via an acid-labile Schiff base linkage.[231] The amphiphilic copolymer was prepared by RAFT of BMDO **CKA29** with 1,2:3,4-di-*O*-

isopropylidene-6-*O*-(2'-formyl-4'-vinylphenyl)-D-galactopyranose (IVDG), a styrenic derivative bearing an aldehyde group and a protected sugar moiety. Once the sugar deprotected, the copolymer became amphiphilic and self-assembled into micelles. Since the vinyl monomer is a styrenic derivative, the incorporation of BMDO **CKA29** was low (15% in the copolymer from a 50 % feed). Nevertheless the amphiphilic copolymer presented good hydrolytic degradability and non-cytotoxicity. The copolymer could thus be conjugated with Dox at a high loading ratio (14 w%) and still self-assemble into micelles. The Dox-release was higher at pH = 5 than at physiological pH due to the imine based linkage and this pH-triggered release is advantageous for the selective release in tumor tissues. In addition it is expected that the galactose shell could lead to site-targeted delivery.

Other biodegradable glycopolymer micelles were also recently prepared.[310] Carbohydrate-coated nanoparticles have the advantage to promote selective and active targeting, but with the drawback that persisting polymer could induce unwanted immune response and toxicity. To tackle this problem the RAFT copolymerization of BMDO **CKA29** with 1-*O*-acryloyl-2,3:4,5-di-Oisopropylidene-β-D-fructopyranose (1-O-A*i*PrFru) was performed using a PCL-based macro-CTA (Figure 113). Once the sugar deprotected, the block copolymer self-assembled into non-spherical egg-shaped micelles. The degradation of the micelles was then investigated *via* an enzymatic system (Lipase *Pseudomonas* sp.) showing extremely rapid dissociation. Both the micelles and the degradation products showed no cytoxicity against healthy human fibroblast HS27 and breast cancer MDA-MB-231 cell lines.

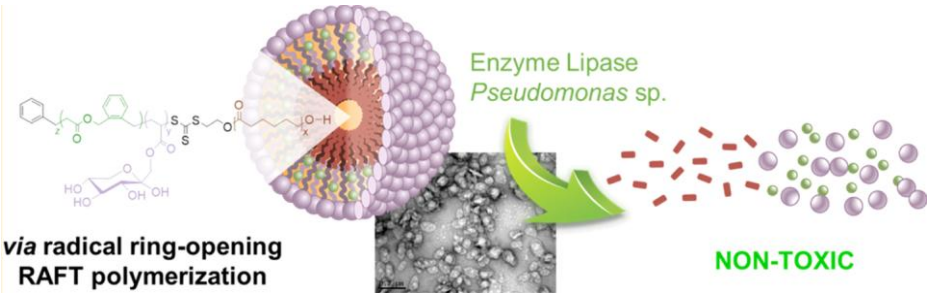


Figure 113. Preparation of biodegradable glycopolymeric micelles by RAFT polymerization. Reproduced with permission from Ref. [310]. Copyright 2016 American Chemical Society.

Landfester and coworkers[15] reported the synthesis of P(**CKA29**), P(**CKA29**-*co*-styrene) and P(**CKA29**-co-MMA) nanoparticles by free-radical miniemulsion (co)polymerization. The (co)polymerizations were performed in the presence of hexadecane using the hydrophobic azo initiator 2,2'-azobis(2-methylbutyronitrile) V59. The influence of the stabilizer (sodium dodecylsulfate (SDS), cetyltrimethylammonium chloride (CTMA-Cl), Tween 200, Tween 40 and Tween 80) on the particles' stability, cellular uptake and cytotoxicity was investigated. It was shown that cationic surfactants resulted in smaller particles, better stabilization but higher toxicity whereas non-ionic surfactant (Tween stabilizers) gave larger particles with good cell viability. Paclitaxel (Pac) was used as model for drug delivery studies and was incorporated into P(**CKA29**) nanoparticles during their synthesis. The anticancer activity of Pac-P(**CKA29**)-Tw80 nanoparticles (Tween 80 as surfactant and 2 wt% Pac loading) was evaluated against HeLa cancer cells and compared to two commercially available Pac formulations (Pac-Hospira and Abraxane). After 24 – 72h of incubation, the synthesized system presented a comparable anticancer activity than the commercially available formulations (Figure 114).

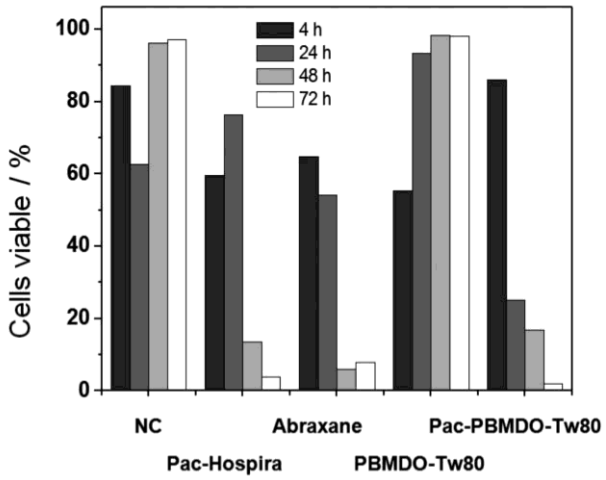


Figure 114. Percentage of viable HeLa cells after incubation of 2, 24, 48 and 72h (cell counting *via* Neubauer chamber) of Pac-P(**CKA29**)-Tw80 encapsulated system and the two commercially available paclitaxel formulations (Pac-Hospira and Abraxane). Reproduced with permission from Ref. [15]. Copyright 2012 John Wiley and Sons.

7.3.2 Biomaterials for gene/DNA transfection

To face diseases caused by genetic disorders, gene therapy is today a very promising research field. Among the different vectors that have been studied so far (e.g., viruses, peptides, polymers, etc.), polycationic synthetic polymers have the particularity to form stable polyplexes with nucleic acids at the nanometer scale. Compared to poly(ethylene imine) (PEI) that has been largely studied for such applications, poly(2-dimethylaminoethyl methacrylate) PDMAEMA presents the advantage of being less toxic. Because of an efficient complexation with DNA, PDMAEMA is a candidate of choice for gene delivery applications but lacks of degradability, hence limiting the *in vivo* use of high molecular masses PDMAEMA. To overcome this problem,

DMAEMA was copolymerized with BMDO **CKA29** or MDO/MDP **CKA27** to introduce hydrolysable ester bonds in the backbone. The synthesis of degradable cationic P(**CKA29**-*co*-DMAEMA)[275] and poly(PEG-*co*-(**CKA29**-*co*-DMAEMA))[236] copolymers tailored for DNA transfection was reported. The lower toxicity of P(**CKA29**-*co*-DMAEMA) compared to PEI was proven, and DLS and electrophoresis showed that after quaternization, the copolymers formed stable polyplexes with DNA. Water solubility could in addition be tuned by changing the ratio [**CKA29**]/[DMAEMA] and the alkyl group length of the quaternization agent (BrC_nH_{2n+1} with n = 2 or 12).

Similarly, the preparation of poly(PEG-*co*-(**CKA27**-*co*-DMAEMA)) block copolymers was also described.[236] These copolymers were synthesized from a PEO macro-azoinitiator to improve the water solubility and MDO/MDP **CKA27** was used instead of BMDO **CKA29** to mimic PCL. Compared to P(**CKA29**-*co*-DMAEMA) copolymers, poly(PEG-co-(**CKA27**-*co*-DMAEMA)) copolymers were thus expected to be more water soluble and more biocompatible and therefore better candidates for DNA transfection. Copolymers from different PEG macroinitiators have been tested (respectively 2000 and 6000 $g.mol^{-1}$), with or without quaternization by bromoethane. The authors proved that the presence of ester bonds in the copolymer backbone led to the degradation of poly(PEG-*co*-(**CKA27**-*co*-DMAEMA)) chains in alkaline conditions. A DLS study confirmed the formation of polyplexes with DNA and showed that their size did not exceed 250 nm. The efficiency of DNA complexation was nevertheless dependant on both the content of DMAEMA and the quaternization. As expected, better complexations were observed with quaternized copolymers. Among the various tested copolymers, the quaternized copolymers with [**CKA27**]/[DMAEMA] = 57/43 in mol% and PEG2000 was found to be the best candidate for DNA transfection whereas the unquaternized counterpart did not show noticeable transfection efficiency (Figure 115).

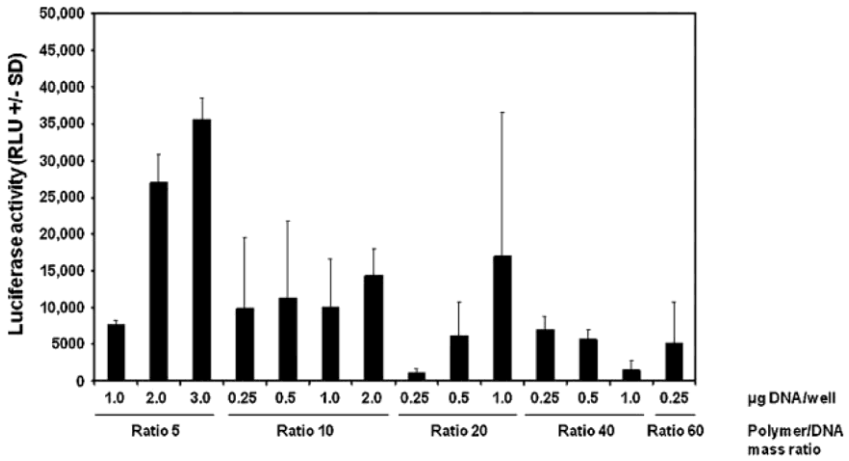


Figure 115. Transfection efficiencies of complexes comprising the quaternized copolymer with [**CKA27**]/[DMAEMA] = 57/43 in mol% and PEG2000 with plasmid-DNA and prepared at different polymer/DNA ratios, as determined by luciferases activities in SKOV-3 ovarian carcinoma cells. Reproduced with permission from Ref. [236]. Copyright 2013 John Wiley and Sons.

Lynn and coworkers[266] prepared a water-soluble cationic polymer by reacting the functional P(VDMA-co-**CKA27)** (see section 5.2.2) with dimethylaminopyridine (DMAP). After post-functionalization, a multi-layered film on silicon substrate was prepared composed of bilayers of P(VDMA-co-**CKA27**)-DMAP with plasmid DNA encoding for GFP. Once incubated in PBS, DNA was released linearly over 25 days. This release profile was consistent with a mechanism of film erosion that is governed by the slow hydrolysis of the CKA27-based ester groups. Cells treated with the released DNA showed fluorescence properties proving that the plasmid was intact after its release.

In addition to CKAs, other cyclic monomers were also used to prepare gene delivery vectors. Paulusse and Wang combined the use of single chain cyclized/knotted nanoparticles

(SCKNP) and SCM monomers to prepare gene delivery cargos that could degrade under reductive conditions.[312] The RAFT polymerization under kinetic control of DAEMA and various diacrylates (TEGDA or DSDA see Figure 116) in presence of 5 % of **SCM7** (Figure 33), led to SCKNP of 10 kDa that could be degraded under reductive conditions (hydrazine hydrate or glutathione). The degradation experiments confirmed both the single chain nature of the nanoparticles and the degradation of the backbone (Figure 116). The SCKNP were then finally tested by examining the Gaussia (G)-luciferase activity and green fluorescence protein (GFP) expression in transfected 3T3 and HeLa cell lines. The advantage of such disulphide-based nanoparticle system is related to the selectivity of the degradation (presence of glutathione that has a concentration 1000 times higher in the intramolecular cytoplasm than in the extracellular matrix) compared to ester-based nanoparticles that can be (slowly) hydrolysed in the extracellular environment. The transfection results presented in Figure 116 proved the efficiency of this system: high transfection efficiency combined with low cytotoxicity.

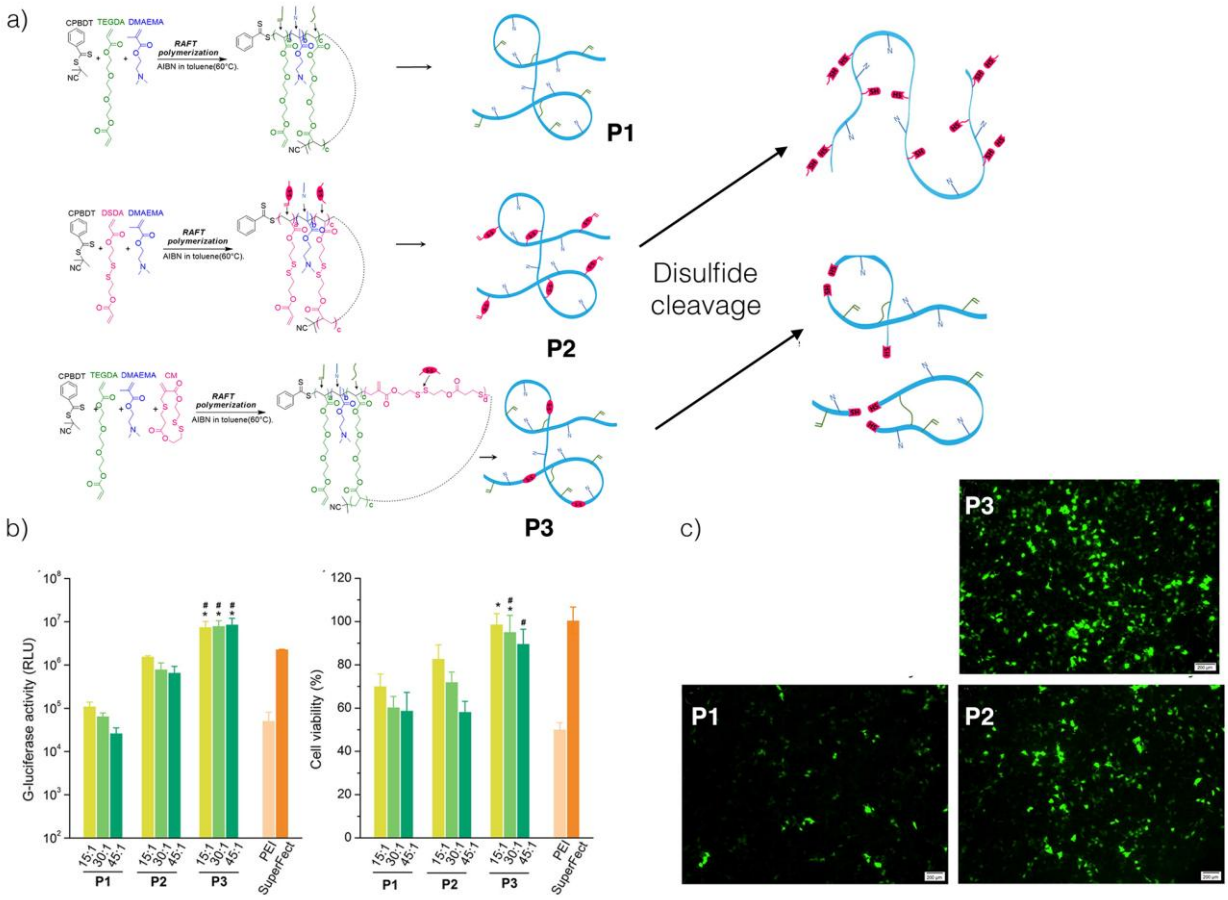


Figure 116. a) Synthesis of three different single-chain cyclized polymers via RAFT copolymerization: non-degradable poly(DMAEMA-*co*-TEGDA) (P1), crosslinked-degradable poly(DMAEMA-*co*-DSDA) (P2) and backbone-degradable poly(DMAEMA-*co*-MDTD-*co*-TEGDA) (P3). b) G-luciferase activity and cell viability of 3T3 cells after transfection. c) GFP expression of 3T3 cells after transfection with P1, P2 and P3/DNA Scale bars are 200 μm. Adapted with permission from Ref. [312]. Copyright 2015 Elsevier.

7.3.3 (Co)polymers for tissue engineering

Three-dimensional (3D) scaffolds that mimic extracellular matrices of great interest in the field of tissue engineering. To be implanted in the body, the scaffold must provide cell adhesion, differentiation and cellular proliferation. These criteria are indeed of crucial importance to prevent rejection of the scaffold by the body. To enable cellular colonization, the synthesized scaffold should thus present a high porosity with controlled pore sizes and interconnected pores. In addition, the role of the scaffold during the tissue (or organ) regeneration process is to bring the mechanical and biochemical support necessary to the healing but this artificial matrix should also disappear once the tissue (or organ) is regenerated. Consequently, this sacrificial use of the scaffold requires a degradable material. Finally, to avoid inflammatory response, the scaffold and its degradation products must be biocompatible. Among the different materials (synthetic or natural) that have been studied for tissue regeneration, hydrogels are promising candidates since they swell well in water and their mechanical properties are close to those of living tissues.

Considering the above-mentioned requirements, Ratner and coworkers[19] designed degradable thermo-sensitive porous PNIPAAm-based hydrogels. To obtain a good control of the pore size and an interconnected porous structure, the authors used a sphere-templating technique based on PMMA microspheres. More precisely, the mixture to polymerize was poured in a mold containing PMMA-microspheres of a chosen diameter (30 – 200 μm). After polymerization and cross-linking reactions, the microspheres were dissolved in a solvent to yield a porous and interconnected scaffold (Figure 117).

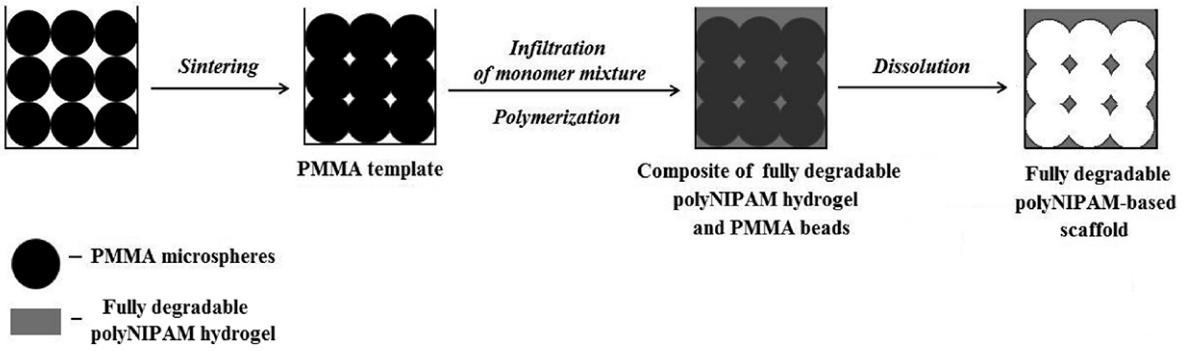


Figure 117. Sphere templating elaboration of degradable PNIPAAm-based scaffold. Reproduced with permission from Ref. [19]. Copyright 2010 American Chemical Society.

The preparation of the scaffold's matrix consisted in the photocopolymerization of NIPAAm with MDO/MDP **CKA27** (20 or 40 mol% in the comonomer mixture) and polycaprolactone dimethacrylate (PCLDMA).[19] The obtained scaffolds were degradable, not cytotoxic and exhibited interconnected size-thermosensitive pores. Scaffolds with pore size around 55 μm were loaded with cells and the authors observed a good cell attachment and infiltration in the scaffold. Figure 118a showed the porous and interconnected structure of the scaffold whereas Figure 118b proved the cellular colonization of the scaffold by NIH3T3 cells that was a model system for many cells.[19]

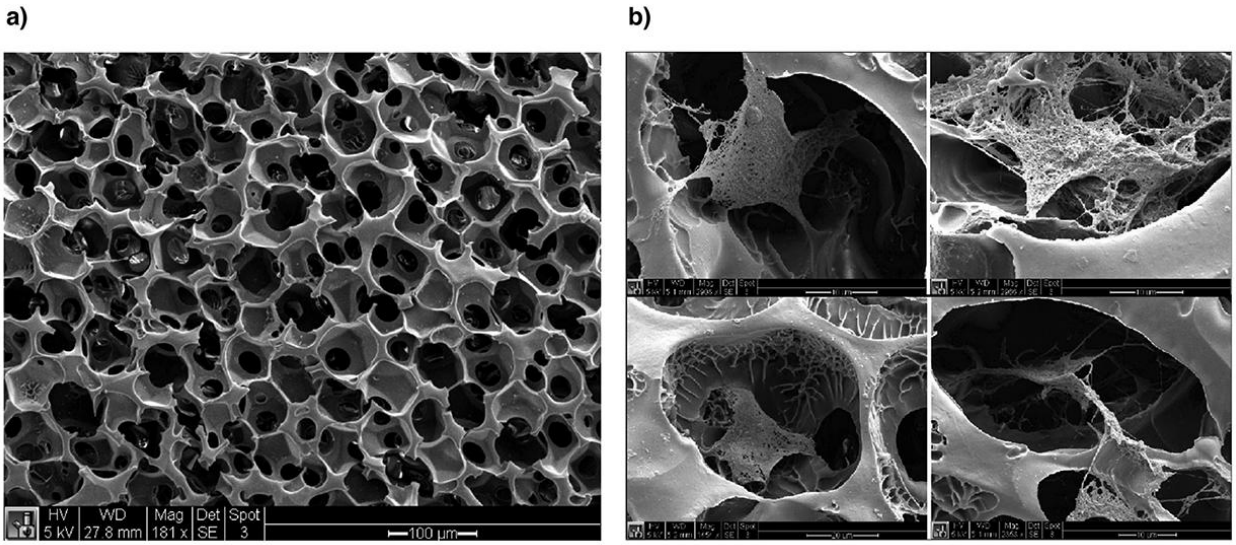


Figure 118. a) SEM image of PNIPAAm-40 based scaffold with 55 µm pore diameter; b) SEM images of cell-loaded PNIPAAm-40-based scaffold cross-section with a 55 µm pore diameter (at 25 °C) (4 different areas of the scaffold). Reproduced with permission from Ref. [19]. Copyright 2010 American Chemical Society.

Matyjaszewski and coworkers[14] studied the elaboration of scaffolds for bone fracture repair. For such a type of applications, the materials should be thermosensitive, biocompatible, degradable and injectable to allow a non-invasive treatment. The authors synthesized P(NIPAAm-*co*-**CKA29**) copolymers by RAFT and ATRP technique. Good degradability and cytocompatibility properties were measured for the P(NIPAAm-*co*-**CKA29**) hydrogels and cross-linked hydrogels were next synthesized by copolymerizing NIPAAm, **CKA29** and poly(ethylene glycol-*co*-glycolic acid) diacrylate (PEG-PGA DA). These copolymers presented the advantage to degrade not only at the cross-linking sites but also within the backbone. The cross-linked hydrogels presented a good cell attachment after incorporation of GRGDS peptides. Unusually, the cross-

linked gels were prepared (by UV photopolymerization) in water. Even if the polymerization time was very short (5 min), the water-sensitivity of **CKA29** was so high that part of the monomer was probably hydrolysed before polymerization.

By a radical copolymerization process from a functional (meth)acrylate monomer with an excess of MDO/MDP **CKA27**, Albertsson[21] and Agarwal[240] proposed a new and easy one-step methodology to elaborate functionalized (degradable) polyesters that could be designed for tissue engineering applications. As seen before, a high and controlled degradability is indeed a key parameter in the elaboration of scaffolds. More precisely, Agarwal and coworkers[240] synthesized alkyne-functionalized PCL-like polyesters by copolymerizing MDP and propargyl acrylate. The copolymers were then postmodified *via* azide-alkyne "click" chemistry to covalently bind PEG chains in the aim to increase the copolymer biocompatibility. Albertsson and coworkers[21] copolymerized MDO/MDP **CKA27** with GMA and then post-modified the P(**CKA27**-*co*-GMA) copolymers by a heparinization reaction that consisted in covalently coupling heparin to the epoxy functions. Without modification, polyesters did not promote cell proliferation and tissue formation. To envision the use of polyester scaffolds for biomedical application, it is then necessary to increase their bioactivity. The strategy followed by the Albertsson team was here to bind heparin to the copolymer and then to immobilize a growth factor (e.g., BMP-2 protein) in a none-covalent manner to enhance cell attachment and differentiation.

7.3.4 (Co)polymers for other biomedical applications

Copolymers synthesized by radical copolymerization from cyclic monomers, and in particular from CKAs such as MDO/MDP **CKA27** or BMDO **CKA29**, have found application in other areas. Some examples are given below.

For instance, biomimetic adhesives were obtained by free-radical copolymerization of MDO/MDP **CKA27** with GMA and OEGMA followed by the coupling of catechol group on the epoxy rings.[338] After cross-linking with the iron complex $Fe(acac)_3$, the adhesive showed good adhesion in PBS, pH 7, 37 °C for at least one week. The synthesized adhesive had high lap shear strength (tests on porcine skin), good enzymatic degradability (in presence of lipases) and low toxicity. These materials were thus promising candidates for medical glue.

Hydrolysable PEGMA-based microspheres were prepared by suspension copolymerization of PEGMA, MDO/MDP **CKA27**, methacrylic acid and a poly(lactide-co-glycolide)-poly(ethylene glycol)-poly(lactide-*co*-glycolide) dimethacrylate (PLGA-b-PEG-b-PLGA DMA), used as cross-linker.[339-341] The obtained microspheres were spherical with a diameter in a 300-500 μm range. These microspheres were easily injected though a catether, which makes them interesting candidates for transient vascular embolization, transient uterine artery occlusion and anti-angiogenic drug delivery. The aim was here to elaborate microspheres that, contrary to non-degradable microspheres, only temporary occlude the vessels from a few hours to a few days and that quickly degrade into fast-eliminated products to prevent inflammatory reactions.

Maynard and coworkers[342] recently presented an elegant methodology to prepare PEGylated protein with a degradable polymer that can be easily cleaved from protein by hydrolysis or reduction. This was achieved by the RAFT-controlled copolymerization of BMDO

CKA29 and PEGMA followed by the covalent attachment to lysozyme *via* a reductible disulphide bond (Figure 119).

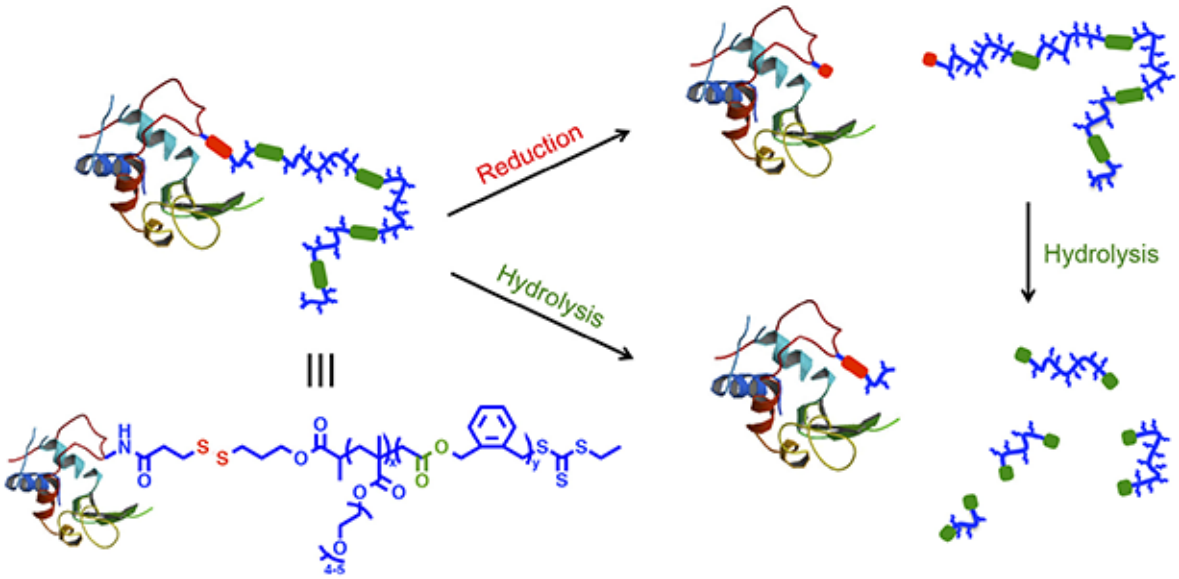


Figure 119. PEGylated protein conjugate released by either reduction or hydrolysis. Reproduced with permission from Ref. [342]. Copyright 2015 Elsevier.

Dove and coworkers showed recently that labelling tags such as fluorescent molecules could be incorporated into PNVP-*b*-P(**CKA27**-*co*-VBr) nanoparticles (with VBr for vinyl bromobutanoate, a VAc derivative).[307] In this work, the copolymers were prepared by RAFT copolymerization of MDO/MDP **CKA27** and VBr from a PNVP macroRAFT agent. The amphiphilic diblock copolymers were then self-assembled by the solvent switch method. Fluorescent dithiomaleimide groups were finally attached to the copolymer backbone *via* azidation and click chemistry (Figure 120). The same team also used P(**CKA27**-*co*-VBr) copolymers (synthesized by RAFT technique) to elaborate functional degradable copolymers.[306] This study showed that the copolymer degradability could be tuned by changing the copolymer

composition (i.e., the proportion of cleavable ester bonds) and that after post-azidation, the copolymer could be functionalized by PEG-alkyne *via* azide-alkyne "click" chemistry.

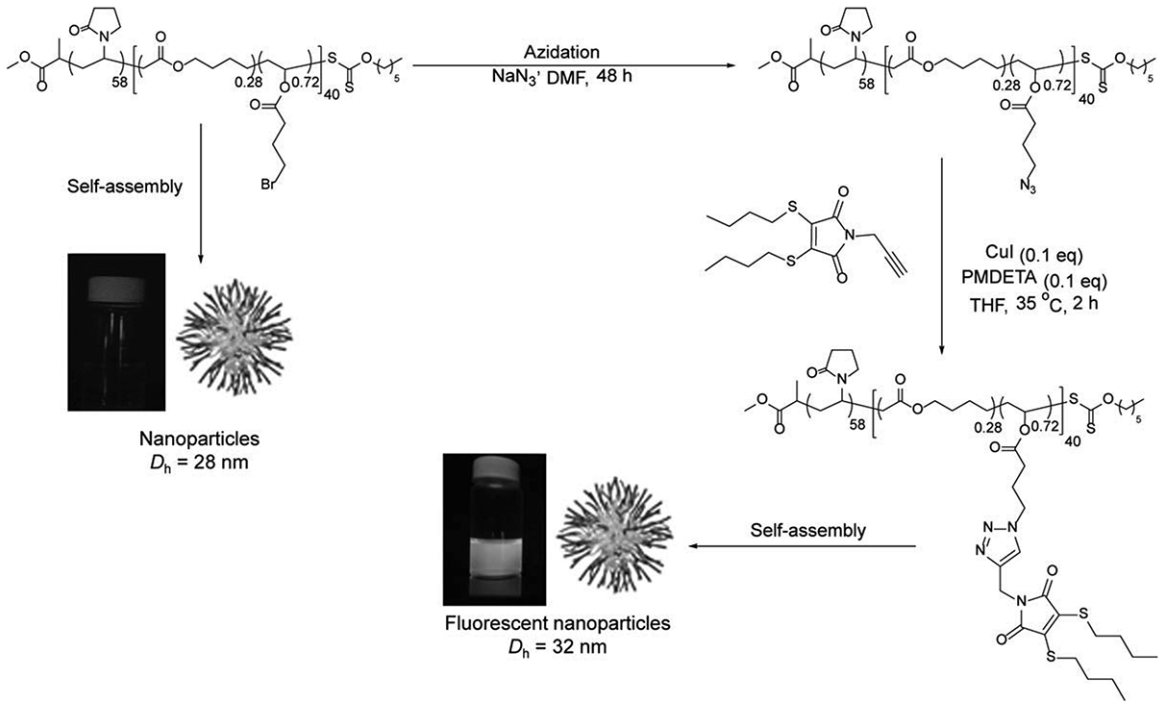
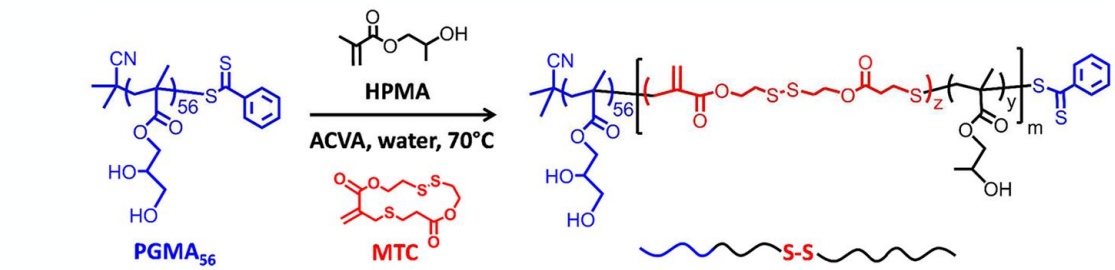


Figure 120. Formation of particles before and after post-polymerization modification with alkyne functional dithiomaleimide. Reproduced with permission from Ref. [307]. Copyright 2015 John Wiley and Sons.

In recent years, many studies were devoted to the preparation of worm-like micelles. These nano-objects can induce morphological transitions into spheres that could be reversible or irreversible, changing the final properties of the materials. SCM and specially **SCM7** (Figure 33) was recently introduced in the hydrophobic part of the amphiphilic P(glycerol methacrylate-*b*-2-hydroxypropyl methacrylate) copolymer made by the PISA-RAFT process.[311] The authors optimized the amount of **SCM7** to 0.5 mol% to still get worm-like micelles combined with good

degradability properties. The addition of tris(2-carboxyethyl)phosphine (TCEP) to an aqueous suspension of the worm-like micelles led to a slow irreversible worm to sphere transition (Figure 121). It has to be noted that the kinetics of the transition seemed far more slower than the kinetics of disulfide bond cleavage (8 days compared to 16 hrs). This phenomenon was mainly attributed to some recombination of the free thiol functions to reform disulphide bonds within the worm.



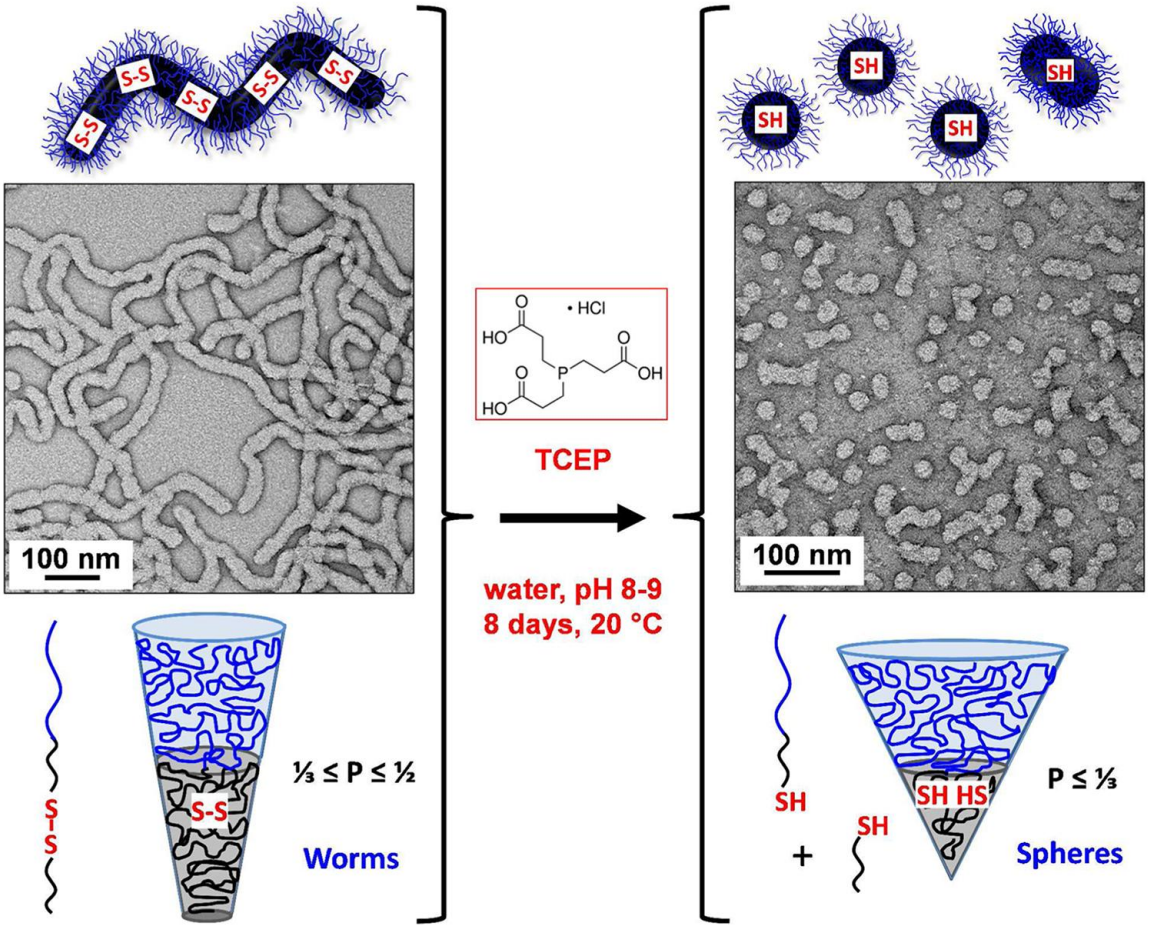


Figure 121. TEM images obtained for a 0.20% w/w aqueous dispersion of $PGMA_{56}$-P($HPMA_{170}$-stat-$MTC_{0.85}$) before and after exposure to TCEP (TCEP/MTC molar ratio = 5.0) at pH 8−9 for 8 days at 20 °C. Cartoon representation of the worm-to-sphere transition observed for a 10% w/w aqueous dispersion of $PGMA_{56}$-P($HPMA_{170}$-stat-$MTC_{0.85}$) worms on exposure to excess TCEP (TCEP/MTC molar ratio = 5.0) at pH 8−9 for 8 days at 20 °C and the corresponding reduction in the packing parameter. Reproduced with permission from Ref [311]. Copyright 2016 American Chemical Society.

7.4 Miscellaneous applications

In addition to degradable and/or low shrinkage materials, (co)polymers prepared by the radical ring-opening (co)polymerization of cyclic monomers have found applications in various different areas.

For instance, the synthesis of PCL-based cationic degradable ionomers was reported by a free radical copolymerization process.[235] Ionomers are (co)polymers containing a low mol% of ionic groups (cationic or anionic) distributed more or less regularly in the backbone or as pendant units. The presence of ionic groups in the (co)polymer resulted in the formation of clusters that altered the physical properties and in general enhanced the mechanical properties, the thermal stability and also the degradation properties. Polyesters are generally synthesized by ROP or polycondensation. In this work, the radical copolymerization of MDO/MDP **CKA27**, MMA and DMAEMA was performed to yield P(**CKA27**-*co*-MMA-*co*-DMAEMA) random terpolymer. The subsequent quaternization with BrC_2H_5 gave the corresponding cationic ionomers (P(**CKA27**-*co*-

MMA-*co*-DMAEMA. BrC_2H_5). Studies by dynamic mechanical analysis (DMA), small-angle X-ray scattering (SAXS) and transmission electron microscopy (TEM) showed that ionic aggregates of 30 nm of diameter were formed and acted as fillers by significantly increasing the Young's modulus. Ionomers with 40 mol% of **CKA27** and 12 mol% of cationic charges presented also good degradability properties when buried in compost.

Kwon and coworkers[343] proved that it was possible to prepare sub-micron spherical biocompatible and degradable particles by radically copolymerizing in dispersion NVP and MDO/MDP **CKA27** in scCO2 by using fluorinated polymeric surfactants (Figure 122). According to the authors, the synthesized microspheres could be used as drug delivery devices.

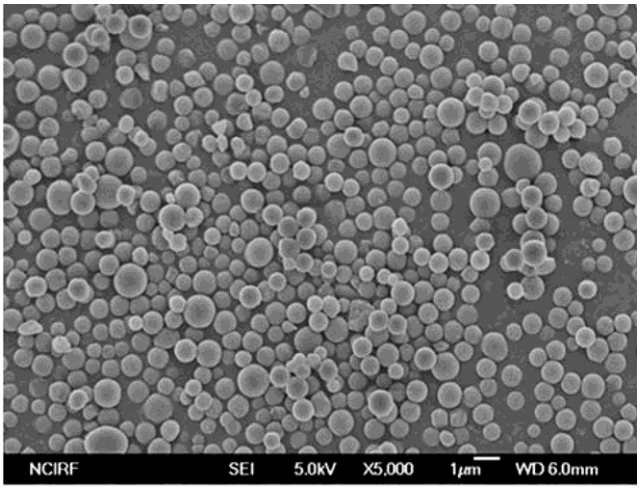


Figure 122. Field emission scanning electron microscopy (FE-SEM) images of copolymer particles with PHDFDMA (poly (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl methacrylate) surfactant. Reproduced with permission from Ref. [343]. Copyright 2008 Springer.

Amphiphilic glycopolymers that self-assembled into degradable biocompatible and aldehyde-functionalized polymeric nanospheres without any surfactant were also reported.[16] The authors also envisioned to use such particles as drug-delivery carriers. Gonsalves and coworkers[258] synthesized P(**CKA27**-*co*-VPA) and P(**CKA27**-*co*-VPE) with VPA for vinylphosphonic acid and VPE for dimethyl vinylphosphonate by free-radical copolymerization with the aim to prepare organic polymer–inorganic hybrid materials. These materials are of great interest for the study of biomimetic processes and as component of biomaterials. Indeed, the presence of ionic groups such as phosphonic acid on a polymer backbone is essential to form polymeric – inorganic hybrid materials, dimethoxyphosphinyl groups providing in particular good nucleation sites for hydroxyapatite formation.

Dove and coworkers[301, 305] reported the elaboration of degradable nanoparticles based on P(**CKA27**-*co*-VAc) copolymers synthesized by the RAFT/MADIX technique. By using functional vinyl monomers (*N*-vinylpiperidone, vinyl chloroacetate or *N*-vinylpyrrolidone) instead of VAc, the authors formed well-defined, functionalized copolymers allowing a good control of the material degradability. The methodology was extended to the elaboration of thermo-responsive block and hyperbranched copolymers (PNVP-*b*-P(**CKA27**-*co*-VAc) cross-linked with divinyl adipate monomer.

The last application that was studied using cyclic monomers and in particular CKA is related to the copolymer self-assembly. Lynn and coworkers[266] prepared block copolymers of PS-*b*-(VDMA-*co*-**CKA27**) using RAFT polymerization. Once prepared, this block copolymer could be post-functionalized to introduce various pendant groups. The interesting feature of all these block copolymers is their self-assembly ability in bulk or when casted as thin film into lamella whose length scale is dependant on the pendant group. Indeed the bulkiness of the amine based group changes the volume fraction of the **CKA27**-co-VDMA block. The ability to tune the length

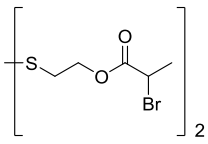
scale in nanostructured morphologies using an universal block copolymer template could have interesting applications in patterning and lithography.

8. Alternatives to cyclic monomers for the synthesis of degradable vinyl-based polymers

The previous section presented the applications (i.e. low shrinkage materials and (bio)degradable materials) in which cyclic monomers have been used. In this last section we will present the alternative to prepare comparable materials still *via* a radical pathway. In the case of low shrinkage materials, alternatives to cyclic monomers lie essentially in the introductions of various fillers and/or functional groups (phosphonic acid, amide, etc.) to ensure better adhesion, stability, lower toxicity and water uptake. Note here that unfortunately there is no today convincing alternative to low shrinkage materials prepared *via* a radical pathway.[317] Contrary to such application, alternative strategies aiming at producing degradable vinyl materials have been developed, spanning from discrete or multiple insertions of labile groups in the polymer backbone to the degradable crosslinking of polymer chains.[344] It is interesting for having a complete picture of the interest of cyclic monomers to prepare vinyl degradable materials to present an overview of the alternative methods based also on a radical pathway to prepare similar materials. Note that, providing they are homogeneously distributed along the chain, a small number of degradable groups in the main-chain can already cause a significant decrease of the overall molar mass and could be sufficient for some applications.

8.1 Multifunctional degradable initiators and chain transfer agents

A simple strategy to insert one central degradable group in a vinyl polymer backbone relies on the use of degradable difunctional radical initiators or chain transfer agents (CTAs).[345] In that case, after divergent chain growth, the M_n will be reduced by half after degradation. This approach became possible by using RDRP techniques (e.g., NMP, ATRP and RAFT) where one central degradable group is positioned between two well-defined polymer blocks. In this context, difunctional RDRP initiators/CTAs based on five main cleavable groups were used (Figure 123): disulfide (**1–7** and **19**), trithiocarbonate (**8–11**), Diels-Alder adduct (**12** and **13**), hemiacetal (**14**), ortho-nitrobenzyl ester (**15** and **16**) and olefin (**18**).



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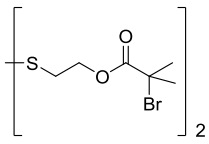

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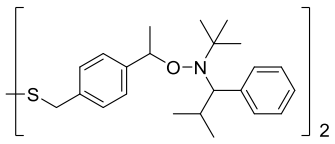

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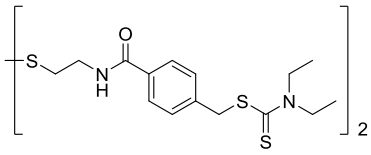

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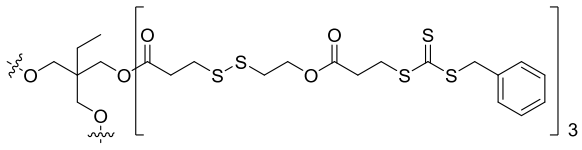

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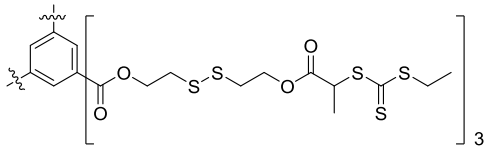

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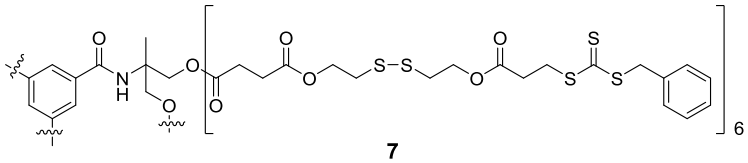

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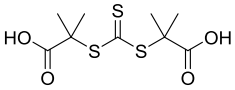

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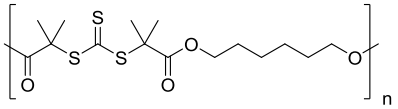

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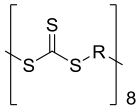

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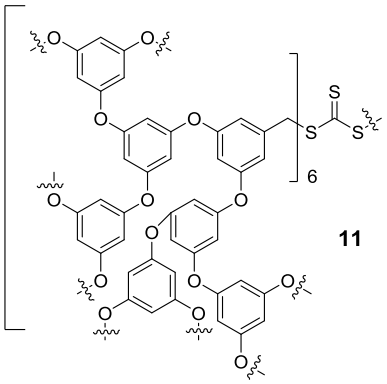

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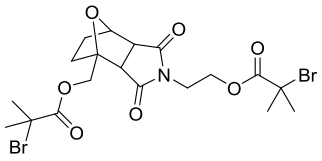

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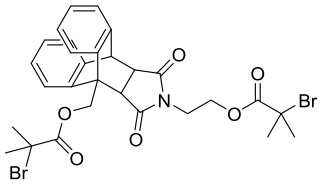

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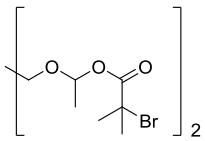

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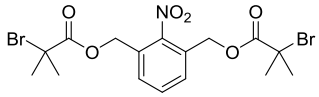

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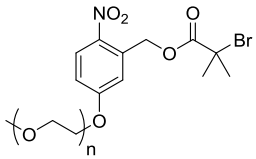

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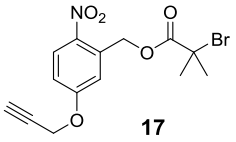

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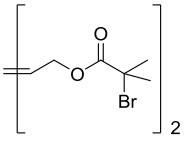

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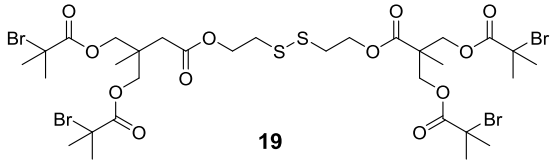

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Figure 123. Structures of the main difunctional degradable reversible deactivation radical polymerization (RDRP) initiators and chain transfer agents (CTA) for the production of polymers with central cleavable groups.

RDRP initiators and CTAs bearing a disulfide moiety have focused a lot of attention likely due to the convenient redox-sensitive degradation that can be advantageously used for bio-related applications. For instance, cellular delivery can be triggered by means of glutathione (GSH), one of the main reducing agents inside cells and the most abundant in the cytosol. Disulfide-containing ATRP (**1** and **2**) and NMP (**3**) initiators, as well as RAFT agent (**4**) have been successfully used to control the polymerization of a broad range of monomers (e.g., S,[346] MMA,[347] NIPAAm,[348] MPC,[348] HPMA,[348] BMA,[349] OEGMA, [349] MHGlcNAc[350] and DMA[351]). It generally gave well-defined materials whose degradation was proven by addition of GSH or dithiothreitol (DTT).

This method can also be adapted to multifunctional RDRP initiators/CTAs bearing one disulfide group per initiating/chain transferring site for the synthesis of the corresponding star polymers with each arm being cleavable. This has been illustrated by the synthesis of 3- and 6-arm star polymers from disulfide-containing RAFT agents (**5–7**).[352-354]

Divergent chain growth from degradable difunctional initiators/CTAs is however refined to the design of polymer blocks of the same nature, giving symmetric architectures with a central degradable function. For example, a single polymerization step will give a homopolymer whereas two consecutive polymerizations of different monomers will conduct to an ABA triblock copolymer. Disulfide-based poly(*N*-isopropyl acrylamide-*b*-poly(2-methacryloyloxyethyl

phosphorylcholine)-*b*-poly(*N*-isopropyl acrylamide (PNIPAAm-*b*-PMPC-*b*-PNIPAAm) triblock copolymer micelles have been designed by two consecutive ATRP steps from **1** (Figure 124).[348] They formed a free-standing gel due to the establishment of disulfide bridges between the micelles but could be nearly quantitatively dissolved after cleavage of the disulfide groups by DTT.

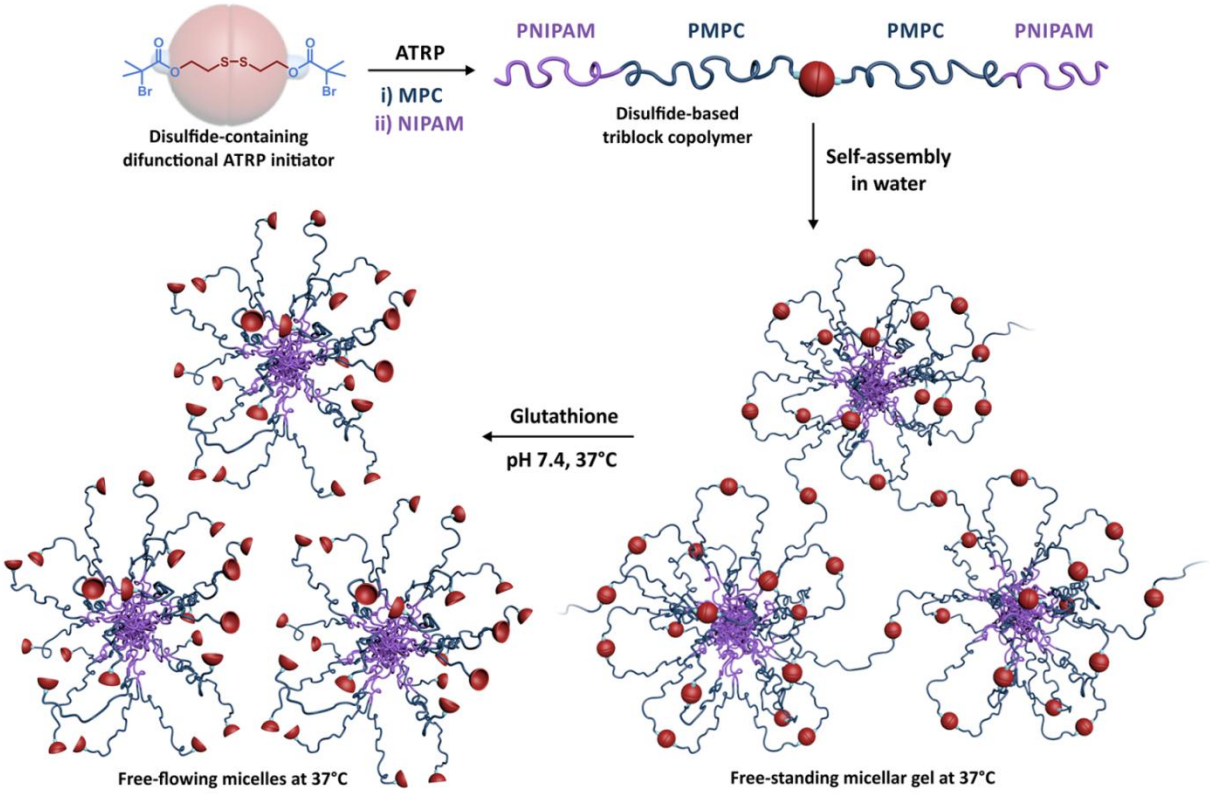

Figure 124. Synthesis of a disulfide-based thermoresponsive poly(*N*-isopropyl acrylamide-*b*-poly(2-methacryloyloxyethyl phosphorylcholine)-*b*-poly(*N*-isopropyl acrylamide (PNIPAAm-*b*-PMPC-*b*-PNIPAAm) triblock copolymer gelator from a cleavable difunctional ATRP initiator. Reproduced with permission from ref. [344]. 2015 Nature Publishing Group.

Trithiocarbonates and dithioesters are also an interesting class of functional groups that can be readily cleaved to thiols under aminolysis (i.e., when reacted with primary amines). Consequently, they have been advantageously incorporated in RAFT agents to produce a variety of different degradable architectures, from linear polymers using **8**,[355] **9**[356] and **10**,[357] to dendritic block copolymers from **11**.[358] As a proof of concept, these materials have been reacted with small amine-containing molecules to show the degradability. In the case of polytrithiocarbonates **9** and **10**, also termed "poly-RAFT agents", they can be used to prepare well-defined polymers with multiple cleavable trithiocarbonate functionalities in the backbone after one polymerization step.[356-357] Note that the number of cleavable trithiocarbonate moieties is governed by the degree of functionality of the polyRAFT agent.

Inducing the formation of Diels-Alder (DA) adducts represent an elegant leverage to confer degradability due to the thermal reversibility of the DA cycloaddition, and can thus give access to self-healing polymers.[359] Interestingly, this reaction enables the formation of two new carbon-carbon bonds without the use of reagents, and the reformation reaction takes place *via* a non-free radical mechanism, thus avoiding non-selective recombination.[360] Bifunctional ATRP initiators **12** and **13** bearing DA adducts, either based on a furan-maleimide adduct or on an anthracene-maleimide adduct, were used to prepare linear PMMA comprising one DA adduct in the center of the polymer chain.[359] Degradation was achieved at high temperature (> 100 °C) and yielded polymer chains with M_n divided by ~2. It was also shown that the anthracene group had a higher thermal stability than the furan group.

Hemiacetal ester can also be embedded into polymers. Compared to acetals and acylals, hemiacetal esters are more reactive toward acid-catalyzed hydrolysis. A bifunctional ATRP initiator bearing two hemiacetal ester groups (**14**) was synthesized and used to prepare conetworks and ensured precise cleavage under acidic conditions (Figure 125).[361]

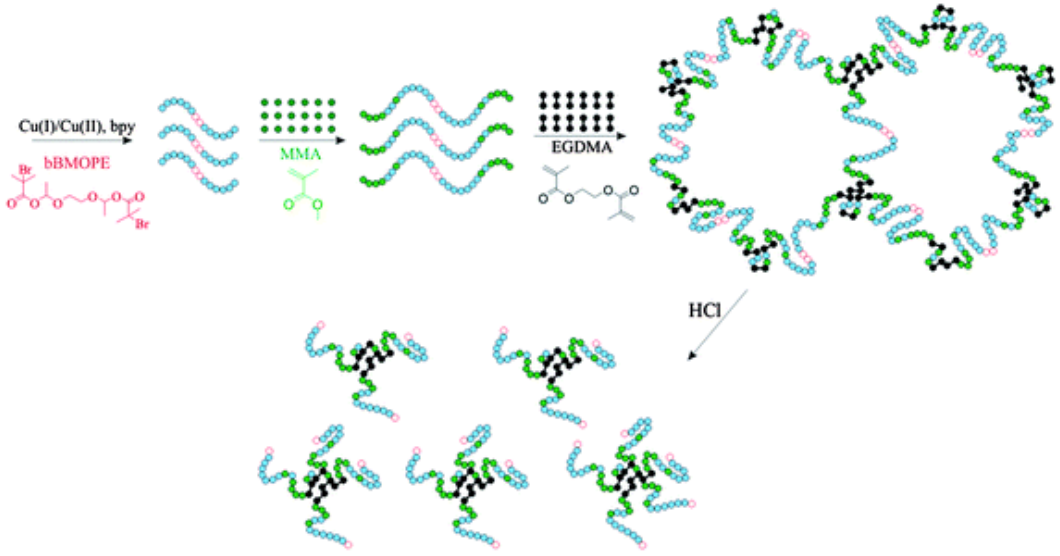

Figure 125. ATRP synthesis and hydrolysis of an end-linked amphiphilic polymer conetworks prepared using a degradable bifunctional initiator. Reproduced with permission for ref. [361]. 2012 RSC.

Using light as a source of degradation is a very appealing approach because it is a non-invasive method that can be temporally and spatially controlled. In this field, ortho-nitrobenzyl alcohol derivatives have been the focus of extensive research and are certainly the most popular photocleavable group. They have been initially used in organic chemistry for the protection of several functional groups (e.g., carboxylic acids, phosphates, alcohols, amines, ketones)[362] and as

a masking group for biological molecules. For instance, the *O*-nitrobenzyl ester group undergoes efficient photocleavage upon UV irradiation leading to *O*-nitrosobenzaldehyde and the corresponding carboxylic acid. This can be applied to the ATRP of S from **15** leading to degradable diblock copolymers that can be cleaved to linear homopolymers decreasing the M_n by two under UV irradiation at 350 nm (Figure 126).[363] When terminal bromine end-groups (inherent to ATRP) were replaced by azide functionalities and further reacted with tetra-alkyne crosslinkers in the presence of Cu(I), degradable model networked were obtained.[363] They were subsequently degraded by UV light at 350 nm to give four-armed star polymers.

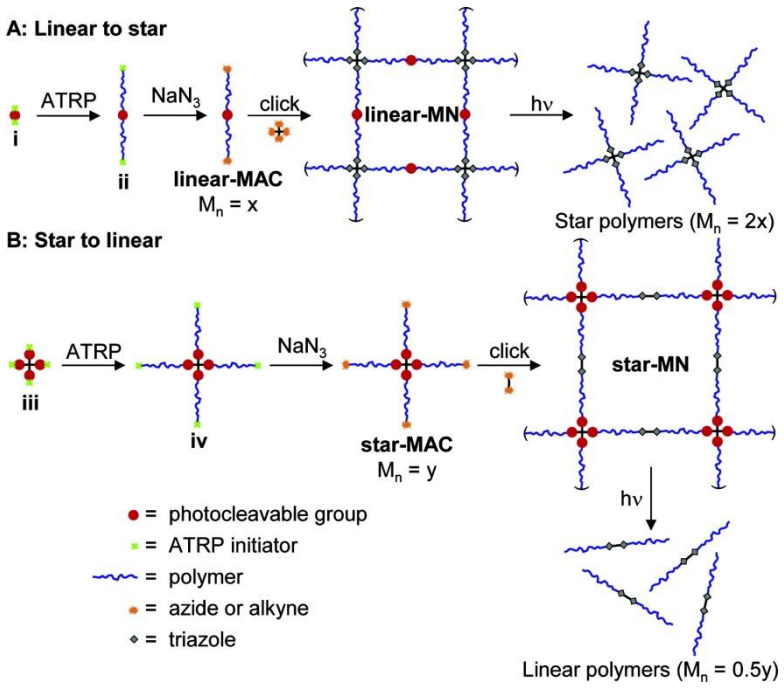

Figure 126. Synthesis of Photocleavable Linear Macromonomers by ATRP and Star Macromonomers by a Tandem ATRP−Click Reaction. Reproduced with permission from ref. [363]. Copyright 2007 American Chemical Society.

A nice extension was also reported using semifluorinated dicyclooctynes as activated cross-linkers allowing copper-free click coupling as more bio-friendly conditions.[364] Photocleavable *O*-nitrobenzyl ester can also be embedded into a monofunctional ATRP macroinitiator **16** attached to a PEG chain for the synthesis of PS-*b*-PEG diblock copolymers for the fabrication of nanoporous PS thin films after cleavage and removal of the PEG block.[365] A similar monofunctional initiator bearing an alkyne group **17** was used for the simultaneous ATRP of S (or *n*BA) and the copper-catalyzed azide-alkyne Huisgen cycloaddition (CuAAC) of azido-terminated PEG (or PS).[358] Photocleavage of the resulting diblock copolymers was achieved by irradiation with UV light at 300 nm, releasing the corresponding linear homopolymer chains.

A difunctional ATRP initiator bearing an alkene group can also lead to well-defined, centrally degradable polymers by ozonolysis.[366] Ozone indeed reacts with alkenes, resulting in the cleavage of the double bond and the formation of carbonyl compounds when this reaction is performed in water. However, when the terminal bromine groups were converted into azides for further crosslinking by click chemistry with multifunctional crosslinkers, degradable networks can be obtained. This was illustrated by ozonolysis of model networks from ATRP of *t*BA initiated by **18** and subsequent crosslinking by click chemistry with tria- and tetra-alkyne crosslinkers.[366]

Different degradation modes can also be implemented into a single macromolecular architecture. For instance, a tetrafunctional ATRP initiatior **19** with a central disulfide linkage and four ester groups bearing the initiating sites yield 4-arm star polymers with two levels of degradability: reductive environments cleave the polymer into two symmetric parts whereas alkaline conditions cut the 4 arms off (Figure 127).[367] This may find applications in drug delivery as unimolecular, degradable nanocarriers may result from increasing the number of cleavable arms as illustrated

by PEG-based star-comb polymers[368] or star-shaped polymers made of a β-cyclodextrin core linked to multiple polymethacrylate chains.[369]

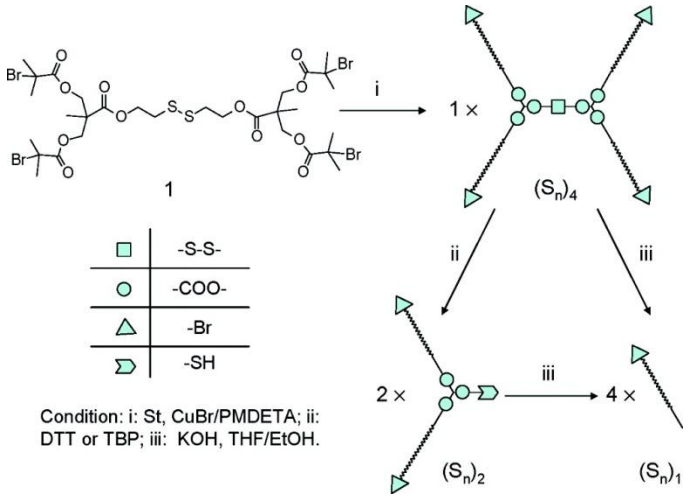

Figure 127. Synthesis of four-arm star polystyrene $(Sn)_4$ from **19** and its degradation products by different cleavage strategies. Reproduced with permission from ref. [367]. Copyright 2010 American Chemical Society.

8.2 Macromolecular coupling approaches

Embedding one central cleavable group can also be achieved by using macromolecular coupling approaches; that is the coupling between two preformed polymers through a labile functionality. For instance, alkoxyamines that cleave at high temperature can be inserted by different techniques.[370-372] Disulfide groups can be positioned between two polymer blocks by reacting together two ATRP-derived polymers; one terminated by a pyridyldisulfide (PDS) group

and one by a thiol group (Figure 128).[373] Non-covalent (supramolecular) interactions can also connect two polymers together, hence yielding dynamic and reversible structures relying on a broad range of stimuli (e.g., redox potential, electric field, temperature, competitive ligand).[374] End-terminated vinyl polymers have been produced by reacting together well-defined polymers end-terminated by complementary moieties from the supramolecular toolbox (e.g., hydrogen bonding, metal coordination, host-guest interaction).[375-378]

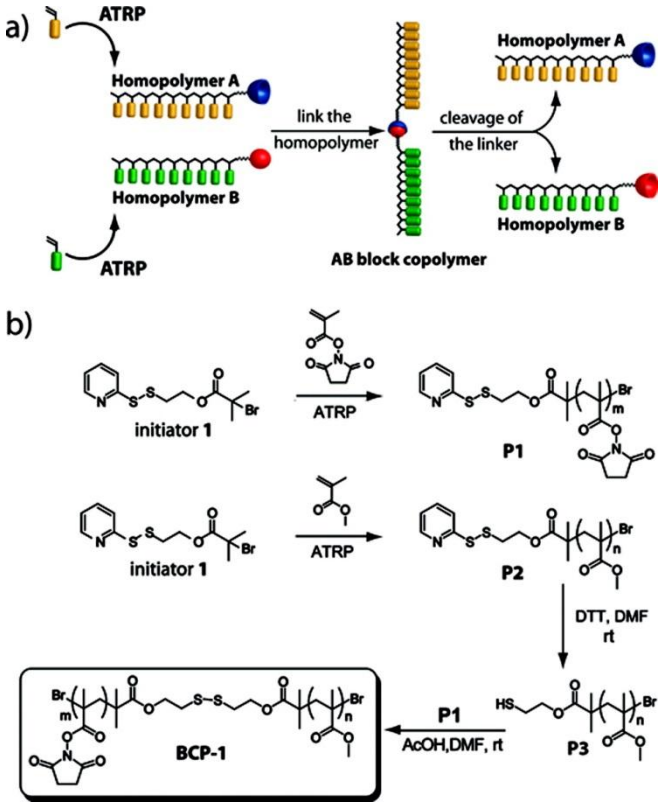

Figure 128. (a) Schematic of the synthetic approach toward diblock copolymers from functional homopolymers by macromolecular coupling. (b) Synthesis of cleavable diblock copolymers from

its homopolymers. Reproduced with permission from ref. [373]. Copyright 2007 American Chemical Society.

Macromolecular coupling approaches can be adapted to produce multisegmented, degradable polymers by using difunctional polymer precursors. In that case, considering that multiple degradable functionalities are present in the resulting copolymer, significant degradation is expected. Multiple thermolabile alkoxyamine moieties can be incorporated into linear polymer chains by different ways including atom transfer nitroxide radical coupling (ATNRC) from ATRP-derived α,ω-dihalogenated polymers and dinitroxides[379] or by nitrone-mediated radical coupling (NMRC) from similar precursors.[380] If dinitroxides contain ester or disulfide moieties, additional chemical and redox degradable properties can be conferred. Another way to produce disulfide-containing multisegmented polymers relies on the reaction between dithiol-terminated polymers prepared by ATRP[346] or RAFT[381-382] under $FeCl_3$ or O_2 oxidation.[346, 381] Finally, multiple disulfide groups can also be inserted by a polycondensation, step-growth procedure from a RAFT-derived macromonomer with a PDS end-group, giving polydisulfides with selective degradability in vitro in the presence of intracellular concentrations of GSH.[383]

Instead of introducing degradable junctions between polymer blocks, labile groups can also be positioned in the backbone of α,ω-functional polymers prior to their coupling together. This has been illustrated by the atom transfer radical polyaddition of divinyl monomers with dibromo-compounds bearing disulfide or ketal functionalities.[384] In a more biological context, multiple insertions of an enzymatically degradable peptide sequence (GFLG) in a vinyl polymer was even reported from water-soluble α,ω-telechelic poly(*N*-(2-hydroxypropyl) methacrylamide)

(PHPMA) chains prepared by RAFT polymerization further linked together by means of a difunctional GFLG sequence *via* CuAAC[385] (Figure 129) or thiol-maleimide[386] coupling. Additional GFLG sequences were inserted in the polymer structure by using GFLG-containing difunctional RAFT agent. The system was shown to be biodegradable and bioresorbable by means of pharmacokinetics and biodistribution studies.[387] This approach was then nicely extended to star PHPMA-drug conjugates by linking PHPMA chains to poly(amidoamine) (PAMAM) dendrimers *via* biodegradable GFLG sequences.[388]

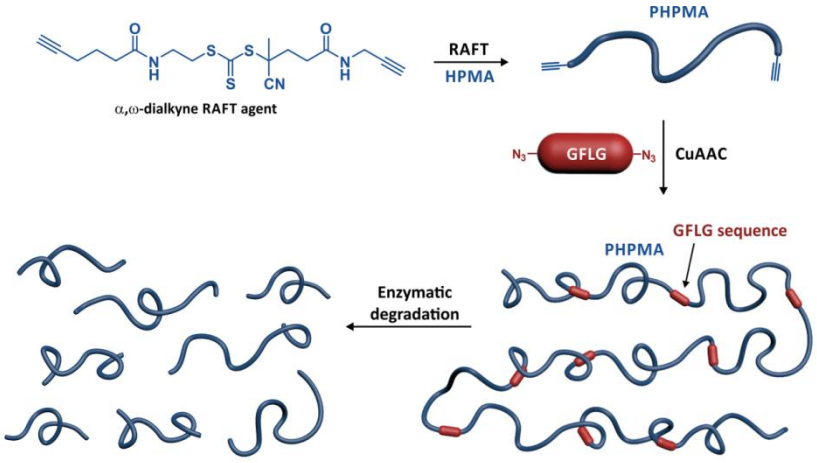

Figure 129. Synthesis of multisegmented poly(*N*-(2-hydroxypropyl) methacrylamide) (PHPMA) copolymer by a combination of RAFT and copper-catalyzed azide-alkyne Huisgen cycloaddition (CuAAC) between PHPMA and α,ω-diazide GFLG peptidic sequence. Reproduced with permission from ref. [344]. 2015 Nature Publishing Group.

8.3 New polymerization mechanisms

In addition to rROP, new polymerization mechanisms leading to a direct insertion of degradable functionalities in the polymer chain have emerged. The most studied one is metal-catalyzed step-growth radical polymerization of monomers possessing unconjugated C=C and active C–Cl bonds (Figure 130).[389] The monomers employed can embed ester groups to confer degradability and can also be copolymerized with traditional vinyl monomer by ATRP.[390] In that case, the method is called simultaneous chain- and step-growth radical polymerization.[389, 391] However, high dispersities are generally obtained which is a feature of step-growth polymerization. Nevertheless, this method has conducted to the design of self-degradable antibacterial copolymers from the copolymerization with an amine-functionalized acrylate.[392]

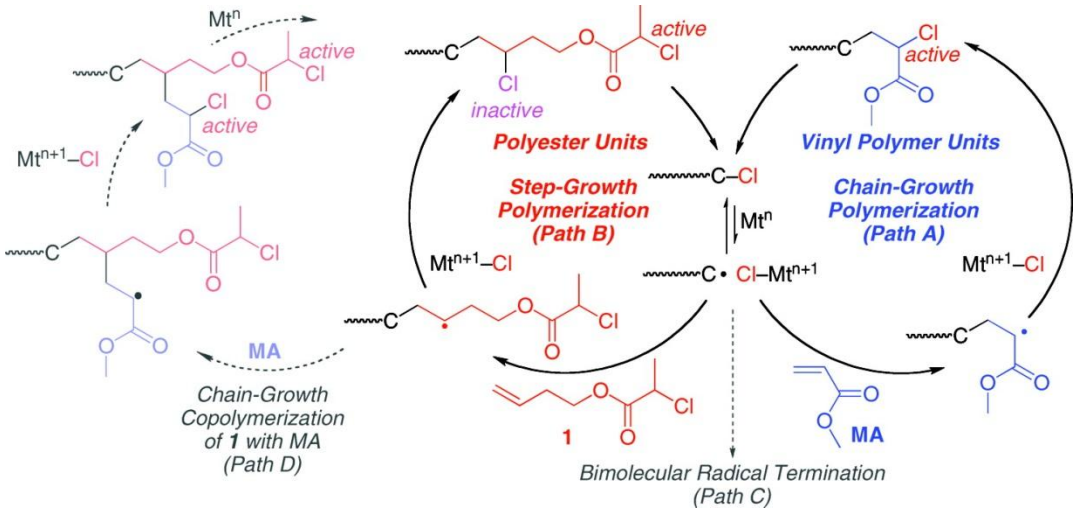

Figure 130. Mechanism of metal-catalyzed simultaneous chain- and step-growth radical polymerization. Path A: chain-growth radical polymerization of MA. Path B: step-growth radical polymerization of 1. Path C: possible bimolecular radical termination. Path D: possible chain-growth radical copolymerization of **1** with MA. Reproduced with permission from ref. [389]. Copyright 2010 American Chemical Society.

Copolymerization of molecular oxygen with vinyl monomers by oxidative polymerization has also been reported to produce degradable vinyl materials *via* the formation of polyperoxides that degrade at high temperatures (T >60 °C).[393] Such copolymerizations can also proceed by RDRP using reversible chain transfer catalyzed polymerization (RTCP) and produce biocompatible materials that can cleave by enzymatic degradation of the –O–O– sequences.[394-395]

8.4 Connecting polymer chains by degradable junctions

Instead of introducing labile groups in the polymer backbone by using either degradable initiators/CTAs, macromolecular coupling approaches or specific polymerization mechanisms, an efficient alternative consists in connecting polymer chains together *via* degradable/reversible linkages.

The most straightforward method to connect polymer chains together in a reversible manner is to use degradable vinyl crosslinkers. It offers interesting advantages over other strategies such as the broad diversity of crosslinkers that can be used (in terms of nature of both the polymerizable group and the degradable functionality) and the ease of synthesis as it only requires the addition of the crosslinker in the reaction medium. Depending on the experimental conditions, using degradable crosslinkers gives access to different kinds of degradable nano-objets. Star polymers with a degradable core can be obtained by the "arm first" method where the degradable core is generated either by coupling monofunctional polymeric chains with cleavable crosslinkers[396] or

by the direct copolymerization of the degradable crosslinker with a macromonomer.[397] This was achieved from PEG-based macromonomers and a disulfide-containing methacrylate, and reducing conditions yielded individual polymeric chains (Figure 131).

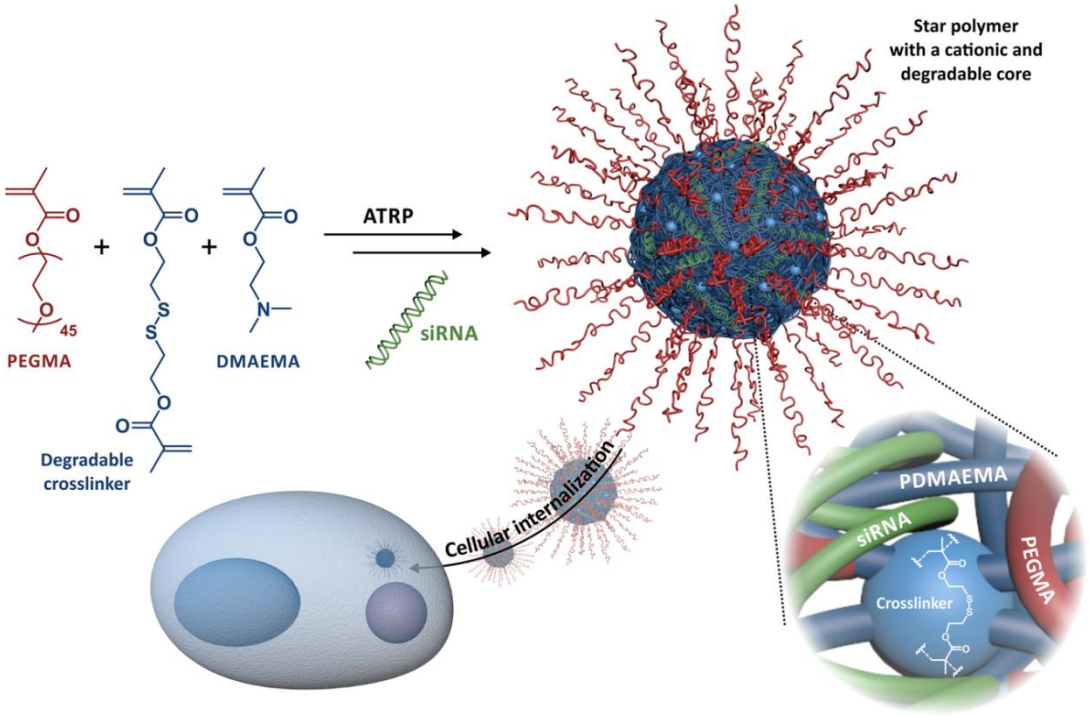

Figure 131. Synthesis of biocompatible PEG-based star polymers with a cationic and degradable core of poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) for small interfering RNA (siRNA) delivery. PEGMA = poly(ethylene glycol) methyl ether methacrylate. Reproduced with permission from ref. [344]. 2015 Nature Publishing Group.

Degradable hyperbranched structures can also be obtained from degradable crosslinkers. Notably, the branching process was shown to be better controlled using RDRP techniques. For instance, ATRP[398] or RAFT[399] conducted in the presence of a redox sensitive crosslinker led to

hyperbranched polymers, whose degradation by DTT led to polymer chains with similar dispersities than the linear polymer obtained without crosslinker. When the polymerization in the presence of a crosslinker goes beyond the gel point, cross-linked 3D polymeric networks are obtained. A representative illustration of this approach is the design of degradable (hydro)gels, by either FRP[400-402] or RDRP.[346, 400, 403-406] RDRP techniques generally provided more homogeneous structures and degradation products compared to those obtained by FRP.[400] For instance, ATRP of different monomers (i.e., HEMA,[403] NIPAAm[405] or DMAEMA[400]) in the presence of a PCL-based divinyl crosslinker, gave hydrogels with different mechanical and physicochemical properties and were successfully degraded hydrolytically.

Degradable micro- and nanoparticles can be prepared from similar copolymerization systems by performing the reaction in aqueous dispersed media (e.g., dispersion, suspension, emulsion, etc.). For instance, cross-linked polyacrylamide microparticles of 0.2–1 μm in diameter were synthesized by inverse free-radical (micro)emulsion polymerization in the presence of acid-sensitive acetal crosslinkers.[402, 407-410] They were used as degradable nanocarriers for therapeutic protein (Figure 132) and nucleic acid delivery. Nanogels (nanoparticulate hydrogels) were also synthesized by inverse miniemulsion ATRP of OEGMA and a disulfide containing crosslinker.[411]

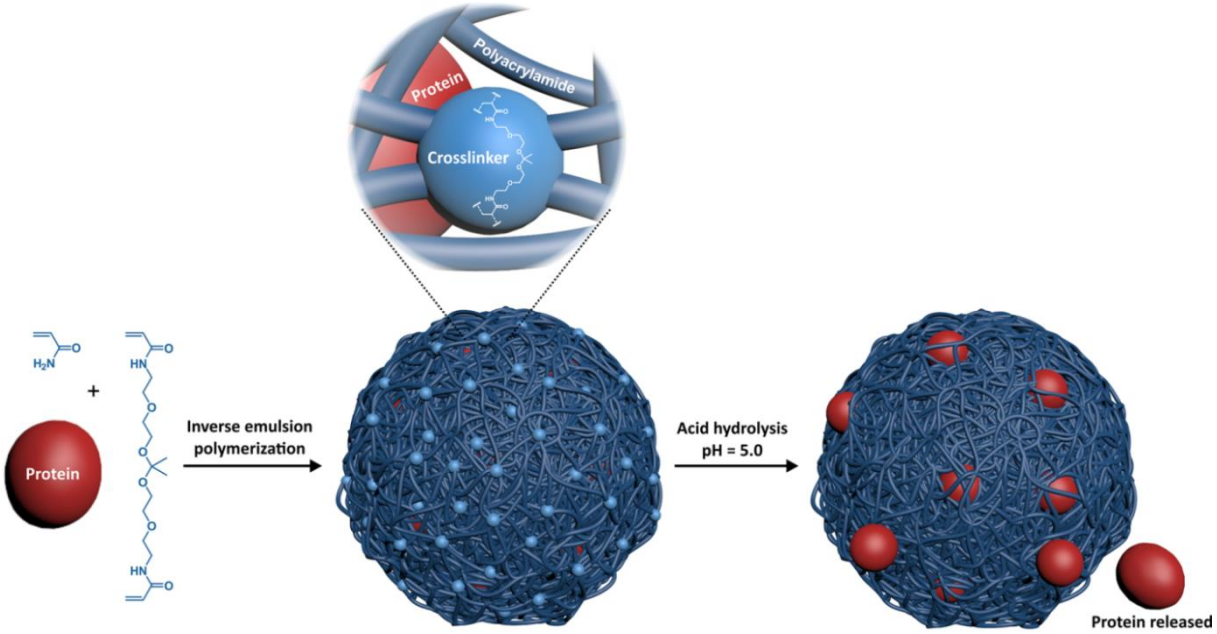

Figure 132. Synthesis of acid-degradable cross-linked polyacrylamide microparticles for protein-based vaccines by inverse emulsion copolymerization between acrylamide and a degradable crosslinker. Reproduced with permission from ref. [344]. 2015 Nature Publishing Group.

The use of inimers, molecules having both an initiator and monomer functionality, represents a simple strategy to achieve degradable junctions between polymer chains. In this case, hyperbranched structures are readily obtained from one single molecule. A typical example is the ATRP of MMA in the presence of a disulfide-containing inimer,[412] giving hyperbranched polymer at monomer conversion above 70% and degraded upon addition of Bu3P in THF.

9. Conclusion and outlook

Since many years the demand of polymer materials with tailored macroscopic properties is constantly increasing for both commodity and high value items. In this context, the radical ring-opening polymerization (rROP) technique of cyclic monomer appears particularly attractive. Indeed, Radical ring-opening polymerization gathers the advantages of both ring-opening polymerization and radical polymerization, that is, the production of polymers having heteroatom and/or functional groups in the main chain but with the robustness, straightforward and mild polymerization conditions of a radical process. However, in many cases the ring-opening process is in competition with the ring-retaining polymerization, leading to undesired repeating units onto the polymer backbone. Numerous monomer families were then tested for an efficient ring-opening behaviour. Among them, the cyclic ketene acetal (CKA) and the vinyl cyclopropane (VCP) derivatives were the most promising compounds and were therefore the most studied. The vinyl cyclopropane derivatives led to low-shrinkage materials that have been widely tested in dental applications and in composites. Recently new efficient structures have been developed that could revitalize this topic in photo-curable coatings.

The cyclic ketene acetal derivatives have been widely studied since after ring-opening, a polyester is formed and such materials are well-known for their (bio)degradability and innocuousness even if they are usually not prepared by a radical pathway. Although the mechanism of its ring opening is simple and leads only to an ester group, it has been shown that only few monomers undergo a complete ring-opening and this restricts the use of this monomer family for a wide range of applications.

Besides the polymerization of new cyclic monomers, the radical ring-opening polymerization is also very attractive since these monomers could also be combined with common vinyl monomers by either conventional free-radical polymerization or by the so-called living /controlled radical polymerization (now Reversible Deactivation Radical Polymerization),

affords original polymers with innovative properties. These new materials found applications in marine antibiofouling, in degradable elastomers and adhesives in (bio)degradable micelles/nanoparticles, etc. Recently the copolymerization of an excess of CKA with functional vinyl monomers led also to the straightforward preparation of functional polyesters that could be hardly prepared by other methods. All these features highlight the interest of the radical ring opening polymerization as a new tool for polymer chemists to prepare advanced macromolecular architectures.

Whereas these advantages, the rROP did not take off yet practically and some challenges have still to be overcome in order to consider the rROP as a convenient tool among the macromolecular engineering panel of techniques. Among the main challenges of the rROP one can mention the competition between the ring-opening process and the radical polymerization of the double bond of the cyclic monomers but also their good insertion in the polymer backbone made from a classical vinyl monomer. Obviously, these phenomena are particularly complicated and rely on multiple parameters such as steric hindrance of the monomer and the derived radical, stabilization of the generated radical, polarity of the monomers but also the media…Therefore, in order to tackle these challenges we do believe that a deep investigation on the physico-chemical behavior of cyclic monomers is now necessary by means of high level molecular modelling approach and a systematic determination of the monomer reactivity ratios. This strategy will definitely help to design improved cyclic monomer structures. Of course, the newly designed cyclic monomer will have to be easily prepared and stable under storage. In these conditions, the rROP is expected to increase the number of conveniently accessible and innovative (bio)degradable polymer compositions suitable for a broad range of domains.

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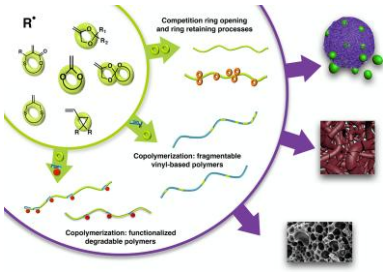

Bios

Antoine Tardy.

Antoine TARDY graduated in Material Science from Aix-Marseille University (Marseille, France), in 2010. He completed his PhD in Chemical Sciences at the Institut de Chimie Radicalaire at Aix-Marseille University under the supervision of Dr Yohann Guillaneuf and Dr Didier Gigmes. Since his graduation in 2014, he has conducted postdoctoral research at the Centre for Advanced Macromolecular Design (CAMD) at The University of New South Wales (Sydney, Australia) in the team of Prof. Per B. Zetterlund. His research interests include Radical Ring-Opening Polymerization (rROP), (controlled) radical polymerization kinetics and mechanism and template polymerization.

Julien Nicolas

Julien Nicolas completed his PhD in 2005 under the supervision of Prof. Bernadette Charleux at the University Pierre and Marie Curie in Paris (France), where he studied nitroxide-mediated polymerization. He then joined the group of Prof. David M. Haddleton at the University of Warwick (UK), as a postdoctoral researcher (Marie Curie Intra-European Fellowship) in the field of polymer-protein bioconjugates. In 2007, he obtained a CNRS researcher position at Institut Galien Paris-Sud (Univ. Paris-Sud) in Châtenay-Malabry (France) and got promoted CNRS research director in 2016. His current research activities lie in advanced macromolecular synthesis and in the design of innovative polymer-based nanomedicines. He is (co)author of more than 75 peer review articles in international journals, 5 patents and 13 book chapters.

Didier Gigmes

Didier Gigmes completed his PhD in organic chemistry in 1998 under the supervision of Prof. Paul Tordo at the University Paul Cézanne in Marseille (France). Then he moved to Elf Atochem North America in Pennsylvania (USA) to work, under the supervision of Gary Silverman, as a post-doctoral in the field of the controlled radical polymerization. In 2001, he was recruited as researcher at CNRS to develop the nitroxide-mediated polymerization (NMP) technique. In 2008, he defended his Habilitation at the University of Provence (Marseille, France) and in October 2010, he was appointed Research Director at the CNRS working at Aix-Marseille University (Marseille, France). Currently, his main concerns are focused on the development and use of new methodologies for the synthesis of advanced polymer materials based on block copolymer self-assembly. Recently he was also involved in the development of original methodologies for Nitroxide Mediated Photopolymerization and the synthesis of versatile photoinitiators. He is (co)author of 250 peer review articles in international journals, 13 patents and 10 book chapters and editor of one book.

Catherine Lefay

Catherine Lefay completed her PhD in 2006 under the supervision of Prof. Bernadette Charleux at the University Pierre and Marie Curie in Paris (France). Her PhD was focused on the synthesis of gradient copolymers by nitroxide-mediated polymerzation and their use as stabilizers for (min)emulsion polymerizations. She then joined in 2006 Pr. Christopher Barner-Kowollik at the Centre for Advanced Macromolecular Design (CAMD, University of New South Wales, Sydney, Australia) to study the elaboration of copolymers by Reversible-

Addition Fragmentation chain Transfer (RAFT) polymerization and ring-opening polymerization (ROP) for hernia repair applications. In 2007, she moved to the Centre for Nutrition and Food Sciences (University of Queensland, Brisbane, Australia) to join the team of Pr. Robert Gilbert and Pr. Mike Gidley where she studied arabinoxylans. Since 2007, she joined the team of Dr. Didier Gigmes as lecturer at Aix-Marseille University (Marseille, France). Her current research areas relie on the synthesis of (co)polymers of interest by nitroxide-mediated polymerization and modification of polysaccharides. She is (co)authors of 18 peer review articles in international journals, 3 patents and 1 book chapter.

Yohann Guillaneuf

Yohann Guillaneuf completed his PhD in 2006 under the supervision of Prof. Denis Bertin at the University of Provence (France), where he studied the kinetics of the nitroxide-mediated polymerization. He then joined the group of Prof. Robert G. Gilbert at the University of Sydney (Australia) and University of Queensland (Brisbane, Australia), as a postdoctoral researcher in both the field of controlled radical polymerization in dispersed media and polysaccharides. In 2010, he obtained a CNRS researcher position at the Institute of Radical Chemistry (Aix-Marseille Université) in Marseille (France). His current research activities deal with advanced macromolecular synthesis via the photo-controlled radical polymerization and the radical ring-opening polymerization. He is (co)author of more than 65 peer review articles in international journals and 5 patents.

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