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Didier Gigmes, Paul H. M. van Steenberge, Didier Siri, Dagmar R. d'Hooge, Yohann Guillaneuf, et al.. Simulation of the Degradation of Cyclic Ketene Acetal and Vinyl-Based Copolymers Synthesized via a Radical Process: Influence of the Reactivity Ratios on the Degradability Properties. Macromolecular Rapid Communications, 2018, 39 (19), pp.1800193. 10.1002/marc.201800193 . hal-02091853

**HAL Id: hal-02091853**
**https://amu.hal.science/hal-02091853**

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# Simulation of the degradation of cyclic ketene acetal and vinyl based copolymers synthesized via a radical process: influence of the reactivity ratios on the degradability properties [a]

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The radical copolymerization of vinyl and cyclic ketene acetal (CKA) monomers is a promising way to prepare degradable vinyl polymers. The reactivity of the comonomer pair is known to be dependent of the vinyl monomer structure that requires to play with experimental conditions (feed ratio, overall monomer conversion, etc.) to target a desired cumulative (average) copolymer composition. Even if the materials is completely degradable, there is no information about the homogeneity of the degraded products. This theoretical study, using kinetic Monte Carlo simulations, allows simulating degradation at the molecular level. It is shown that disparate reactivity ratios (styrene/CKA, etc.) and also a composition drift at high conversion can lead to an inhomogeneous degraded product compared to systems with similar reactivity ratios (vinyl ether/CKA, etc.). The use of RDRP techniques does not influence the final degraded products and is only useful for the design of advanced macromolecular architectures before degradation.

[a] **Supporting Information** ((bold)) is available from the author.

# 1. Introduction

Degradable polymers are today of great interest in a wide range of applications including disposable materials, packaging and medicine. In particular, (bio)degradable materials are used to elaborate resorbable sutures, scaffolds and various drug delivery systems.[1-2] Among the different degradable polymers, aliphatic polyesters like polycaprolactone (PCL), polylactide (PLA), polyglycolide (PGA), and poly(lactide-*co*-glycolide) (PLGA) are probably the most studied ones thanks to their biocompatibility and degradability properties enabling their use in humans. Aliphatic polyesters[3] are commonly synthesized by ring-opening polymerization (ROP), a polymerization technique that requires generally drastic synthetic conditions, the use of a catalyst (that requires FDA approval for biomedical applications) and that is limited to a narrow range of monomers.

Vinyl polymers like polystyrene or poly(meth)acrylics for example are other classes of materials also largely used for various applications. These polymers present the advantages to be easily prepared by free radical polymerization (FRP) that does not require specific synthesis conditions and that is compatible with a wide range of monomers. Reversible deactivation radical polymerization (RDRP) techniques like nitroxide-mediated polymerization (NMP)[4], atom-transfer radical polymerization (ATRP),[5] and reversible addition fragmentation chain transfer polymerization (RAFT)[6] allowed in addition to elaborate sophisticated (co)polymers with controlled compositions, architectures and functionalities.[7] Nevertheless, the main drawback of these vinyl-based materials is their lack of degradability since the main polymer chains do not possess degradable functionalities (like ester groups for example).[8] This limitation has been overcome with the development of degradable vinyl copolymers prepared by the radical ring-opening (co)polymerization (rROP) of vinyl monomers with cyclic monomers introducing labile groups in the vinyl polymer backbone.[8-9] Among the different cyclic monomers reported in the literature and polymerized by rROP, cyclic ketene acetal (CKA) monomers originally developed by Bailey

*et al.*[10] have been the most studied ones.[9, 11] In particular, five and seven-membered ring monomers like 2-methylene-4-phenyl-1,3-dioxolane (MPDL) and 2-methylene-1,3-dioxepane (MDO) or 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) respectively are of great interest thanks to their good stability and their well-described synthesis. Their copolymerization by rROP with vinyl monomers like styrene (S), methyl acrylate (MA), methyl methacrylate (MMA), vinyl acetate (VA) or vinyl ether (VE) enables the elaboration of degradable vinyl materials.[9, 12] Their hydrolytic degradation that can be performed under different conditions (few hours to several days in deionized water, phosphate-buffered saline (PBS) or under accelerated conditions in presence of KOH or HCl) is nevertheless difficult to precisely quantify and can be reported according to different criteria (soluble or not in the medium, weight loss measurements etc.). Generally, the most common method to evaluate the copolymer degradation consists in following the decrease of the number-average molecular weight ($M_n$) with time. For example, Albertsson et al.[13] reported that MDO/glycidyl methacrylate (GMA) copolymers with a cumulative mole fraction of MDO units in the copolymer ($F_{MDO}$) of 0.42 (synthesized with an initial MDO feed composition ($f_{MDO,0}$) of 0.65) lost 25% and 60% of their initial $M_n$ after 133 days of hydrolysis at 37 °C in PBS and deionized water respectively. In the case of MDO/VA copolymers, Agarwal *et al.*[14] studied the hydrolytic degradation of copolymers with $F_{MDO}$ = 0.73 (synthesized with $f_{MDO,0}$ = 0.76) in 5wt% KOH methanol solution. After 20 h of hydrolysis, the authors observed a full solubilization of the sample in the medium and liquid chromatography–mass spectrometry (LCMS) analysis revealed the presence of only oligomers of molecular weight ranging between 131 and 263 g.mol$^{-1}$. Another example of vinyl/CKA copolymer degradation study was proposed by Wu et al.[15] who studied the system MDO/S. In the case of copolymer with $F_{MDO}$ = 0.20 (synthesized with $f_{MDO,0}$ = 0.78), they observed a decrease of $M_n$ from 6400 to 1160 g.mol$^{-1}$ with an increase of the dispersity from 1.45 to 2.66 after 10 h of methanolysis in chloroform.

It is here important to note that in the case of the rROP of styrene or methacrylate vinyl monomers with MDO, the incorporation of the CKA monomer in the final copolymer is very weak (*i.e.* the mole fraction of CKA units in the copolymer, $F_{CKA}$ is always lower than the mole fraction of CKA in the feed, $f_{CKA}$). This phenomenon can be explained by the strong difference between the vinyl and CKA reactivity ratios ($r_{vinyl}$ and $r_{CKA}$ respectively) with $r_{CKA}$ values generally very low (and close to 0) compared to the $r_{vinyl}$ ones ($r_{MDO}$ = 0.023 and $r_{MA}$ = 26.53[16]; $r_{MDO}$ = 0.021 and $r_S$ = 22.6;[17] $r_{MDO}$ = 0.04 and $r_{MMA}$ = 3.5[18] for example). The only noticeable exceptions concern the systems MDO/VAc[14] and MDO/VE[12] with reactivity ratios both close to 1 ($r_{VE}$ = 1.61 and $r_{MDO}$ = 0.73; $r_{VA}$ = 1.53 and $r_{MDO}$ = 0.47). In this case, one can expect a more homogeneous and statistical repartition of the cleavable ester units all along the polymer chain and consequently a narrow distribution of the fragmented chains length after degradation. On the opposite, in the case of comonomers with highly different reactivity ratios, the monomer with the lowest reactivity (*i.e.* the CKA monomer) will be incorporated only after a noticeable polymerization of the more reactive monomer (*i.e.* the vinyl monomer). Heterogeneous chains with different chain length should consequently be observed after degradation. Depending of the kind of targeted application, the presence of long and non-degradable vinyl polymer residue could be highly problematic like in medicine for example and the choice of the CKA monomer crucial to obtain the more suitable degradable copolymer. To have a more precise knowledge of the degradability properties of such vinyl-based polymers, it appears therefore relevant to have a complete description of the incorporation of the labile units into the individual backbones and to investigate if this incorporation could be finely tuned to control the length of the degraded copolymer chains.

To confirm this point of view and study the influence of the nature of the comonomer pair (*i.e.* the reactivity ratio values) on the degradability properties of copolymers prepared by the rROP of CKA and vinyl monomers, we theoretically followed with a deterministic Predici solver and an advanced stochastic solver the evolution of the cumulative copolymer

composition in vinyl moieties ($F_{vinyl}$) with the overall molar monomer conversion, and the explicit variation of the monomer sequences stochastically. The main drawback of more basic modeling techniques is related to their incapability to obtain a differentiation between the monomer sequences of individual chains. Explicit modeling techniques are required to obtain such a high level of microstructural detail. These methods are usually based on a matrix representation of the propagation event history of a representative number of macrospecies along the polymerization, following a kinetic Monte Carlo (*k*MC) algorithm.[19-20] With this approach,[21-22] the theoretical degradation of the polymer chains could thus be investigated at the molecular level.

MDO was chosen as model CKA monomer, and S, MMA, VA or VE as vinyl monomer (Figure 1). More precisely, S and MMA were chosen as model vinyl monomers to illustrate the case where $r_{vinyl}$ and $r_{CKA}$ are highly different, whereas VA and VE illustrate the case where $r_{vinyl}$ and $r_{CKA}$ are both close to 1.

This theoretical study confirms the crucial role of the reactivity ratios on the degradability properties of the materials and that as expected, the system MDO/VE or VA furnishes the more suitable system for biomedical application, *i.e.* with degraded chains of similar and small length.

## 2. Results and Discussion

### 2.1. Methodology

The aim of this work is to model the incorporation of degradable CKA monomer units in the backbone of a non-degradable polymer prepared by the radical polymerization of common vinyl monomers. The kinetic scheme we used to perform the modeling is a classic one with i) the decomposition of a radical initiator (AIBN for instance) followed by the radical addition

of the initiator radicals onto the two monomers to initiate the polymerization, ii) chain propagation using a terminal model, and iii) termination of the various macroradicals. The average kinetic rate coefficients used in this model were selected from the literature and as discussed in ESI, they only aim at giving a qualitative description of the polymerization kinetics.

Besides this conventional radical polymerization scheme, a living/controlled radical polymerization (or reversible deactivation radical polymerization (RDRP)) scheme was also studied. We chose a simple model where a stable free radical is added to a propagating one, leading to an (pseudo-)equilibrium between dormant and active species (the corresponding parameters and assumptions are discussed in ESI). The initiator was also changed to have an unimolecular initiating system instead of a bimolecular one. Modeling was performed to have the complete description of the copolymerization process. In particular, matrix-based *k*MC modeling provided a fine description of the copolymer chain composition with the discrete position of the two monomers along the individual backbones.[21-22] These backbones were then theoretically degraded and the distribution of the obtained side-products compared in the case of comonomer pairs with different reactivity ratios and under controlled or free radical conditions (Figure 1).

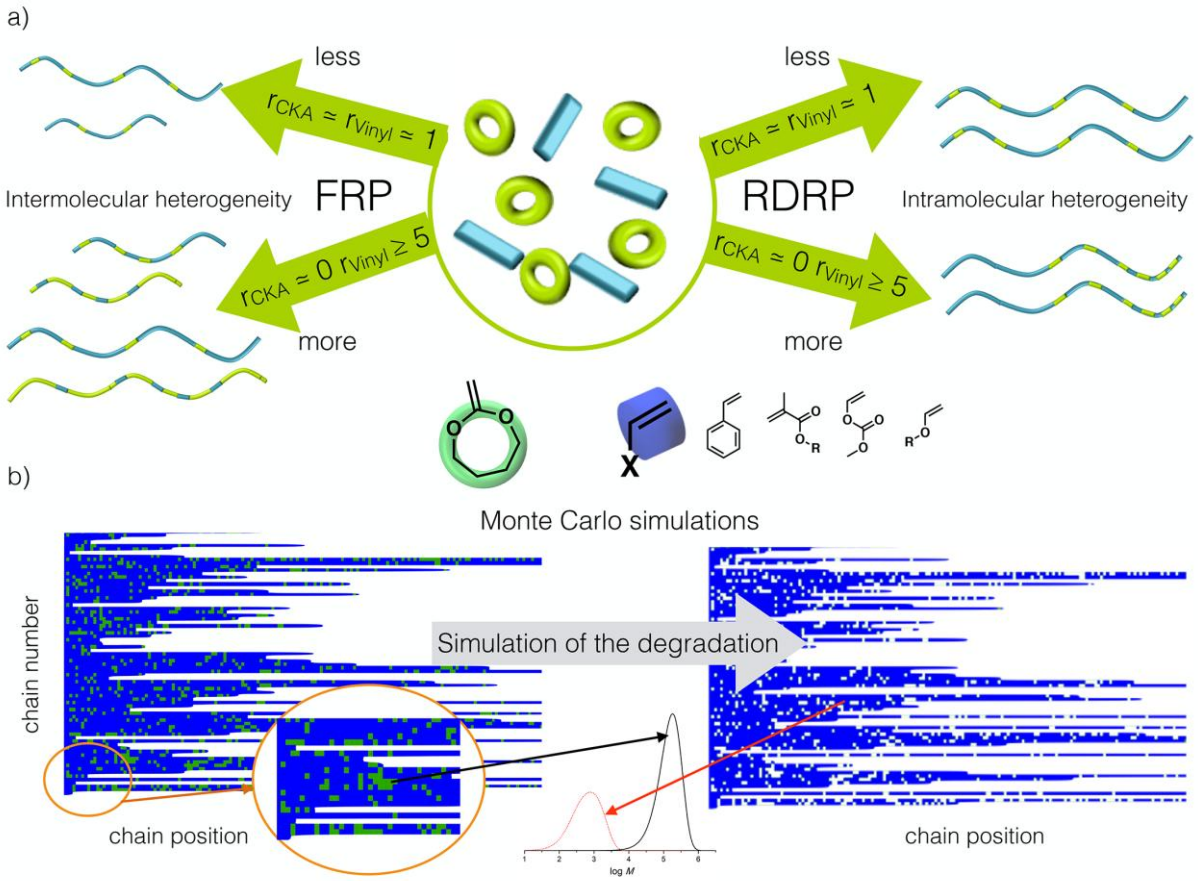



**Figure 1.** a) Influence of the reactivity ratios $r_{vinyl}$ and $r_{CKA}$ on the copolymer structure, i.e intra or intermolecular heterogeneity. blue: vinyl monomer – green CKA monomer 2-methylene-1,3-dioxepane (MDO) b) Simulation of the degradation of the individual chains, as obtained by kinetic Monte Carlo simulations and the corresponding computed SEC traces for both pristine and degraded chains.

## 2.2. Average incorporation of vinyl and degradable monomer units

We first studied the evolution of the cumulative (average) mole fraction of different vinyl monomers units in the copolymer ($F_{vinyl}$) with the overall molar conversion (Fig 2). Styrene and methacrylics illustrate the case where the vinyl reactivity ratio ($r_{vinyl}$) is very high compared to $r_{CKA}$ ($r_{MDO}$ = 0.021 and $r_S$ = 22.6;[17] $r_{MDO}$ = 0.04 and $r_{MMA}$ = 3.5[18]) whereas VAc and VE are examples of vinyl monomers where $r_{vinyl}$ and $r_{CKA}$ are both close to 1 ($r_{VE}$ = 1.61 and $r_{MDO}$ = 0.73;[12] $r_{VAc}$ = 1.53 and $r_{MDO}$ = 0.47[14]). Please note here that whatever the

radical process (controlled or free radical polymerization), the evolution of $F_{vinyl}$ with the overall molar conversion is similar. These two cases will consequently not be discriminated in this part of the work.

Different copolymerization systems were simulated using initial mole fractions of vinyl monomer in the feed ($f_{vinyl,0}$) ranging between 0.25 and 0.75. The theoretical incorporation of the vinyl monomer units in the copolymer backbones was also compared to all currently available literature data, as reported under different conditions of *e.g.* temperature, initiator and monomers (S,[10, 17, 23-24] (meth)acrylics,[10, 25-29] VAc,[14, 30] and VE (symbols on Figure 2)). There is no more data available since in many studies only the degradable material is targeted and information on either the initial feed ratio or the final copolymer composition or overall monomer conversion are not given. The good agreement between experimental and theoretical values confirms the relevance and accuracy of the simulations. It is here important to note that $r_{vinyl}$ being higher than $r_{CKA}$, in all cases $F_{vinyl}$ is higher than $f_{vinyl}$ and in addition, in the case of styrene and methacrylate derivatives, low $F_{vinyl}$ values cannot be reached even if a large excess of CKA is used. As expected, in the case of styrene and methacrylate derivatives and with $f_{vinyl,0}$ = 0.5 or 0.25, there is a high copolymer composition drift as the reaction feed is rapidly depleted from the more reactive monomer (*i.e.* vinyl monomer). This drift of composition is not observed with VE and VA since the values of $r_{vinyl}$ and $r_{CKA}$ are close one to each other. The pronounced decrease of $F_{vinyl}$ with overall monomer conversion creates highly heterogeneous chains in terms of composition. In the case of a FRP process, chains formed at the beginning of the reaction will have a higher content of vinyl monomer than the ones formed at higher overall conversion, leading to intermolecular heterogeneity (Figure 1). The polymer chains formed at the beginning of the polymerization will therefore be less degradable than the ones formed at the end. In the case of a controlled system, the composition drift will be observed along each copolymer backbone and thus a gradient

copolymer is obtained, with intramolecular heterogeneity (Figure 1). A heterogeneous distribution of the polymer residues is then expected, the beginning of the chains being less degradable than the final part.

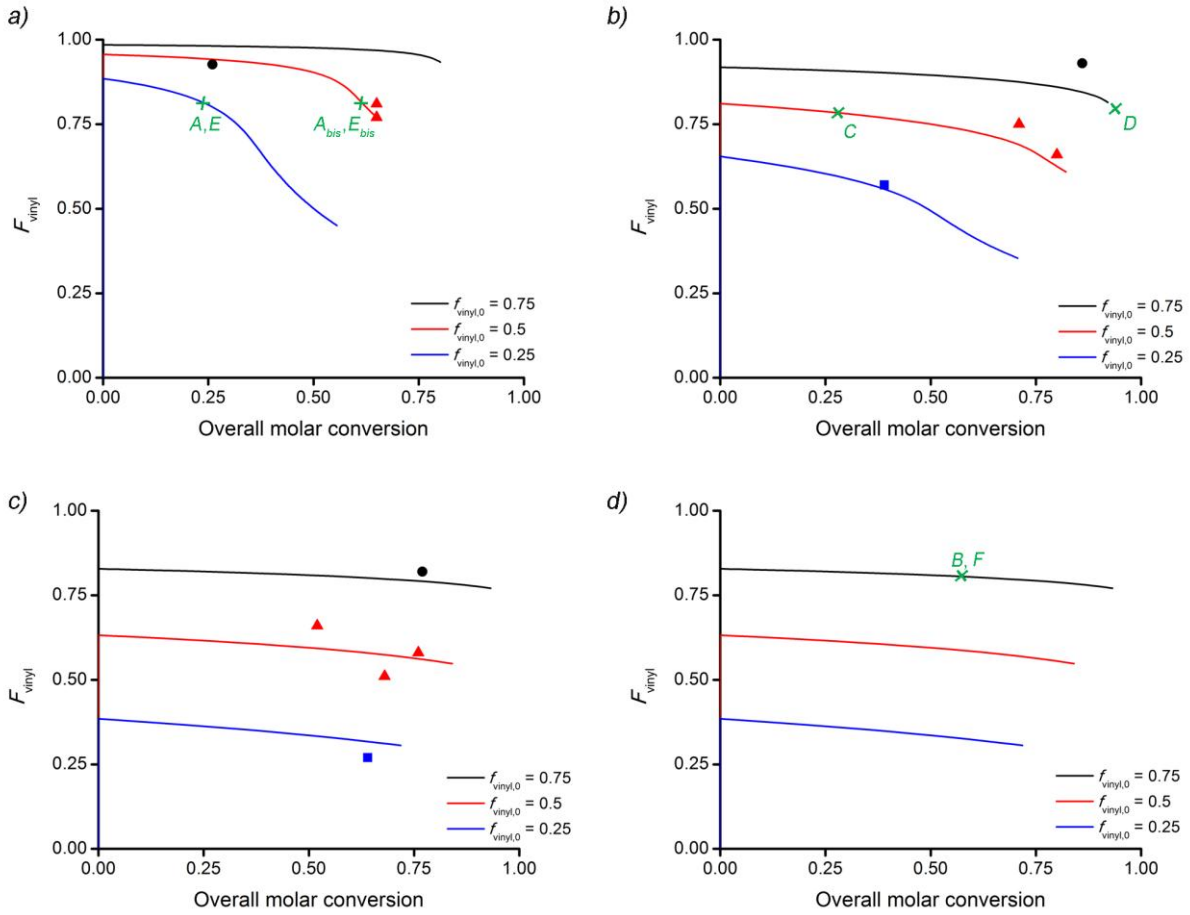



**Figure 2.** Evolution of the cumulative (average) mole fraction of vinyl units in the polymer $F_{vinyl}$ as a function of the overall molar conversion at different initial feed ratio $f_{vinyl,0}$ for a) Styrene derivatives – CKA pair. b) Methacrylate derivatives – CKA pair. c) Vinyl acetate – CKA pair. d) Vinyl ether derivatives – CKA pair. The symbols represent experimental data extracted from literature.[10, 17, 23-24],25-29,[14, 30] The green crosses represent the various theoretical materials whose degradation is further investigated at the molecular level, so beyond an average characterization. They have in common a $F_{vinyl}$ of 0.8. The reported cases A-F are described in Table S1 and Table 1.

## 2.3. Theoretical degradation at the molecular level

The degradation of vinyl/CKA copolymer chains was theoretically studied by *k*MC simulations in the case of S, MMA, and VE vinyl monomers, with or without a drift of

composition and by using a free (FRP) or a controlled radical polymerization (RDRP) process. In all cases the same cumulative copolymer composition in vinyl monomer units was targeted, namely $F_{vinyl}$ = 0.80. For systems having highly different reactivity ratios, it is possible to counter-balance the difference in reactivity by adjusting the initial feed ratio to obtain the desired cumulative copolymer composition and thus different experimental conditions (see Table 1 and Table S1 in ESI and crosses in Figure 1) can be used: i) in the case of S (*i.e.* when $r_{vinyl} >> r_{CKA}$), one can start the reaction with $f_{vinyl,0}$ = 0.25 and stop the polymerization at 23-26 % overall monomer conversion (cases A and E in Table 1) or start with $f_{vinyl,0}$ = 0.50 and stop the polymerization at 63 % overall monomer conversion (cases Abis and Ebis in Table 1); ii) in the case of VE (*i.e.* if $r_{vinyl}$ and $r_{CKA}$ are both close to 1), one can start the reaction with $f_{vinyl,0}$ = 0.75 and stop the polymerization at 55 % overall monomer conversion (cases B and F in Table 1). The difference between the cases A/E and B/F is the use of a RDRP technique. In each case the theoretical initial average segment length of the vinyl monomer unit $<L_{1,inst}>_0$ could be determined *a priori*.[20] For perfect hydrolysis and in the absence of composition drifting, this property yields the (number) average chain length of the degradation product.

As the final cumulative copolymer composition is identical, a simple thought is that the total decomposition of the polymer chains should lead to similar degradation products, at least on an average basis. The theoretical approach we follow allows us to study in a straightforward manner – on the molecular level - the influence of a drift of composition, the reactivity ratio values and the technique of polymerization (RDRP or not) on the degraded material properties and in particular on the dispersity of the degraded polymer ($Đ_{after}$ values) and the presence of long chains ($X_{m,after}$ and $X_{n,after}$ values; mass vs. number average chain length). The results are gathered in Table 1. In this table, “before” and “after” refer to respectively before and after

hydrolysis. The "before hydrolysis" properties were directly calculated from the *k*MC output whereas the "after hydrolysis" properties were calculated indirectly by superposing instantaneous Schulz-Flory segment length distribution with $<L_{vinyl,inst}>$ as the instantaneous average segment length at each 1% overall monomer conversion increment (see ESI for details). Besides dispersity, we also added in Table 1 the relative standard deviation (or coefficient of variation; CV) that has been recently presented by Harrisson[31] and Fierens *et al.*[32] as a better illustration of structural variation.

**Table 1.** Average polymer properties before and after hydrolysis when targeting a vinyl copolymer composition of 0.80 (Figure 1).

| case | polym. | system | $Đ_{before}$ | CV | $X_{n,before}$ | $X_{m,before}$ | $Đ_{after}$ | CV | $X_{n,after}$ | $X_{m,after}$ | Conv. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **A** | FRP | S/MDO | 1.9 | 0.95 | 287 | 555 | 9.0 | 2.83 | 5 | 42 | 0.26 |
| **Abis** | FRP | S/MDO | 2.5 | 1.22 | 251 | 628 | 17.1 | 4.01 | 7 | 123 | 0.63 |
| **B** | FRP | VE/ MDO | 2.0 | 1.00 | 878 | 1735 | 3.3 | 1.52 | 2 | 7 | 0.55 |
| **C** | FRP | MMA/MDO | 1.9 | 0.95 | 1003 | 1897 | 4.2 | 1.79 | 3 | 11 | 0.27 |
| **D** | FRP | MMA/MDO | 3.1 | 1.45 | 371 | 1145 | 5.2 | 2.05 | 3 | 15 | 0.93 |
| **E** | RDRP | S/MDO | 1.1 | 0.32 | 37 | 42 | 9.4 | 2.90 | 5 | 47 | 0.23 |
| **Ebis** | RDRP | S/MDO | 1.1 | 0.32 | 103 | 111 | 17.2 | 4.02 | 7 | 124 | 0.63 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **F** | RDRP | VE/ MDO | 1.2 | 0.45 | 89 | 103 | 3.3 | 1.52 | 2 | 7 | 0.55 |

Very interestingly, whatever the technique of polymerization (FRP or RDRP), the polymer chains after degradation present the same dispersity and the average length. The technique of polymerization does not consequently play an important role on the material degradation properties. The combination of RDRP and CKA polymerization is thus relevant to prepare interesting macromolecular architectures before degradation but do not improve or change their degradation properties

The results secondly showed that one of the key parameters is the presence of a drift of composition. Indeed, when a drift of composition is observed before reaching the targeted copolymer composition (case Abis, Table 1), for a similar (average) polymer backbone, the dispersity of the residual chains clearly increases after degradation (*Đ* increases from 2.5 to 17.1) whereas in the case A (with no/limited drift of composition), the dispersity only increases from 1.9 to 9. In addition, longer degraded segments are observed after a drift of composition ($X_{m,after}$ = 123 and 42 for cases Abis and A respectively from close $X_{m,before}$ values (628-555), and $X_{n,after}$ = 7 and 5 for cases Abis and A respectively from close $X_{n,before}$ values (251-287), Table 1). Cases C and D showed similar results but with a lower extent due to a lower composition drift. The influence of the composition drift is well observed on the Figure S1 that represents the change of the instantaneous $<L_{vinyl,inst}>$ versus overall monomer conversion in which the average segment length decreases from 25 to 2 between the beginning and the end of the polymerization.

The visualization of the composition drift is also well depicted in Figure 3, where the discrete microstructure of polymer chains is represented for cases E, Ebis, and F. As a linear growth of

the polymer chain is expected due to the RDRP mechanism, a composition drift should lead to a gradient-like structure. For case E and F (Figure 3(a) and (c)) the two monomer units are more or less well homogenized (randomly distributed) along the backbone but in case Ebis (Figure 3(b)), a higher amount of CKA monomer (in red) at the chain end is well evidenced.

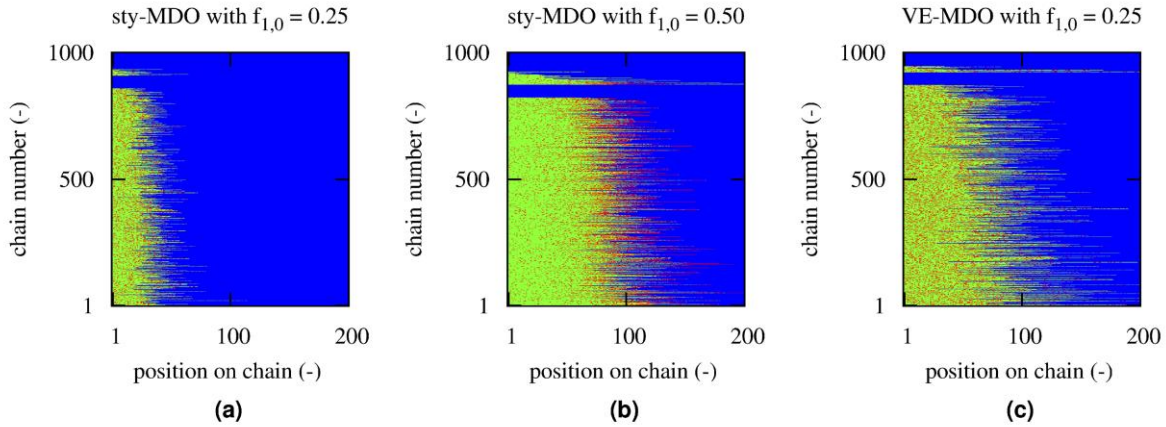



**Figure 3**: Visualization of individual chains (red CKA monomer unit – green vinyl monomer unit - blue: absence of monomer) before and after hydrolysis at $F_{vinyl}$ = 0.8. Initial number of monomer molecules: (a) 2 $10^6$, (b) 2 $10^6$, and (c) 2 $10^7$; cases E, Ebis, and F in Table 1.

As expected, the value of the monomers reactivity ratios also strongly influences the characteristics of the chains after degradation and a homogeneous incorporation of both monomers, *i.e.* if the monomers reactivity ratios are both close to 1 (cases with VE and MDO), furnishes more homogeneous (low $Đ_{after}$ values) and shorter chains (low $X_{n,after}$ and $X_{m,after}$ values) after degradation (Table 1). More precisely, without a drift of composition and in the case of a FRP, with styrene ($r_S$ = 22.6 and $r_{MDO}$ = 0.021, case A) and MMA ($r_{MMA}$ = 3.5 and $r_{MDO}$ = 0.04, case C), the dispersity is multiplied by a factor 4.6 and 2.2 respectively after

degradation, whereas with VE ($r_{VE}$ = 1.61 and $r_{MDO}$ = 0.73, case B) the dispersity is only multiplied by a factor a 1.7. The fragments after degradation with VE are also shorter ($X_{n,after}$ = 2 and $X_{m,after}$ = 7) than with S (5 and 42 respectively) or MMA (3 and 11 respectively) (Table 1). In summary, the more noticeable increase of dispersity with degradation and the longer degraded fragments ($X_{n,after}$ = 7 and $X_{m,after}$ = 124) are then unsurprisingly observed in the cases Abis and Ebis, *i.e.* with different monomer reactivity ratios and after a drift of composition. On the contrary, the cases B and F furnish the more homogenous material after degradation (light increase of Đ) with the shorter chains (lower $X_{n,after}$ and $X_{m,after}$ values).

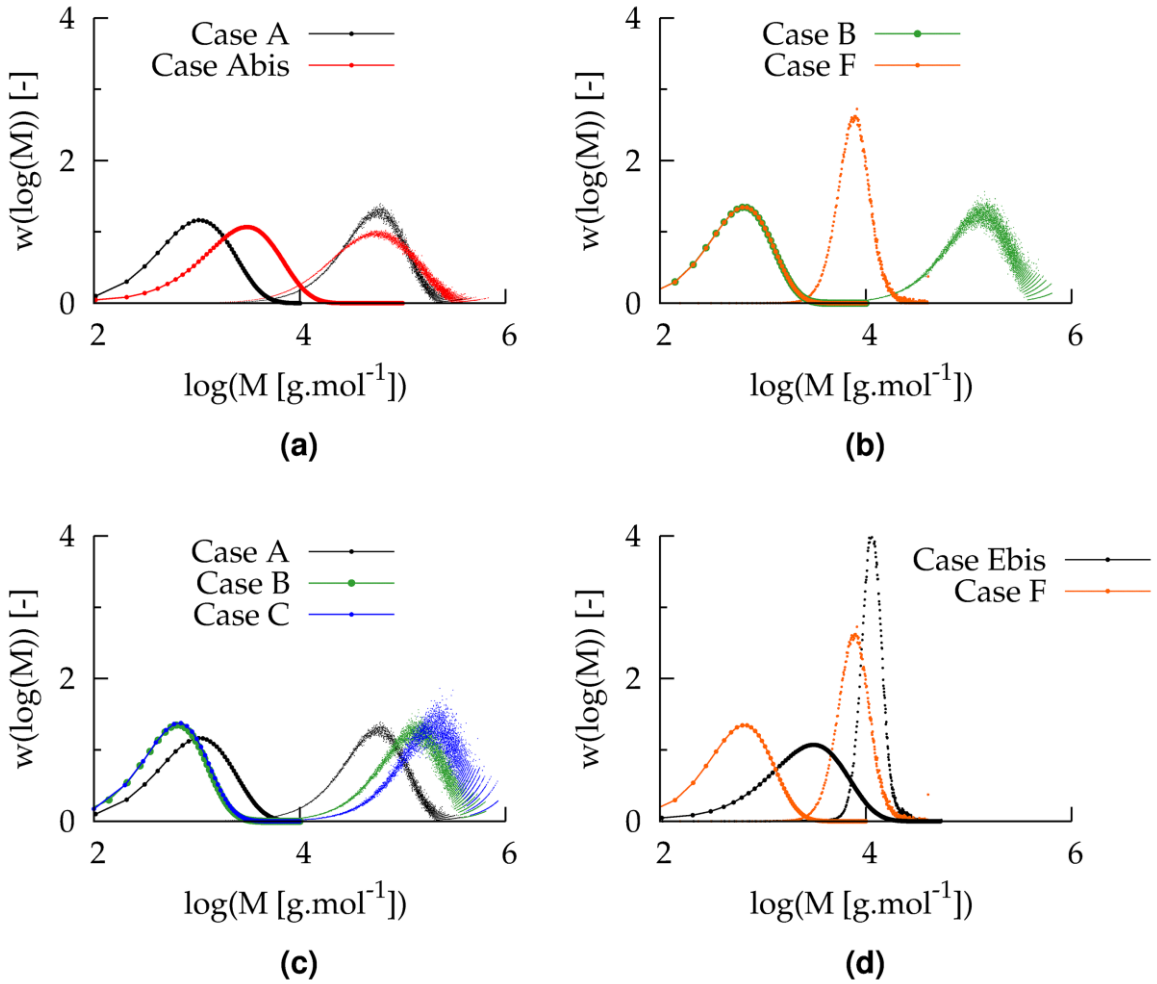


**Figure 4.** SEC trace before and after hydrolysis of copolymers according to various parameters a) Composition drift in FRP Case A (26 % conv) and Abis (67 % conv); b) RDRP vs FRP polymerization Case B (FRP) and Case F (RDRP); c) Reactivity ratios Case A (22.6/0.021), Case B (1.61/0.73) and Case C (3.5/0.04); d) Comparison of the most heterogeneous and homogeneous RDRP degradation products Cases F and Ebis respectively; in every subplot the degraded product is located on the left side of the pristine product (same color).

It is also possible to determine the full molar mass distribution of the degraded chains from the length of the chain residues. These distributions are obtained from the kinetic Monte Carlo simulations and thus are dependent on the initial number of molecules. The latter number is sufficiently high for the scope of the present work, although some limited scattering is obtained in the higher chain length region in Figure 4. The comparison of the molar mass distribution (w(log(M)) vs log(M), Figure 4) before and after theoretical degradation confirms all the previous findings and clearly proves that more homogeneous and shorter degraded chains are expected with the VE/MDO system, whereas the S/MDO system with $f_{\text{vinyl},0} = 0.50$ and after 63% conversion and with a drift of composition furnishes long and heterogeneous polymer chains after degradation. The degraded materials and the resulting fragmented chains are then significantly different, whereas the final copolymers have similar (average) molar masses and compositions.

## 4. Conclusions

In summary, the homogeneity of the incorporation of degradable ester units through vinyl based polymer backbones *via* the radical copolymerization of vinyl and cyclic ketene acetal

monomers has been investigated. Depending on the vinyl monomer structure and thus on the reactivity ratios, experimental conditions have to be carefully chosen to counter-balance the different reactivities and to target a cumulative (average) copolymer composition. Nevertheless the degradability of such materials is in the literature only roughly investigated and the homogeneity of the degradation product not characterized in detail. By matrix-based *k*MC simulation, it is possible to completely describe the composition of the original copolymer and the derived degradation product on the molecular level and to investigate the key parameters that could influence the complete molar mass distribution of the residual oligomers. At the view of this study, the radical technique of polymerization does not influence the material properties after degradation, whereas the presence or not of a drift of composition during the synthesis and the values of the comonomer reactivity ratios are on the contrary of prime importance. When targeting a given final cumulative copolymer composition, a system with no or limited drift of composition and with monomers of reactivity ratios both close to 1 gives shorter and more homogeneous chains after degradation. Such properties could be of high importance when targeting biomedical applications.

## Supporting Information

Supporting Information is available from the author.

**Acknowledgements**: The authors thank the French National Research Agency (ANR-15-CE08-0019) for financial support. P.H.M.V.S. and D.R.D acknowledge the Fund for Scientific Research Flanders (FWO) through a postdoctoral fellowship.

Received: Month XX, XXXX; Revised: Month XX, XXXX; Published online:

DOI: 10.1002/marc.((insert number)) ((or ppap., mabi., macp., mame., mren., mats.))

Keywords: degradable polymer, kinetic Monte Carlo simulation, cyclic ketene acetal, radical ring-opening polymerization, reactivity ratio

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