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DFT-calculation-assisted prediction of the copolymerization between cyclic ketene acetals and traditional vinyl monomers†

Antoine Tardy,[a] Noémie Gil,[a] Christopher M. Plummer,[a] Chen Zhu,[b] Simon Harrisson,[b,c] Didier Siri,[a] Julien Nicolas,[b] Didier Gigmes,[a] Yohann Guillaneuf *[a] and Catherine Lefay *[a]

The radical ring-opening polymerization (rROP) of cyclic ketene acetals (CKAs) by free radical or controlled radical mechanisms attracts considerable research interest as it presents an alternative route for the synthesis of aliphatic polyesters. These monomers can undergo radical addition to their C=C double bonds which subsequently leads to propagation by ring opening. CKA/vinyl monomer copolymerization appears to be an elegant method to produce partially or fully degradable copolymers depending on the proportion of the ester functionality incorporated into the copolymer backbone. Although this approach seems promising, some important limitations still remain. Owing to DFT calculations, we are now able to understand the reactivity of CKAs and common vinyl monomers. Indeed, the calculations confirm that cross-addition is not a key parameter for the copolymerization and the reactivity ratios are linked to the homopolymerization rate coefficients of the comonomer pair. In particular, it was demonstrated that trifluoromethyl vinyl acetate (CF_3VAc) should provide alternating copolymers. These structures were confirmed experimentally with reactivity ratios close to 0 for the MDO/CF_3VAc system (MDO = 2-methylene-1,3-dioxepane). A solid understanding of the reactivity of CKA monomers which allows for the tunable incorporation of main-chain functionalities into copolymers would open up exciting prospects in the field of degradable materials.

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Introduction

Radical polymerization remains one of the primary polymerization techniques due to several advantages such as its compatibility with a broad range of monomers, experimental conditions that only require the removal of oxygen, *etc*. In addition to these advantages, radical polymerization has also witnessed the advent of controlled/living radical polymerization (CLRP) techniques that allow for the preparation of polymer chains with well-defined length, composition and end-groups.[1] Recently the extension of CLRP to include a photochemical process has also led to both temporal and spatial control of the polymerization, giving the possibility to finely tune the polymer chains.[2] To date, the main disadvantage of the radical polymerization process is the non-degradability of the resulting polymer backbone since only C–C bonds are produced. Several strategies have been developed to address this problem.[3] Among them, the use of cyclic ketene acetals (CKAs) is one of the most promising routes. After radical addition to the exo-methylene moiety, these cyclic monomers are able to fragment into an ester group and a new alkyl radical that can propagate the chain (Fig. 1a).[4,5] In particular, five- and seven-membered ring CKA monomers (Fig. 1b) such as 2-methylene-4-phenyl-1,3-dioxolane (MPDL), 2-methylene-1,3-dioxepane (MDO) and 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) are widely used owing to their good stability and high tendency for ring-opening.

When a copolymerization is performed with a vinyl monomer, the consumption of CKA monomers creates an ester moiety in the polymer backbone that will confer (bio) degradability to the resulting polymer (Fig. 1c). The copolymerization of CKA with common vinyl monomers has been exten-

[a]*Aix-Marseille-Univ, CNRS, Institut de Chimie Radicalaire, UMR 7273, F-13397 Marseille, France. E-mail: catherine.lefay@univ-amu.fr*
[b]*Université Paris-Saclay, CNRS, Institut Galien Paris-Saclay, 92296 Châtenay-Malabry, France*
[c]*Laboratoire de Chimie des Polymères Organiques (LCPO), UMR 5629, CNRS, ENSCBP, University of Bordeaux, Pessac, France*

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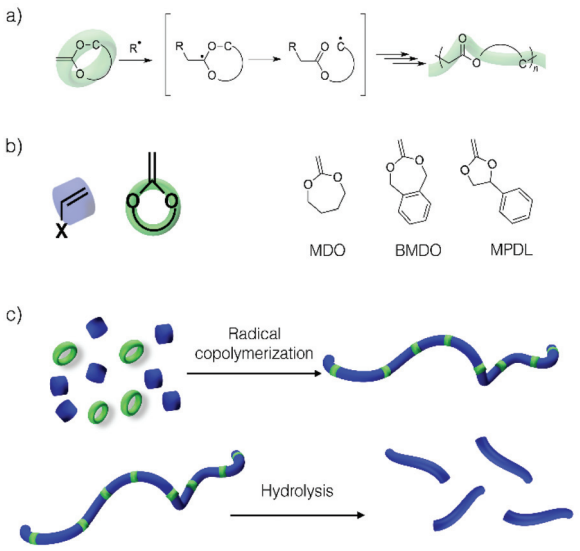
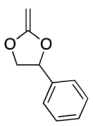
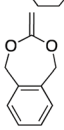


Fig. 1 (a) Radical ring-opening polymerization (rROP) of cyclic ketene acetals (CKAs). (b) Structures of the most used CKA monomers. (c) Preparation of degradable vinyl-based polymers by the radical copolymerization of CKAs and common vinyl monomers.

Table 1 Initial CKA feed ratio ($f_{CKA,0}$) and overall CKA molar composition of the polymer (F_{CKA}) during the copolymerization of CKAs with various vinyl monomers

CKA	Vinyl monomer	$f_{CKA,0}$	F_{CKA}	Ref.
	Styrene	50	23	6
	4-Vinylanisole	50	19	
	MMA	50	33	
	MMA	50	25	
	Vac	50	49	
	Vac	50	34	
	Styrene	50	32	7
	4-Vinylpyridine	50	34	
	MMA	50	40	
	VAc	50	40	
	Styrene	50	27	8
	MMA	50	24	
	Styrene	50	31	
	4-Vinylanisole	50	33	
	MMA	50	13	

sively studied.[4,5] The radical copolymerization of CKA monomers under various experimental conditions and with many common vinyl monomers such as styrenic, (meth)acrylate derivatives and vinyl acetate (VAc) enables the preparation of polymeric materials with enhanced (bio)degradable properties compared to the standard materials. Nevertheless, whatever the system studied, the primary limitation of their copolymerization with vinyl monomers is the weak reactivity of the cyclic monomer resulting in their low incorporation into the final copolymer and a high discrepancy between the initial monomer feed ratio and the final copolymer composition (Table 1).[4,5]

The particular reactivity of CKAs can be attributed to the strong nucleophilic character of the double bond. Nevertheless, the radical addition of electrophilic radicals (such as those derived from acrylates and methacrylates) onto nucleophilic CKA-derivative radicals does not promote a high incorporation of the cleavable ester units into the copolymer backbone. Surprisingly VAc has been identified as one of the most interesting monomers to be copolymerized with CKA.[6,9–12] In the case of MDO as the CKA monomer, the reactivity ratios were indeed both close to 1, enabling the synthesis of a nearly statistical copolymer (r_{MDO} = 0.47 and r_{VAc} = 1.53).[9]

Recently we investigated[13] the copolymerization of CKA monomers with vinyl monomers (methyl acrylate and VAc), and concluded, with the assistance of quantum chemistry and frontier molecular orbital analyses, that the differences in the reactivity observed between vinyl monomers were attributed to the rate of addition of the vinyl-based radicals onto the vinyl monomers and not to the rate of cross-addition between the vinyl radical and the CKA monomer. Such findings helped to discover a new copolymerization pair: CKA/vinyl ethers.[13] Indeed, such systems afford random copolymers with MDO, thereby giving functional polyesters that could be used in a broad range of applications.[13,14]

To expand our understanding of radical CKA copolymerization with vinyl monomers, and to find other relevant CKA/vinyl monomer pairs to copolymerize, the reactivity of model CKAs (MDO or BMDO) with a large range of vinyl monomers was investigated. In particular, after determining the enthalpy of addition for nucleophilic, electrophilic and ambiphilic–electrophilic primary, secondary and tertiary radicals onto BMDO using quantum calculations, the reactivity ratios of several monomer couples were theoretically evaluated.

Indeed, the kinetics of a copolymerization can be described simply by using the terminal model. This approach is based on the assumptions that the growth of the chains depends on the reactivity of the radicals at the end of the chain, and that the propagation reactions are irreversible. The copolymerization of two monomers M_1 and M_2 is then summarized by four possible propagation reactions, two homopropagation reactions (k_{11} and k_{22}) and two cross-propagation reactions (k_{12} and k_{21}). The reactivity ratios defined as $r_1 = k_{11}/k_{12}$ and $r_2 = k_{22}/k_{21}$ allow the evaluation of the microstructure of the copolymer chains.

Based on these results, 1-(trifluoromethyl)vinyl acetate (CF_3VAc, Fig. 2) appeared as a promising new candidate to copolymerize with MDO to give an alternating copolymer. These theoretical results were then confirmed by experimental copolymer synthesis and detailed NMR characterization. This system is therefore a novel way to prepare degradable fluorinated polymers that could have many different interesting applications, such as biomedical imaging.

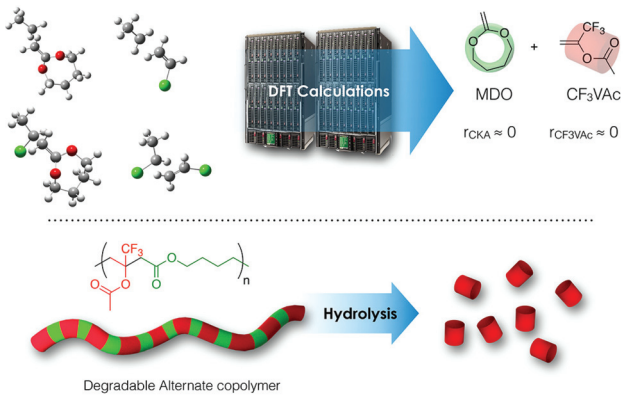


Fig. 2 Theoretical reactivity ratios determined by DFT calculations and the new CKA/vinyl monomer pair: MDO and trifluoromethyl vinyl acetate (CF_3VAc).

Experimental section

Materials

2-Methylene-1,3-dioxepane (MDO) was prepared following a previously described protocol.[6] 1-(Trifluoromethyl)vinyl acetate (CF_3VAc) was purchased from Apollo Scientific. Diethyl azobisisobutyrate (DEAB) was kindly provided by Arkema. All other reagents and solvents were purchased from Sigma-Aldrich and Acros Organics and were used as received.

Characterization

^1H and ^{13}C NMR spectra were obtained on a Bruker Advance DPX 300 MHz spectrometer at 300 MHz (^1H) and 75.5 MHz (^{13}C). The ^1H chemical shifts were referenced to the solvent peak for acetone-*d*6. All integrations of the ^1H NMR spectra were normalized to a peak at 7.5 ppm relating to bromobenzene which was used as an internal reference. SEC analyses were performed using an EcoSEC system from TOSOH equipped with a differential refractometer detector. THF was used as an eluent with 0.25 vol% toluene as a flow marker at a flow rate of 0.3 mL min^{-1} after filtration using Alltech PTFE membranes with a porosity of 0.2 μm. The column oven was maintained at 40 °C, and the injection volume was 20 μL. One ResiPore pre-column (50 mm, 4.6 mm) and two ResiPore columns (250 mm, 4.9 mm) from Polymer Laboratories were used in series. The system was calibrated using polystyrene standards from Agilent in the range of 580–400 000 g mol^{-1}.

CF_3VAc and MDO radical copolymerization

In a typical polymerization reaction, 0.2 mmol of thermal initiator (DEAB), 2–4 droplets of bromobenzene (used as an internal reference for NMR) and 8 mmol of monomer were placed in a flask previously rinsed with triethylamine. The homogenized mixture was then syringed into a Wheaton prescored ampule of 2 mL which was also previously rinsed with triethylamine. Afterward, the mixture was degassed by three cycles of freeze–pump–thaw and the ampule was then sealed. The ampule was then placed in a preheated oil bath at a specific temperature. After a prescribed time, the ampule was removed and placed in ice-cold water, and then opened. The reaction mixture was dissolved in $CDCl_3$ to obtain the ^1H and ^{13}C NMR spectra of the crude polymers and then dried and redissolved in THF to obtain the GPC distributions. Finally, the solution was precipitated in pentane.

Results and discussion

Determination of the activation enthalpy of the reaction of addition of radicals onto BMDO

In a previous study,[13] it was demonstrated that the difference in reactivity observed between VAc and methyl acrylate (MA) copolymerizations in the presence of MDO arises from the rate of addition of the vinyl-based macroradicals onto the vinyl monomers ($k_{vinyl-vinyl}$), as opposed to the rate of cross-addition of the vinyl-based macroradicals onto the CKA monomers ($k_{vinyl-CKA}$). Such findings led us to propose vinyl ether derivatives as good comonomers for CKA polymerization. To obtain a deeper understanding of the copolymerization mechanism, we extended our previous study to a large quantity of alkyl radicals. Although more expensive in calculation time, the use of BMDO in the calculations seemed simpler because the monomer has a greater rigidity and therefore fewer possible conformations after addition. To perform the calculation of polar radical addition activation energies on various alkenes, the UB3-LYP/6-31G(d) method was used.[15,16] This commonly used method was previously validated by Fisher and Radom,[17] indicating that it allows for a good estimation of the energy barriers at a moderate calculation cost. The effectiveness of this DFT method for free radical addition reactions with polar effects has been confirmed more recently, even with the lowest level of theory (6-31G(d)).[18] We therefore modelled the addition reactions of various primary, secondary and tertiary carbon-based radicals from various families, *i.e.*, nucleophilic (alkyl, methoxyalkyl, hydroxyalkyl, acetylalkyl, chloroalkyl); apolar–nucleophilic (aromatic, methyl); electrophilic–ambiphilic (cyanoalkyl, phosphonoalkyl, methoxycarbonylalkyl, and methylcarbonylalkyl) and electrophilic (trifluoromethylalkyl, trifluoroacetonyl – FAc•, and cyclic malonyl – cMal•). The structures and calculation results for UB3-LYP/6-31G(d) are presented in Table S1†, and the activation enthalpies are compared in Fig. 3.

In this work, it was considered that the enthalpies of activation $\Delta H^{\ddagger}$ and the activation energies E_a are similar and that the $\Delta H^{\ddagger}$ values consequently give consistent information of the energetical barrier. Considering apolar radicals (Me-, alkyl, aromatic), there is a linear correlation between the activation energy and the enthalpy of reaction comparable to the Evans–Polanyi–Semenov equation (see Fig. S1†) as already observed by Fischer and Radom.[17] For all other radicals, a deviation of the values below this line is observed, demonstrating the presence of polar interactions during the addition of these radicals to the CKA monomer.[17] Thus, we concluded that the DFT calculation with the UB3-LYP/6-31G(d) method should be

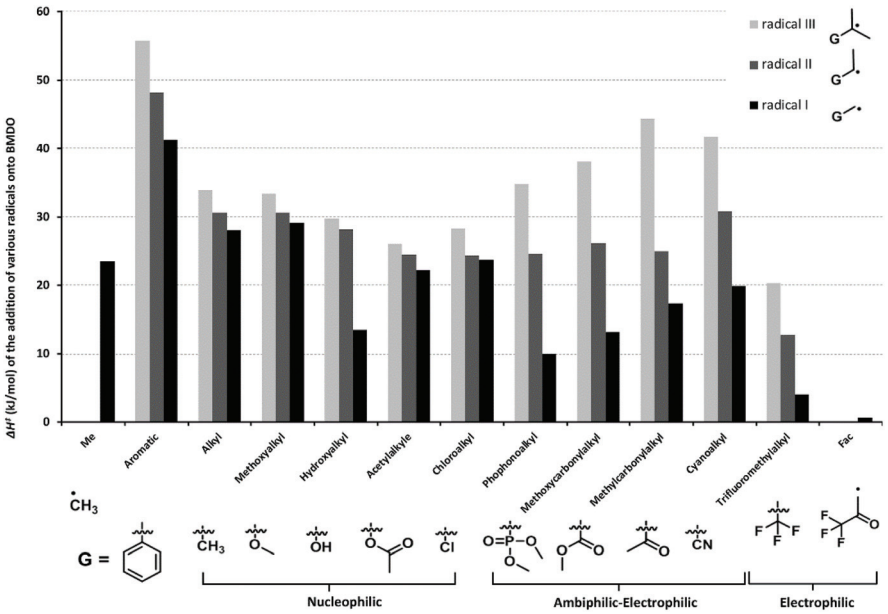


Fig. 3 Calculated activation enthalpies $\Delta H^{\ddagger}$ for the addition of various radicals onto the BMDO monomers using the UB3-LYP/6-31G(d) level of theory.

sufficient to identify behavioral trends since similar trends were observed compared to common radical addition onto alkenes.[17] On the other hand, it was also with the aim of "averaging" potential non-systematic errors that the study was undertaken on a large number of radicals. The analysis of Fig. 3 also provides many insights. First, the additions of all nucleophilic radicals were performed with a low activation barrier ($\Delta H^{\ddagger}$ < 35 kJ mol^{-1}). Besides, nucleophilic radicals present different energy barriers depending on the type of primary, secondary or tertiary radicals. In fact, apart from the addition of the hydroxymethyl (MOH$^{\bullet}$) radical, which seems to be an outlier, the enthalpies of activation of the primary radicals are of the order of 22 to 29 kJ mol^{-1}, whereas they are slightly higher for tertiary radicals at between 26 and 34 kJ mol^{-1}. Additions of secondary nucleophilic radicals are intermediate ($\Delta H^{\ddagger}$ = 24 to 31 kJ mol^{-1}). On the other hand, there is a clear difference in the enthalpy of activation concerning the additions of electrophilic–ambiphilic radicals. In particular, primary radicals show a high reactivity towards the CKA double bond ($\Delta H^{\ddagger}$ = 10–20 kJ mol^{-1}) whereas their tertiary analogs present much more difficulty ($\Delta H^{\ddagger}$ = 35–44 kJ mol^{-1}).

This large difference can be explained by steric hindrance which increases and reduces the reactivity of the tertiary radical, but there should be the same effect for nucleophilic radicals, which is not the case. From another point of view, the electrophilic behavior of primary radicals is modified into a more ambiphilic behavior by the addition of two electron-donating methyl substituents.

Finally, a major difference with nucleophilic radicals is that electrophilic–ambiphilic radicals exhibit forms of resonance, so tertiary radicals are particularly stabilized and therefore less reactive. Indeed, when we look at the enthalpies of addition (Table S1†), we observe that the addition of the tertiary radicals 2-methoxycarbonyl-2-propyl (PEst$^{\bullet}$), 2-cyano-2-propyl (PCN$^{\bullet}$) and 2-methylcarbonyl-2-propyl (PCO$^{\bullet}$) is not very stabilizing (ΔH_r = −23, −27 and −10 kJ mol^{-1}, respectively) in the same way as that of the styryl radical (ΔH_r = −26 kJ mol^{-1}) and cumyl radical (ΔH_r = −6 kJ mol^{-1}). For all other radical additions, the enthalpies are higher and indicate more thermodynamically favorable reactions. The addition of truly electrophilic radicals such as FAc$^{\bullet}$ or radicals with a mesomeric donor but inductively electron-withdrawing trifluoromethyl (CF_3) groups is extremely fast, which is to be expected since the philicity of these radicals is completely opposite to that of the CKA double bond. This reactivity seems to be confirmed with the addition of the cMal$^{\bullet}$ radical, which even seems to present no energy barrier (Table S1†). Nevertheless, the geometry of the corresponding transition state is not comparable with the others because it is not possible to avoid the presence of hydrogen bonds with one of the carbonyls of the cMal$^{\bullet}$ radical.

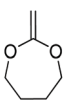
The most important point to note is that for secondary radicals, whether nucleophilic or electrophilic–ambiphilic, the calculations carried out give identical enthalpies of activation, of the order of 25–30 kJ mol^{-1}. Since the propagation of the monomers such as MA and VAc takes place *via* secondary radicals, these singular results could perhaps explain the particular reactivity of CKAs in copolymerization. It has been shown that the most inaccurate UB3-LYP calculations concern species with an oxygen atom directly linked to the reactive center (hydroxymethyl (MOH$^{\bullet}$), 2-hydroxy-2-propyl (POH$^{\bullet}$) and 2-methoxy propylene monomer radicals).[18] Since CKAs possess two oxygen atoms linked to the double bond, the calculations performed here may not be sufficiently reliable. In addition,

the UB3-LYP/6-31G(d) level of theory is known to overestimate the stabilization of radical species[19] and this may be the reason for the low reactivity of electrophilic–ambiphilic tertiary radicals. Recently, Mardirossian and Head-Gordon[20] reported that the root mean square deviation for barrier heights could reach ~6 kcal mol^{-1}, and that absolute values have to be taken with care.

To confirm these results, we thus used other DFT methods, namely BMK[21] with various levels of theory and G3(MP2)RAD,[19,22] which are both known to describe well the reactivity of radicals. In that case, we also initially focused on MDO as it has less atoms, thus saving computational time, and alkyl radicals that mimic the propagating macroradicals. The results are presented in Table 2. It can first be observed that the UBMK/6-31G(d) method indicates values of the same order of magnitude as UB3-LYP while at the UBMK/6-311++G(2dp3df) level of theory, the energy estimates are on average 10 kJ mol^{-1} above the previous values. In contrast, the G3(MP2)RAD method gives rather low values. The results of the calculations that are theoretically more accurate are much more nuanced than the first estimate for the various radicals I, II and III. Indeed, whereas with the UB3-LYP method, the $\Delta H^{\ddagger}$ value of methoxycarbonylalkyl radicals increases from primary to tertiary radicals (methoxycarbonylmethyl radical (MEst$^{\bullet}$) < 2-methoxycarbonylethyl radical (EEst$^{\bullet}$) < 2-methoxycarbonyl-2-propyl radical (PEst$^{\bullet}$)), the UBMK method hardly differentiates between secondary and tertiary radicals but separates them from the addition of a primary radical. Even more surprisingly, it seems from the G3(MP2)RAD method that all methoxycarbonylalkyl radical additions are performed with the same ease ($\Delta H^{\ddagger}$ = 13 ± 1 kJ mol^{-1}) without steric hindrance being important.

Furthermore, in contrast to the results obtained with UB3-LYP/6-31G(d), the addition of the tertiary radical 2-acetyl-2-propyl radical (PAc$^{\bullet}$) to CKA is easier than to its secondary counterpart 2-acetyl-ethyl radical (EAc$^{\bullet}$) according to all other methods. On the other hand, the low reactivity of PCN$^{\bullet}$ and EEst$^{\bullet}$ radicals towards CKA (relative to PEst$^{\bullet}$ and EAc$^{\bullet}$ radicals)

Table 2 Activation enthalpies $\Delta H^{\ddagger}$ for the addition of various secondary alkyl radicals onto the MDO monomer using various levels of theory

			$\Delta H^{\ddagger}$ (kJ mol^{-1})			
Radical		Monomer	UB3-LYP/6-31G(d)	UBMK/6-31G(d)	UBMK/6-311++G(2dp3df)	G3(MP2)RAD
MEst$^{\bullet}$			10.45	14.27	19.59	12.26
EEst$^{\bullet}$			23.62	24.06	32.27	14.58
PEst$^{\bullet}$			35.45	25.02	34.50	13.46
PCN$^{\bullet}$		MDO 	38.66	35.14	43.94	20.39
EAc$^{\bullet}$			23.83	27.94	37.23	18.67
PAc$^{\bullet}$			25.35	25.94	36.64	11.06
EEt$^{\bullet}$			30.67	33.06	43.53	27.24
EEst$^{\bullet}$		VAc 	27.59	27.38	—	18.35
EAc$^{\bullet}$		MA 	5.28	1.84	—	0.40

is confirmed by all calculation methods. The key information to be taken from these calculations is the following: while the UB3-LYP/6-31G(d) method gives similar results concerning the addition of the "nucleophilic" EAc$^{\bullet}$ and "electrophilic" EEst$^{\bullet}$ radicals to the double bond of CKA, the last three methods agree that the addition of the EEst$^{\bullet}$ radicals is favored over EAc$^{\bullet}$ with a lower enthalpy of activation of about 4 kJ mol^{-1}. This difference between the calculated energy barriers is more in line with what is expected *a priori*; however, it remains low for radicals of opposite philicities. It is also observed that the addition of EEst$^{\bullet}$ radicals to CKA is slightly more favorable than the same addition to vinyl acetate, which shows that a larger difference in philicity is slightly favorable for the addition. In any case, the enthalpies of activation obtained for the addition of the various radicals to the nucleophilic double bond of CKA remain high and of a completely different order of magnitude than that for the model addition of a nucleophilic radical (EAc$^{\bullet}$) on an electrophilic double bond (MA) – the classic example of the polar effect in radical chemistry ($\Delta H^{\ddagger}$ extremely low).

Evaluation of the reactivity ratios

This theoretical study aiming at determining the $\Delta H^{\ddagger}$ values for the addition of different vinyl-based radicals to CKA monomers was then completed by the study of the reactions of cross-additions and self-addition to obtain all the rate constants of addition involved in the copolymerization scheme (Table S2†).

The theoretical reactivity ratios (at 70 °C) were then determined from the ratio of the rate constants of self-addition compared to cross-addition. The reactivity ratios obtained for the different systems are presented in Table 3. For such evaluation, the UB3-LYP method was used, considering that the errors among the various alkyl radicals are similar and will be compensated. The reactivity ratios calculated in this work have values with similar orders of magnitude to those reported in the literature; the cases of styrene ($r_{CKA} = 10^{-2}$, $r_{vinyl} = 10$–10^{2}), vinyl acetate ($r_{CKA} = 10^{-1}$, $r_{vinyl} = 1$), methyl acrylate (MA) and methyl methacrylate ($r_1 = 10^{-1}$–10^{-2}, $r_2 = 10^{1}$) attest the pertinence of the UB3LYP/6-31G(d) method. The values of the rate constants are relatively well approximated even if the absolute values of the activation energies are not correct. In addition, and as previously observed, the vinyl ether monomer (VE) appears to be a monomer of choice for copolymerization with CKA to obtain a random copolymer (r_1 and r_2 are both close to 1). This approach has been previously validated on the MDO/vinyl ether pair.[13]

The aim of this work was to obtain a better understanding of the reactivity of different couples of vinyl/CKA monomers, and also to try to identify any other systems of interest for producing degradable vinyl-based copolymers with a high rate of CKA incorporation.

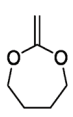
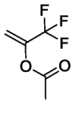
Isoprene is an interesting vinyl monomer since it is a major component of elastomers[26,27] and has been recently shown to be a promising carrier for drug delivery[28–30] *via* a prodrug approach. The theoretical calculations of the reactivity ratios between isoprene and MDO did not let us envision that an efficient random degradable polyisoprene could be prepared *via* its radical copolymerization with CKA monomers. Nevertheless, a low incorporation of cleavable ester groups seemed possible. We then performed the polymerization of isoprene at 115 °C in dioxane for 30 hours in the presence of 0–75 mol% of MDO as the CKA monomer and initiated by dicumyl peroxide to favor CKA incorporation. Polyisoprenes with an M_n value close to 10 000 g mol^{-1} were obtained showing between 5 and 7 mol% of ester units in the polymer backbone (see the ESI† for details). Such polymers were then degraded under accelerated conditions and showed a close to 50% decrease in M_n (Fig. 4).

The nature of the CKA monomer was also investigated. A similar isoprene polymerization was also performed using BMDO as a CKA monomer. In order to favor CKA incorporation, only an initial feed ratio of 75 mol% CKA was used. Even with this large excess of CKA, the conversion was less than 2% of CKA, thus showing almost no incorporation of degradable bonds into the polyisoprene chains.

The theoretical reactivity ratios (Table S3†) between BMDO and isoprene were then computed using the same methodology used in Table 3, providing $r_{BMDO} = 6.5 \times 10^{-3}$ and $r_{isoprene} = 150$. This result confirms the very difficult incorporation of CKA, in agreement with the experimental data.

Unlike isoprene, and based on this theoretical study, a potentially interesting copolymerization system was noticed since the CF_3VAc/MDO pair presents theoretical reactivity ratios both close to 0, thus being expected to produce alternat-

Table 3 Theoretical reactivity ratios at 70 °C between MDO and various vinyl monomers, and comparison with the experimental data

	CKA	STY	IP	VE	VAc	VC	VDC	VP	MA	MMA	AN	CF_3VAc
												
Theoretical reactivity ratio (70 °C)	$r_{CKA} = \frac{k_{ethyl-CKA}}{k_{ethyl-vinyl}}$	**0.013**	**0.02**	**0.97**	**0.23**	**0.068**	**0.013**	**0.007**	**0.003**	**0.006**	**0.001**	**0.006**
	$r_{vinyl} = \frac{k_{vinyl-vinyl}}{k_{vinyl-CKA}}$	**92**	**9.5**	**0.99**	**4.3**	**3.4**	**0.42**	**4.8**	**10**	**17**	**1.48**	**0.16**
Experimental reactivity ratio	r_{CKA}	0.021[23]	—	0.73[13]	~0.5[9]	—	—	—	0.023[24]	~0.1[25]	—	—
	r_{vinyl}	22.6[23]	—	1.61[13]	~1.6[9]	—	—	—	26.5[24]	~4[25]	—	—

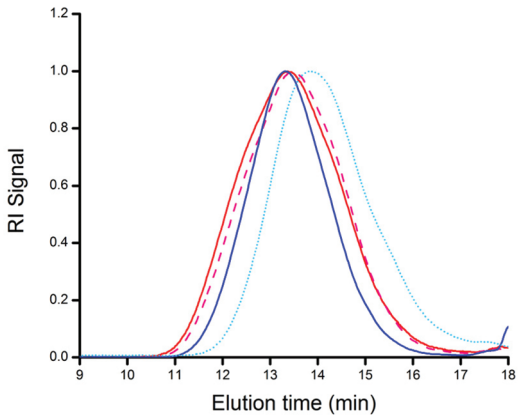


Fig. 4 SEC chromatograms of polyisoprene (red) and poly(isoprene-*co*-MDO) (blue) before (solid) and after (dash and dot) accelerated degradation experiments (24 h THF, KOH, 5 wt% in MeOH).

ing copolymers. Such kinds of alternating copolymers were already obtained using maleic anhydride[31] and maleimide monomers.[32–34] Another interesting aspect of CF_3VAc is the presence of a mesomeric electron-donating acetate function and an inductively electron-withdrawing CF_3 group. Thus, the formation of charge transfer complexes (possible with a mesomeric electron-withdrawing group) that could lead to low cycle opening[35] should be avoided.

Copolymerization of MDO with CF_3VAc

To confirm these theoretical results, we first studied the homopolymerization of the two monomers. Homopolymerization of CF_3VAc is known to be difficult.[36,37] The best results observed by Haas[38] are oligomers with 30% conversion in the presence of benzoyl peroxide at 70 °C for 8 days. We thus performed such homopolymerizations at 70 °C for 12–15 hours with 3 mol% of diethyl azobisisobutyrate (DEAB) as the initiator. The results showed a maximum conversion of 40% (Fig. S2†). On the other hand, the molar masses obtained were about 20 000 g mol^{-1}, which is surprisingly high even though we used the conventional PS calibration. Under the same experimental conditions, MDO reaches a conversion plateau of *ca.* 80% after about 6 hours (Fig. S2†).

We thus performed various copolymerizations with different initial molar ratios of MDO and CF_3VAc ($[MDO]_0 : [CF_3Vac]_0$ = 18 : 82, 45 : 55 and 82 : 12) and stopped them after 6 hours of reaction time at 70 °C with 3 mol% of DEAB as the initiator. The ^1H NMR analyses of the crude products (Fig. 5a) show markedly different behaviors when the composition of the initial medium is varied. Indeed, for initial compositions with 18 and 82% of MDO, a significant amount of the excess monomer remains unreacted after 6 hours, as can be observed in Fig. 5a (peaks α, β, γ, δ and ε), whereas for an initial molar composition of 45%, the two monomers almost completely reacted within 6 hours.

This difference is even more striking when we look at the consumption of the monomers. Indeed, it can be seen in Fig. 5b that monomer consumption is extremely rapid and the conversion plateau (90%) is almost reached after only 2 hours. Moreover, the conversion of the two monomers followed the same trend. The system is therefore strongly accelerated when both monomers are present in an equimolar fashion.

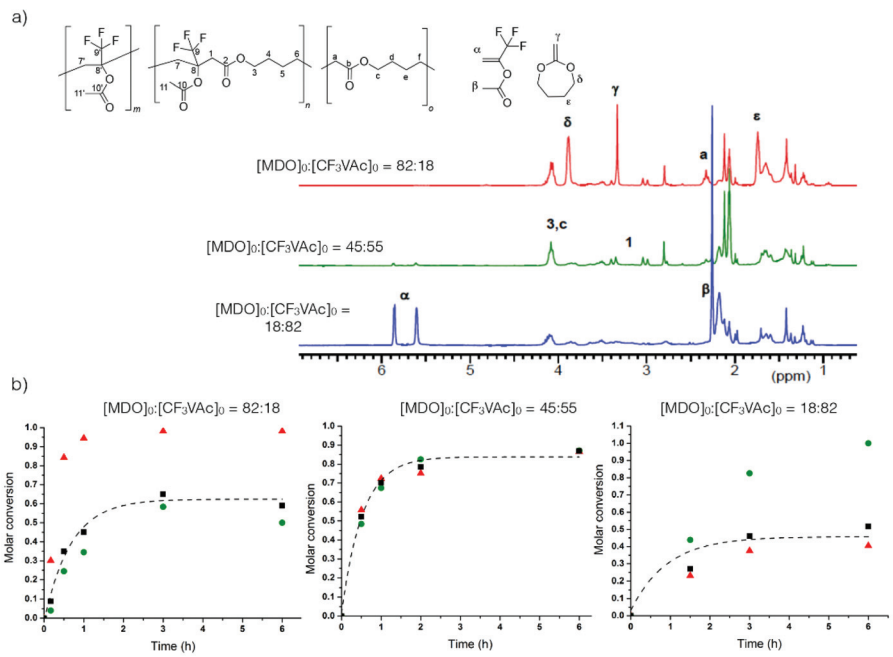


Fig. 5 (a) Crude ^1H NMR analysis of the bulk copolymerization of MDO and CF_3VAc. (b) Molar conversion of CF_3VAc (▲) and MDO (●) and overall conversion (■) for the bulk copolymerization of MDO and CF_3VAc.

This is confirmed by the other two polymerization kinetics (Fig. 5b) where the total conversions only reached 40–60%. When MDO is introduced in excess, copolymerization is rapid until the CF_3VAc monomer is consumed, and then stops at *ca.* 20% conversion of MDO, the characteristic peak of which can be observed in the ^1H NMR spectrum (Fig. 5a). Conversely, when CF_3VAc is introduced in excess, the polymerization stops at 40% molar monomer conversion. It is important to note that the initiator system used for these copolymerizations is the same as that used for the homopolymerization of each of the monomers.

Using this kinetic study, we determined the reactivity ratios by fitting the evolution of the feed ratio *versus* the overall molar conversion (Fig. 6), using the Skeist equation and a non-linear least squares method (NLLS).[13,39] This method provides reactivity ratios of $r_{CF_3VAc} = 0.11$ and $r_{MDO} = 0.07$, in good agreement with the calculated values. Concerning the molar masses of the polymers, they were determined by SEC calibrations using an apparent PS calibration and are presented in Table S4.†

The chemical structures of the obtained polymers are truly dissimilar to the standards, and thus the molar masses are not necessarily comparable. Nevertheless, for copolymers containing a majority of CKA, masses around 10 000 g mol^{-1} are well within the expected range for a radical polymerization of MDO. The masses obtained during a copolymerization initiated with the molar ratio of the monomers being 45 : 55 are much higher which again confirms the better reactivity of this system. The dispersity begins to increase when the amount of the introduced MDO monomer is higher owing to transfer reactions which are known to occur during MDO polymerization.[40,41]

It should also be noted that the molar masses obtained at the beginning of the polymerization are higher than those obtained at the end when the initial feed ratio is not equimolar. This can perhaps be explained by the preparation of polymer chains of a different nature (*i.e.*, homopolymers) with different reactivities when all the alternating copolymers have been formed.

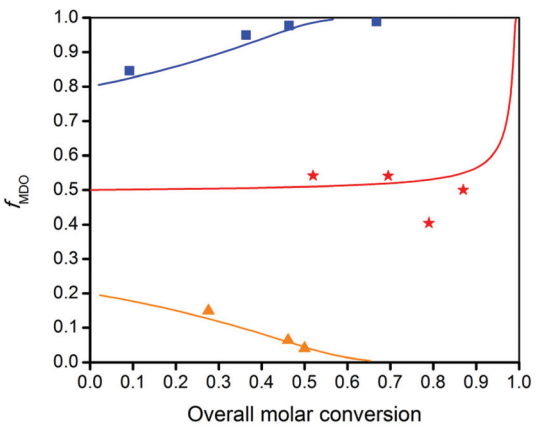


Fig. 6 Experimental and theoretical MDO monomer composition *versus* overall molar conversion with $r_{CF_3VAc} = 0.11$ and $r_{MDO} = 0.07$ during the bulk copolymerization of CF_3VAc and MDO at 70 °C initiated with 3 mol% of DEAB.

Characterization of the copolymer

To confirm the theoretical results and the synthesis of an alternating copolymer, we analyzed the copolymer obtained from an equimolar ratio of MDO and CF_3VAc at 70 °C with 3 mol% of DEAB as the initiator. A homopolymer of the CF_3VAc monomer was prepared under similar conditions before the NMR peak assignment of the copolymer (Fig. S3†). The absence of the acetal peaks generally observed at *ca.* 100 ppm and the presence of ester functionalities at 170 ppm in the ^{13}C NMR spectra (Fig. 7, top) both provide proof of the ring-opening of the MDO monomer. This was confirmed by 2D HMBC NMR analysis which attributed the peak at 169 ppm to the polycaprolactone ester function (coupling between proton 3 and carbon 2, Fig. 5a). The peak at 170.2 ppm was attributed to the acetyl group of CF_3VAc based on the coupling between carbon 10 and proton 11. These results prove that the copolymerization of MDO with CF_3VAc takes place with quantitative ring-opening of the CKA monomer. The full ring-opening of the MDO monomer is essential for introducing cleavable ester functions into the copolymer backbone, thereby enabling the production of degradable materials.

The alternating structure of the copolymer was confirmed by 2D NMR HSQC-ED (Fig. 8b) by the presence of specific couplings between carbon signals at 34.4 and 37.3 ppm with a doubled triplet at 2.1–2.3 ppm and a doubled doublet at 3.0–3.3 ppm, respectively, with the absence of a strong correlation characteristic of the homopolymers of MDO and CF_3VAc. The significant coupling observed between proton 1

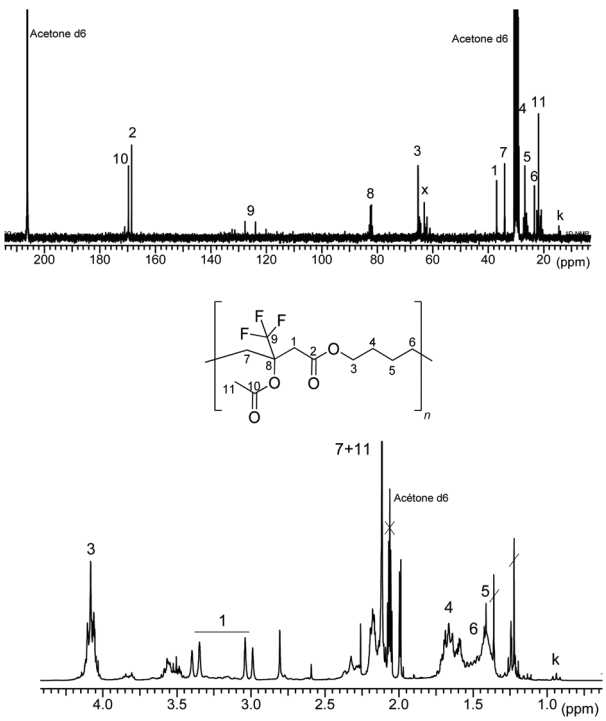


Fig. 7 ^{13}C NMR (top) and ^1H NMR (bottom) spectra of the copolymer obtained from the initial molar ratio $[MDO]_0 : [CF_3VAc]_0 = 0.45 : 0.55$.

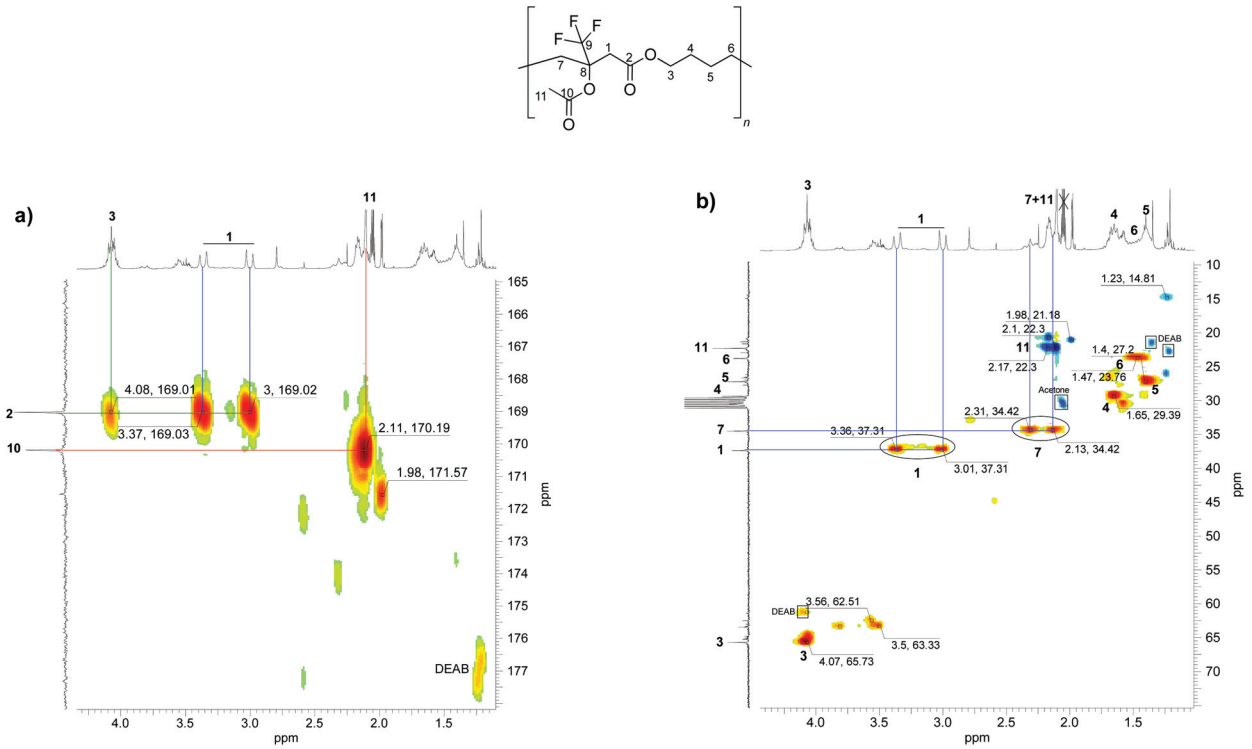


Fig. 8 2D (a) HMBC (heteronuclear multiple bond correlation) NMR spectrum (acetone-*d*6) for the copolymer poly(MDO-*alt*-CF_3VAc). (b) HSQC (heteronuclear single-quantum correlation-multiplicity edited) NMR spectrum (acetone-*d*6) for the copolymer poly(MDO-*alt*-CF_3VAc).

and carbon 2 provides additional evidence of the presence of an alternating structure (Fig. 8a).

This detailed NMR study thus confirmed that the copolymerization of MDO with CF_3VAc with an equimolar initial molar ratio of monomers ($[MDO]_0 : [CF_3VAc]_0 = 0.45 : 0.55$) gives alternating copolymers with 100% ring-opening of the MDO monomer. It should be noted that Maynard and Sawamoto recently showed that degradable methacrylate-based copolymers with a pendant fluorinated group could also be prepared by the copolymerization of BMDO and fluorinated methacrylate.[42] Our system is thus another straightforward methodology for the preparation of degradable fluorinated copolymers with the fluorinated group directly linked to the backbone and not only present as a pendant group.

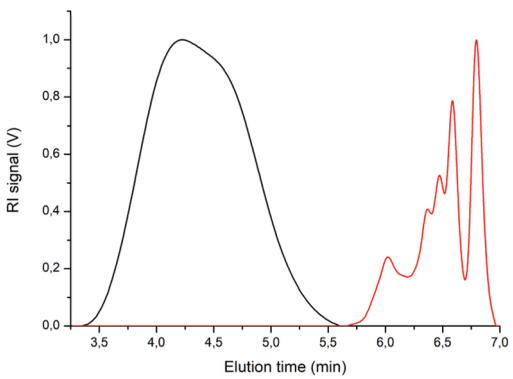


Fig. 9 SEC chromatograms of poly(MDO-*alt*-CF_3VAc) before (dark) and after (red) accelerated degradation experiments.

Degradation and formulation studies

The prepared alternating copolymers were subsequently subjected to degradation tests. Hydrolysis in solution was first investigated under accelerated conditions using 5% potassium hydroxide in THF. The degradation was monitored by SEC and the results of such degradation tests are shown in Fig. 9.

The results showed a total degradation in less than 15 minutes for a pristine polymer of M_n = 26 000 g mol^{-1}, $Đ$ = 3.4. This kinetics is similar to the ones of other degradable CKA-containing copolymers.[33,43] The degradation led to oligomers with an M_n value below 400 g mol^{-1}, in agreement with an alternating copolymer structure.

The hydrophobic poly(MDO-*alt*-CF_3VAc) copolymer was then formulated into nanoparticles in the presence of surfactants using the nanoprecipitation technique as previously performed for poly(MDO-*co*-CEVE) copolymers.[14] Briefly, nanoparticles were formulated at 1 mg mL^{-1} in the presence of 1 wt% of F127 Pluronic as the surfactant. We thus obtained a stable nanoparticle suspension with an intensity-averaged hydrodynamic diameter (D_z) of 242 nm and a particle size distribution of 0.181 (Fig. 10). This result showed that highly fluorinated nanoparticles could be prepared using a degradable polymer and let us envision their use in biomedical imaging.

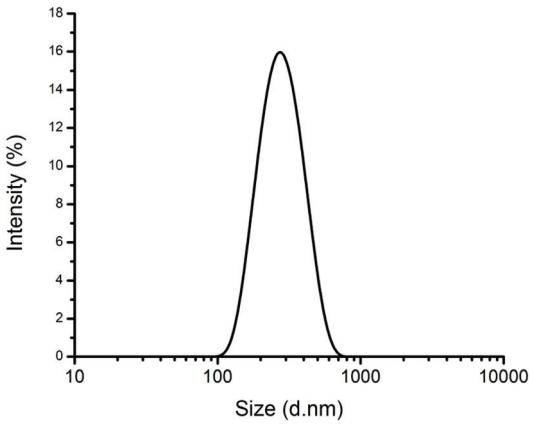


Fig. 10 Volume size distribution of poly(MDO-*alt*-CF_3VAc) nanoparticles measured by DLS.

Conclusion

One of the primary advantages of the radical ring-opening polymerization of CKA monomers consists of their copolymerization with common vinyl monomers, thereby allowing the introduction of ester units into vinyl-based polymer backbones and thus conferring (bio)degradability. This study therefore aimed to rationalize the copolymerization behaviors of CKA monomers with common vinyl monomers *via* DFT calculations. For example, the theoretical determination of the reactivity ratios allowed us envision a low but possible introduction of ester units into a polyisoprene backbone which was later confirmed by experimental studies.

Efficient copolymerization of CKA monomers was found to only be achievable with non-activated comonomers such as vinyl ether or vinyl acetate, or as an alternating copolymerization with maleimides through charge transfer complexes. In this work, we first confirmed this behavior and then extended the alternating copolymerization to trifluoromethyl vinyl acetate (CF_3VAc). The latter system was therefore studied experimentally, and the alternating structure of the copolymer was confirmed by NMR. Degradation studies were performed under accelerated conditions and showed the total degradation of the polymer chains. Finally, nanoparticles of this highly fluorinated degradable copolymer were then obtained by a nanoprecipitation technique. This novel material could potentially find applications in biomedical imaging.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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