

Review

## RAFT Polymerization of Vinyl Esters: Synthesis and Applications

Simon Harrisson, Xuan Liu, Jean-Noël Ollagnier, Olivier Coutelier, Jean-Daniel Marty and Mathias Destarac \*

IMRCP, UMR CNRS 5623, Université de Toulouse, 118 route de Narbonne, F-31062 Toulouse, Cedex 9, France; E-Mails: harrisson@chimie.ups-tlse.fr (S.H.); liu@chimie.ups-tlse.fr (X.L.); ollagnier@chimie.ups-tlse.fr (J.-N.O.); coutelier@chimie.ups-tlse.fr (O.C.); marty@chimie.ups-tlse.fr (J.-D.M.)

\* Author to whom correspondence should be addressed; E-Mail: destarac@chimie.ups-tlse.fr; Tel.: +33-5-61-55-69-68; Fax: +33-5-61-55-81-55.

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**Abstract:** This article is the first comprehensive review on the study and use of vinyl ester monomers in reversible addition fragmentation chain transfer (RAFT) polymerization. It covers all the synthetic aspects associated with the definition of precision polymers comprising poly(vinyl ester) building blocks, such as the choice of RAFT agent and reaction conditions in order to progress from simple to complex macromolecular architectures. Although vinyl acetate was by far the most studied monomer of the range, many vinyl esters have been considered in order to tune various polymer properties, in particular, solubility in supercritical carbon dioxide (scCO<sub>2</sub>). A special emphasis is given to novel poly(vinyl alkylate)s with enhanced solubilities in scCO<sub>2</sub>, with applications as reactive stabilizers for dispersion polymerization and macromolecular surfactants for CO<sub>2</sub> media. Other miscellaneous uses of poly(vinyl ester)s synthesized by RAFT, for instance as a means to produce poly(vinyl alcohol) with controlled characteristics for use in the biomedical area, are also covered.

**Keywords:** reversible addition fragmentation transfer (RAFT); xanthate; dithiocarbamate; vinyl ester; poly(vinyl acetate); poly(vinyl alcohol); block copolymer; supercritical carbon dioxide

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## 1. Introduction

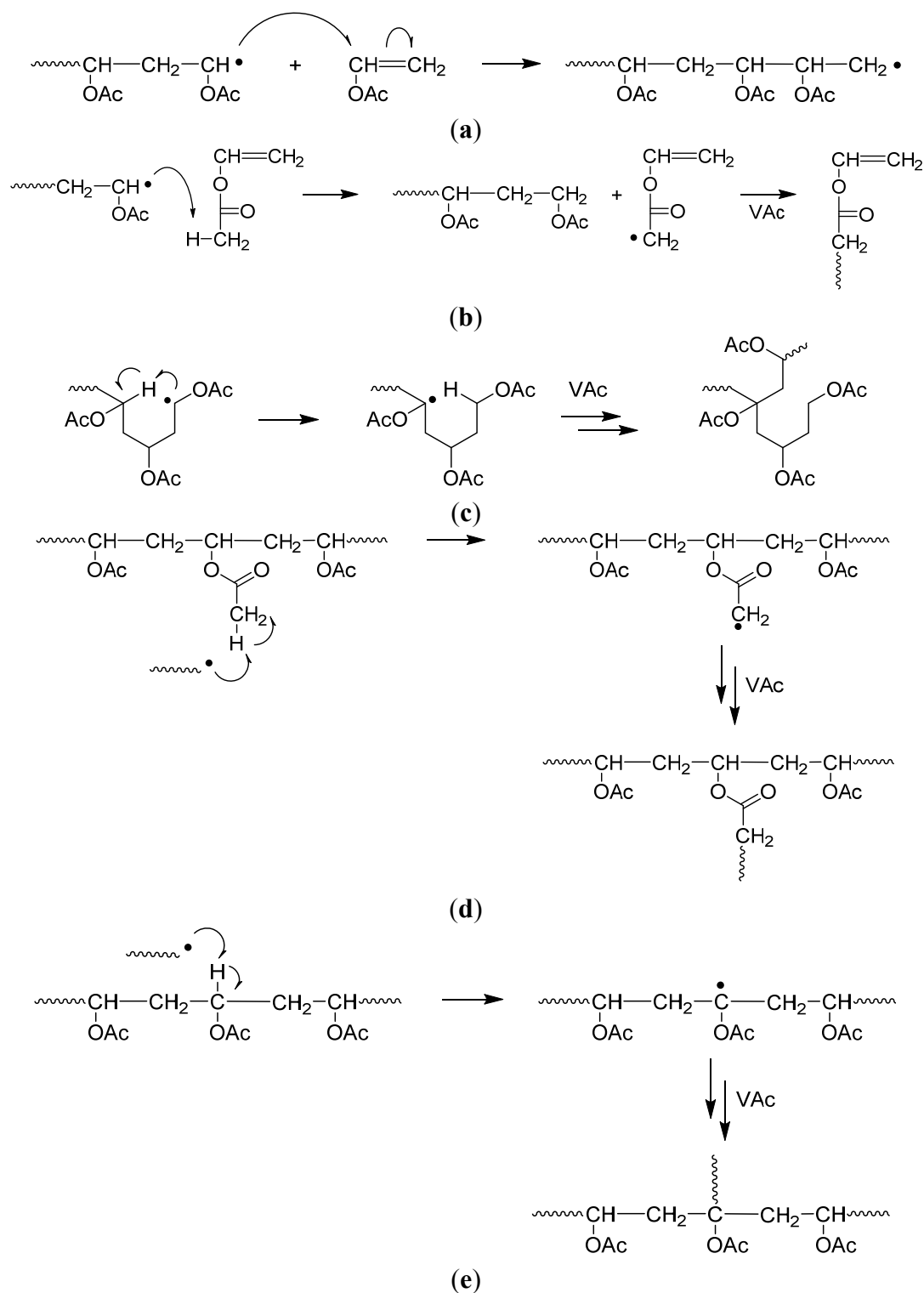
Poly(vinyl ester)s have a rich history in polymer research and industrial production [1]. They are produced by free-radical polymerization. In particular, poly(vinyl acetate) (PVAc) and statistical copolymers of vinyl acetate (VAc) with higher vinyl alkylates, have found application as adhesives for porous substrates (e.g., wood, paper and cloth), emulsion paints and as powder additives for construction materials. PVAc is also known as a precursor for poly(vinyl alcohol) (PVA) [2] and poly(vinyl acetate phthalate), which are important industrial polymers in the coatings area. This broad range of applications can be explained by the large variety of commercially available vinyl ester monomers.

The structure and properties of poly(vinyl ester)s can be finely adjusted by proper selection of the ester group. Hence amorphous and semi-crystalline poly(vinyl ester)s with large ranges of glass transition temperature ( $T_g$ ) and melting points ( $T_m$ ) can be produced. Playing on the free volume of the polymer chain and the strength of polymer–polymer interactions can also influence the behavior of poly(vinyl ester)s in solution. A recent example is the solubility of PVAc in supercritical carbon dioxide (scCO<sub>2</sub>) that can be enhanced via the copolymerization of VAc with hindered [3–6] or fluorinated vinyl esters [7–9]. The kinetics of hydrolysis of the ester group can also be strongly affected by steric hindrance and polar effects. For instance, hydrolysis times ranging from a few minutes to 24 h were observed for trifluoroacetate, acetate, or 2,2-bis(trifluoromethyl)propionate [10].

One of the main reasons for making poly(vinyl ester)s is their use as starting materials for the preparation of PVA with enhanced syndiotactic character. This interest was justified by dramatic changes in the solubility, gelation, and crystallization properties of PVA depending on its tacticity [11,12]. The nature of the vinyl ester monomer can influence the stereochemistry of chain propagation and thus the tacticity of the resulting polymer, although only to a limited extent due to the sp<sup>2</sup> nature of the radical center. This can be achieved by playing on either steric hindrance or polar effects by using bulky [13–15] or polar [14,16] substituents. Use of specific solvents [17,18]—particularly fluoroalcohols [16,19–22]—or addition of Lewis acids [23] constitute other options to induce higher syndiotacticities [19]. For these reasons, vinyl esters represent a large palette of monomers for creating materials with tuneable properties such as  $T_g$ ,  $T_m$ , solubility (*i.e.*, in scCO<sub>2</sub>), alkaline resistance and tacticity.

In vinyl ester polymerization, the very different reactivities of the growing radicals (high) and the monomer (low) result in a high level of chain transfer reactions and main chain irregularities (Scheme 1), which make the production of uniform polymers rather difficult. In addition to a high propensity for chain transfer to solvent in comparison with other monomers [24] (p. 295), a significant contribution of chain transfer to monomer [25] and polymer [26] (Scheme 1) resulting in the formation of branched polymer has been revealed in VAc polymerization. In addition, some regioirregularities are present along the PVAc backbone with 1%–2% head-to-head addition (Scheme 1), their relative abundance tending to increase with increasing temperature [27–29].

**Scheme 1.** Chain transfer reactions in polymerization of vinyl esters. (a) Head-to-head addition; (b) Chain transfer to monomer; (c) Intramolecular chain transfer to polymer (backbiting); (d,e) Intermolecular chain transfer to polymer.



As vinyl esters can only be polymerized by free radical polymerization, the possibilities for macromolecular engineering have long been limited. The advent of reversible-deactivation radical polymerization [28] has led to an increased interest in poly(vinyl ester)s by enabling the control of the main characteristics of polymer chains such as molar mass and molar mass distribution, end-groups

and architecture. Numerous recent studies have focused on complex polymer architectures with original solid state morphologies [30–33], PVA-based surfactants [34,35] or poly(vinyl ester)s with enhanced solubility in  $\text{scCO}_2$  [3–8]. To date, iodine-transfer polymerization (ITP) [36], organoheteroatom-mediated polymerization (OMRP) [28,37], cobalt-mediated polymerization (CoMRP) [38] and reversible addition-fragmentation chain transfer (RAFT) polymerization [39] have been proven efficient in the radical polymerization of vinyl esters. However, ITP, OMRP and CoMRP suffer drawbacks of different kinds. Firstly, PVAc derived from ITP undergoes decomposition of the iodide chain end to form an aldehyde [40]. OMRP based on methyl telluride compounds is only efficient to synthesize low molecular weight PVAc owing to the accumulation of low-activity inverted VAc-TeMe adducts during polymerization [28]. While high molar mass PVAc samples with low dispersities are accessible by CoMRP, this technique is applicable only to a narrow range of monomers, which hampers its development. In contrast, RAFT technology using xanthates and dithiocarbamates [41,42] is of particular interest for its ease of application, versatility and compatibility with a large range of monomers with very different reactivities including vinyl esters.

The intent of this article is to give an extensive review of the works associated with the study and use of vinyl ester monomers in RAFT polymerization since its discovery in the late nineties. Although previous general reviews have covered both synthetic aspects [43–48] and to a lesser extent the applications [49–51] of RAFT, no such work has focused on a single important class of polymers from synthesis to applications. This document will cover all vinyl ester monomers which have been polymerized with a RAFT agent. An important part will be dedicated to the influence of R and Z groups of the RAFT agent on the kinetics of chain transfer and overall homopolymerization, and on the degree of control of the macromolecular characteristics of the polymers formed. Specific parts on macromolecular engineering—*i.e.*, stars, hyperbranched and end-functional homopolymers—and heterogeneous polymerization of vinyl esters will be developed. Also, a detailed section will be dedicated to the copolymerization of vinyl esters to produce block and graft copolymers either by RAFT strategies only or through transformation chemistries. Finally, the use of RAFT-derived poly(vinyl ester)s as precursors to PVA, as  $\text{CO}_2$ -philic polymers or surfactants, and in several other applications will be described.

## 2. Homopolymerization

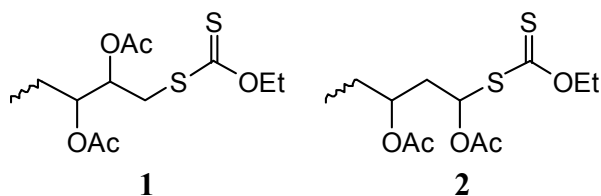
### 2.1. Polymer Structure

The high reactivity of the poly(vinyl ester) propagating radical leads to a high rate of occurrence of side reactions such as head-to-head addition and chain transfer to solvent, monomer and polymer. Most available data concerns VAc but the reactions should take place to a similar degree in other vinyl esters. As a result of these chain-breaking events, RAFT of vinyl esters cannot yield controlled polymers up to high  $M_n$  (typically  $> 10^5$  g/mol) while maintaining low dispersities ( $D = M_w/M_n < 1.2$ ). This is in contrast to an ideal RAFT polymerization in which the proportion of terminated chains depends only on the rate of initiation.

**Head-to-Head Addition.** Head-to-head addition in VAc (Scheme 1a) accounts for 1.23% of additions at 25 °C, increasing to 1.95% at 110 °C [29]. The resulting primary radical is likely to form a

strong C-S bond on reaction with a RAFT agent, effectively deactivating the chain. Indeed, calculations suggest a difference in bond dissociation energy of 3–6 kcal/mol in the C–S bonds of structures **1** and **2** (Scheme 2), resulting from head-to-head addition and head-to-tail addition, respectively [52]. Although never studied in detail, it can be assumed that the difference in reactivity of **1** and **2** contributes to some extent to the observed increase of dispersities at high  $M_n$  during RAFT polymerization of VAc [53]. It should be noted that this difference is less pronounced for RAFT than for most other controlled radical polymerization techniques, with the exception of CoMRP. In CoMRP, the stronger primary Co–C sigma bond resulting from head-to-head addition is compensated by a weaker interaction between Co and the carbonyl group of the terminal monomer unit, resulting in a negligible overall difference in stability between the two adducts [52].

**Scheme 2.** Dormant chains resulting from head-to-head (**1**) and head-to-tail (**2**) propagation of VAc followed by addition to a xanthate during reversible addition fragmentation chain transfer (RAFT) polymerization.



**Branching.** In classical radical polymerization of VAc, it has been reported that chain transfer to monomer occurs predominantly on the acetate position [54] to yield a reactive macromonomer (Scheme 1b) whose copolymerization is responsible for the formation of long-chain branches and can influence the time of gelation in bulk polymerization of VAc [55]. Chain transfer to polymer occurs both intra- (Scheme 1c) and intermolecularly (Scheme 1d and 1e), leading to the formation of short and long branches, respectively. Intramolecular chain transfer (or backbiting) leading to 2,4-diacetoxybutyl branches was evidenced by several groups [56,57]. This side reaction is favored by low monomer concentrations, *i.e.*, at high conversions and in starved feed polymerizations. Two main types of branching are observed when intermolecular chain transfer occurs (Scheme 1): the side chains can be bound to the main chain via an ester group after transfer on acetate methyl hydrogens (Scheme 1d) and also directly by a carbon-carbon bond when transfer occurs on methine (Scheme 1e) or methylene hydrogens of the backbone [24] (p. 323). The principal pathway for chain transfer in VAc polymerization is by hydrogen abstraction from the methyl side group [26]. The relative proportions of chain transfer to polymer according to paths (Scheme 1d) or (Scheme 1e) is a key parameter because (Scheme 1d) generates hydrolyzable long chain branches whereas (Scheme 1e) is responsible for the formation of non-hydrolyzable branches. Therefore, it influences the magnitude of reduction of  $DP_n$ , the degree of branching and the change in molar mass distribution after saponification of PVAc to form PVA. It has been reported that chain transfer to polymer is strongly influenced by the process conditions [58]. In conventional radical polymerizations, the degree of branching initially increases with conversion in bulk, before levelling off at 0.13 mol % at 60% conversion. Higher levels of branching (up to 0.75 mol %) are encountered in emulsion polymerization as a result of the higher polymer concentrations in the vicinity of the propagating radicals. Lower levels of branching have

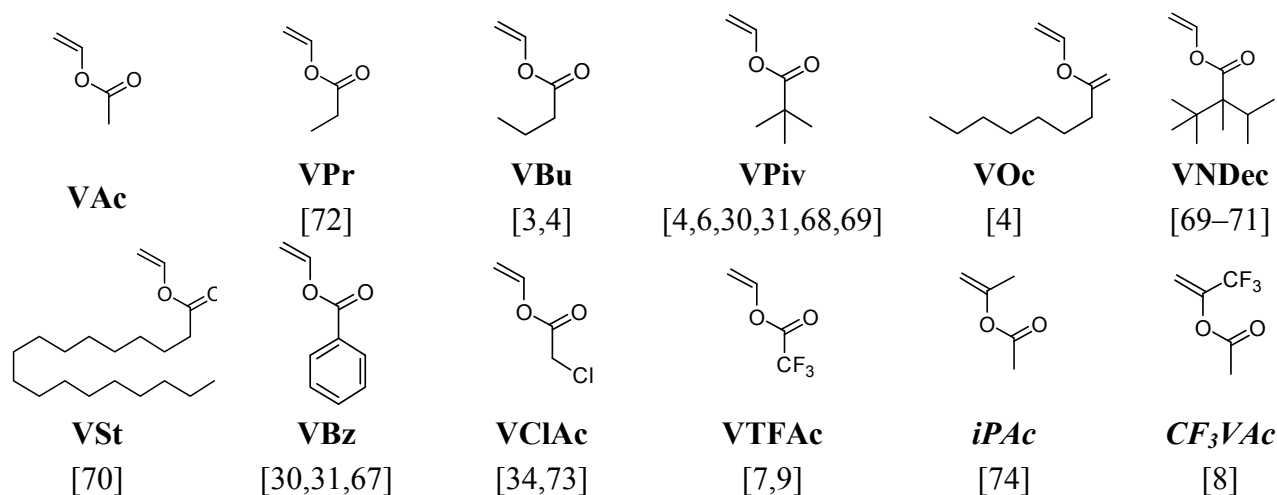
been observed in controlled radical polymerizations, for example 0.045 mol % in CoMRP at 40 °C [52], although this may simply be a result of the lower temperature. Reduction in the degree of branching has been observed in controlled radical polymerizations of butyl acrylate, attributed either to the narrower chain length distribution obtained in controlled polymerizations (fewer reactive short chain radicals) [59] or to reduced conformational freedom of the chain end immediately after activation of the dormant polymer [60]. While these effects should apply equally to vinyl esters, no experimental evidence for reduction of branching in RAFT polymerizations of vinyl esters has been published.

**Tacticity.** Small variations in tacticity can have a large effect on the properties of PVA, with increased syndiotacticity leading to large changes in solubility, gelation and crystallinity. The tacticity of polyvinyl esters can be influenced by the use of bulky or polar side groups, or through the control of solvent effects—in particular fluoroalcohols. RAFT polymerization has been used to prepare PVAs with racemic diad content ranging from 53% to 56% [9] by copolymerization of VAc and vinyl trifluoroacetate (VTFAc) in varying proportions. Use of fluoroalcohol solvents such as (CF<sub>3</sub>)<sub>3</sub>COH at 0 °C allowed the production of narrowly-dispersed PVAc containing up to 62.3% racemic diads [61]. Stereoblock copolymers of PVAc, containing atactic and syndiotactic segments, could be produced by partially polymerizing VAc in bulk at 60 °C, then adding hexafluoroisopropanol and cooling to 0 °C to complete the reaction. Finally, Zelikin *et al.* recently reported the preparation of highly syndiotactic PVAc oligomers (racemic diad content of 69% ± 8%) using *S*-(*N*-phthalimido)methyl *O*-ethyl xanthate as chain transfer agent [62]. High syndiotacticities were only observed at 50 °C while using a high concentration of RAFT agent ([VAc]/[RAFT] = 33); the same RAFT concentration at 60 °C or a lower RAFT concentration at 37 °C resulted in atactic polymer (racemic diad content of 53%). Fractionation of the syndiotactic oligomers allowed the separation of a sample of PVAc with a racemic diad content of 78%, the highest value yet reported.

## 2.2. Vinyl Ester Monomers

A wide range of vinyl esters are available, either commercially or by transition metal-catalyzed transvinylation of VAc with the corresponding acid [63,64]. By far the majority of reported RAFT polymerizations concern VAc. The first successful example of RAFT of VAc employed xanthate transfer agents and was reported by Rhodia and Zard in a 1998 patent [65] and soon after in an article in 2000 [66]. CSIRO researchers independently reported the xanthate-controlled polymerization of VAc and vinyl benzoate (VBz) in a 1999 patent [67]. Other commonly used vinyl esters include vinyl pivalate (VPiv) [4,6,30,31,68,69], vinyl butyrate (VBu) [3,4], and vinyl neodecanoate (VNDec) [69–71]. A complete list of vinyl esters which have been polymerized by RAFT is shown in Scheme 3.

**Scheme 3.** Vinyl esters in RAFT (co)polymerization. RAFT homopolymerization of monomers in *italics* has not been reported.



The halogenated esters vinyl chloroacetate (VClAc) [34,73] and VTFAc [7,9] are more susceptible to hydrolysis than VAc. Block copolymers of these monomers with VAc allow the preparation of PVA-PVAc block copolymers by selective hydrolysis [9,34]. The increased electronegativity of the ester substituent had a negligible effect on the degree of control over the polymerization.

The isopropenyl esters isopropenyl acetate (*iPAc*) [74] and 1-(trifluoromethyl)vinyl acetate (*CF<sub>3</sub>VAc*) [8] have been copolymerized with VAc. Addition of 10% *iPAc* or *CF<sub>3</sub>VAc* to a VAc polymerization had no effect on the control of the polymerization. Further addition of up to 50% *CF<sub>3</sub>VAc* resulted in increased polydispersities (up to 1.7) although control over molecular weight was maintained. *CF<sub>3</sub>VAc* cannot be homopolymerized under radical conditions [75]; no data is available on the RAFT-mediated homopolymerization of *iPAc*.

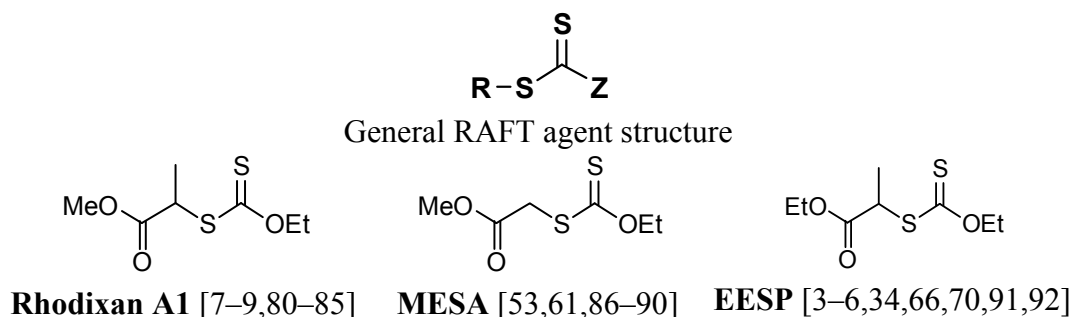
A recently-reported route to functionalized vinyl esters with interesting biological applications utilizes enzymatic selective transesterification of divinyl esters of dicarboxylic acids to prepare *O*-vinyl dicarboxylate esters of a wide range of sugars [76] and biologically-active sugar derivatives such as ribavirin [77], cytarabine [78] and fluorodeoxyuridine [78]. Transesterification is catalyzed by lipase immobilized on acrylic resin and proceeds in yields of 40%–85% depending on the substrate and solvent used. Several such monomers have been polymerized using conventional radical techniques and their self-assembly and drug-release behavior has been evaluated [78,79]. No reports currently exist of RAFT polymerization of this class of monomers, although the preparation of biologically-active polymers of controlled architecture should be of substantial interest for drug delivery applications.

### 2.3. Selection of RAFT Agents

The most important decision before attempting RAFT polymerization of a vinyl ester is the choice of an appropriate RAFT agent. RAFT agents typically consist of a thiocarbonylthio group with two substituents, denoted R and Z (Scheme 4). The Z group determines the stability of the intermediate radical adduct while the R group primarily affects the rate at which the RAFT agent is consumed.

Three of the most commonly used RAFT agents for the polymerization of vinyl esters are shown in Scheme 4.

**Scheme 4.** Commonly used RAFT agents in polymerization of vinyl esters.



The sulfur atoms of the thiocarbonylthio group can be replaced by selenium, with *N,N*-dimethyl diselenocarbamates providing moderate control over the polymerization of VAc and VPiv [68]. Alternatively, the RAFT agent can be synthesized *in situ*, as exemplified by the use of isopropylxanthic disulfide [71,93]. Addition of a poly(vinyl ester) radical to either of the C=S double bonds of the disulfide results in formation of a xanthate RAFT agent and a thiocarbonylthiyl radical which does not reinitiate polymerization. Combination of the thiocarbonylthiyl radical with another polyvinyl ester radical results in formation of a second RAFT agent.

**Choice of Z Group.** Z groups which strongly stabilize the intermediate radical adduct cause retardation or even inhibition of vinyl ester polymerization. This is a result of the low degree of stabilization of the propagating radical—if the RAFT adduct is strongly stabilized, fragmentation is discouraged and termination reactions between radical adducts or radical adducts and propagating radicals become important. Thus RAFT agents such as dithioesters and trithiocarbonates which are highly effective for polymerization of styrene (S) or acrylates inhibit the polymerization of vinyl esters [94]. Xanthates and *N*-aryl dithiocarbamates, which provide less stabilization of the radical adduct, provide effective control over both molecular weight and dispersity, while *N,N*-dialkyl dithiocarbamates provide control over molecular weight but produce polymers with relatively broad molecular weight distributions [41].

On the basis of *ab initio* calculations Coote and coworkers proposed that fluorodithioformates (Z = F) should serve as universal RAFT agents, able to control the polymerization of S as well as VAc [95,96]. The fluoro substituent destabilizes the radical adduct, favoring fragmentation, without deactivating the C=S double bond towards radical addition. This class of RAFT agents has proved difficult to synthesize, however, with only two reports of polymerizations (of S [97] and ethylene [98]) in the presence of fluorodithioformates.

Stenzel *et al.* [86] studied the polymerization of VAc in the presence of several *O*-aryl and *O*-alkyl xanthates. Within a series of *S*-methoxycarbonylmethyl *O*-aryl xanthates carrying *p*-methoxy, *p*-fluoro, *p*-carboxylic acid and *p*-methoxycarbonyl substituents, ability to control the polymerization (as measured by the dispersity of the polymer at ~25% conversion) improved as the electron-withdrawing effect of the substituent decreased. However, there was a concomitant decrease in the rate of polymerization, with inhibition times of up to 8 h observed for the *p*-methoxyphenyl xanthate and up



to 12 h for the *p*-fluorophenyl xanthate. A similar trend was observed for *S*-methoxycarbonylmethyl *O*-alkyl xanthates, with the degree of control over dispersity increasing from *O*-methyl (less electron donating) through *O*-ethyl to *O*-isopropyl (more electron donating). As for the *O*-aryl xanthates, inhibition times increased with the electron-donating ability of the substituent, with total inhibition of polymerization observed for *S*-methoxycarbonylmethyl *O*-*tert*-butyl xanthate. In the case of the *O*-*tert*-butyl xanthate, theoretical calculations have shown that scission of the *O*-*tert*-butyl bond to form a *tert*-butyl radical is competitive with scission of the *S*-PVAc bond [99]. This will result in conversion of the RAFT agent to an unreactive carbonyl compound, as well as the generation of *tert*-butyl radicals which are relatively slow to reinitiate polymerization of VAc ( $k_{\text{add}} = 4200 \text{ L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$  at 298 K [100]), providing another possible cause for the inhibition of polymerization observed. The best balance between inhibition (<2 h) and control over polymerization ( $\bar{D} \approx 1.2$ ) was obtained with the *O*-ethyl xanthate, MESA (Scheme 4).

In the case of dithiocarbamates, conjugation of the nitrogen lone pair with the thiocarbonyl group reduces the double bond character of the C=S bond, resulting in low rates of radical addition [101]. Substitution of the nitrogen with electron-withdrawing or resonance-stabilizing substituents such as carbonyl or phenyl groups hinders this delocalization [41,45]. Thus *S*-diethyl malonyl *N,N*-diphenyl dithiocarbamate is a relatively effective RAFT agent for the polymerization of VAc ( $\bar{D} = 1.3\text{--}1.6$ ) while the analogous *N,N*-diethyl dithiocarbamate gives PVAc with dispersity of 1.8 [41]. Use of more electron-withdrawing *N*-carbonyl substituents allows the production of narrowly distributed polymer ( $\bar{D} \leq 1.3$ ), but results in significant retardation of the polymerization [41].

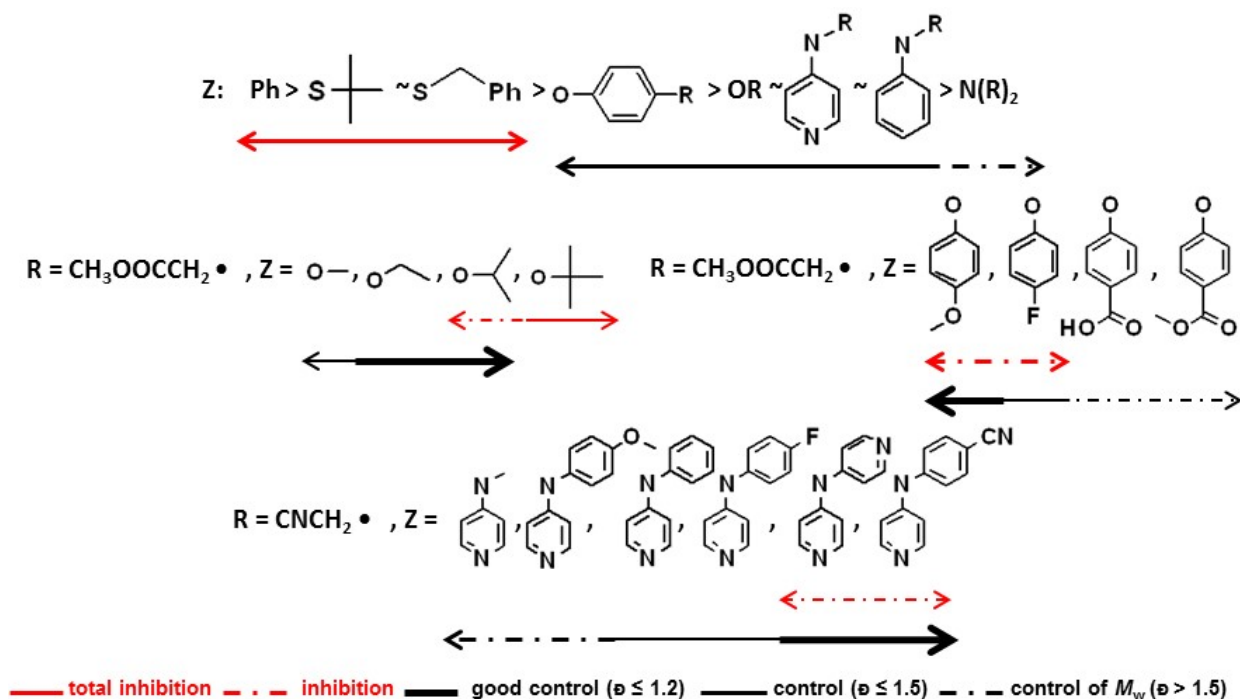
Polymerizations of VAc have been carried out in the presence of a series of *N*-aryl *N*-(4-pyridyl) *S*-cyanomethyl dithiocarbamates with substituents of varying electron-withdrawing ability [102]. In contrast to the trend observed with xanthates [86], the apparent chain transfer constant of the RAFT agent increased with the electron-withdrawing nature of the substituent, from 93 for *N*-(*p*-methoxyphenyl) *N*-pyridyl *S*-cyanomethyl xanthate to over 320 for *N*-(4-pyridyl) *N*-(*p*-cyanophenyl) *S*-cyanomethyl dithiocarbamate. All measured *N,N*-diaryl dithiocarbamates had higher apparent chain transfer constants and were more effective at controlling the polymerization of VAc than *N*-methyl *N*-(4-pyridyl) *S*-cyanomethyl dithiocarbamate, suggesting that the resonance-stabilizing ability of the substituent is of equal or greater importance than its electron-withdrawing ability in determining the activity of the RAFT agent. As for the xanthates, the most active RAFT agents caused significant retardation of the polymerization. Thus, the best compromise between narrow dispersity and acceptable retardation was found with the methoxyphenyl, phenyl and fluorophenyl substituted dithiocarbamates of intermediate activity.

Substituent effects on control over dispersity and retardation of polymerization kinetics are summarized in Scheme 5 for xanthates and *N*-aryl dithiocarbamates.

The *N*-pyridyl dithiocarbamates discussed above are also known as switchable RAFT agents [42], as protonation of the pyridyl group results in the formation of a RAFT agent of comparable activity to a dithioester or trithiocarbonate. In their protonated form, these dithiocarbamates are capable of controlling the polymerization of more activated monomers such as acrylates and S, but inhibit the polymerization of vinyl esters and *N*-vinyl monomers such as *N*-vinyl carbazole [42]. Switching between protonated and deprotonated forms of the dithiocarbamate allows the production of

narrowly-distributed diblock copolymers containing monomers which cannot usually be controlled by the same RAFT agent [42,103,104].

**Scheme 5.** Guidelines for selection of Z groups for control of vinyl ester polymerizations. Red lines indicate inhibition of polymerization; black lines indicate degree of control over molecular weight and dispersity.



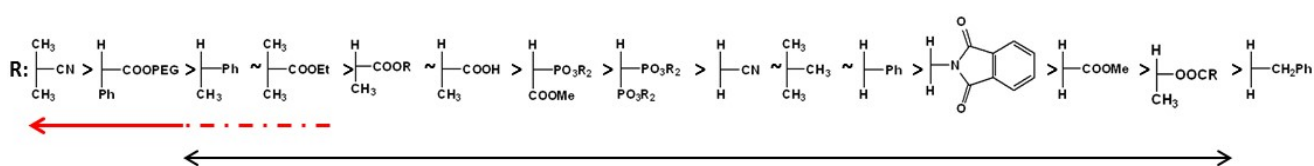
**Choice of R Group.** The S-substituent, or R-group of the RAFT agent must be a good homolytic leaving group in order to facilitate fragmentation of the RAFT agent after addition of the propagating radical. It must also be capable of reinitiating the polymerization at a rate comparable to that of propagation. This is particularly important in the polymerization of vinyl esters, which are substantially less reactive towards radical addition than monomers such as S or acrylates which carry radical-stabilizing substituents. The 2-cyanoisopropyl radical, for example, adds to S with a rate constant of  $2410 \text{ L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$  at 315 K; the corresponding rate constant for VAc is only  $41 \text{ L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$  [100]. As the rate constant of propagation of VAc is  $6100 \text{ L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$  at 313 K [105], use of a 2-cyanoisopropyl R-group would be expected to result in substantial retardation. Less stabilized radicals such as tert-butyl or cyanomethyl react more rapidly with VAc (rate constants of  $4200 \text{ L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$  and  $12,000 \text{ L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ , respectively), while strongly electrophilic radicals such as trifluoroacetyl and 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl (a cyclic malonyl radical) add very rapidly (rate constants of  $4.0 \times 10^5 \text{ L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$  and  $2.0 \times 10^5 \text{ L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$  respectively) [100].

These rate constants are reflected in experimental results of RAFT polymerizations. Use of strongly stabilized R-groups such as 2-cyanoisopropyl [67,106] or  $\alpha$ -(PEGoxycarbonyl) benzyl [107] result in near-total inhibition of VAc or VBz polymerization due to slow reinitiation. Good control over polymerization is obtained with 1-phenylethyl [72,108] though very long inhibition times (10–48 h) are observed.

Poorly stabilized leaving groups, on the other hand, disfavor fragmentation of the RAFT agent, leading to low apparent chain transfer constants. An *S*-(2-phenylethyl) substituted xanthate had no effect on the polymerization of VAc [72], due to the lack of stabilization of the primary 2-phenylethyl radical. Similarly use of a methyl 3-propionyl leaving group [109] in emulsion polymerization of VAc did not lead to control of molecular weight, although retardation of the polymerization was observed.

In between these extremes, a wide range of R-groups may be employed to good effect, including esters of 1-acetyl [86–90,108,110–113], 2-propionyl [3–9,30,31,34,66,69,70,80–82,85,89,91,107,114–123] and 2-methyl-2-propionyl [67,91], 2-acetic acid [124], 2-propionic acid [106,114,125], *t*-butyl [106], cyanomethyl [67,102], benzyl [72,126–130], acetoxymethyl [108], 1-acetoxyethyl [90,108], pivaloyloxymethyl [90] or 1-pivaloyloxyethyl [30] groups. Some unusual leaving groups which have been used to control VAc polymerization include *N*-phthalimidomethyl [62,131], which can be transformed via hydrazinolysis to an amine group, and methylene bis(phosphonate) esters [53]. Some guidelines for selection of an R-group are given in Scheme 6.

**Scheme 6.** Guidelines for selection of R groups for control of vinyl ester polymerizations. Red line indicates inhibition of polymerization, black line indicates control over molecular weight and dispersity.



#### 2.4. Controlled Architectures: Stars, Hyperbranched and End-Functional Polymers

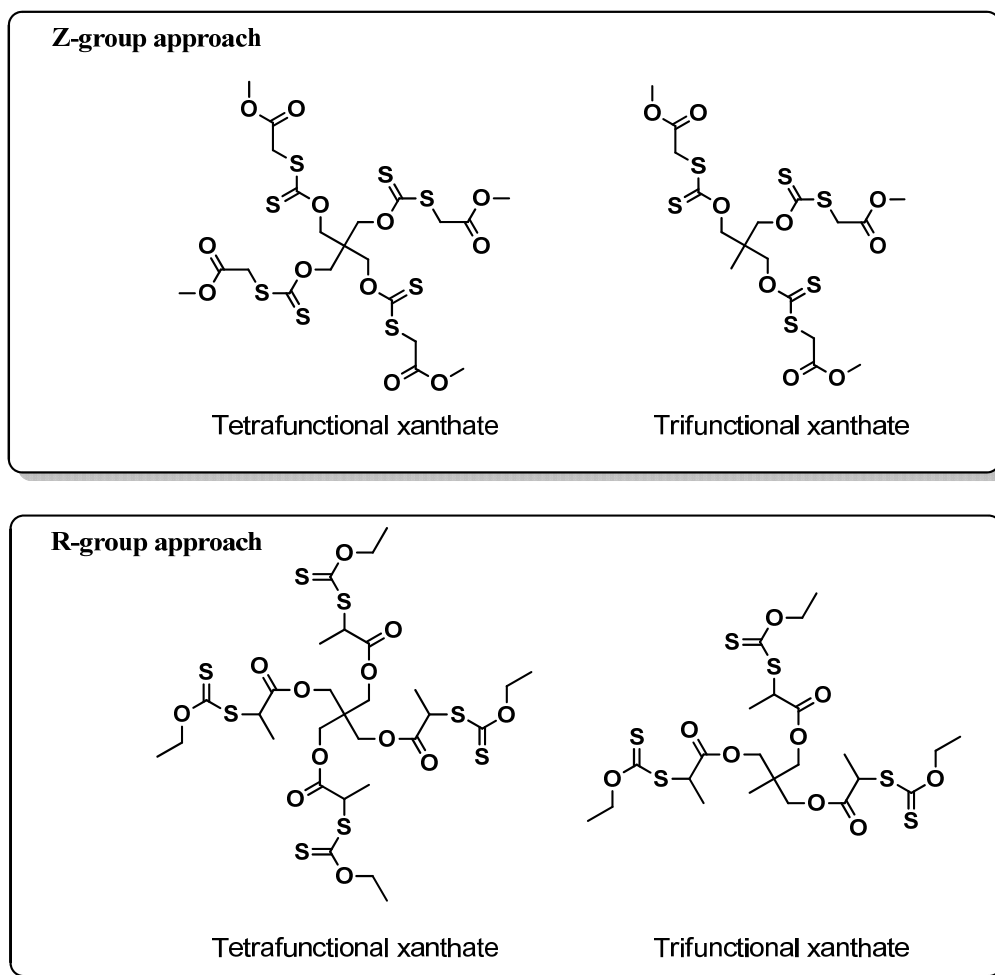
Several different kinds of controlled PVAc architectures have been reported, with starlike PVAc being by far the most common. The main strategy to produce star-shaped polymers is to use tri- or tetra-functional xanthate agents through two different approaches: “R-group approach” or “Z-group approach”, depending on whether the core of the RAFT agent is linked to the R or Z group (Scheme 7).

In 2004, Stenzel *et al.* [80] developed a series of multifunctional xanthates based on the R-group approach and obtained star-shaped PVAc with comparable polymerization kinetics and retardation to those obtained with Rhodixan A1. Molecular weights were found to be in good agreement with theory while dispersities broadened with conversion. In a subsequent paper [69] the authors compared the R-group approach to the Z-group approach in VAc polymerization and concluded that the R-group approach afforded better-defined star polymers, and was the only way to obtain star-shaped PVA after hydrolysis of the star PVAc, as the Z-group approach would result in hydrolysis of the core of the star shaped polymer. Recently the Z-group approach has been used by Zhang *et al.* [122] to synthesize PVAc oligomers with different topologies, to study their behavior in *scCO*<sub>2</sub>.

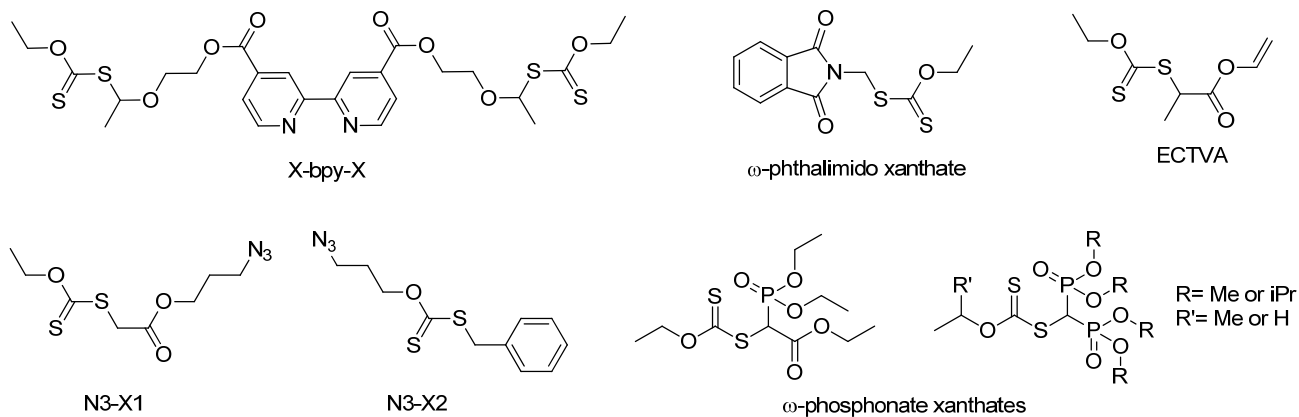
A route to hyperbranched PVAc was proposed independently by Schmitt *et al.* [83] and Zhou *et al.* [132] in 2011, using a xanthate with a polymerizable vinyl ester function on the R group (ECTVA, Scheme 8). Homopolymerization of ECTVA led to hyperbranched P(ECTVA) while its copolymerization with VAc gave highly branched P(ECTVA-*co*-VAc) (Scheme 9). By varying the relative concentration in ECTVA and VAc in the copolymerization, it was possible to modulate both

the number of branch points and the length of the branches. Both hyperbranched and highly-branched xanthate-functionalized PVAc could then be used as macro-RAFT agent for the synthesis of starlike PVAc by chain extension.

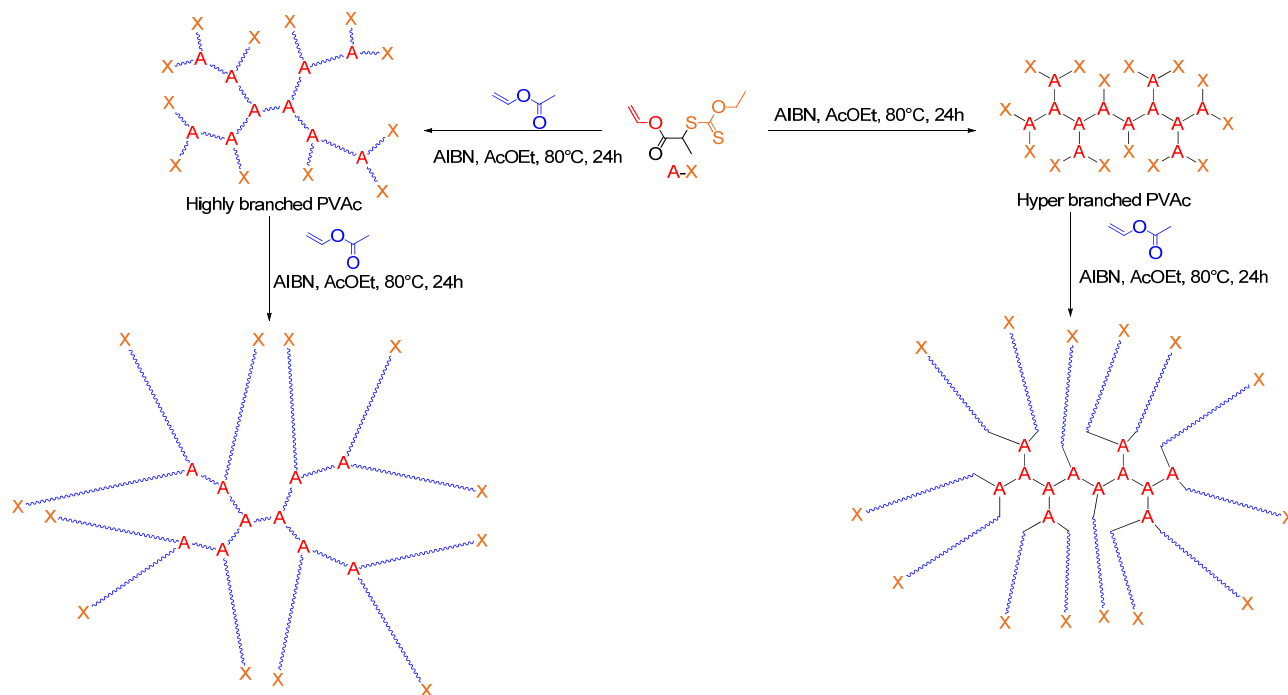
**Scheme 7.** Structure of R and Z-designed tri and tetra xanthate RAFT agents.



**Scheme 8.** Structure of  $\omega$ -functionalized xanthates.



**Scheme 9.** Synthesis of highly branched and hyperbranched poly(vinyl acetate) (PVAc) and the corresponding chain extension.



One last category of PVAc controlled architectures is end-functionalized PVAc, which can be synthesized by RAFT polymerization of VAc in the presence of a functional xanthate. The new functionality can extend the domain of application of PVAc by modifying its properties. For instance, Dufils *et al.* [53] developed a series of phosphonated xanthate agents (Scheme 9) allowing the controlled polymerization of VAc in the range 2000–20,000  $\text{g}\cdot\text{mol}^{-1}$  with good control of both molar masses and chain end fidelity, as revealed by MALDI-TOF spectrometry. In order to apply PVAc in extraction of metal ions in  $\text{scCO}_2$ , Zhang *et al.* [123] developed a bipyridine bis(xanthate) (X-bpy-X, Scheme 8) allowing the controlled polymerization of VAc. In this case, two polymer chains grow from the functional bis(xanthate), putting the bipyridine in the middle of the PVAc.

An elegant example of functional PVAc has been published by Smith *et al.* [62] with an  $\omega$ -amino-PVA obtained by RAFT polymerization of VAc. In order to overcome the incompatibility of the amine and xanthate functions, the authors developed a phthalimido xanthate [131] (Scheme 8) and controlled the polymerization of VAc up to 60,000  $\text{g}\cdot\text{mol}^{-1}$  with dispersities below 1.44. The terminal amine is revealed by hydrazinolysis of the phthalimide and  $\omega$ - $\text{NH}_2$  PVA can be obtained by saponification. Further reaction with Traut's and Ellman's reagents allows the preparation of  $\omega$ -thiol functionalized PVA, which can subsequently be conjugated to oligopeptides [133].

The new function introduced by the functional xanthate can also serve as a platform for further functionalization. Since the development of click chemistry, the azido function has become one of the most used functionalities for such a task. Quémener *et al.* [111] developed a azido-xanthate (N3-X1, Scheme 9) functionalized on the R group and used it to control the polymerization of VAc up to 35,000  $\text{g}\cdot\text{mol}^{-1}$  with dispersities under 1.18. The presence of the azido function was revealed by IR spectroscopy and indirectly by SEC after copper-catalyzed azide-alkyne coupling (CuAAC) with  $\omega$ -alkynyl-polystyrene showed no residual starting material. Chen *et al.* [128] followed the same strategy

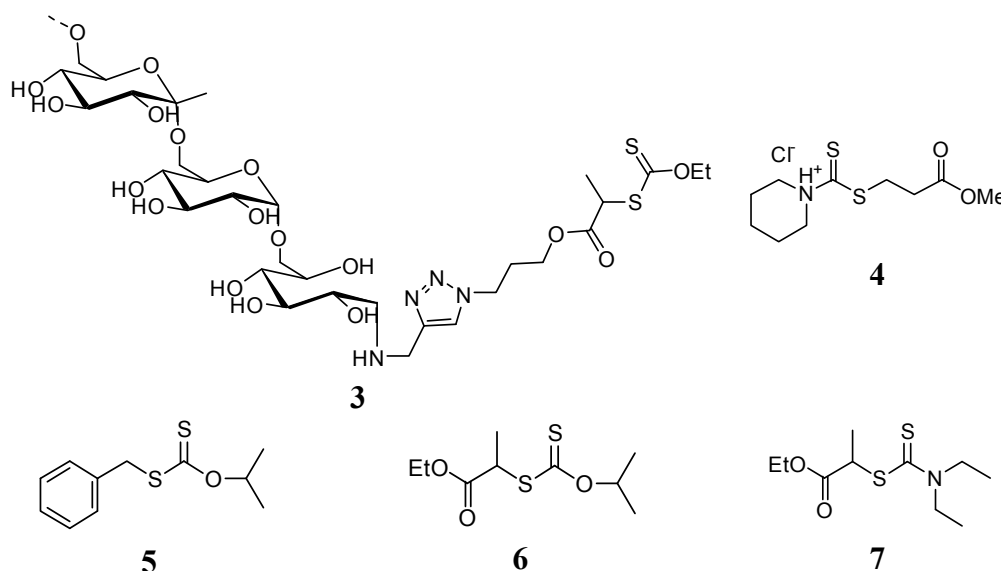
to introduce a fluorescent probe at the end of a PVAc by using a slightly different xanthate (N3-X2, Scheme 9) with the azido function linked to the Z group. While  $^1\text{H-NMR}$  and IR analysis of the CuAAC coupling product suggested that total conversion of the terminal azide function into triazole had taken place, UV-Vis analysis indicated only 69% of fluorescent functionalization, which was tentatively attributed to loss of the azide end group.

### 3. Heterogeneous Polymerizations

Heterogeneous processes, in particular emulsion polymerization, form by far the most important industrial source of poly(vinyl ester)s [1]. Despite this, there are relatively few reports of the RAFT polymerization of vinyl esters in heterogeneous media such as emulsion, suspension, or solid-supported polymerizations.

**Emulsion Polymerization.** The first emulsion polymerization of VAc in the presence of a RAFT agent was reported in 2008, with the use of a xanthate-modified dextran (**3**, Scheme 10) as a reactive stabilizer [115]. The dextran was first functionalized with an alkyne group, then alkyne-azide click chemistry was used to attach an azide-functional xanthate RAFT agent which had previously been shown to be effective in controlling the solution polymerization of VAc. In emulsion, however, relatively poor control over the polymerization was obtained. In particular, while an increase in  $M_n$  with conversion was observed, dispersities were very high (up to 5.6). Nevertheless, the emulsions were effectively stabilized using 2–6 wt % of xanthate-functionalized dextran, while similar concentrations of native or propargylamine-functionalized dextrans failed to stabilize the latex (Figure 1).

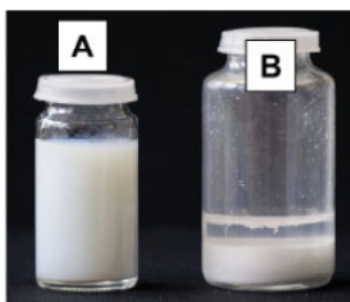
**Scheme 10.** RAFT agents used in emulsion polymerization of vinyl esters. Best control was obtained using dithiocarbamate **7**.



A more recent study [109] used an unusual dithiocarbamate RAFT agent carrying a primary methyl 3-propionyl leaving group (**4**, Scheme 10). Addition of the RAFT agent to emulsion polymerizations of VAc resulted in retardation of the polymerization kinetics, confirming its involvement in the reaction. A slight decrease in molecular weight was observed as the concentration of RAFT agent was increased, with dispersities ranging from 1.5 to 3.5. In all cases molecular weight in the presence of the

RAFT agent was greater than that obtained in the absence of the RAFT agent, which was ascribed to the suppression of chain transfer to polymer or monomer in RAFT polymerizations, as previously proposed by Schork *et al.* [60]. The primary nature of the leaving group and high molecular weights obtained during the polymerization suggest that the RAFT agent did not undergo addition-fragmentation chain transfer, although reversible addition to the C=S double bond may have taken place, causing the observed retardation.

**Figure 1.** Comparison of latex stability (1 day after polymerization). Latex **A**: 6 wt % xanthate-functionalized dextran. Latex **B**: 6 wt % native dextran. Reproduced with permission from reference [115].



Finally, Nomura *et al.* [134] compared the effectiveness of a series of xanthates and dithiocarbamates in controlling the emulsion polymerization of VAc. Polymerizations were moderately well controlled by *O*-isopropyl xanthates with *S*-benzyl (**5**, Scheme 10) or *S*-(ethyl 2-propionyl) (**6**) substituents, with good agreement between targeted and theoretical  $M_n$  and dispersities of around 1.6–2.0. Best results, however, were obtained using *N,N*-diethyl *S*-(ethyl 2-propionyl) dithiocarbamate (**7**), which gave a linear relationship between  $M_n$  and conversion and polydispersities of 1.4–1.5. The presence of terminal groups derived from the RAFT agent was confirmed by MALDI-TOF mass spectroscopy. The resulting emulsions were stable and comprised particles of average diameter 58 nm by DLS, with dispersity of 1.2.

**Miniemulsion Polymerization.** Miniemulsions, composed of droplets ranging from 50–500 nm in size, are more amenable to controlled radical polymerization than conventional emulsions, as polymerization occurs within the monomer droplets and thus transfer of reagents (specifically the control agent) across the aqueous phase is not required [135]. The controlled miniemulsion polymerization of VAc was reported independently by two groups in 2005 [87,88], both using MESA as chain transfer agent. Each group used a similar miniemulsion recipe containing SDS and hexadecane as cosurfactants, and reported dispersities of 1.2–1.7 (increasing with conversion) and molecular weights that increased as a function of conversion. The increase of dispersity with conversion was attributed to the loss of terminal xanthate functionality as a result of chain transfer reactions. The major difference between the two studies was the use of oil-soluble [87] or water-soluble [88] azo initiators. Use of an oil-soluble initiator, AIBN, led to good agreement between theoretical and experimental molecular weight, although high initiator concentrations were required in order to reach a limiting conversion of 80%. The use of water-soluble initiators resulted in faster kinetics and higher limiting conversions, but produced polymer with experimental molecular weight which was approximately double the expected value. This was attributed to the formation of VAc

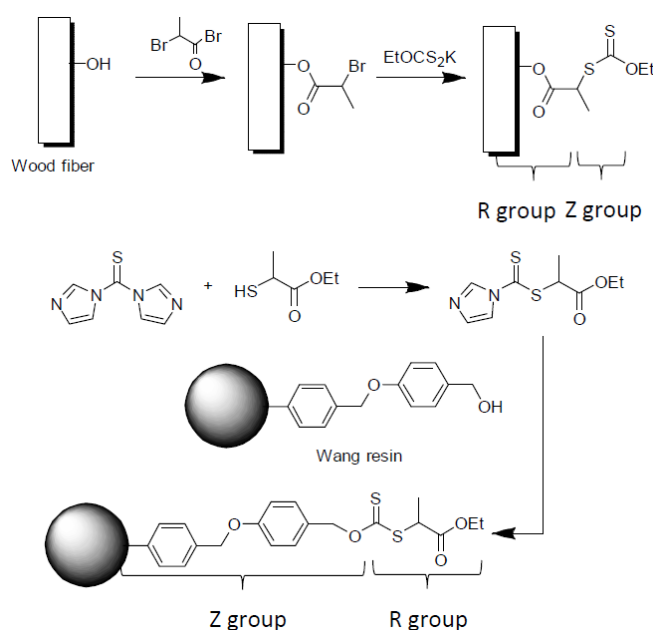
oligomers in the aqueous phase as a result of the use of a water-soluble initiator and the relatively high aqueous solubility of VAc. Both groups reported the formation of stable emulsions with particles of  $140 \pm 90$  nm (water soluble initiator) or  $220 \pm 20$  nm (oil soluble initiator).

A more recent study [113], however, found comparable levels of control over molecular weight and dispersity using either AIBN (oil-soluble) or potassium persulfate (KPS, water-soluble) initiators. In each case, molecular weight was approximately 20% greater than theory, while dispersity was comparable to previous studies. The polymerization proceeded more rapidly and to a higher final conversion in the presence of KPS than AIBN, which may reflect more efficient initiation of VAc by the sulfate radical anion compared to the cyanoisopropyl radical. This study used methyl (methoxycarbonothioyl)sulfanyl acetate (MMSA) in place of MESA.

**Suspension Polymerization.** The RAFT-mediated suspension polymerization of VAc was recently reported [136], using *N*-methyl-*N*-phenyl *S*-cyanomethyl dithiocarbamate as the chain transfer agent. Spherical particles with a relatively narrow size distribution were produced. While control over molecular weight was relatively poor, the resulting polymers could be used as macroRAFT agents for further chain extension.

**Solid-Supported Polymerization.** Solid-supported RAFT polymerizations of VAc have been carried out using xanthate-modified Wang resins [92] or wood fibers [137]. In each case, solution polymerization of VAc was carried out in the presence of both the solid supported RAFT agent and additional free RAFT agent. The two approaches differed in the nature of the attachment of the RAFT agent to the substrate. In the case of the Wang resin, attachment was via the Z group, allowing facile cleavage of the grafted polymer by heating the washed particles in a solution of *t*-amyl peroxyacetate. The objective of grafting from the wood fibers, however, was to create a firmly-bound coating of PVAc, hence attachment via the R group was chosen. The contrasting methods of functionalization are shown in Scheme 11.

**Scheme 11.** Preparation of solid supported RAFT agents.





Both approaches gave good control over molecular weight, but the best control over dispersity was achieved with the Wang resin, with dispersities of around 1.5 which could be reduced to as little as 1.15 by the addition of free EESP (see Scheme 4 for structure). By contrast, polymerization of VAc in the presence of modified wood fiber led to dispersities of around 1.8, even in the presence of free EESP. It should be noted that the polymerizations in the presence of modified wood fiber were carried out in bulk to conversions of around 80%, compared to less than 30% for the Wang resin polymerizations which were carried out in toluene solution.

#### 4. Copolymerization of Vinyl Esters

Copolymerization of vinyl esters with other monomers allows the modulation of properties such as solubility, hydrolytic stability and tacticity, providing access to combinations of properties which cannot be found in the respective homopolymers. Vinyl esters form part of a class of monomers termed “less activated monomers” (LAMs) which are characterized by electron-rich double bonds and lack of a radical-stabilizing substituent. As such, they are most readily copolymerized with other LAMs. Copolymerization with “more activated monomers” (MAMs) such as S or methyl acrylate (MA), which carry a radical-stabilizing substituent, generally results in substantial composition drift as the MAM is preferentially incorporated into the copolymer.

The application of RAFT polymerization to copolymerization of vinyl esters intensifies this preference for LAM/LAM copolymerization. Most RAFT agents which are effective for MAMs cause substantial retardation in LAM polymerizations, while those that are effective for LAMs have low chain transfer constants in MAM polymerization. Preferential consumption of the MAM during the copolymerization causes the comonomer composition to change from MAM-rich early in the copolymerization to LAM-rich at later stages. Thus it can be difficult to find a RAFT agent which provides effective control throughout the polymerization. If this challenge can be overcome, however, it is possible to exploit the composition drift to produce polymers with gradient and even block-like structures, consisting of a MAM-rich segment of near constant composition, a short transitional segment, and finally a segment of LAM homopolymer.

##### 4.1. Copolymerization with Less Activated Monomers

Most examples of RAFT copolymerization of vinyl esters involve copolymerizations with monomers of similar reactivity, such as other vinyl esters, vinyl lactams, and *N*-vinyl carbazole (NVK).

There are numerous examples of copolymerizations of VAc with other vinyl esters, frequently driven by a desire to introduce bulky groups into the polymer chain which will reduce polymer–polymer interactions and improve solubility in scCO<sub>2</sub>. Examples include copolymerizations with VBu [3,5], VPiv [4,6] and vinyl octanoate (VOc) [5]. In all cases, the composition of the copolymer closely matches that of the monomer feed, reflecting the similar reactivity of the vinyl ester double bonds. Control over molecular weight and dispersity is similar to that obtained with the corresponding homopolymers. When these polymers are used as stabilizers in the dispersion polymerization of *N*-vinyl pyrrolidone (NVP), the terminal xanthate group reacts with the growing poly(NVP) radicals to anchor the stabilizer to the polymer particles [3–6].

Also with the aim of increasing solubility in  $\text{scCO}_2$ , RAFT copolymerizations of VAc with the fluorinated vinyl esters VTFAc [7,9] and  $\text{CF}_3\text{VAc}$  [8] have been reported. The introduction of fluorine reduces the electron density of the double bond, with the result that these fluorinated vinyl esters show a tendency towards alternation in copolymerization with vinyl esters such as VAc (Table 1).

**Table 1.** Reactivity ratios of fluorinated vinyl esters in copolymerization with vinyl acetate (VAc).

Monomer	$r_{\text{VAc}}$	$r_{\text{fluorinated monomer}}$	azeotropic composition (% VAc)	Reference
VTFAc	0.60	0.32	37	[138]
$\text{CF}_3\text{VAc}$	0.25	0.20	48	[139]

The copolymerization of VTFAc and VAc has an azeotropic composition at 37% VAc, with some composition drift to be expected at monomer feeds on either side of this composition. In a conventional polymerization, this will result in the formation of a blend of polymers of varying compositions. In a controlled polymerization such as RAFT, however, the composition drift is expressed as a gradient in composition within each chain. All chains have a similar composition gradient, resulting in a more homogeneous product. Copolymerizations of VTFAc and VAc were well-controlled across the full range of compositions using Rhodixan A1 as RAFT agent, with dispersities of approximately 1.1–1.3 and  $M_n$  close to theoretical values. Lower dispersities ( $\sim 1.1$ ) were obtained for polymers of molecular weight around 4000 [7], while higher molecular weights ( $M_n = 15,000 \text{ g}\cdot\text{mol}^{-1}$ ) gave higher dispersities ( $D \sim 1.3$ ) [9], potentially indicating the occurrence of chain transfer to solvent (ethyl acetate), monomer or polymer. A parallel study of the VPiv/VTFAc copolymerization [9] gave good control of molecular weight and dispersities of around 1.1, reflecting the lower susceptibility of vinyl pivalate to undergo chain transfer reactions. The syndiotacticity of the VTFAc/VAc copolymers varied from 53% to 56% as the VTFAc content was increased from 0 to 100%. While this difference appears minor, small increases in syndiotacticity can have a dramatic effect on the gelation properties of PVA and the mechanical characteristics of the resulting hydrogels [140]. Thus copolymerization of VAc with VTFAc (and other monomers which display enhanced syndiotacticity such as VPiv [141,142] or vinyl diphenylacetate [141]) may provide a simple route to the preparation of PVA hydrogels with tunable properties.

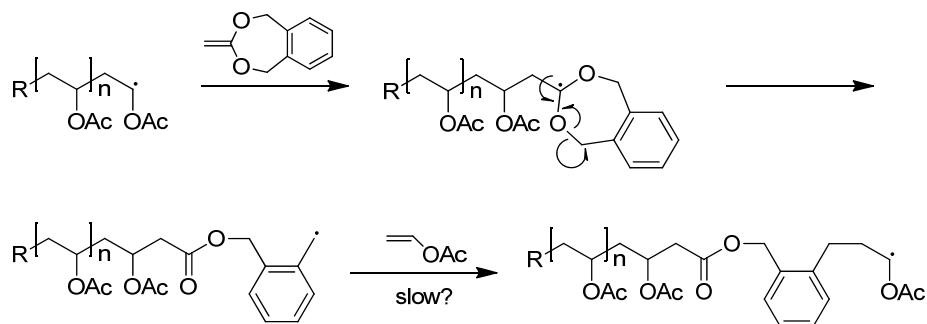
The trifluoromethyl group of  $\text{CF}_3\text{VAc}$  has an even stronger effect on the reactivity of the vinyl group, resulting in a strong tendency to alternate with VAc and greatly reduced ability to homopolymerize [8]. Nevertheless, good agreement was obtained between experimental and theoretical  $M_n$  for molecular weights up to 4000  $\text{g}\cdot\text{mol}^{-1}$  in Rhodixan A1-mediated copolymerizations of VAc and  $\text{CF}_3\text{VAc}$  containing up to 50%  $\text{CF}_3\text{VAc}$ , although dispersities increased from 1.2 to 1.5 and final conversion decreased from 77% to 29% as the concentration of  $\text{CF}_3\text{VAc}$  increased from 10 mol % to 50 mol % [8].

Moving beyond vinyl esters, Zhu *et al.* [143] have reported the copolymerization of NVK and VAc in the presence of *S*-benzyl *O*-ethyl xanthate at VAc monomer fractions ranging from 25% to 67%. Polymerizations proceeded to 80%–90% conversion in 48 h at 70 °C.  $M_n$  increased linearly with conversion, and was close to the theoretical value, while dispersities were in the range 1.3–1.35. Copolymers of NVK and VAc are enriched in NVK relative to the feed composition, as indicated by

reactivity ratios of 1.9 for NVK and 0.12 for VAc, which may result in significant composition drift during the polymerization. The use of RAFT will cause this composition drift to be expressed as a composition gradient within the polymer chains, resulting in a more homogeneous product than could be obtained in a conventional polymerization.

A final example of controlled radical copolymerization with vinyl esters is the copolymerization of VAc with the cyclic ketene acetal 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) [84]. BMDO polymerizes via a radical ring-opening mechanism which inserts ester groups into the polymer backbone (Scheme 12). While BMDO is relatively unreactive towards most MAMs, the use of VAc as a comonomer allowed the preparation of copolymers with BMDO contents only slightly lower than that of the monomer feed. Only low conversions of polymer could be achieved, with a maximum conversion of 45% obtained at 5% BMDO, decreasing to 18% at 30% BMDO. This may be due in part to the choice of toluene as a solvent, which undergoes degradative chain transfer to VAc (*i.e.*, chain transfer resulting in reduced molecular weight and inhibition as a result of slow addition of the solvent radical to the monomer) with a chain transfer constant of approximately  $3 \times 10^{-3}$  [144]. Further inhibition may be due to slow reinitiation of VAc by the benzylic ring-opened BMDO radical, by analogy with the slow addition of benzyl radical to VAc. The polymers produced could be chain extended with VAc (albeit with a substantial fraction of dead polymer) and degraded by hydrolysis of the backbone esters in refluxing KOH/MeOH. In a recently-published article [73], Hedir and coworkers overcame many of these limitations by copolymerization of VAc or VClAc with 2-methylene-1,3-dioxepane (MDO). This monomer is an analogue of BMDO, but lacks the aromatic ring substituent. The polyethylene-like ring-opened radical adds much more rapidly to VAc than the benzylic ring-opened radical of BMDO. Addition of a crosslinking agent, divinyl adipate (DVA) to the copolymerization resulted in the formation of hydrogels. The authors demonstrated degradation of the copolymers in methanolic potassium hydroxide, and were able to prepare poly(NVP-*block*-VAc) diblock copolymers and poly(VAc-*co*-MDO-*co*-DVA) core- poly(NVP) shell hydrogels through the use of a poly(NVP) macroxanthate.

**Scheme 12.** Radical ring-opening copolymerization of 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) with VAc [84].



#### 4.2. Copolymerization with More Activated Monomers

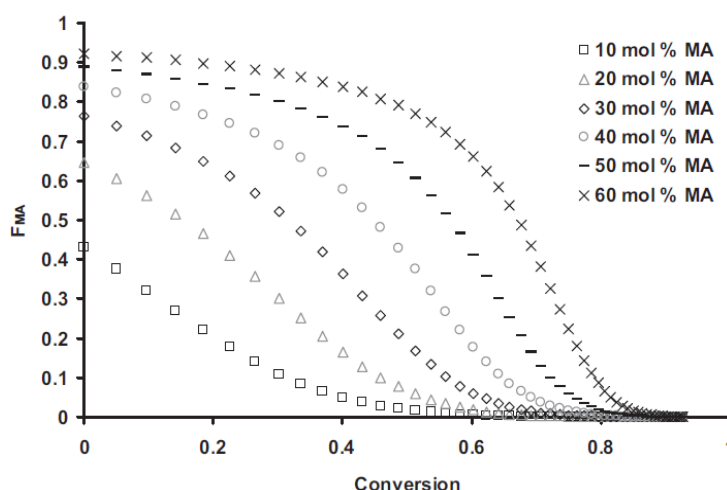
Compared to copolymerizations with LAMs, there are relatively few examples of RAFT copolymerizations of vinyl esters with more activated monomers, due to the difficulty of controlling these polymerizations. For example, copolymerization of acrylic acid and VAc in the presence of

benzyl dithiobenzoate, an effective RAFT agent for acrylic acid but strongly retarding for VAc, did not proceed beyond a limiting conversion of 32% [145], suggesting that the polymerization stopped once the acrylic acid was consumed.

A rare counterexample is the copolymerization of VAc with dibutyl maleate (DBM) [146]. This monomer pair forms a strictly alternating copolymer, due to the inability of DBM to homopolymerize and the strong preference of VAc-terminal radicals to add to DBM rather than VAc. Thus a 50:50 mixture of the two monomers displays no composition drift during polymerization and can be controlled using a xanthate RAFT agent, with molecular weights ranging from 2900–6400 g·mol<sup>−1</sup> and polydispersities ranging from 1.1 to 1.2. The alternating structure of the copolymer was confirmed by MALDI-TOF MS, which revealed polymers of composition (VAc-*alt*-DBM)<sub>n</sub>-VAc-xanthate as the major component of the mass distribution.

The strong composition gradients observed in copolymerizations of LAMs and MAMs have been turned to advantage in the case of MA [45,147] and *t*-butyl acrylate (*t*BA) [67,67,126] to prepare block-like copolymers in a one-pot process. CSIRO researchers reported the copolymerization of a mixture of *t*BA (24 mol %) and VAc (76 mol %) using the chain transfer agent *O*-pentafluorophenyl *S*-benzyl xanthate [67]. This chain transfer agent provides moderate control over the polymerization of *t*BA, with an apparent chain transfer constant of 2.7. The copolymerization proceeded to 68% conversion, and the polymer produced had a monomodal mass distribution with a final dispersity of 1.31. Given the strong difference in reactivity between alkyl acrylates and vinyl esters, the *t*BA should polymerize first to produce an initial block containing low levels of VAc, followed by homopolymerization of the residual VAc after all *t*BA was consumed.

**Figure 2.** Instantaneous copolymer composition as a function of conversion for copolymerizations of methyl acrylate (MA) ( $r_{MA} = 8.2$ ) and VAc ( $r_{VAc} = 0.17$ ). Reproduced with permission from reference [147].



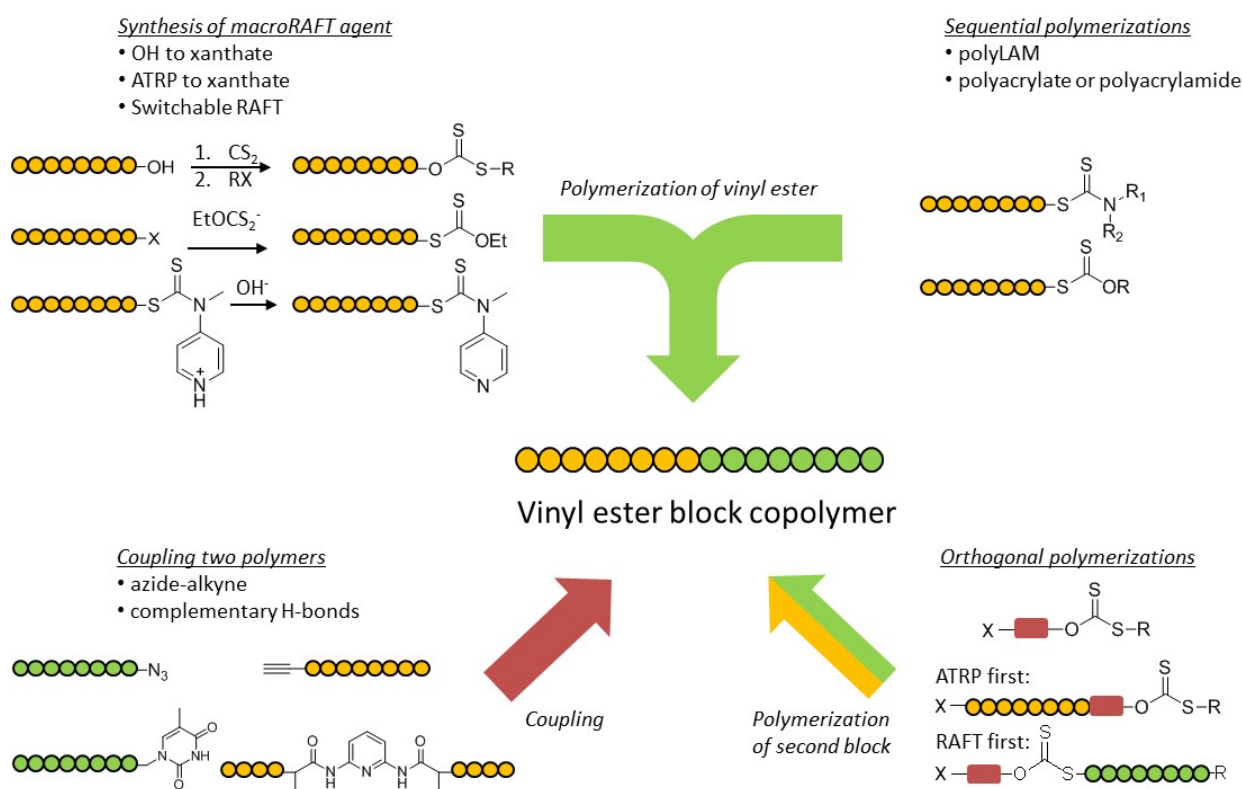
In subsequent work [45,147], the copolymerization with MA was reported in greater detail, this time using *O*-ethyl *S*-cyanomethyl xanthate as the RAFT agent. In a bulk copolymerization containing 34 mol % MA [45], copolymer containing 69 mol % MA with dispersity 1.54 was obtained at 50% conversion. At this stage, all MA had been consumed, and subsequent polymerization resulted in chain extension with VAc homopolymer. At 70% conversion, the polymer had a dispersity of 1.34 and an

overall MA content of 49 mol %. Copolymerizations containing up to 60 mol % MA could be controlled using this process [147], although the degree of control over the polymerization worsened as the MA content increased, both in terms of the dispersity of the final product (1.3 at 10% MA *vs.* 1.6 at 60% MA) and the agreement between theoretical and experimental molecular weight. Regular sampling of the reaction mixture allowed the determination of the instantaneous copolymer composition as a function of conversion (Figure 2), which should be expressed as a composition gradient in each polymer chain.

## 5. Block and Graft Copolymers

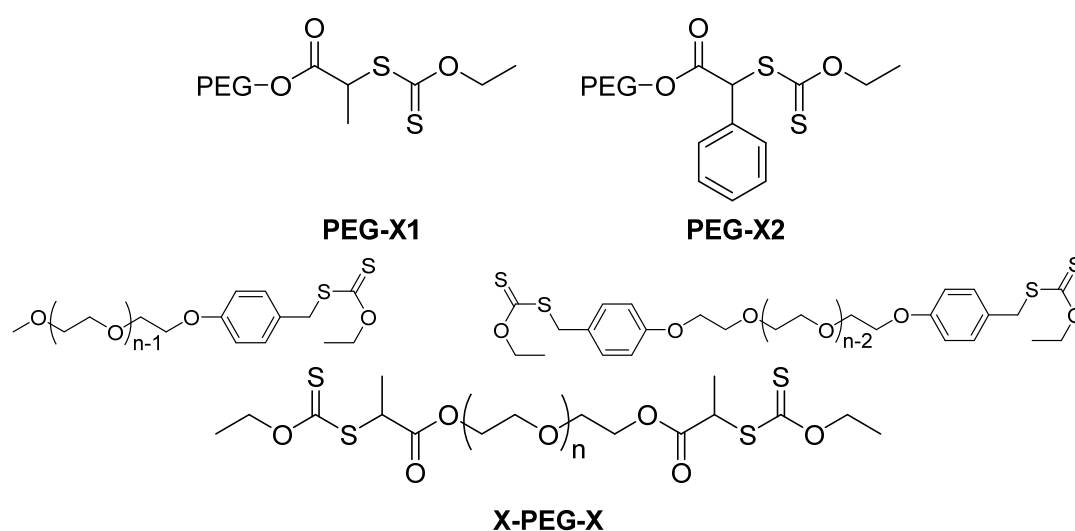
A key feature of RAFT polymerization is the ability to prepare block and graft copolymers by chain extension of a macroRAFT agent. Chain extension from poly(vinyl ester) macroRAFT agents presents particular challenges, however, due to the lack of stabilization of the poly(vinyl ester) macroradical. The alternative route, involving polymerization of a vinyl ester from a previously prepared macroRAFT agent, requires careful selection of the Z group, as only a limited number of Z groups are effective at controlling the polymerization of VAc. To address these challenges, numerous techniques have been developed for the preparation of a wide range of block and graft copolymers containing one or more vinyl ester blocks. These are summarized in Scheme 13, and can be broken down into four categories, *viz.*: (1) Preparation of a macroRAFT agent from a preformed polymer; (2) Use of a bifunctional RAFT agent which can also control an orthogonal polymerization in which the RAFT agent is unreactive; (3) Sequential polymerizations, using the product of the first polymerization as a macroRAFT agent for the second polymerization; and (4) Coupling two pre-formed polymers, typically using azide-alkyne click chemistry.

**Scheme 13.** Synthetic routes to vinyl ester block copolymers.



**Preparation of a MacroRAFT Agent from a Preformed Polymer.** *O*-ethyl xanthate-terminated poly(ethylene glycol) (PEG-xanthate) is the most commonly used macroRAFT agent in chain extension of PVAc to yield amphiphilic copolymers. In 2007, based on their previous work revealing the selective initialization in RAFT polymerization of VAc for specific leaving groups [106], Pound *et al.* [107] modified commercial mono- or dihydroxyl end-functional PEGs into macroCTAs by introduction of a xanthate moiety, and then used them in RAFT-mediated polymerization of VAc. PEG-*b*-PVAc diblock copolymer was obtained when the macroCTA had a propionyl ester leaving group (PEG-X1, Scheme 14), whereas under the same experimental conditions the macroCTA with a phenylacetyl ester leaving group (PEG-X2, Scheme 14) inhibited the polymerization.

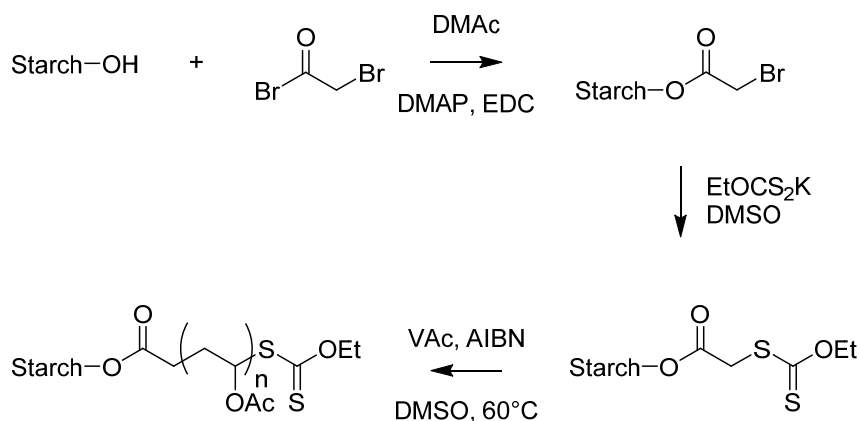
**Scheme 14.** PEG-functionalized RAFT agents.



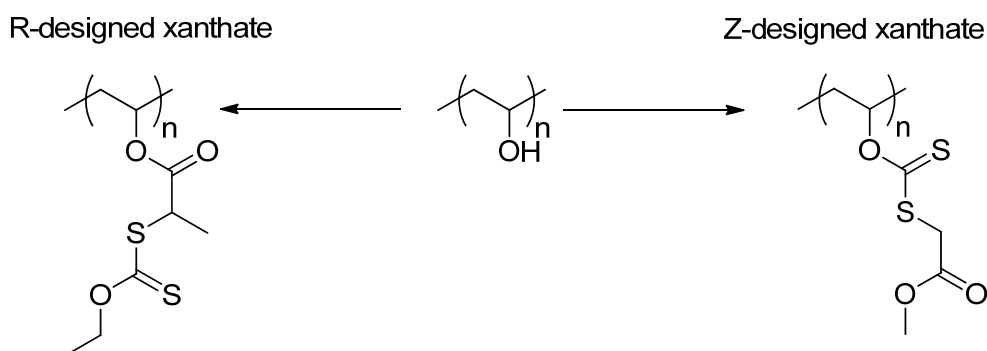
Later in 2009, Tong *et al.* reported a series of well-defined poly(ethylene oxide)-*b*-poly(VAc) (PEO-*b*-PVAc) and PVAc-*b*-PEO-*b*-PVAc with different molecular weights of both PVAc and PEO blocks were synthesized through RAFT polymerization by using a new type of xanthate end-functionalized PEO-CTA, in which the xanthate group was connected to PEO with an ether linkage (Scheme 14) [129]. The corresponding well-defined PEO-*b*-PVA and PVA-*b*-PEO-*b*-PVA were then achieved by hydrolysis of these PVAc-containing polymer precursors in the presence of *n*-propylamine. Chen *et al.* [118] also synthesized a series of oligo(VAc)-*block*-poly(EO)-*block*-oligo(VAc) copolymers (X-OVAc-*b*-PEG-*b*-OVAc-X, where X stands for xanthate group) in THF by using X-PEG-X as macroRAFT agent (Scheme 14).

Lipscomb *et al.* [31] used the same macroCTAs to obtain a series of poly(vinyl ester)/poly(ethylene oxide) triblock copolymers (PVAc-*b*-PEO-*b*-PVAc, PVPiv-*b*-PEO-*b*-PVPiv, PVBz-*b*-PEO-*b*-PVBz). The thermal, morphological, and mechanical properties of the triblock copolymers were examined.

A similar route was used to prepare amphiphilic starch-*g*-PVAc [148]. A starch-based xanthate was synthesized by successive reactions of starch with bromoacetyl bromide and potassium ethyl xanthate (Scheme 15). The graft polymer was prepared by RAFT polymerization of VAc in DMSO at 60 °C. The resulting copolymer self-assembled into micelles in aqueous solution.

**Scheme 15.** Preparation of a starch-based RAFT agent and starch-PVAc graft copolymer.

MacroRAFT agents can also be prepared through the chemical modification of a polymer derived from RAFT. For instance, Bernard *et al.* [149] synthesized two different types of PVA modified with xanthate lateral groups in order to obtain PVA-*g*-PVAc copolymers using both R-group and Z-group approaches (Scheme 16). The Z strategy led to partially functionalized PVA which was insoluble in VAc, making further bulk VAc polymerization impossible. Polymerization was attempted in dioxane but no reaction was observed even after 5 days at 60 °C. The macro RAFT agents obtained via the R strategy allowed the polymerization of VAc in bulk, but the resulting PVAc combs were accompanied by linear polymer chains at low to moderate conversion and a high molecular weight shoulder.

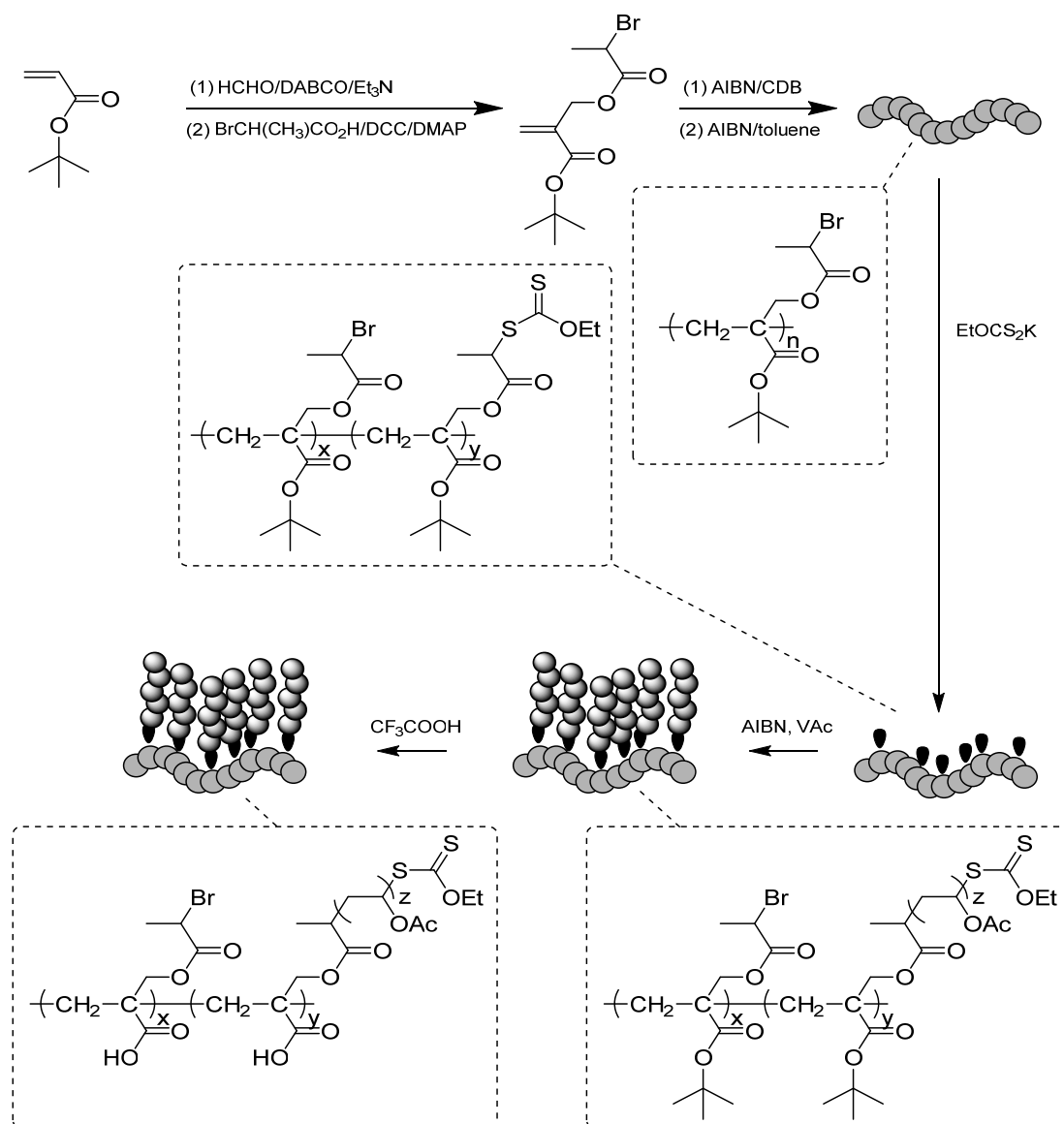
**Scheme 16.** Strategy for the R and Z-designed PVAc combs.

In an alternative fashion, a new Br-containing acrylate monomer, namely *tert*-butyl-2-((2-bromopropanoyloxy) methyl) acrylate, was synthesized and polymerized via RAFT to obtain a well-defined homopolymer [150]. Then it was transformed into xanthate-functional macroRAFT agent to polymerize with VAc and yield graft copolymer (Scheme 17). Selective acidic hydrolysis of the backbone *t*-butoxy groups gave PAA-*g*-PVAc amphiphilic copolymers which aggregated in water and brine to form spherical micelles. The diameters of the micelles increased with increasing ionic strength of the solution.

ATRP precursors were also transformed into macroRAFT agents by Shipp and co-workers [151]. For instance, P(*t*BA), synthesized via ATRP, was allowed to react with sodium *O*-ethyl xanthate to transform the bromine end group into a xanthate moiety. The resulting macroRAFT agent was used to prepare P(*t*BA)-PVAc diblock copolymers. Matyjaszewski *et al.* synthesized a macroRAFT agent

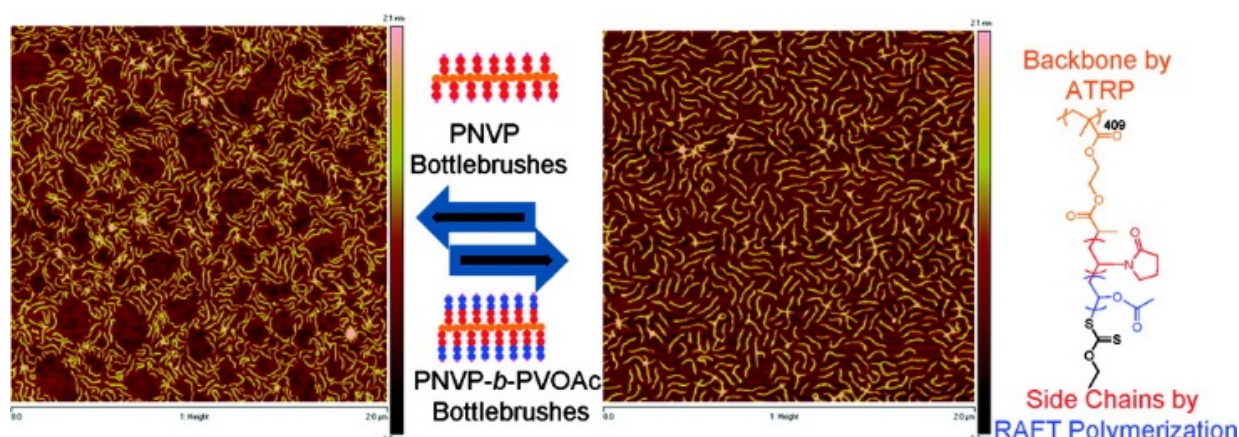
(poly(2-((2-ethylxanthatepropanoyl)oxy)ethyl methacrylate, PXPEM) by attaching xanthate chain transfer agents onto each monomeric unit of poly (2-hydroxyethyl methacrylate) (PHEMA) prepared by ATRP. Polymerization of VAc [152] or sequential polymerizations of NVP and VAc [153] in the presence of PXPEM allowed the formation of molecular brushes (Figure 3).

**Scheme 17.** Synthesis of PAA-g-PVAc amphiphilic graft copolymer. Reproduced with permission from reference [150].



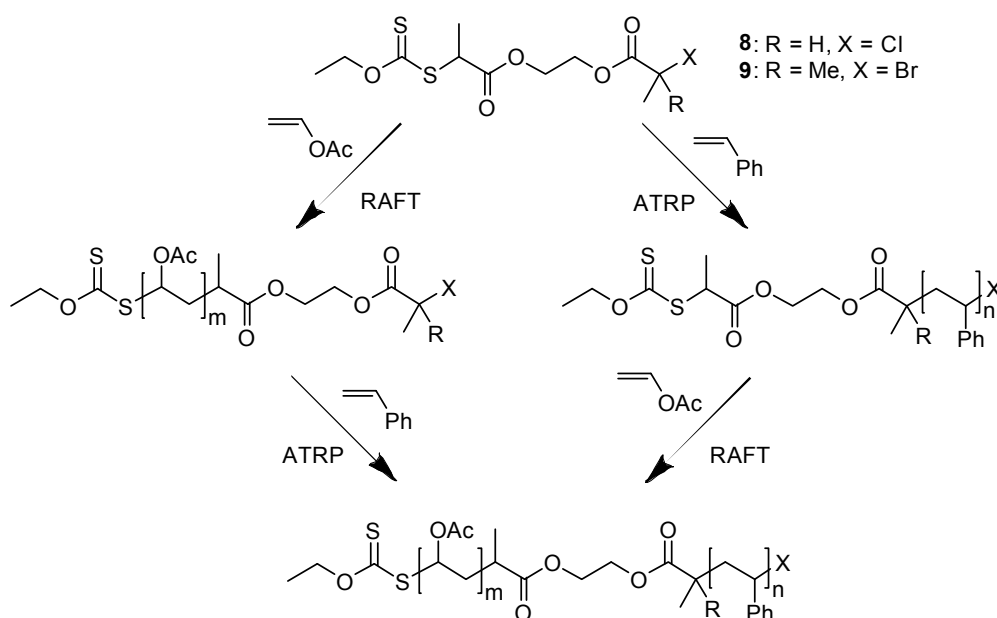


**Figure 3.** Molecular brushes by RAFT polymerization from an ATRP-derived macroxanthate. Reproduced with permission from Nese *et al. ACS Macro Lett.* **2011**, *1*, 227 [153]. Copyright 2011 American Chemical Society.



**Orthogonal Polymerizations.** An alternative process for the synthesis of PVAc-containing block copolymers was proposed by Matyjaszewski and co-workers in 2011 [116]. They employed the successive RAFT polymerization of VAc and ATRP of (meth)acrylates or styrenic monomers with a bromoxanthate iniferter (Scheme 18) and allowed the preparation of well-defined ( $1.15 \leq D \leq 1.24$ ) block copolymers.

**Scheme 18.** Synthesis of PVAc containing block copolymers by sequential ATRP and RAFT copolymerization.

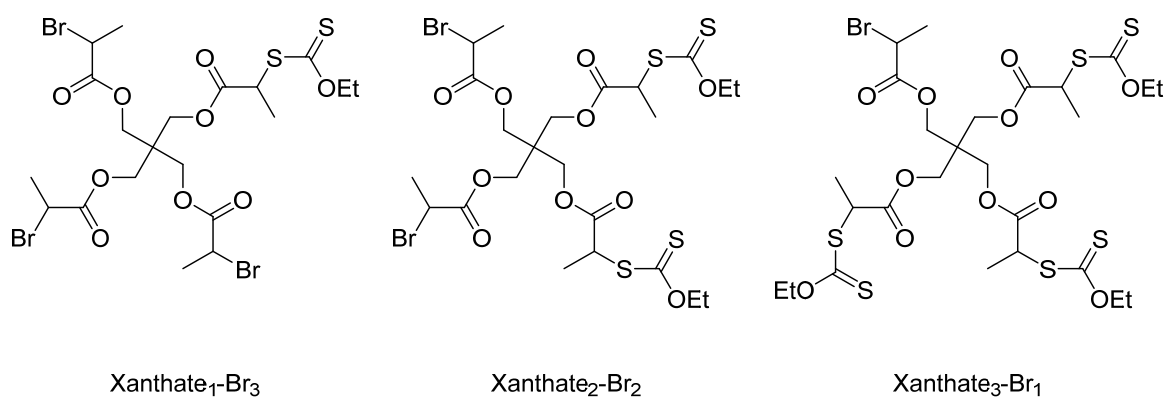


The same year, two difunctional compounds, *S*-(2-chloropropionyethoxycarbonylmethyl) *O*-ethyl xanthate (**8**) and *S*-(2-bromo-2-methylpropionyethoxycarbonylmethyl) *O*-ethyl xanthate (**9**), with an activated halide group and a xanthate group in the molecule were synthesized [108]. Thus, **8** was first used to mediate the radical polymerization of VAc, followed by ATRP of S, while **9** was used first to initiate the ATRP of S, followed by the RAFT polymerization of VAc. The obtained results indicate

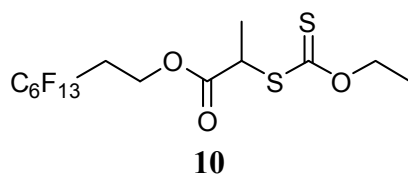
that either the radical polymerization of S or that of VAc was controlled, and well-defined PVAc-*b*-PS was obtained. However, in the latter case, chain transfer to xanthate during S polymerization cannot be ruled out considering the established moderate transfer constant of the PS propagating radical to *O*-ethyl xanthates ( $0.5 < C_{tr} < 0.8$ ) [154].

Later, three tetrafunctional bromoxanthate agents (Xanthate<sub>3</sub>-Br, Xanthate<sub>2</sub>-Br<sub>2</sub>, and Xanthate-Br<sub>3</sub>, Scheme 19) were synthesized [120], and then the PS<sub>*n*</sub>-*b*-PVAc<sub>4-*n*</sub> (*n* = 1, 2, and 3) miktoarm star-block copolymers containing PS and PVAc chains with controlled structures were successfully prepared by successive RAFT and ATRP chain-extension experiments using VAc and S as the second monomers, respectively.

**Scheme 19.** Tetrafunctional xanthate<sub>*n*</sub>-Br<sub>4-*n*</sub> agents for preparation of miktoarm star-block copolymers PVAc<sub>*n*</sub>-*b*-PS<sub>4-*n*</sub>.



**Sequential RAFT Polymerizations.** For the copolymerization of VAc with less activated monomers such as vinyl esters (VPiv [30,124], VBz [30,124], VNDec [71], VClAc [34], VTFAc [9]) and NVP [153,155,156], the process was carried out in two steps. The first segment (PVAc or PVP) was synthesized via RAFT polymerization by using xanthate or dithionodisulfide [71], and then the second monomer (VAc or other vinyl esters) was added to obtain the corresponding block copolymers. Most of the copolymers were well-controlled. In another contribution [121], Ameduri and co-workers synthesized a fluorinated xanthate, **10**, and successfully used it in the radical copolymerization of vinylidene fluoride (VDF) and 3,3,3-trifluoropropene (TFP). Subsequently, well-controlled poly(VDF-*co*-TFP)-*b*-oligo(VAc) was prepared, which could be hydrolyzed to form poly(VDF-*co*-TFP)-*b*-oligo(vinyl alcohol).

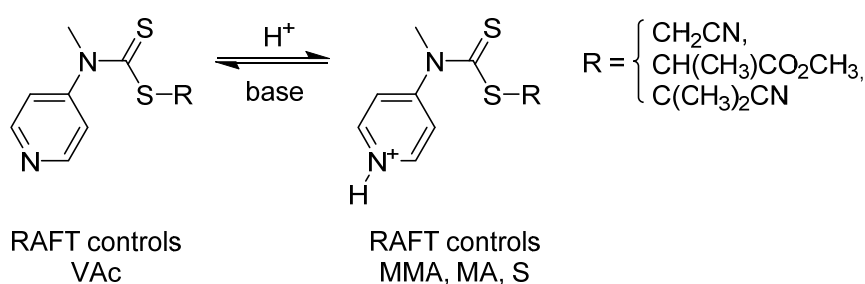


There are only limited examples of RAFT agents which can allow the controlled copolymerization of VAc with more activated monomers. In order to successfully synthesize a MAM-LAM block copolymer by RAFT, the MAM monomer should be polymerized first. This is because of the poor leaving ability of the P(LAM) group; P(LAM) macroRAFT agents have low chain transfer constants in MAM polymerizations. Generally, xanthates or *N*-aryl dithiocarbamates are used, as these provide

good control over the vinyl ester block, and moderate control over the MAM block. Xanthates [157,158] were used to produce block copolymers of poly(1,1-dihydroperfluorooctylacrylate) and poly(VAc) (PFOA-*b*-PVAc) for use as CO<sub>2</sub>-philic surfactants. Our group reported the use of Rhodixan A1 to produce poly(*N,N*-dimethyl acrylamide)-block-poly(vinyl acetate) (PDMA-*b*-PVAc) with relatively narrow dispersities for the same application [82]. An *N,N*-diaryldithiocarbamate, 2-(diethylmalonyl) *N,N'*-diphenyldithiocarbamate [159] was used to prepare PS-*b*-PVAc, with moderate control over the PS block (chain transfer constant of ~2.7) and good control over the PVAc block (chain transfer constant of ~26). In addition dithioester and trithiocarbonate [94] were employed to prepare poly(butyl acrylate-*b*-VAc), although with significant retardation of the VAc polymerization, and diselenocarbonate [68] was used to prepare P(*t*BA)-PVAc diblock copolymer.

The other approach to incorporate PVAc segments in controlled architectures with MAMs is through the use of switchable RAFT agents. This approach was demonstrated with the use of *N*-4-pyridinyl-*N*-methylthiocarbamate derivatives [42,103,104] to prepare polyMAM-block-polyLAMs. The *N*-4-pyridinyl-*N*-methylthiocarbamate provide effective control over polymerization of LAMs and when protonated also provide excellent control over the polymerization of MAMs (Scheme 20).

**Scheme 20.** Switchable RAFT agents.



#### *Coupling Two Polymers—Typically by Click Chemistry*

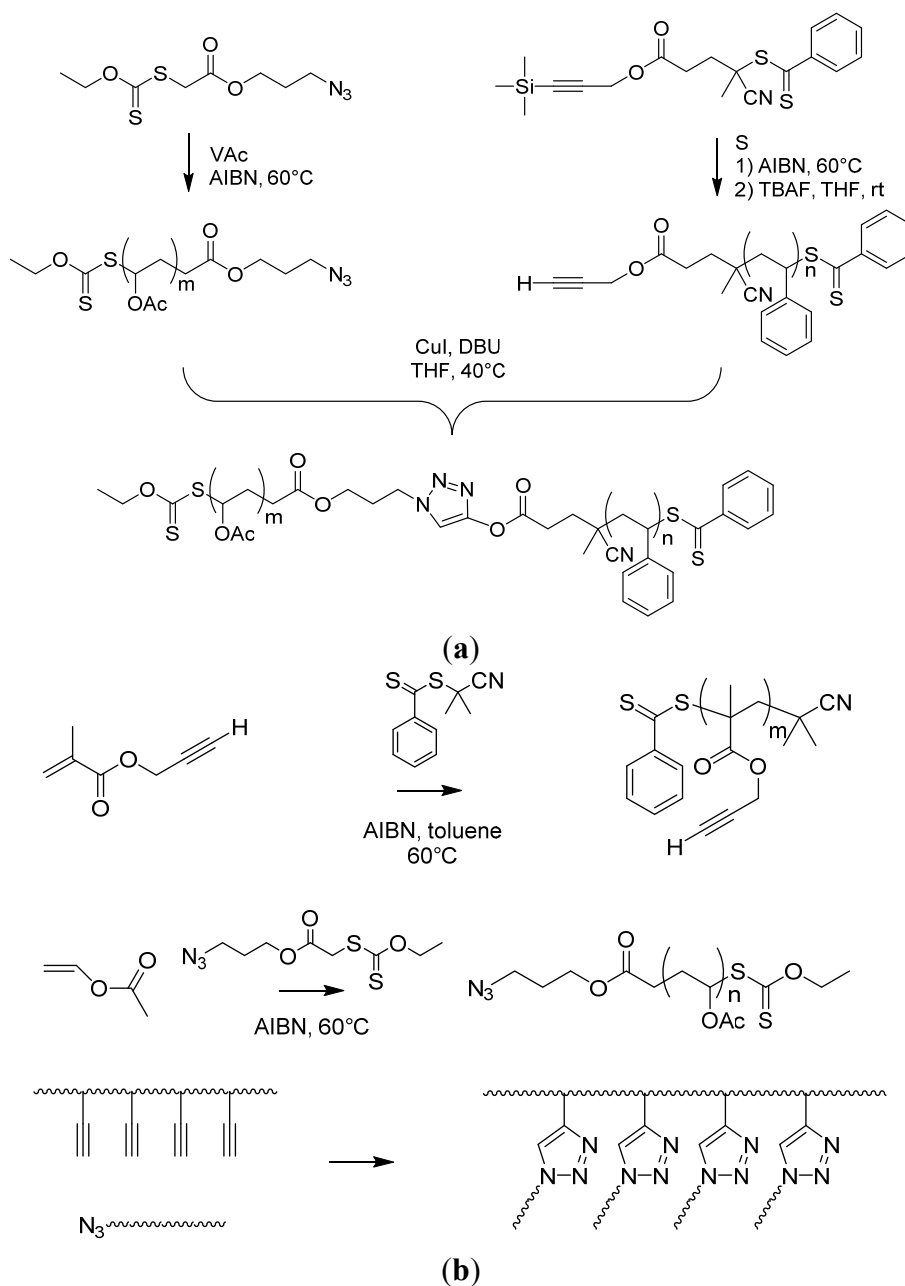
With the introduction of “click” chemistry, PVAc-based copolymers like PS-*b*-PVAc have been successfully achieved. Stenzel and coworkers [111] synthesized PVAc and PS with terminal azide and alkyne group respectively through RAFT polymerization by using functional RAFT agents. Well-defined block copolymer, PS-*b*-PVAc was prepared via “click” chemistry between these two homopolymers (Scheme 21a). Later they used a similar approach to prepare well-controlled amphiphilic glycopolymer poly(VAc)-block-poly(6-*O*-methacryloyl mannose) [112] as well as PVAc comb polymers [117] (Scheme 21b).

A similar method was used to prepare alkyne-functional poly(VAc) and subsequently couple it to azide-functionalized starch [148]. The resulting starch-PVAc conjugate formed spherical micelles in aqueous solution with average diameter of *ca.* 100 nm.

While the previous examples involved azide or alkyne functionalization of the R-group, Zhu *et al.* prepared a RAFT agent with an azide functionality on the Z group, namely *O*-(2-azido-ethyl) *S*-benzyl dithiocarbonate (AEBDC, Scheme 22). Use of AEBDC to mediate RAFT polymerization of VAc gave rise to well-defined PVAc homopolymer with an azido group [128]. This was coupled to an  $\alpha$ -alkyne functionalized, chromophore-bearing polystyrene which had been prepared using the RAFT agent 2-(3-ethynylphenylazophenoxy carbonyl)prop-2-yl-9H-carbazole-9-carbodithioate (EACDT) to obtain

a PS-*b*-PVAc block copolymer [130]. The use of the Z group as a site for azide functionalization allows a straightforward synthesis of the functionalized RAFT agent in 2 steps from chloroethanol, but has the disadvantage that the two blocks of the copolymer are linked by a thermally and hydrolytically labile xanthate group.

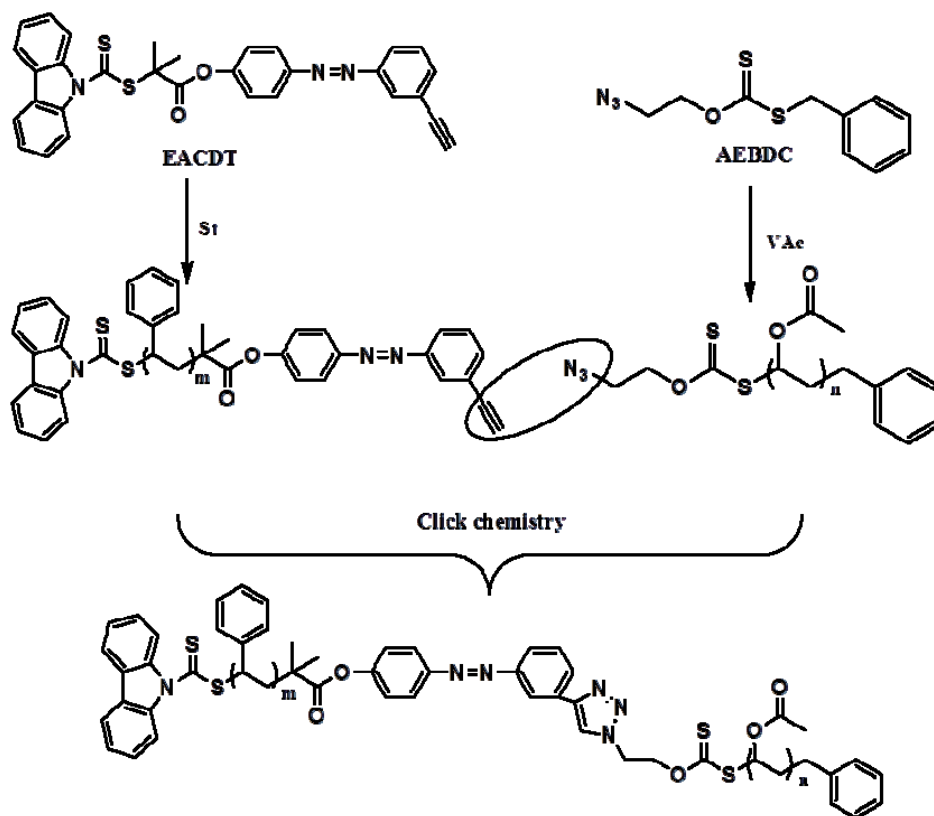
**Scheme 21.** Click coupling of azide-functional PVAc to alkyne-functional polymer to prepare block (a) and comb (b) polymers.



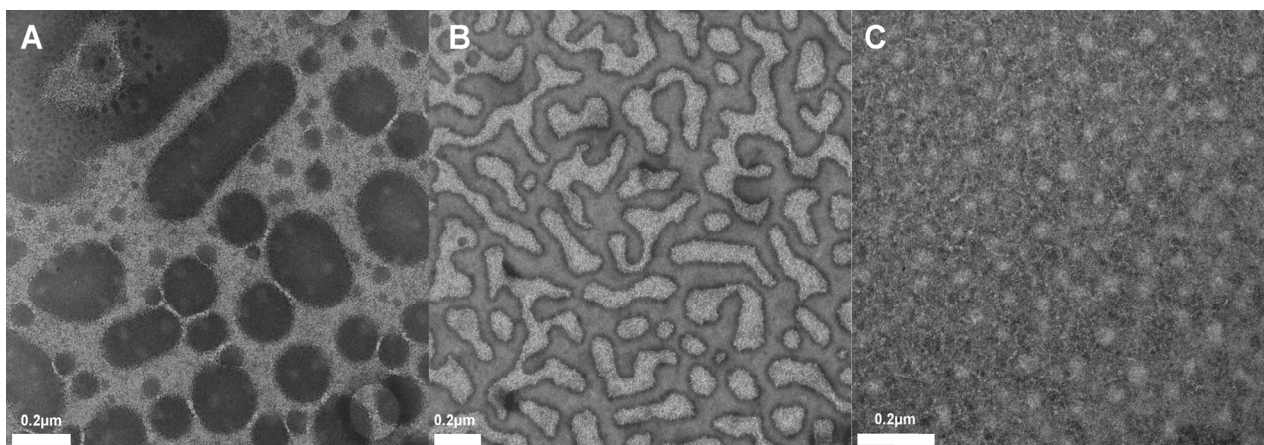
Bernard *et al.* prepared PVAc-(PS)<sub>2</sub> miktoarm star polymers through a non-covalent approach incorporating complementary hydrogen-bonding units [119]. A thymine-functional xanthate was synthesized and used to prepare thymine-functional PVAc. This was then mixed with PS which contained a central 2,6-diamidopyridine (DAP) unit. In both cases the H-bonding units were incorporated into the R group of the RAFT agent to avoid loss of functionality through hydrolysis. The

equilibrium constant of association between the two polymers was measured as  $80\text{--}90\text{ L}\cdot\text{mol}^{-1}$ , and blends of the two polymers formed microphase-separated structures consistent with a block copolymer. By contrast, blends of DAP-functionalized PS with unfunctionalized PVAc resulted in poorly stabilized, macrophase-separated domains (Figure 4).

**Scheme 22.** Click coupling of PVAc and polystyrene via a fluorescent linker.



**Figure 4.** TEM pictures of 1/1 blend of unfunctionalized PVAc (uPVAc)/2,6-diaminopyridine-functionalized polystyrene (PS-DAP-PS) (A), 0.5/0.5/1 blend uPVAc/thymine-functionalized PVAc (THY-PVAc)/PS-DAP-PS (B), and 1/1 blend of THY-PVAc/PS-DAP-PS (C). Reproduced with permission from Chen *et al. Macromolecules* **2010**, *43*, 5981 [119]. Copyright 2010 American Chemical Society.



## 6. Applications of RAFT Poly(vinyl ester)s

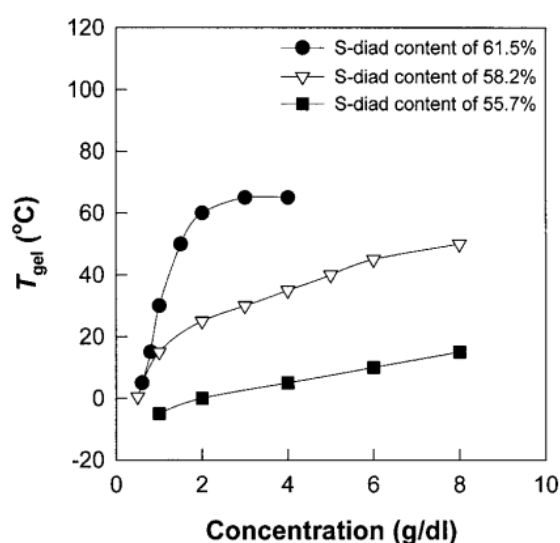
Poly(vinyl ester)s find applications in many fields including paper sizing, adhesives, paints, and construction materials. RAFT has been successfully applied to the synthesis of poly(vinyl ester)-based polymers with various architectures and compositions, as described above. While it will not replace conventional radical polymerization for the preparation of commodity poly(vinyl ester)s, RAFT is a powerful tool for the preparation of (co)polymers for specialized applications that require good control of architecture.

### 6.1. Poly(vinyl ester)s as Precursors to PVA

PVAc is a precursor of PVA which is the largest volume water-soluble polymer produced commercially. PVA is a material with diverse applications, FDA approval for several uses and clinical application in humans [160]. In addition PVA demonstrates bioadhesive properties and is increasingly used in pharmaceutical industries due to its non-toxic, non-carcinogenic properties [161–164].

RAFT polymerization was used to obtain the first example of PVA with controlled molecular weight and terminal amine functionality for bioconjugation [62]. Moreover it has been shown that the RAFT mechanism can be used to prepare highly syndiotactic polymer, allowing the formation of stronger physical hydrogels [69,165]. Syndiotactic PVA has different properties to atactic PVA as a result of increased intermolecular hydrogen bonding between the adjacent chains. Figure 5 illustrates the effect of syndiotacticity on gelation temperature. The solution of high molecular weight syndiotactic PVA (HMW s-PVA) with higher syndiotacticity was gelled at higher temperature and had larger gel region in the sol-gel diagram than atactic PVA of similar molecular weight.

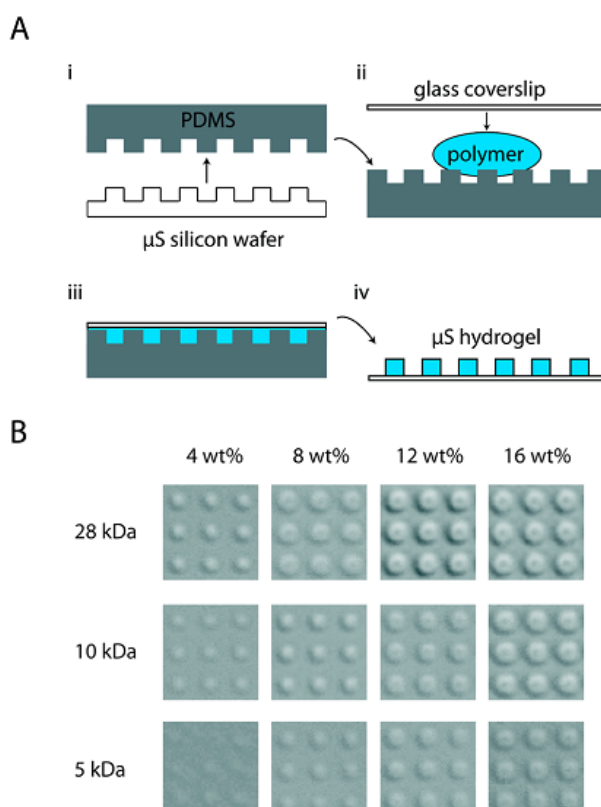
**Figure 5.** Gelation temperature of HMW s-PVA/DMSO/water solution measured by test tube tilting method. Reproduced with permission from Choi *et al. Macromolecules* **2001**, *34*, 2964 [165]. Copyright 2001 American Chemical Society.



Hydrogels of PVA are three-dimensional polymer networks with interesting properties for biotechnology and biomedicine. Zelikin *et al.* [166] have investigated physical hydrogels of PVA as biodegradable surface-adhered materials for substrate-mediated drug release devices. PVA chains with

narrow polydispersities (1.1–1.2) and molecular weights of 5, 10, and 28 kDa have been synthesized via RAFT. These polymers formed robust hydrogel matrices while undergoing gradual erosion suitable for delayed release. The hydrogels were loaded with enzymes to achieve *in situ* conversion of an externally added prodrug, thus giving rise to surface-adhered enzymatic microreactors. Microtransfer molding ( $\mu$ TM) was used to assemble the surface-adhered PVA hydrogels (Figure 6). Retention of the enzymatic cargo within microstructured hydrogels and conversion of model prodrugs has been characterized in depth using polymer molecular weight and concentration of polymer solution used for assembly of hydrogels as tools of control over properties of the matrix. The assembled biointerfaces demonstrated controlled degradation and durability of enzymatic activity with lifetimes of at least one week and the possibility to tune these properties by varying the molecular weight of the PVA. This process was developed further by functionalization of the adhered PVA with Traut's reagent, followed by treatment with an activated disulfide of thiocholesterol to form a cholesterol-functionalized hydrogel [167]. Alternatively, the use of  $\omega$ -thiol functional PVA allowed conjugation of the PVA with oligopeptides by thiol-disulfide exchange, either before or after formation of surface-adhered hydrogels [133].

**Figure 6.** (A) Schematic illustration of the assembly of microstructured ( $\mu$ S) PVA hydrogels. (i) PDMS stamps are produced on a silicon wafer with 2  $\mu$ m sized features; (ii) the polymer solution is placed between a PDMS stamp and a coverslip; (iii) fills the cavities of the stamp; and (iv) undergoes initial dehydration affording coverslip-adhered  $\mu$ S PVA thin films upon detachment of the coverslip. Subsequent polymer hydrogelation is achieved via polymer coagulation using aqueous  $\text{Na}_2\text{SO}_4$ . (B) DIC micrographs of surface-adhered  $\mu$ S PVA hydrogels prepared using polymers with varied molecular weights (5, 10, and 28 kDa) and solutions with polymer content from 4 to 16 wt %. Reproduced with permission from Fejerskov *et al. Langmuir* **2012**, 29, 344 [166]. Copyright 2012 American Chemical Society.

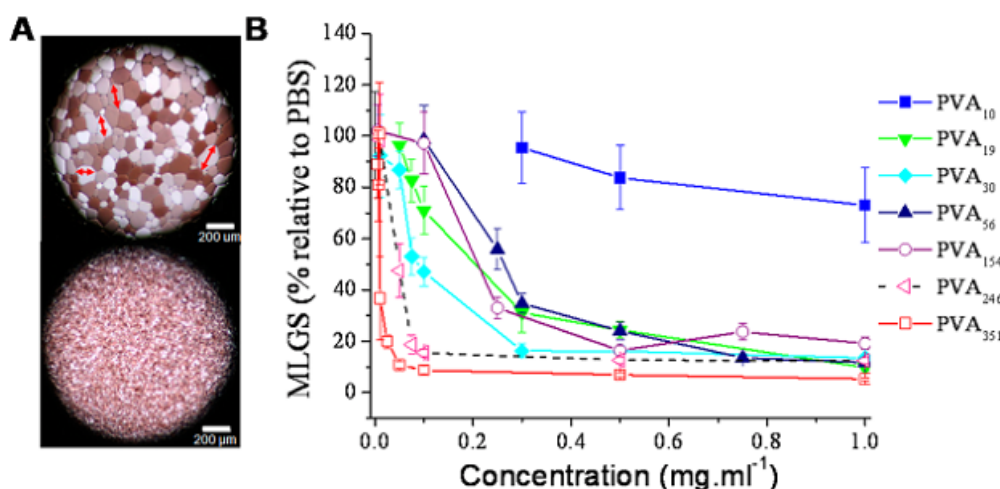




PVP-*b*-PVAc amphiphilic block copolymers have been used to stabilize suspension polymerization for making crosslinked poly(VNDec/ethylene glycol dimethacrylate) microspheres [168]. Kostov and co-workers [121] synthesized a new fluorinated surfactant derived from block copolymers of VAc and the fluoroalkenes vinylidene fluoride (VDF) and 3,3,3-trifluoropropene (TFP). After hydrolysis of the PVAc block, the copolymers P(VDF-*co*-TFP)-*b*-PVA and PVA-*b*-P(VDF-*co*-TFP) showed good solubility in water and surface tension comparable to that of ammonium perfluorooctanoate surfactant.

Congdon *et al.* [74] have demonstrated the potential of RAFT for applications involving VAc as polymeric mimics of antifreeze (glyco)proteins. PVA is the most effective synthetic polymer for inhibition of ice recrystallization. The reasons for the reactivity of PVA compared to other macromolecules bearing hydroxyl groups are still unknown. The formation and growth of ice is a serious problem in many technological processes such as storage and distribution of human tissue for regenerative and transplantation medicine [169,170]. RAFT was used to synthesise well-defined polymers in order to understand the role of molecular weight and the tolerance for structural modification such as hydrophobicity on the antifreeze activity. Previous studies have used commercially available PVA which is polydisperse and poorly characterized. The critical chain length at which PVA begins to inhibit ice recrystallization was between 10 and 20 repeat units. This minimum length was essential for strong interactions with ice surface. Increasing the chain length further gave rise to increased activity which was maintained at concentrations as low as 0.05 mg·mL<sup>-1</sup> (Figure 7).

**Figure 7.** Ice recrystallization inhibition activity of PVA homopolymers as measured by the splat assay. (A) Example micrographs showing ice crystals grown in PBS alone (upper) and with PVA351, 1 mg·mL<sup>-1</sup>; (B) Ice recrystallization inhibition activity as a function of polymer concentration. MLGS = mean largest grain size relative to a PBS control, expressed as %. Error bars represent the standard deviation from at least three measurements. Reproduced with permission from *et al. Biomacromolecules* 2013, 14, 1578 [74]. Copyright 2013 American Chemical Society.



Incorporation of either hydrophilic or hydrophobic functional groups by means of comonomers led to a reduction in activity above approximately 20 mol %. The solution conformation of inhibitor and

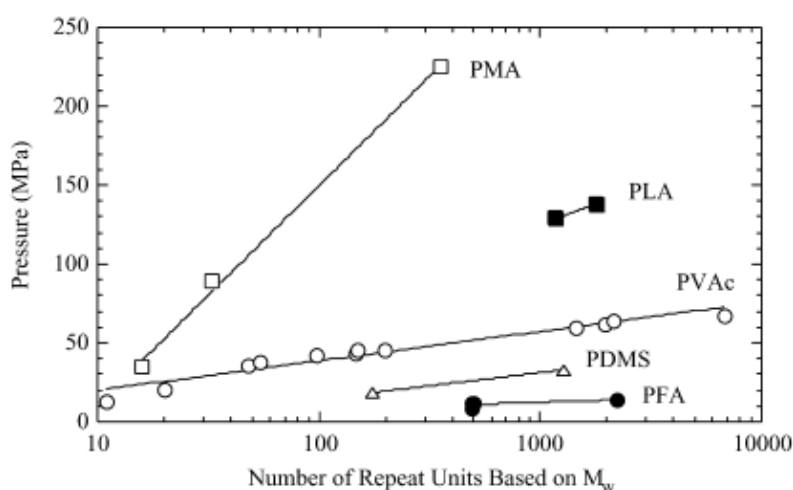


orientation of hydrophobic (water repelling units) is fundamental for inhibition of ice recrystallization and thus control of polymer architecture is crucial for the design of efficient cryoprotectors.

## 6.2. CO<sub>2</sub>-Philic Polymers and Surfactants

Over the last decade precision polymers of poly(vinyl ester)s have caught the attention of a good part of the scCO<sub>2</sub> research community. Supercritical CO<sub>2</sub> is one of the few solvents not regulated as a volatile organic solvent by the U.S. Environmental Protection Agency. In addition its cost is low and it possess moderate critical conditions, *i.e.*,  $T_c = 31.1\text{ }^{\circ}\text{C}$ ,  $P_c = 7.38\text{ MPa}$ ,  $\rho_c = 0.468\text{ g}\cdot\text{cm}^{-3}$ . Nevertheless, despite numerous attractive features and widespread applications, scCO<sub>2</sub> is generally a poor solvent because of its very low dielectric constant and polarizability per volume. CO<sub>2</sub> is a thermodynamically good solvent only for relatively non-polar low molecular weight compounds or fluorinated poly(meth)acrylates. To a lesser extent, perfluoropolyethers and poly(dimethylsiloxane) also show significant solubilities in scCO<sub>2</sub>. These polymers all have weak polymer–polymer interactions, as illustrated by their low surface tensions [171]. This is the principal driving force to solubilize polymers in scCO<sub>2</sub>. Additional factors such as the entropy of mixing and favorable polymer–solvent enthalpic interactions—principally based on Lewis acid–Lewis base (LA–LB) interactions—play a secondary role. In this regard, PVAc is of great interest as its acetate groups can act as Lewis bases while polymer–polymer interactions remain moderate [172]. Due to their strong and multidentate LA–LB interactions with CO<sub>2</sub> and the existence of a cooperative hydrogen bond, PVAc and vinyl ester based polymers are an attractive alternative to fluorinated and silicon-based materials (see Figure 8).

**Figure 8.** Cloud point pressure at ~5% polymer concentration and 298 K for binary mixtures of CO<sub>2</sub> with PMA, poly(lactide) (PLA), PVAc, poly(dimethyl siloxane) (PDMS), and poly(fluoroalkyl acrylate) (PFA) as a function of number of repeat units based on  $M_w$ . Reproduced with permission from reference [173].



In their pioneering work, Rindfleisch *et al.* observed, at approximately 35 °C, a cloud point pressure around 700 bar for 5 wt % of PVAc ( $M_n = 125,000\text{ g}\cdot\text{mol}^{-1}$ ) in scCO<sub>2</sub> [173,174]. In later work, 5 wt % polymer was also identified as the cloud point pressure maximum [175]. However PVAc is only moderately CO<sub>2</sub>-philic compared to fluoropolymers and polysiloxanes due to its stronger

polymer–polymer interactions. Therefore a significant decrease of solubility is observed with increasing molar mass [171]. Controlled radical polymerization methods, among them the RAFT process, are thus the method of choice to control the polymerization of non-conjugated monomers such as VAc and to evaluate accurately the effect of degree of polymerization on solubility. Thus, at a CO<sub>2</sub> density of 0.88 g·cm<sup>−3</sup> (*i.e.*, 22 MPa and 40 °C), 1 wt % of PVAc<sub>1.8k</sub>-Xa (Xa standing for the *O*-ethyl xanthate end of Rhodixan A1) was fully soluble. At 0.94 g·cm<sup>−3</sup>, 0.81 wt % of PVAc<sub>3.8k</sub>-Xa was solubilized while only 0.38 wt % of PVAc<sub>5.8k</sub>-Xa was detected at the same density [82].

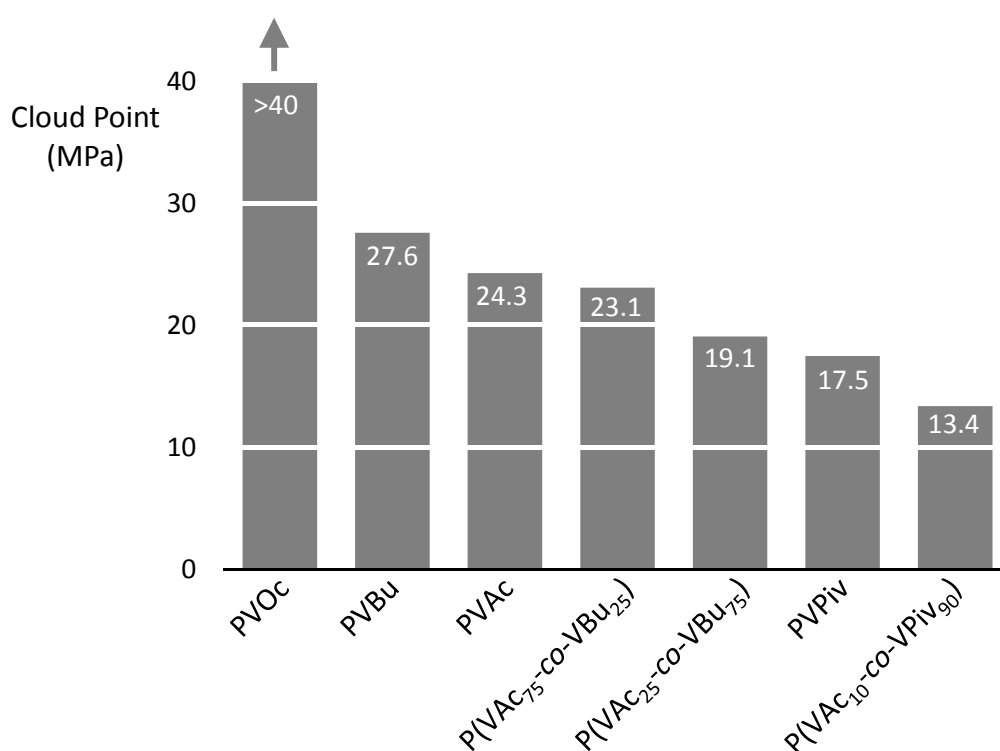
Along with the chain length, the nature of the chain end group may play an important role on the solubility of polymers in scCO<sub>2</sub>. Hence, the xanthate group was suggested to significantly lower the solubility of P(VAc-*alt*-DBM) copolymers as concluded from a comparison between samples synthesized by telomerization and by RAFT polymerization [146]. On the contrary, other studies demonstrated no substantial differences of solubility in scCO<sub>2</sub> for a xanthate-capped PVAc (PVAc<sub>3.8k</sub>-Xa) and a xanthate-free equivalent (PVAc<sub>4.2k</sub>-H) since they were respectively soluble in proportions of 0.89 wt % and 0.87 wt % at 35 MPa [82]. In addition, the xanthate can be turned into a solubility enhancer via the introduction of a fluorinated Z-group [68]. As an example, incorporation of a C<sub>6</sub>F<sub>13</sub> moiety at the  $\omega$ -end of the synthesized (co)polymers significantly increased the solubility of PVAc<sub>3.8k</sub>-FXa: 1 wt % of this sample was soluble at conditions down to 30 MPa and 40 °C. At higher molecular weights, these differences were less marked as the influence of the terminal group was weaker. Additionally, topology effects were studied and revealed the positive impact of branching on the solubility of PVAc [122].

As depicted in Figure 9, other vinyl esters were less soluble in scCO<sub>2</sub>. Therefore, different strategies, based on the synthesis of copolymer, have been described to enhance the solubility of vinyl esters (and more specifically of PVAc). To do so, a large palette of monomers has been suggested in the literature. By varying the vinyl ester group, linear aliphatic or branched structures, and fluorinated moieties were thus demonstrated to successfully enhance the solubility of PVAc-based copolymers in binary or ternary mixtures of scCO<sub>2</sub>. Those strategies aim at increasing the entropy of mixing of PVAc-based copolymers or at enhancing polymer–scCO<sub>2</sub> enthalpic interactions (potentially through the decrease of polymer–polymer interactions).

Therefore, VAc was copolymerized with sterically-hindered comonomers including other vinyl ester and maleate monomers. Using VBu, the cloud point pressure of a 50:50 copolymer of VAc and VBu ( $M_n = 2400$  g·mol<sup>−1</sup>) at 40 °C and 0.2 % wt was observed at 172 bar, which was 14 bar lower compared to a PVAc of equivalent  $M_n$  [3]. In a ternary mixture of polymer (5 % wt), CO<sub>2</sub> and NVP (15 % wt) at 35 °C, the decrease in pressures was even in the order of 53 bars between a PVAc ( $M_n = 9600$  g·mol<sup>−1</sup>) and 25:75 VAc:VBu copolymer ( $M_n = 9900$  g·mol<sup>−1</sup>) [5]. In each case, the monomer ratio 25:75 was most favorable. These enhancements of solubility were attributed to a higher free volume as a result of the lower  $T_g$  of the copolymer (−6 °C against 23 °C for the PVAc sample). At equivalent  $M_n$ , increasing the side chain length from VBu to VOc even shifted the cloud point pressure to 182 bar for a 75:25 copolymer of VAc and VOc [5]. Using the same heuristics, the solubility of a 50–50 alternating copolymer of VAc and DBM ( $M_n = 2400$  g·mol<sup>−1</sup>) was evaluated [146]. The cloud point pressure at 35 °C and 0.2 % wt was observed around 190 bar which was quite close to the aforementioned equivalent PVAc sample. The attribution of these enhanced solubilities solely to the entropy of mixing is controversial. It is difficult to decouple the effects arising from the entropy of

mixing and from lower polymer–polymer interactions induced by steric hindrance. A good example of this is provided by the case of VPiv. In their study on the solubility of copolymers of VAc and VPiv, Birkin *et al.* demonstrated that a 10:90 copolymer with a  $M_n$  of  $8900 \text{ g}\cdot\text{mol}^{-1}$  showed a phase transition around 134 bar and  $35^\circ\text{C}$ , which represents the lowest cloud point pressure for this type of copolymer [4]. This was related to enhanced entropy of mixing while the reported  $T_g$  was approximately  $65^\circ\text{C}$ —higher than the  $T_g$  of PVAc itself. In this case at least, it is clear that entropy of mixing does not provide a sufficient explanation. Interestingly, a PVPiv homopolymer of equivalent  $M_n$  was more  $\text{CO}_2$ -soluble than PVAc, contrary to PVBu and PVOC homopolymers [5].

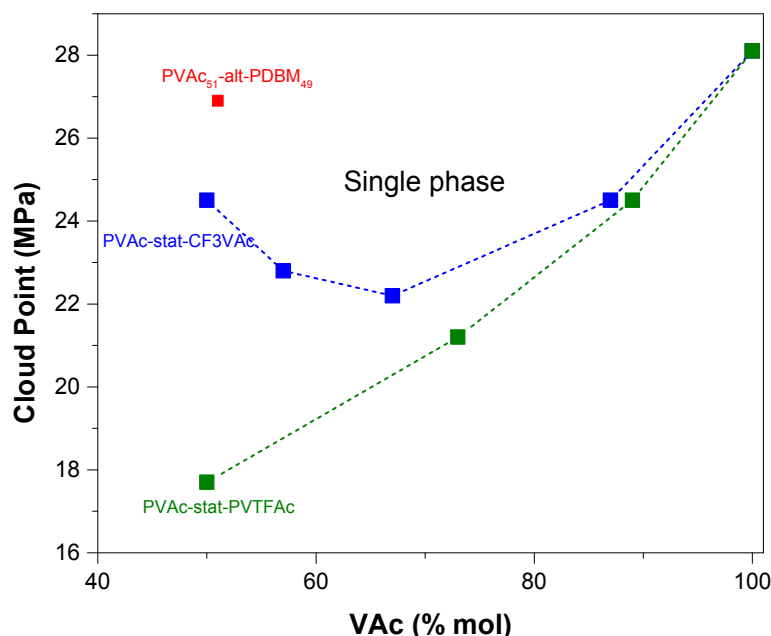
**Figure 9.** Cloud point pressure at ~5% polymer concentration and 15% *N*-vinylpyrrolidone at 308 K for ternary mixtures of  $\text{CO}_2$  with PVAc, PVBu, PVOC and PVPiv, and copolymers that enhance  $\text{CO}_2$  solubility with  $M_n$  near 10 k.



More recently other strategies have focused on the enhancement of polymer– $\text{scCO}_2$  enthalpic interactions. Such a goal can be reached by reducing polymer–polymer interactions. Thus the incorporation of the fluorinated monomer, VTFAc, in PVAc- and PVPiv-based polymers dramatically increased their solubility (see Figure 10) [7,9]. Both DFT calculations and surface tension measurements demonstrated that this effect arises mainly from a decrease of polymer–polymer interactions while at the same time a slight decrease of polymer– $\text{CO}_2$  interactions was calculated. However, these copolymers are extremely sensitive to both hydrolysis and temperature, which limits their potential application. The use of  $\text{CF}_3\text{VAc}$  can circumvent those drawbacks [8]. The presence of a trifluoromethyl group on the alpha position of the acetate group lowers the surface tension of the polymer chains without hindering the formation of acetate– $\text{CO}_2$  complexes or reducing thermal or chemical stability. For this copolymer the lowest  $P_{\text{cloud}}$  was observed at a VAc– $\text{CF}_3\text{VAc}$  molar

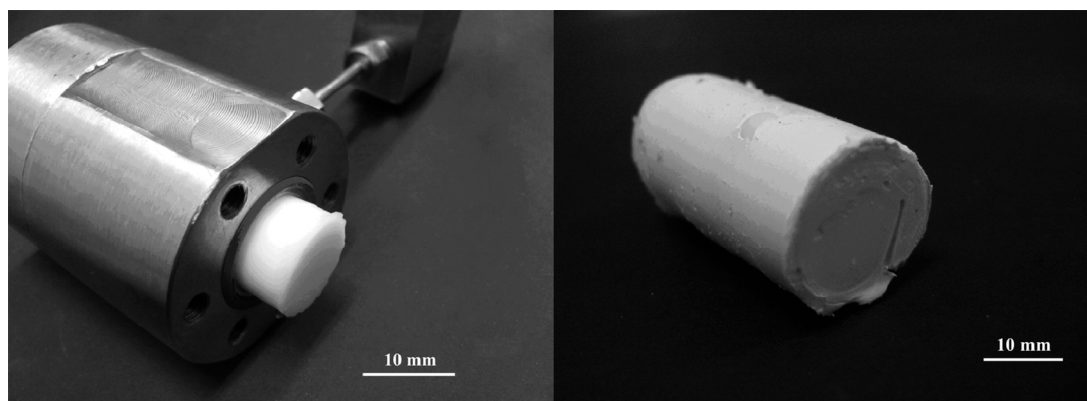
composition of 66:33 (see Figure 10) [8]. Once again this effect results from the decrease of polymer–polymer interactions while preserving an equivalent level of polymer–solvent interactions. In both cases, the observed cloud points are lower than that of poly(VAc-*alt*-DBM).

**Figure 10.** Cloud point pressure of P(VAc-*stat*-CF<sub>3</sub>VAc), P(VAc-*stat*-PVTFAc), P(VAc-*alt*-DBM), (0.2 wt % of polymer at 40 °C) as a function of VAc molar percentage.



While poly(vinyl ester)s exhibit moderate solubilities under mild conditions in scCO<sub>2</sub>, their use as CO<sub>2</sub>-philic building blocks in macromolecular engineering has scarcely been reported. To date, there are only a few examples using RAFT agents such as PDMA [82], PEG [118], or PVTFAc [9] -based amphiphilic diblock PVAc copolymers. Chen *et al.* [118] synthesized a series of oligo(VAc)-block-poly(EO)-block-oligo(VAc) which were extremely effective in the production of C/W emulsions with enhanced stability, leading to porous emulsion-templated materials based on polyacrylamide (Figure 11).

**Figure 11.** Photograph of a low-density C/W emulsion templated PAM-based materials. The materials obtained conform closely to the cylindrical interior of the reaction vessel. Reproduced with permission from Chen *et al.* *Macromolecules* **2010**, *43*, 9355 [118]. Copyright 2010 American Chemical Society.



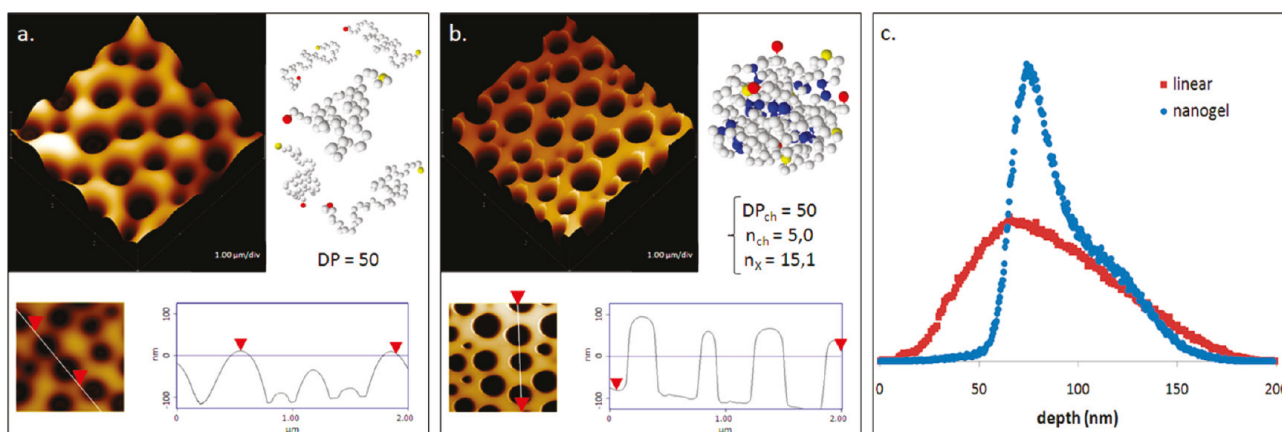
Macromolecular surfactants can be used to extract metal ions in scCO<sub>2</sub>. While liquid or supercritical CO<sub>2</sub> is an attractive alternative to conventional solvent for extraction, direct extraction of metal ions in neat scCO<sub>2</sub> is impossible because of its low solvent power. When metal ions are chelated with suitable organic ligands, their solubility can be significantly increased. Some highly CO<sub>2</sub>-philic fluorinated or siloxane-based ligands are in removing various metals from solid and liquid matrices [176–179]. Zhang *et al.* [123] have developed an extraction method using RAFT polymerization in order to functionalize a bipyridine group with VAc oligomers. Their results show that the solubility of the functional polymer was lower than that of unfunctionalized PVAc of similar molecular weight, and decreased with increasing molecular weight. The lowest cloud point was observed at 16.3 MPa with  $M_{n,GPC} = 1900 \text{ g}\cdot\text{mol}^{-1}$ . The extraction efficiency reached 98% for Ni<sup>2+</sup> complexes and 88% for Co<sup>2+</sup> and Cu<sup>2+</sup> complexes at 25 °C.

### 6.3. Other Applications

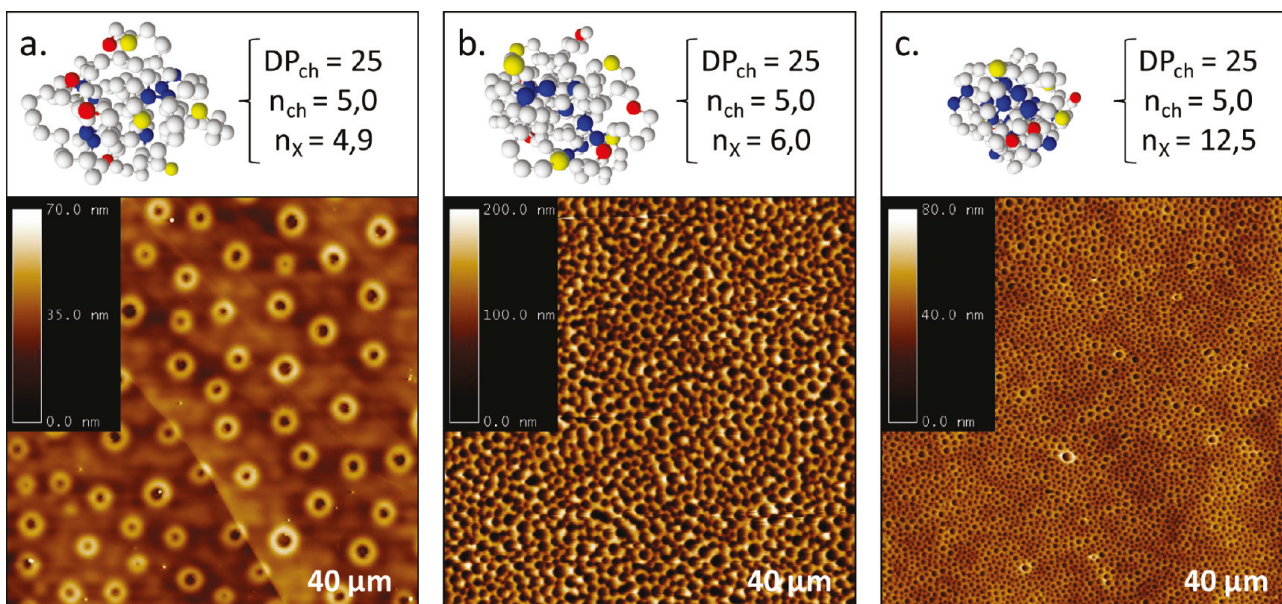
The design of branched PVAc by RAFT has also allowed the synthesis of nanogels by controlled radical crosslinking copolymerization (CRCC) [180]. VAc was copolymerized with divinyl adipate as crosslinker with similar structure. The resulting nanogels with different crosslinking densities were used to prepare porous films [181]. The goal was to compare the influence of their internal structure on the surface topography and also to compare the structure of porous surfaces made by same linear homologues with equivalent degree of polymerization. The network structure of nanogels with smaller chain length enhanced the patterning of the topography of the porous surface. However, linear PVAc with higher chain length compared to their crosslinked homologs gave rise to porous surfaces while PVAc nanogels constituted of primary chains having the same length gave films with deeper and better-defined voids. These results suggest that the network structure is highly influenced by the degree of polymerization and the crosslinking density (Figures 12 and 13).

The properties of natural wood fibers can be improved by grafting polymers onto the surface of fibers. The polymer coating can then enhance the resistance of wood against external stressors such as humidity, fungi, and fire. Since the first surface-initiated controlled radical polymerization (SI-CRP) from polysaccharide [182], many studies have been realized by synthesizing various polymers by SI-CRP from cellulose nanocrystals [183], fibers [184] or Whatman filter paper [185,186]. Tastet *et al.* [137] have proceeded to the grafting of poly(PVAc, PnBA, PS, and cationic amphiphilic PS-based copolymers from raw wood fibers. In this application, PVAc is of interest for its adhesive properties. The polymer grafting was performed by RAFT after derivatizing the wood fibers with xanthate chain transfer agents in such a way that the R group was covalently bound to the surface of the wood fibers. This strategy allowed straightforward grafting of the polymer chain to the fiber surface. The polymer-fiber attachment proved to be stable under humidity and temperature stress. These studies demonstrate the versatility of RAFT for the control of well-defined vinyl ester based (co)polymers.

**Figure 12.** Atomic force microscopy (AFM) topography images and profiles for films prepared on graphite by spin coating nanogel solutions in THF/H<sub>2</sub>O (98/2 vol %/vol %) at a concentration of 10.0 mg/mL. (Inset) Theoretical structure. DP<sub>ch</sub>: degree of polymerization of the constitutive chains. N<sub>ch</sub>: average number of constitutive chains. N<sub>x</sub>: average number of cross-link. (a) Linear polymer (DP = 50). (b) Nanogel (DP<sub>ch</sub> = 50; synthesis parameter: Co = 2050 mol/kg [Xa]<sub>0</sub> = 5.00 × 10<sup>-2</sup> mol/kg and x = 12.10%). (c) Depth histograms corresponding to surfaces obtained with linear polymers (squares) and nanogels (circles) as shown in a and b, respectively. Reproduced with permission from Poly *et al. Langmuir* **2011**, 27, 4290 [181]. Copyright 2011 American Chemical Society.



**Figure 13.** AFM topography images for films prepared by spin coating, on graphite, nanogel solutions in THF/H<sub>2</sub>O (98/2 vol %/vol %) at a concentration of 10.0 mg/mL. (Inset) Theoretical structure. DP<sub>ch</sub>: degree of polymerisation of the constitutive chains. n<sub>ch</sub>: average number of constitutive chains. n<sub>x</sub>: average number of cross-links. (a) Nanogel 1 (x = 7.87%). (b) Nanogel 2 (x = 9.60%). (c) Nanogel 3 (x = 20.03%). Reproduced with permission from Poly *et al. Langmuir* **2011**, 27, 4290 [181]. Copyright 2011 American Chemical Society.



## 7. Conclusions

The development of RAFT technology has revitalized the field of radical polymerization of polyvinyl esters by enabling the preparation of materials with well-defined length, functionality, and architecture. Since the first reports of controlled polymerization of VAc using the Rhodixan A1 xanthate, a plethora of polyvinyl esters with controlled architectures have been prepared. These include end-functional, di- and tri-block, gradient, comb, star and hyperbranched (co)polymers. RAFT exhibits several advantageous features for the polymerization of vinyl esters compared to other RDRP strategies, such as the possibility of copolymerizing VAc with monomers of dissimilar reactivities provided that the RAFT agent is chosen in a judicious manner. Due to their commercial availability, a great variety of vinyl esters have been studied in homopolymerization and copolymerization under RAFT conditions. After nearly 20 years of intensive research, the key role of R and Z groups of RAFT agent in vinyl ester polymerization is now well understood. For most cases, xanthate RAFT agents (sometimes referred to as MADIX agents) are the best choice, as they control both  $M_n$  and dispersity without significantly affecting the overall kinetics.

The preparation of copolymers of vinyl esters, either statistical or block, presents specific challenges due to the unstable poly(vinyl ester) radical and relatively unreactive vinyl ester double bond. Much research has been carried out to address these challenges. This review contains examples of the RAFT statistical copolymerization of vinyl esters with both MAM and LAM monomers, and a large section has been dedicated to synthetic techniques for the preparation of block and graft copolymers.

An emerging body of work deals with heterogeneous (*i.e.*, emulsion, miniemulsion and suspension) polymerizations of VAc. Control of macromolecular characteristics is typically inferior to that of solution polymerization but the formed particles display good colloidal stability. This is an area which deserves more attention, given the ubiquity of heterogeneous processes in the industrial production of vinyl esters.

As RAFT technology matures, attention is increasingly turning to applications of controlled and functional poly(vinyl ester)s. Of particular interest is the preparation of polyvinyl esters with enhanced solubility in  $scCO_2$ . PVAc is moderately soluble in  $scCO_2$ , and its solubility can be further increased by the introduction of bulky side groups or fluorinated substituents. Poly(vinyl ester)-based block copolymers have been used to stabilize both water-in- $CO_2$  and  $CO_2$ -in-water emulsions, while xanthate-terminated polyvinylalkylates have been used as reactive stabilizers for dispersion polymerization. The preparation of well-defined PVA for biomedical applications is also a growing area, as PVA is a non-toxic, FDA-approved polymer which forms strong physical hydrogels. The control over functionality and architecture offered by RAFT polymerization should find many applications in this domain.

Poly(vinyl ester)s are produced industrially in enormous quantities using conventional free radical polymerization, and find applications as coatings and adhesives in areas ranging from construction materials to cheese rinds and chewing gum. As this review shows, RAFT technology provides a route to a wide range of well-defined and functionalized vinyl ester-based polymers and copolymers. The combination of the attractive properties of poly(vinyl ester)s with the structural control offered by RAFT should lead to many new and diverse applications for this important class of polymers.



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## Author Contributions

The text was written as a collaborative effort between all authors.

## Conflicts of Interest

The authors declare no conflict of interest.

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