

The Reversible Addition-Fragmentation Chain Transfer (RAFT) Polymerization of Cyanoacrylates

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ABSTRACT

Chapter 1 gives a general overview of cyanoacrylate chemistry with a focus on radical polymerization.

Chapter 2 begins with a review of available Reversible-Deactivation Radical Polymerization (RDRP) techniques. Reversible Addition Fragmentation Chain Transfer (RAFT) was chosen in order to establish the first controlled/living polymerization of cyanoacrylates. Small molecular RAFT agents provided chain transfer in terms of reductions in molecular weight, but little evidence of control/living character in ethyl cyanoacrylate (ECA) polymerizations.

Chapter 3 describes RAFT polymerizations of ECA, *n*-butyl cyanoacrylate (*n*-BuCA) and phenylethyl cyanoacrylate (PECA) using poly(methyl methacrylate, MMA) as macroRAFT agent. Gel Permeation Chromatography (GPC) with refractive index (RI) detection indicated control/living character with unimodal and narrow molecular weight distributions (MWDs) shifting to higher MW with conversion. However, MWs were significantly below theoretical values based on monomer to RAFT agent ratios. Formation of non-living chains was evidenced by RAFT of poly(MMA)-*b*-poly(cyanoacrylate) with further MMA. Although triblock formation was indicated, bimodality in RI traces indicated some chains were not extended.

Chapter 4 examines livingness using GPC with UV-detection for RAFT end-group analysis. The UV polymer peak remained narrow and shifted to higher molecular weight with increasing conversion. There were however, low MW peaks absent in the GPC RI data observed by UV, which indicated loss in living chains from the degradation to unsaturated dead polymer and dithiobenzoic acid (DTBA). The generation of DTBA was proposed to lead to a plethora of reactions, which ultimately increase the number of chains, thus rationalising the observed increase in RI dispersity with increasing conversion, and MWs deviating below theoretical values. UV-analysis of triblocks indicated RAFT end-group decomposition occurs at a markedly higher rate for CA polymers compared to poly(MMA). This chapter concludes with ideas for future work to control the radical polymerization of cyanoacrylates.

ABBREVIATIONS

α	alpha
ACA	allyl cyanoacrylate
ACN	1,1'-azobis(cyclohexanenitrile)
AIBN	2,2'-azobis(2-methylpropionitrile)
AMRP	aminoxyl mediated radical polymerization
AN	acrylonitrile
ATRP	atom transfer radical polymerization
β	beta
<i>b</i>	block
Bu	butyl
BPO	benzoyl peroxide
<i>c</i>	fractional conversion
C	celsius
C	coulomb
CA	cyanoacrylate
CCC	4-(((2-carboxyethyl)thio)carbonothioyl)thio)-4-cyanopentanoic acid
CDSPA	4-cyano-4-[(dodecylsulfanylthiocarbonyl) sulfanyl] pentanoic acid
CPDB	cyanoisopropyl dithiobenzoate
CPMPC	2-cyanopropan-2-yl <i>N</i> -methyl- <i>N</i> -(pyridin-4-yl)carbamodithioate
CSIRO	Commonwealth Scientific and Industrial Research Organisation
CTPA	4-cyano-4-(phenylcarbonothioylthio)pentanoic acid
CuAAC	Copper(I)-catalyzed Azide-Alkyne Cycloaddition
DDMAT	2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid
DTBA	dithiobenzoic acid
DCHPC	dicyclohexyl peroxydicarbonate
DFT	density functional theory
DMF	<i>N,N</i> -dimethylformamide
DPRP	depolymerization – repolymerization
DSC	differential scanning calorimetry
DTA	dynamic thermal analysis

ECA	ethyl cyanoacrylate
Et	ethyl
f	initiator efficiency
g	gram
GPC	gel permeation chromatography
h	hour
Hept	heptyl
Hz	hertz
[I]	initiator concentration
IUPAC	International Union of Pure and Applied Chemistry
K	equilibrium constant
k_{act}	rate constant for activation
k_c	rate coefficient of combination
k_d	rate coefficient of initiator decomposition
k_{deact}	rate constant for deactivation
k_p	propagation rate coefficient
k_{Ri}	reinitiation rate coefficient
k_t	termination rate coefficient
k_{tr}	rate coefficient of chain transfer
L	litre
LAM	less activated monomer
[M]	monomer concentration
M	molar
m	metre
m/z	mass to charge ratio
MA	methyl acrylate
MAM	more activated monomer
MCA	methyl cyanoacrylate
Me	methyl
MESA	methyl (ethoxycarbonothioyl)sulfanyl acetate
mg	milligram

MHz	megahertz
mL	millilitre
μm	micrometre
min	minute
mm	millimetre
MMA	methyl methacrylate
mmol	millimole
M_n	number average molecular weight
$M_{n,\text{th}}$	theoretical number average molecular weight
mol	mole
MSA	methane sulfonic acid
MW	molecular weight
M_w	weight average molecular weight
M_w/M_n	polydispersity
MWD	molecular weight distributions
<i>n</i> -BuCA	<i>n</i> -butyl cyanoacrylate
nm	nanometre
NMP	nitroxide mediated polymerization
NMR	nuclear magnetic resonance
OCA	octyl cyanoacrylate
ω	omega
PECA	phenylethyl cyanoacrylate
PEG	polyethylene glycol
Ph	phenyl
pK_a	acid dissociation constant
PLP	pulsed-laser polymerization
p	pyroelectric coefficient
PRE	persistent radical effect
RAFT	reversible addition-fragmentation chain transfer
RDRP	reversible-deactivation radical polymerization
RI	refractive index

RITP	reversible iodine transfer polymerization
R_p	rate of polymerization
s	second
SEC	size exclusion chromatography
St	styrene
T	tritium
t	time
T_c	ceiling temperature
T_g	glass transition temperature
TBB	tri- <i>n</i> -butyl borane
TBBO	tri- <i>n</i> -butyl borane oxide
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
THF	tetrahydrofuran
TIPNO	2,2,5-trimethyl-4-phenyl-3-azahexane-3-aminoxyl
TrH	transfer agent
UV	ultraviolet
VAc	vinyl acetate
wt%	weight percent
w/v	weight per volume
w/w	weight per weight

CHAPTER 1

INTRODUCTION TO CYANOACRYLATES

1.0 GENERAL INTRODUCTION

1.1 Introduction and Use of Cyanoacrylates

Cyanoacrylates are a family of vinyl monomers renowned for their reactivity, instant adhesive properties and wide ranging application areas.^[1-4] Short chain cyanoacrylates, like methyl (MCA) and ethyl (ECA) have found great utility as the major components of industrial and household instant adhesives or “super glues”, including those manufactured at Henkel under the Loctite brand (**Table 1.0**).^[5,6] Longer chain cyanoacrylates such as butyl (*n*-BuCA) and octyl (OCA) have utility as surgical suture replacements for skin and tissue adhesives.^[7-12] Poly(cyanoacrylates) have gained recognition for numerous biomedical applications due to their favourable biocompatibility, biodegradability and low toxicity.^[13] Colloidal nanoparticles based on cyanoacrylates have shown great promise in the field of drug and vaccine delivery.^[14-20] In forensics, cyanoacrylates are used in latent fingerprint development, whereby cyanoacrylate vapours adhere to the trace amino acids present in the fingerprint residue rendering them visible to the naked eye and can be further visualised when luminescent dyes are added to the cyanoacrylate.^[21]

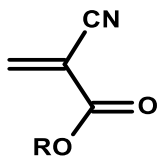
Structure	R	Abbreviation	Uses
	Me	MCA	Loctite 496 Super Bonder
	Et	ECA	Loctite 401 Instant Adhesive
	<i>i</i> -Propyl	<i>i</i> -PrCA	Root canal sealant
	<i>n</i> -Butyl	<i>n</i> -BuCA	Skin / surgical adhesive
	2-Octyl	2-OCA	Skin / surgical adhesive
	Allyl	ACA	High temperature adhesive
	Methoxyethyl	β-MeOCA	Low odour adhesive
	Ethoxyethyl	β-EtOCA	Low odour adhesive
	Phenylethyl	PECA	Adhesive tapes

Table 1.0 Structure and commercial uses of common cyanoacrylates.

Due to its unsaturated ester group, allyl cyanoacrylate (ACA) has the ability to undergo crosslinking reactions at elevated temperatures, a feature that gives it utility as a thermally resistant adhesive.^[5] Methoxyethyl (β -MeOCA) and ethoxyethyl (β -EtOCA) have lower vapour pressures compared to shorter chain cyanoacrylates and are often used as low odour adhesives. Additionally, these adhesives avoid a phenomenon characteristic of their shorter chain counterparts known as “blooming”, whereby polymerized monomer vapour is deposited as a fine chalky powder on the surface near an adhesive bond-line and thus are sometimes referred to as “low-bloom” adhesives.^[4] Phenylethyl cyanoacrylate (PECA) differs from the previously named cyanoacrylates in that it is a solid and is utilized in industrial adhesive tapes and films.^[22]

The general monomer chemistry, synthesis, modes of polymerization, and the physical characteristics of the resulting polymers along with several toxicological evaluations have been detailed in a number of reviews.^[4-6,23-26] After a general overview of reactivity and properties (section 1.2), the focus of this chapter is the radical polymerization of cyanoacrylates.

1.2 Cyanoacrylates: Reactivity and General Properties

1.2.1 Reactivity

The high reactivity of cyanoacrylates is attributed to the strong electron-withdrawing nitrile (CN) and ester (CO₂R) groups attached to the α -carbon of the double bond (**Figure 1.0**).

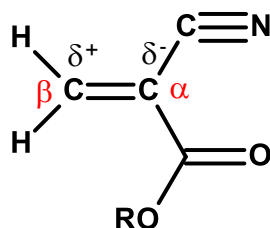
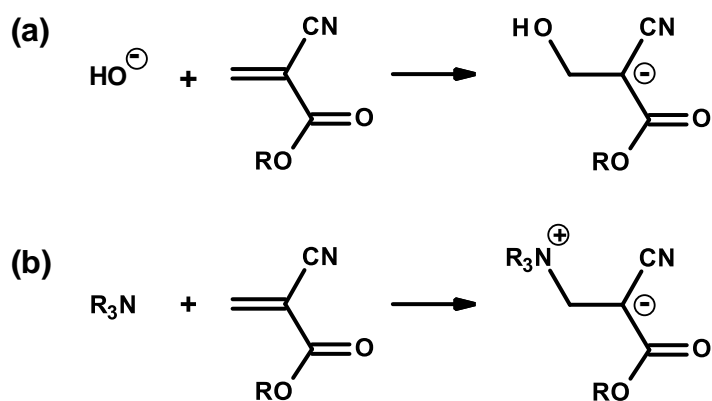


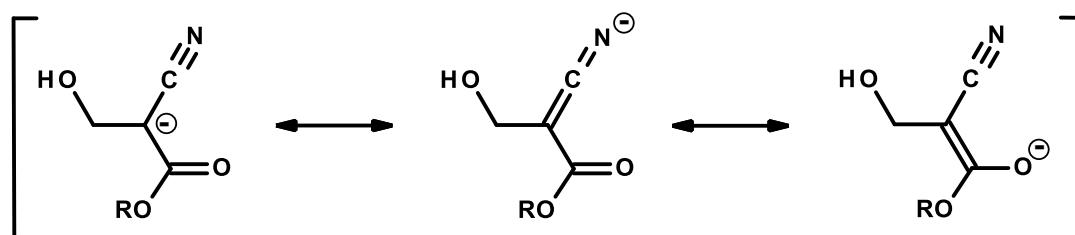
Figure 1.0. Polarization of the cyanoacrylate double bond.

The β -carbon of cyanoacrylates is activated toward nucleophiles, such as anions, as well as weak bases, water, and alcohols (**Scheme 1.0(a)**). In an adhesive context, polymerization or curing occurs through rapid initiation from the thin film of moisture commonly found on the surface of most materials.



Scheme 1.0 (a) Anionic and (b) Zwitterionic initiation.

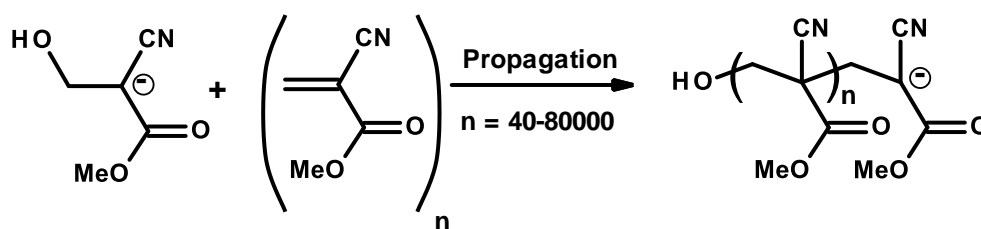
Initiation can rapidly occur upon contact with anions, as well as with non-dissociated base species, such as tertiary amines and tertiary phosphines leading to zwitterionic polymerization (**Scheme 1.0(b)**). Regardless of whether cyanoacrylate polymerization is initiated by anionic or non-dissociated nucleophilic base, a propagating carbanion is formed on the β -carbon, which is resonance stabilized through the CN and CO_2R groups (**Scheme 1.1**).



Scheme 1.1. Resonance stabilization of cyanoacrylate α -carbanion adduct.

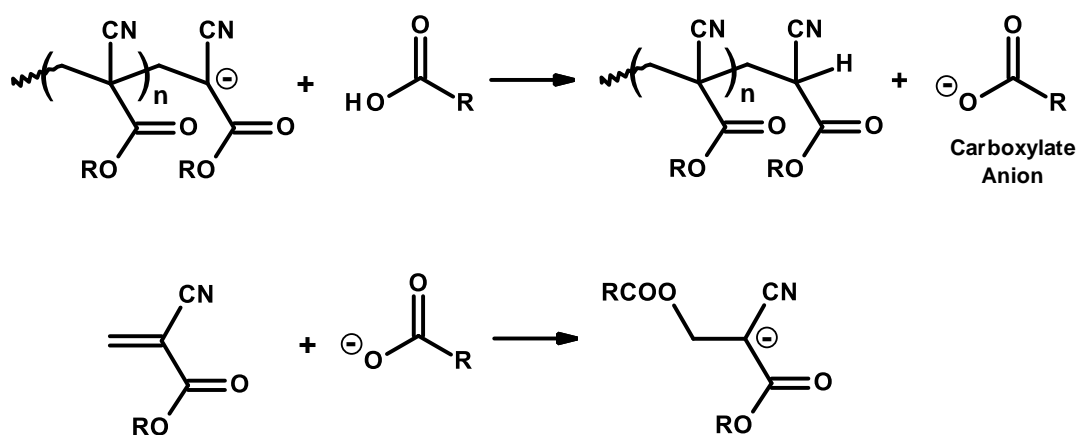
The stabilization of the negative charge through delocalization at the α -carbon atom in combination with the sterically unhindered and highly electrophilic nature of the β -carbon makes the cyanoacrylate molecule uniquely reactive. The carbanion adds to another monomer molecule to generate a dimeric species, which in turn reacts with more monomer until a high molecular weight polymer is

formed, typically in the range of 10^5 – 10^7 g.mol⁻¹ (**Scheme 1.2**).^[27] The poly(cyanoacrylate) molecular weights are not greatly affected by temperature, but can be affected by pH.^[28] Polymerization kinetics have been studied in detail by Pepper and co-workers with various initiators in dilute solutions using adiabatic calorimetry techniques.^[29-39] Solution polymerizations of *n*-BuCA in THF at 20 °C using tetrabutylammonium salts as initiators gave extremely fast rates of polymerization with propagation rate coefficient (k_p) values close to 10^6 L.mol⁻¹s⁻¹.^[29] The k_p values for cyanoacrylates are significantly greater than the anionic polymerization of methyl methacrylate (MMA), with $k_p = 775$ L.mol⁻¹s⁻¹ initiated by a tetraphenylphosphonium salt under similar experimental conditions of 20 °C in THF.^[40] Rapid initiation of cyanoacrylate polymerization leads to characteristics close to those of ideal living polymerization with molecular weights in approximation to theoretical values based on the monomer/initiator ratio.^[30]



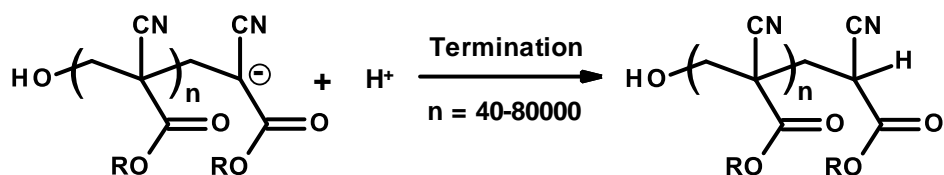
Scheme 1.2. Anionic polymerization: Propagation of cyanoacrylates.

Propagation of cyanoacrylate polymerization will continue until available monomer is consumed or until a chain transfer or termination step intervenes. It is believed that some chain-transfer reactions can occur in the presence of weak acids, such as the carboxylic acids formed from hydrolysis of cyanoacrylate monomer.^[1] Transfer of a proton to the propagating carbanion will terminate the growth to produce a dead chain, however, the resulting conjugate base (carboxylate anion) is able to initiate a new growing polymer chain by addition onto monomer (**Scheme 1.3**). Strong acids will act as chain terminators by protonation of the anion and will rapidly kill the polymerization (**Scheme 1.4**). In the case of strong mineral acids (e.g. sulfuric acid), the conjugate base is not nucleophilic enough to initiate further anionic polymerization.



Scheme 1.3. Chain-transfer in cyanoacrylate polymerization.

The investigations carried out by Pepper et al. demonstrated that in the absence of strong acid the polymerization has no intrinsic termination reactions and the poly(cyanoacrylate) carbanions are stable enough to remain active even after addition of small amounts of common terminating agents such as water, oxygen or CO₂.^[29-39] The polymer chain stability is in stark contrast to other common anionically polymerizable monomers like styrenics or (meth)acrylates for example where, in the case of organolithium-initiated anionic polymerizations, the introduction of trace amounts of air or moisture terminates polymer growth by reacting with the active chain end anions or the (often organometallic) initiator. With the latter conventional anionic polymerizations, stringent experimental conditions including inert atmospheres and glove boxes are a requirement.^[41]



Scheme 1.4. Termination of propagating chain with strong acid.

1.2.2 General Polymer Properties

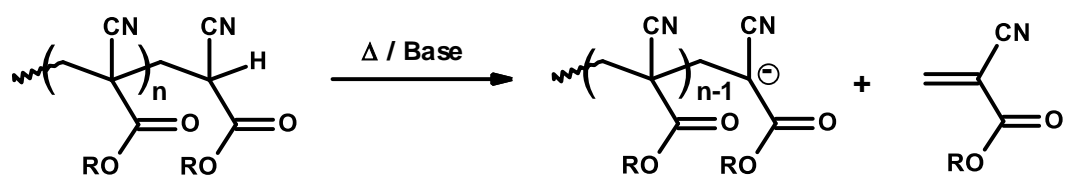
Poly(cyanoacrylates) are colourless, thermoplastic materials with physical properties dependent on their ester side chain. The glass transition temperatures (T_g) of common poly(cyanoacrylates) are shown in **Table 1.1**. In general, the T_g values for poly(cyanoacrylates) decrease with increasing ester chain length and steric bulk. T_g values can however, vary depending on the method employed for determination such as dilatometry (see later in text for definition) and dynamic thermal analysis (DTA).^[42] Additionally, the means of polymer sample preparation (anionic or radical polymerization), polymerization temperature and resulting molecular weight can impact T_g values.^[42,43]

Poly(cyanoacrylate)	T_g , °C	Ref
MCA	160	[42]
ECA	150	[44]
<i>n</i> -BuCA	130	[43]
2-OCA	10	[1]
ACA	90	[43]
β -MeOCA	85	[1]

Table 1.1. Glass transition temperatures (T_g) of poly(cyanoacrylates).

Poly(cyanoacrylates) have relatively poor thermal stability and start to degrade slightly above their glass transition temperature and significantly less than their ceiling temperature (T_c).^[45] The latter is the temperature at which the rate of polymerization and depolymerization of the polymer are equal.^[46] Thermal behaviour of isolated polymers however, can be very complex and degradative reactions other than depolymerization will often occur at temperatures below the ceiling temperature. Poly(ECA) for example, begins to degrade at around its T_g of approximately 150 °C, whereas its T_c has been measured as 276 °C.^[44] Rather than a random chain scission, thermal degradation occurs through a depolymerizing or

“unzipping” mechanism that starts at the chain terminus, whereby the polymer chains undergo retro-polymerization to reform monomer (**Scheme 1.5**).^[47-49]



Scheme 1.5. Unzipping mechanism of poly(cyanoacrylates).

Poly(cyanoacrylates) are very susceptible to degradation on contact with water^[50,51] and basic solutions.^[52] Degradation occurs in common organic solvents that can often contain traces of basic impurities. Robello reported that adventitious base present as impurities in solvents are sufficient to promote degradation.^[53] Han et al. stored a solution of poly(ECA) in acetone at room temperature, periodically tested the solution by gel permeation chromatography (GPC), and showed the polymer peak gradually disappearing over time.^[54] The terminal proton at the end of the dormant polymer chain is expected to be acidic due to the presence of the adjacent electron-withdrawing nitrile and ester functional groups. The acid dissociation constant (pK_a) value for this terminal proton has not been reported in literature however, for comparison the structurally similar compounds of diethyl 2-methylmalonate and methyl malonitrile have pK_a values of 17 and 12.4 respectively (**Figure 1.1**).^[55,56]

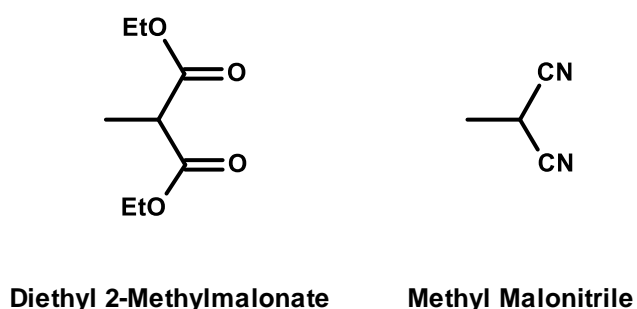


Figure 1.1. Structures of diethyl 2-methylmalonate and methyl malonitrile.

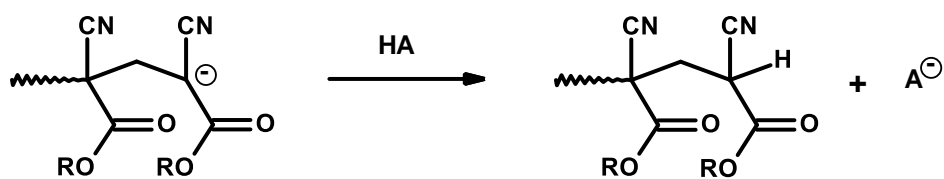
Ryan and McCann demonstrated that addition of tetrabutylammonium hydroxide (TBAOH) to poly(*n*-BuCA) in THF at 21 °C deprotonated the chain end and led to a rapid depolymerization process.^[52] The unzipped monomer is then instantly repolymerized in the presence of the base to form much lower molecular weight so-called “daughter” polymers in a depolymerization-repolymerization reaction (DPRP). The reaction was monitored by GPC and showed that “parent” and “daughter” polymer peak areas remained almost directly proportional to one another throughout, indicating a near quantitative conversion of unzipped monomer from the “parent” polymer to the “daughter” polymer which gradually increases in molecular weight. Similarly, solutions of *n*-BuCA monomer in THF underwent instantaneous polymerization upon addition of millimolar quantities of TBAOH to give initially high molecular weight polymer followed by rapid depolymerization and subsequent repolymerization to give lower molecular weight daughter polymer.

This depolymerization-repolymerization reaction was confirmed by Robello et al. in their studies into the degradation of various poly(cyanoacrylates).^[53] In this case the added base was not a necessity as degradation occurred in simple solutions of poly(cyanoacrylates) in acetonitrile and acetone incubated at 50 °C. Robello et al. reported that the degradation could be effectively inhibited by addition of acetic acid. As with the findings of the previous McCann and Ryan degradation study, the initial high molecular weight peak observed by GPC gradually disappeared over time and was accompanied by the simultaneous appearance of lower molecular weight peaks, indicating that the polymer chains are in dynamic equilibrium with their monomers. Robello and co-workers attempted to stop the unzipping process by end-capping the polymer chain with 4-bromobenzylbromide, which proved unsuccessful as no aromatic protons were observed by ¹H NMR of the polymer.^[53]

1.3 The Radical Polymerization of Cyanoacrylates

1.3.1 Cyanoacrylate Inhibitors and Precautions for Radical Polymerization

Cyanoacrylates are routinely stabilized against anionic polymerization by addition of precise levels (parts per million) of strong organic or mineral acid inhibitors. These act by terminating the cyanoacrylate anion or zwitterion species by proton transfer before significant chain growth occurs (**Scheme 1.6**).



Scheme 1.6. Chain termination using anionic inhibitors.

Various anionic inhibitors^[57] have been reported, such as SO₂,^[57] SO₃,^[58] sulfonic acids,^[59] sulfones,^[60] boric acid chelates,^[61] P₂O₅,^[62] Sb₂O₅,^[62] HPO₃,^[62] maleic anhydride,^[62] maleic acid,^[62] FeCl₃,^[62] HF,^[58] NO,^[58] alkyl sulfates,^[60] alkyl sulphides,^[60] alkyl sulfones,^[60] MeSO₃H,^[63] MeCO₂H,^[64] CF₃CO₂H,^[65] oxonium and phosphonium compounds.^[66] Cyanoacrylates can be polymerized via a radical mechanism however, sufficient amounts of anionic inhibitor must be used in order to suppress anionic polymerization in favour of the radical pathway. Over-stabilization with anionic inhibitors should be avoided due to hydrolysis of the monomer ester functionality leading to interference with the polymerization.^[67]

Commercial cyanoacrylates will often contain radical inhibitors such as hydroquinone, catechol, *p*-methoxyphenol, butylated hydroxyanisole, and related phenolic compounds (**Figure 1.2**) to suppress radical polymerization, which can be triggered with high temperatures or UV-light.^[68,69] In order to study the radical polymerization of cyanoacrylates, inhibitors should be removed by distillation prior to commencing the reaction. Any glassware that will come in contact with cyanoacrylates should be acid washed, acetone rinsed, and oven dried before use. Distilled monomer should ideally be stored in tightly closed high density polyethylene (HDPE) at sub-zero temperatures.

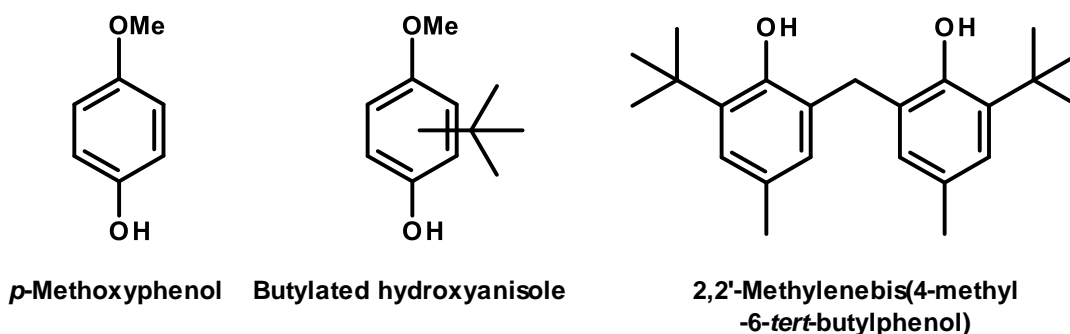


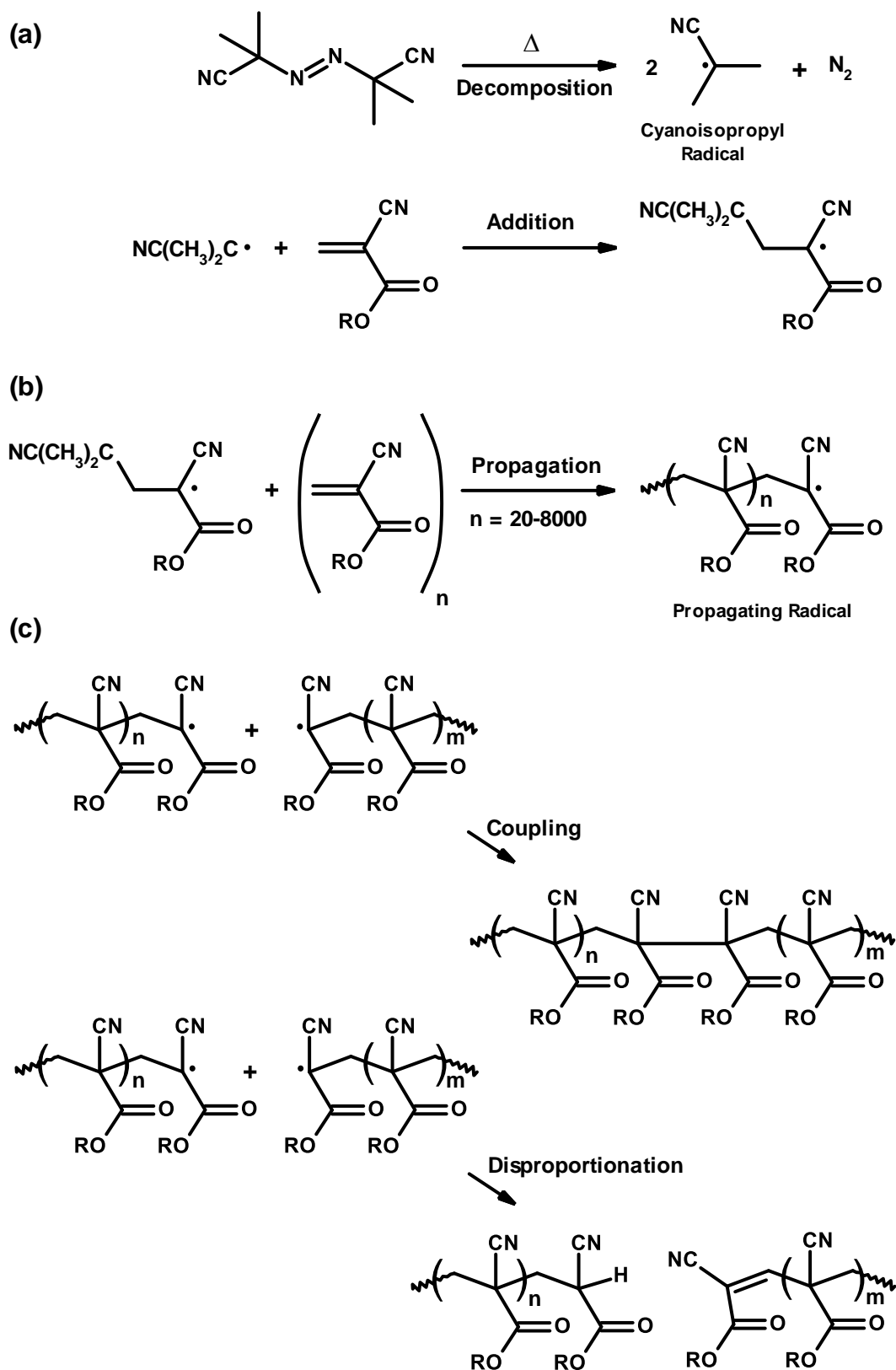
Figure 1.2. Examples of radical inhibitors.

For solution polymerizations, attention should be paid to the inhibitor contained within commercial solvents which can often be nucleophilic in nature. In some instances commercial solvents, e.g. THF, have been found to contain impurities which can cause polymerization of cyanoacrylates.^[70] Similarly, any non-solvents used to isolate poly(cyanoacrylates) by precipitation should be inhibited with strong acid (e.g. methanesulfonic acid)^[71] to prevent anionic polymerization of residual monomer.

1.3.2 General Mechanism

Once the appropriate inhibitor for anionic polymerization is added, cyanoacrylates can be polymerized radically (**Scheme 1.7**). Initiation takes place in two steps; the first involves the thermal homolysis of the initiator to give a pair of radicals. The initiator depicted in **Scheme 1.7(a)** is 2,2'-azobis(2-methylpropionitrile) (commonly known as AIBN), an azo-initiator frequently used with cyanoacrylates.

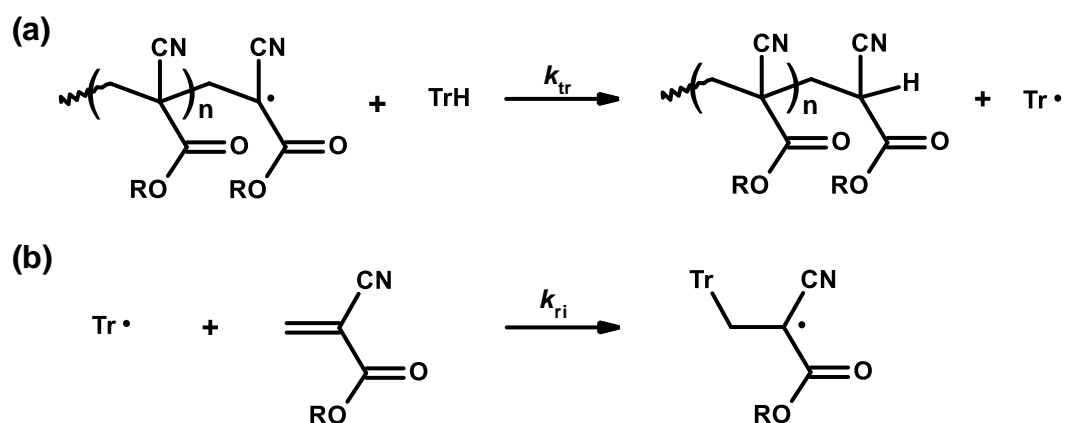
After thermal decomposition into a pair of cyanoisopropyl radicals, the second step is the addition of the initiating cyanoisopropyl radical onto the cyanoacrylate monomer to form a propagating radical (**Scheme 1.7(b)**). Rapid addition of this propagating radical onto successive monomer units can occur hundreds or even thousands of times, increasing the polymer chain length with each addition until terminating events take place (**Scheme 1.7(c)**). The process of initiation, propagation and termination take place for each propagating species typically in the order of less than one second, or at most, a few seconds.^[72]



Scheme 1.7. (a) Initiation (b) Propagation and (c) Termination in the conventional radical polymerization of cyanoacrylates.

For radical polymerization there are two different means of termination; coupling and disproportionation, which give three different end groups. Termination by coupling occurs when two growing chains combine to give a single dead chain. Termination by disproportionation takes place when a β -hydrogen atom is abstracted from one propagating chain resulting in a chain with a hydrogen terminus and the other with an unsaturated chain-end.

Another occurrence in conventional radical polymerization is chain transfer reactions (k_{tr}), whereby a propagating radical is terminated usually by hydrogen atom abstraction and a new radical species is created (**Scheme 1.8(a)**).



Scheme 1.8. (a) Transfer and (b) Reinitiation of transfer agent (TrH) during chain-transfer reactions in cyanoacrylate radical polymerization.

The newly created radical can then add to a monomer unit (k_{ri}) and reinitiate polymerization (**Scheme 1.8(b)**). Chain transfer can take place in several ways: transfer to monomer, to polymer, to initiator and to solvent. Transfer to monomer can occur if the monomer has labile hydrogen that can be readily abstracted. Transfer to polymer can occur when a polymer chain radical abstracts a hydrogen atom from somewhere on the backbone of another polymer chain which terminates one chain but allows the other to branch and continue growing. Transfer to initiator will terminate a polymer chain radical but creates a new radical initiator. Transfer to solvent results in the abstraction of a hydrogen from a solvent molecule to generate a solvent molecule radical. For example, Magee et al. demonstrated that chain transfer to solvent strongly influences the maximum

attainable molecular weight in the conventional radical polymerization of acrylamide monomers in various alcohol solvents.^[73]

The use of organohalides, such as CBr₄, as transfer agents in radical polymerization for a number of different vinyl monomers have been reported.^[74] In the radical polymerization of *n*-butyl acrylate, the use of CBr₄ as chain transfer agent lead to significantly reduced branching during the reaction as chain lengths became shorter with increasing CBr₄ concentration and the rate of backbiting reactions decreased.^[75] Additionally, at high CBr₄ concentrations any midchain radicals that are formed via backbiting processes are terminated through transfer to CBr₄, where a Br atom is abstracted.

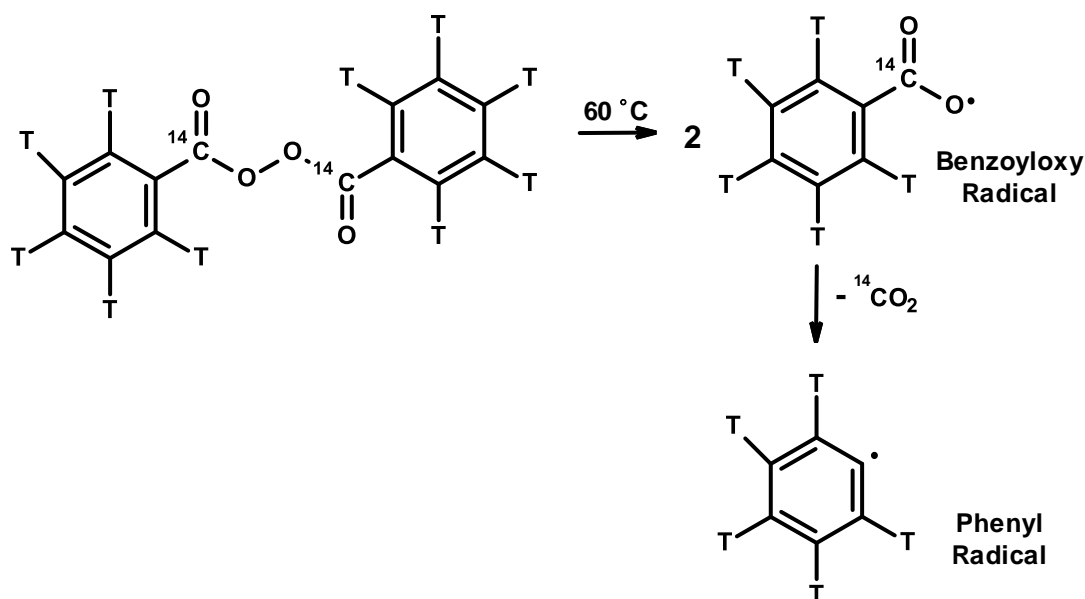
Tang et al. attempted to utilize CBr₄ as a chain transfer agent in the homopolymerization of ECA with the intended dual function of limiting the polymer chain length before gelation occurred, and to provide bromine terminated chains that could be further functionalized in “click” type reactions.^[65] It was found that transfer of bromine atoms to the propagating poly(cyanoacrylate) radicals was very inefficient even when the transfer agent was used in high concentrations.

1.3.3 Mechanistic Radical Homopolymerization Studies

Various common azo and peroxide radical initiators have been employed to initiate cyanoacrylate polymerization. AIBN and benzoyl peroxide (BPO) being the most frequently used, with the former being preferred.

When BPO is used as a radical initiator, both benzoyloxy and phenyl radicals participate in initiation as the benzoyloxy radical decomposes to give a phenyl radical through loss of carbon dioxide. Methyl cyanoacrylate (MCA) showed low reactivity towards the benzoyloxy radical with initiation occurring largely through addition of the more nucleophilic phenyl radical onto the monomer, as detected using doubly isotopically labelled BPO with Carbon-14 and Hydrogen-3 (T) (**Scheme 1.9**).^[76] For the polymerization of MCA at 60 °C, the number of phenyl α -end

groups on the polymer were found to be approximately twice that of benzoyloxy end groups.



Scheme 1.9. Initiation with doubly isotopically labelled BPO.

Chappelow et al investigated the use of tri-*n*-butyl borane oxide (TBBO) as the radical initiator for several monomers, ethyl-2-isocyanatoacrylate, 2-isocyanatoethyl methacrylate and ECA (**Figure 1.3**).^[77]

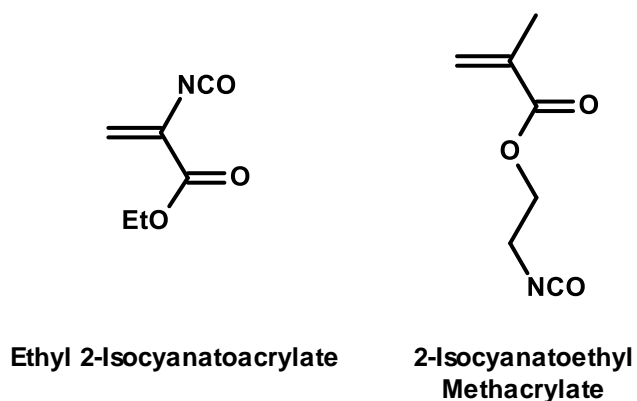
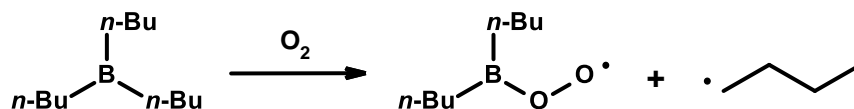


Figure 1.3. Structures of ethyl 2-isocyanatoacrylate and 2-isocyanatoethyl methacrylate.

The initiating radical is generated from the auto-oxidation of the alkylboron compound from the air to give the alkyl borane peroxide and butyl radicals (**Scheme 1.10**).^[78] Homopolymerizations of ECA were carried out using 1.8 wt% of TBBO in THF at room temperature (22 – 25 °C). After 21 hours poly(ECA) was

isolated by precipitation into hexane in greater than 70% conversion, however, polymer formed via anionic polymerization cannot be ruled out since no anionic inhibitor was employed.



Scheme 1.10. Auto-oxidation of tri-*n*-butyl borane (TBB).

The earliest report on the kinetics of the radical polymerization of cyanoacrylates was by Canale et al. in 1960 who carried out bulk polymerization of MCA using a boron trifluoride acetic acid complex as anionic inhibitor and AIBN as initiator.^[79] The bulk parameter $k_p/k_t^{0.5}$ was determined as $0.021 \text{ L}\cdot\text{mol}^{-1}\text{s}^{-1}$ at $60 \text{ }^\circ\text{C}$, although an acceleration in rate was observed at initial stages. This is significantly higher than the $k_p/k_t^{0.5} = 0.0144 \text{ L}\cdot\text{mol}^{-1}\text{s}^{-1}$ for MMA and $k_p/k_t^{0.5} = 0.00166 \text{ L}\cdot\text{mol}^{-1}\text{s}^{-1}$ for styrene (St) measured under the same conditions.^[79] The rate of polymerization (R_p) was measured by dilatometry for a series of initiator concentrations [I].

Dilatometry is an accurate means of determining the conversion of monomer to polymer by measuring the change in volume that occurs upon polymerization. The $k_p/k_t^{0.5}$ was obtained from the initial slopes of the first-order plot according to equation 1, where k_p is the propagation rate coefficient, k_t is the termination rate coefficient, k_d is the rate coefficient of initiator decomposition, f is the initiator efficiency, t is time, and [M] and [I] are the concentrations of monomer and initiator respectively.

$$\ln \frac{[M]_0}{[M]} = \left(\frac{k_p}{k_t^{0.5}} \right) (fk_d[I]_0)^{0.5}t \quad (1)$$

Solution polymerizations of MCA were also carried out in isobutyronitrile and nitromethane however, no kinetic data was obtained in these solvents. Poly(MCA) was found to be insoluble in common aromatic solvents, such as benzene and toluene (in the case of benzene the polymer precipitated as a swollen gel). The homopolymer was insoluble in alcohols, ketones (acetone, methyl ethyl ketone)

and chlorinated solvents (chloroform, 1,2-dichloroethane). Bevington et al. used 1,3-propane sultone (0.3 wt%) as inhibitor in their study on the radical polymerization of MCA in bulk and in solutions of 1,4-dioxane at 60 °C using AIBN and BPO as initiator.^[80] The inhibitor had negligible effects on the rate of radical polymerization of MCA at 60 °C even at high concentrations in excess of 2.6×10^{-2} M. Although the polymer was found not to be soluble in dioxane, it was deemed an acceptable diluent for the polymerization of MCA at 60 °C.

In a recent study looking at the preparation of highly branched cyanoacrylate containing polymers, Tang et al. studied the homopolymerization of ECA in two different solvents.^[65] ECA (1.13 M) was polymerized in acetonitrile and in toluene using AIBN (1.13×10^{-2} M) as initiator at 65 °C. The polymerization appeared to be 50% faster in toluene than in acetonitrile due to an apparent poorer solubility of the polymer in the former less polar solvent.

In 1983 Yamada et al. gave the first determination of the absolute rate coefficients for propagation (k_p) and termination (k_t) for the radical polymerization of ECA using the rotating sector method.^[81] The rotating sector method is so named as it refers to a rotating disc from which a sector-shaped portion is cut out, the disc is placed in between the reaction system and a non-laser light source to cause periodic interruption of light.^[82] The cycling of light and dark periods allows the parameter τ_s , known as the average lifetime of a growing radical under steady-state conditions to be calculated. Once τ_s is known, from equation 2 k_p and k_t values can be calculated.

$$\tau_s = \frac{k_p[M]}{2k_t(R_p)} \quad (2)$$

The rotating sector method was used to determine the k_p and k_t values for the bulk polymerization of ECA at 30 °C in the presence of two different anionic inhibitors. Polymerizations containing 7.0 wt% acetic acid had values of $k_p = 1622 \text{ L}\cdot\text{mol}^{-1}\text{s}^{-1}$ and $k_t = 4.11 \times 10^8 \text{ L}\cdot\text{mol}^{-1}\text{s}^{-1}$, whereas polymerizations containing 0.5 wt% of propane sultone gave values of $k_p = 1610 \text{ L}\cdot\text{mol}^{-1}\text{s}^{-1}$ and $k_t = 4.04 \times 10^8 \text{ L}\cdot\text{mol}^{-1}\text{s}^{-1}$. The close proximity of these values indicated that anionic polymerization was

adequately suppressed by both inhibitors, and that the rate coefficients were representative of the radical polymerization. The k_p values for ECA were close to those determined at 30 °C using the same method for ethyl chloroacrylate and was attributed to the nitrile group attached to the α -carbon of the double bond having the same stabilization effect on the propagating radical as the chlorine substituent at the same position.^[83] **Table 1.2** gives a comparison of experimentally measured k_p for cyanoacrylates and similarly α -substituted monomers using the rotating sector method. The k_p values for ECA are over 3.5 times higher than those measured for MMA and *n*-butyl methacrylate, while more than double the value for methyl acrylate.^[84,81] Yamada's determination of k_p for the polymerization of ECA was in agreement with data derived from more recent density functional theory (DFT) computational modelling.^[85]

In 2015, the k_p for *n*-BuCA was estimated to be about 7 times lower ($k_p = 226 \pm 32$ L.mol⁻¹s⁻¹) at 30 °C than that reported by Yamada (above).^[86] The k_p was obtained by extrapolation of experimental data for the copolymerization of *n*-BuCA with MMA using the more accurate pulsed-laser polymerization coupled with size exclusion chromatography (PLP-SEC) technique. PLP uses pulsed laser irradiation to oscillate between the light and dark periods however, the pulse width is greatly shorter (nanoseconds) compared to the cycle time of the rotating sector method (seconds). The key advantage of PLP is that it allows for k_p to be calculated directly without the need to couple it to the termination rate constant and has led to greater reproducibility of kinetics results compared to the discrepancies in experimental data observed for the rotating sector method. Consequently, PLP is now the International Union of Pure and Applied Chemistry (IUPAC) preferred method for k_p determination.^[87] **Table 1.3** gives a comparison of experimentally measured k_p for cyanoacrylates and other α -substituted monomers using PLP. It is difficult to draw direct comparisons between k_p values obtained from the rotating sector method and those obtained by PLP, since variations in experimentally reported k_p values from different studies can reflect differences in data interpretation and the dependence of kinetic parameters on polymerization conditions. The discrepancy in the k_p measured for the two different cyanoacrylate

monomers by two different techniques is alarming, however, it is worth highlighting that the value obtained by Rooney et al. is an extrapolation rather than a direct PLP measurement. Existing methods for reliable k_p determination are constantly being improved and new techniques are being developed.

Monomer	k_p (L.mol ⁻¹ s ⁻¹)	Ref.
ECA	1610-1622	[81]
Ethyl chloroacrylate	1660	[83]
Ethyl fluoroacrylate	1120	[88]
MMA	450	[84]
<i>n</i> -Butyl methacrylate	369	[89]
Methyl acrylate	720	[81]
St	106	[90]

Table 1.2. k_p values at 30 °C for α -substituted monomers using the rotating sector method.

Contrary to **Table 1.2**, the PLP data in **Table 1.3** suggests that k_p values for CAs are closer to those of methacrylate monomers. Perhaps the CO₂R and CN substituents adjacent to the propagating radical allow significant stabilization (by steric and electronic effects) thus greatly slowing down the rate of radical polymerization of CAs compared to that of for example acrylates (which polymerize about 70 times faster).

Monomer	k_p (L.mol ⁻¹ s ⁻¹)	Ref.
<i>n</i> -BuCA	226 ± 32	[86]
MMA	375	[91]
<i>n</i> -Butyl methacrylate	753 ^a	[92]
Methyl acrylate	15851	[93]
St	107	[94]

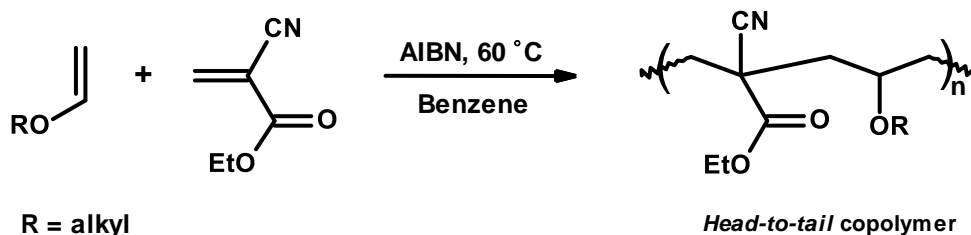
^a Measured at 50 °C

Table 1.3. k_p values at 30 °C for α -substituted monomers using the PLP-SEC method.

As with radical polymerization of other acrylic monomers such as MMA, termination of poly(cyanoacrylates) occurs predominantly by disproportionation.^[95] The hydrogen-atom terminated (non-functionalized) polymer chains are susceptible to the same degradation by base catalysed unzipping that occurs with anionically formed poly(cyanoacrylates), whereas the chains with the unsaturated terminus do not unzip and are more stable.^[52] Consequently, radically formed poly(cyanoacrylates) exhibit greater stability than those formed by anionic polymerization. This improved stability was noted by Robello et al. during degradation studies of poly(cyanoacrylates).^[53] Samples of poly(cyanoacrylate) derived from nucleophilic initiation completely degraded when incubated in acetonitrile at 50 °C for 24 hours, whereas only a small portion of samples derived from radical polymerization degraded under the same conditions. Manipulation of GPC data using a Gaussian numerical algorithm function for peak fitting enabled deconvolution of the GPC curves which allowed Robello et al. to approximate that 80% of these polymer samples were terminated through disproportionation and 20% by combination.

1.3.4 Mechanistic Radical Copolymerization Studies

One key benefit to radical polymerization, which is difficult to achieve through anionic means is the ease of copolymerization with other monomers, generating polymers with unique and varying properties. Cyanoacrylates form alternating *head-to-tail* copolymers when radically copolymerized with electron rich monomers such as vinyl ethers (**Scheme 1.11**).^[96-99]



Scheme 1.11. Radical copolymerization of ECA and vinyl ether.

For a vinyl monomer M_1 being copolymerized with monomer M_2 , the reactivity ratios r_1 and r_2 can be thought of as the tendency of the propagating chain end species to self-propagate and enchain its own type of monomer over that of the other monomer. Although it has been met with criticism, historically the Q and e scheme, developed by Alfrey and Price 70 years ago, has been used as a measure of monomer and radical reactivity on a quantitative basis in terms of correlating structure with reactivity and can be used to predict reactivity ratios.^[100] The Q and e values are related to the extent of resonance stabilization and polarity of the monomer and are approximated from its copolymerization kinetic data whereby the parameter Q describes resonance factor (and to a certain degree the steric factor) of the monomer and the parameter e describes the polar factor. Q and e values assigned to monomers are correlated against the arbitrarily selected reference value of $Q = 1$ and $e = -0.80$ for styrene. The values of Q and e increase with increasing monomer reactivity and increasing electron deficiency of the carbon-carbon double bond. Negative values of e indicate an electron rich double bond. The values for MCA were reported by Otsu et al. as $Q = 17$ and $e = 2.48$ respectively, from the bulk copolymerization with MMA in the presence of acetic acid in a sealed tube at 60 °C using AIBN as initiator.^[101] The authors noted that the monomers showed a high tendency for alternation with rates of

copolymerization decreasing as cyanoacrylate monomer concentration increased. The modes of derivation for Q and e values based on suggestions from Jenkins^[102] or McFarlane, Reilly and O'Driscoll^[103] where parameters for both Q and e could be experimentally determined without the necessity of an arbitrary assignment or without equating the polarities of conjugate monomers and radicals has led to the improved methods of assessment for reactivity ratios. Recent values of Q and e values for MCA have been reported as 4.91 and 0.91 respectively.^[104] The values of Q and e for some common monomers are shown in **Table 1.4**.

Monomer	Q	e
Ethyl vinyl ether	0.018	-1.80
Vinyl Acetate (VAc)	0.026	-0.88
St	1.00	-0.80
Isoprene	1.99	-0.55
1,3-Butadiene	1.70	-0.50
MMA	0.78	0.40
Acrylamide	0.23	0.54
MA	0.45	0.64
MCA	4.91	0.91
Acrylonitrile (AN)	0.48	1.23

Table 1.4. Q and e values for common monomers.^[104]

In the second publication of a series studying the reactivity of MCA, Kinsinger et al. examined the radical copolymerization of MCA with a wide variety of monomers including acrylic esters, styrenes, vinyl esters/ethers/halides/sulfides, allylic monomers and unsaturated hydrocarbons.^[105] As part of this study, the reactivity ratios of MCA (M_1) with a number of reference monomers in benzene solutions at 60 °C using AIBN as initiator were calculated, the most important of which was that of MMA (M_2), reported as $r_1 = 0.25$ and $r_2 = 0.04$, given that MMA has been one of the more frequently studied co-monomers with cyanoacrylates (**Table 1.5**). In 2016, the reactivity ratios of ECA and MMA were simulated on PROCOP software by Tang et al. based on their experimental copolymerization data in toluene at 65 °C.^[65]

These values were reported as $r_1 = 0.15$ and $r_2 = 0.02$, which are not too dissimilar to those reported by Kinsinger. Over the years, a series of reactivity ratios for cyanoacrylates with a variety of other monomers have been calculated from various studies and are summarized in **Table 1.5**.

CA (M_1)	Monomer (M_2)	r_1	r_2	Medium	Ref.
MCA	MA	1.2	0.1	Benzene	[105]
MCA	MMA	0.25	0.04	Benzene	[105]
MCA	St	0.03	0.01	Benzene	[105]
MCA	α -Methyl St	0.001	0.05	Benzene	[105]
MCA	VAc	0.5	0.005	Benzene	[105]
MCA	MMA	0.13	0.10	Bulk	[101]
ECA	MMA	0.85	0.41	Bulk	[106]
ECA	MMA	0.16	0.08 ^a	bulk	[81]
<i>n</i> -BuCA	MMA	0.236	0.057 ^b	bulk	[86]

^a Measured at 30 °C, ^b Measured at 50 °C

Table 1.5. Reactivity ratios of cyanoacrylates with other monomers at 60 °C.

Han and Kim carried out extensive studies on the stability and degradation of copolymers from the radical copolymerization of ECA with MMA using AIBN at 60 °C with methane sulfonic acid as anionic inhibitor.^[106] These copolymers were found to be random in nature with a strongly alternating tendency. Due to this alternation in the copolymer system, the inclusion of MMA units in the polymer backbone close to the chain terminus was believed to be the reason for suppressing the unzipping degradation of the polymer. The copolymers were found to have increasing thermal stability and improved stability in solutions of acetone with increasing MMA content.

Like cyanoacrylates, methylene esters of malonic acid are a group of electron deficient monomers which can be polymerized both anionically and radically. Polyakova et al. studied the anionic and radical copolymerization of a series of alkyl and fluoroalkyl methylene malonates with ECA using a molar feed of 5 – 50%.^[107] Bulk anionic copolymerizations were carried out using a tributyl lithium catalyst as

initiator at 20 °C, whereas bulk radical copolymerizations were carried out using dicyclohexyl peroxydicarbonate (DCHPC) (**Figure 1.4**) and BPO at 40 °C and 60 °C respectively, to generate the random copolymers (**Scheme 1.12**)

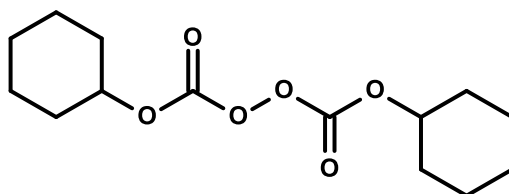
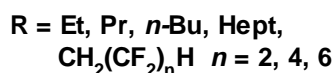
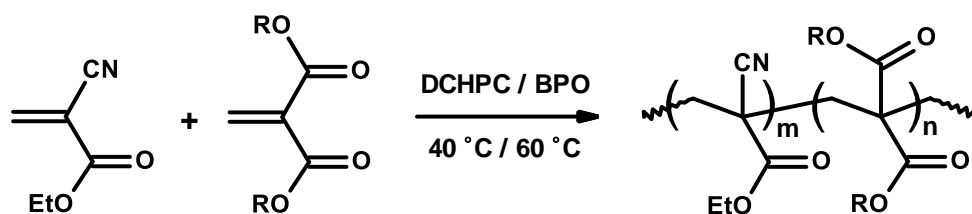


Figure 1.4. Structure of dicyclohexyl peroxydicarbonate (DCHPC).

The radically generated copolymers were found to give higher yield of copolymer than the anionic copolymerization. Additionally, the fluoroalkyl methylene malonates were observed to have increased reactivity toward ECA for radical copolymerization than their non-fluorinated counterparts as determined by elemental analysis. The mechanical and chemical properties of cured polymer from ECA based adhesive formulations containing 10% of alkyl and fluoroalkyl methylene malonates were tested. Formulations containing fluoroalkyl methylene malonate were found to have improved thermal and hydrolytic stability compared to the control formulation based on ECA alone.



Scheme 1.12. Copolymerization of ECA with alkyl/fluoroalkyl methylene malonates.

Copolymerizations of cyanoacrylates with simple alkenes have been reportedly difficult to achieve. Kinsinger et al. detailed their lack of success in attempting to copolymerize 1-octene with MCA, which largely resulted in cyanoacrylate homopolymer being formed.^[105] Sperlich and Eisenbach overcame this issue by employing $\text{CF}_3\text{CO}_2\text{H}$ or $\text{ZnCl}_2 \cdot \text{OEt}_2$ as complexing agents in the copolymerization of ethylene with ECA to form alternating copolymers.^[108] Alternating copolymers with

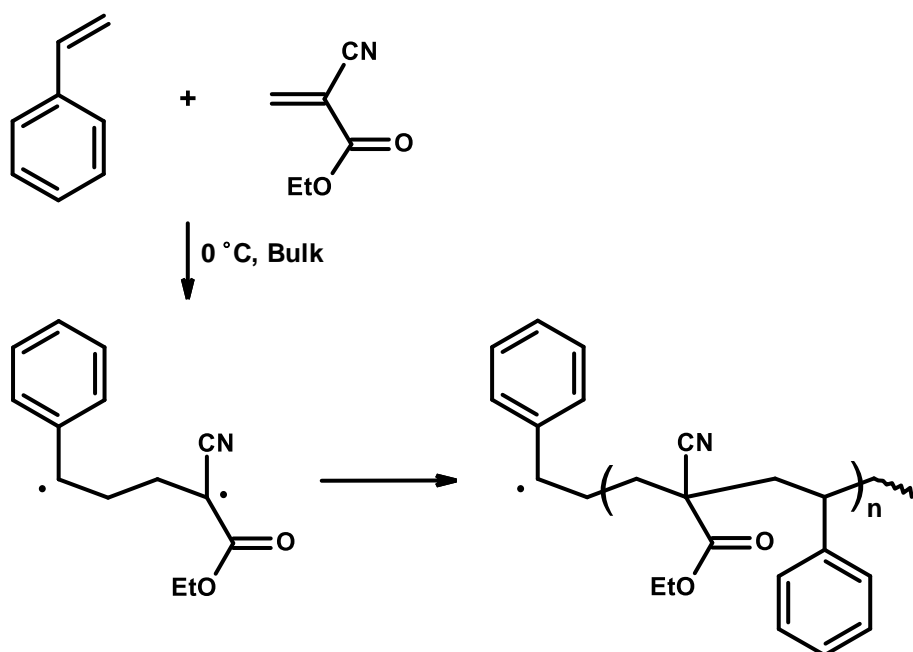
ethylene are of special interest as they exhibit crystallinity and this morphology can have unique thermal and mechanical properties.^[109] Copolymerizations were carried out in a pressure reactor using DCHPC as initiator with reaction components added together at -80 °C before being heated to 40 °C and maintained at that temperature for 15 hours. The concentration of complexing agent was found to have significant influence on the degree of alternation of the copolymer.

Dikov et al. reported on the radical graft copolymers of ECA onto poly(butadiene-*co*-acrylonitrile) using bulk polymerizations of ECA at 60 – 80 °C in the presence of up to 2 wt% of the dissolved polymer with BPO as initiator and TsOH (1 wt%) as anionic inhibitor.^[110] Graft polymerization is useful as it allows combination of two polymers which would otherwise be incompatible. Solution copolymerizations with ECA were also carried out in toluene at 80 – 90 °C with up to 75 wt% poly(butadiene-*co*-acrylonitrile) present. IR spectra of the resulting polymers gave superposition of the individual polymer spectra and were considered a good indication of a successful graft polymerization.

Piezoelectric materials can create electricity when subjected to a mechanical stress and conversely can generate a strain by the application of an electrical field. Piezoelectrics have great significance for electronic systems in a wide variety of applications such as sensors, speakers, actuators, microphones, microelectronic mechanical systems, semiconductors, robotics, etc.^[111] Polymers can act as piezoelectric materials whereby polymer functionality can repel or attract each other when an electrical field is applied. Hall et al. synthesized a large number of novel, nitrile containing copolymers and studied their piezoelectric properties in terms of their pyroelectric coefficients.^[112] Copolymers of MCA and ECA with VAc and isopropenyl acetate were included in this study with copolymerization reactions using AIBN in benzene at 60 – 65 °C with 7 wt% of acetic acid. Poly(cyanoacrylate) (10 – 20 wt%) solutions in cyclopentanone were spin coated onto conductive InSnO coated glass slides to give 2 – 5 µm films followed by heating at 130 – 160 °C in an oven under an inert nitrogen atmosphere. A set

electrical field was applied at temperatures close to T_g and after cooling to room temperature overnight the pyroelectric coefficient values (p) were measured. A copolymer of ECA and VAc gave a value of $p = 6.7 \mu\text{C}\cdot\text{m}^{-2}\text{K}^{-1}$, one of the highest values recorded in the study, in contrast to the value of $p = 1.94 \mu\text{C}\cdot\text{m}^{-2}\text{K}^{-1}$ measured for a copolymer of AN and VAc.

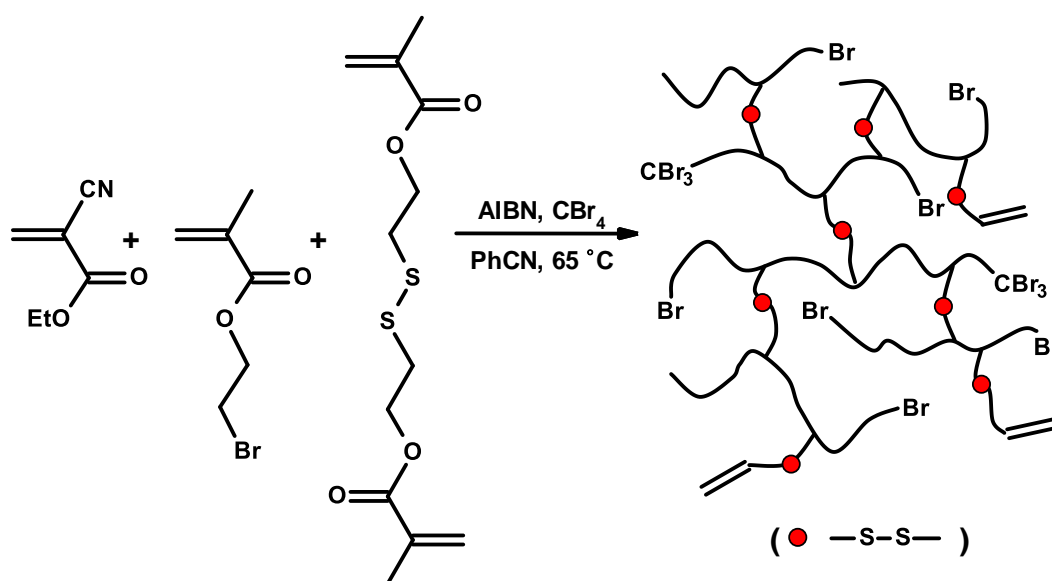
When cyanoacrylates are added directly to certain electron rich vinyl monomers, spontaneous copolymerization can occur without the requirement of an external initiator, even at room temperature and is believed to occur through the formation of diradical intermediates.^[113,114] The spontaneous copolymerization with cyanoacrylates has been reported for a number of electron-rich monomers such as St, *p*-methoxy St, α -methyl St, α -acetoxy St, and isobutylene.^[105,115] The addition of St to ECA is illustrated in **Scheme 1.13**. After the formation of the intermediate diradical species, the electron-deficient ECA radical centre rapidly reacts with another St monomer to form a new benzylic radical, which in turn further reacts with an ECA monomer and an alternating copolymer develops.



Scheme 1.13. Spontaneous copolymerization of St with MCA.

1.3.5 Synthetic Copolymerization Studies

Branched cyanoacrylate copolymers were recently reported by Tang et al. using ECA and small amounts of haloethyl methacrylates in the presence of CBr_4 and bis(2-methacryloyloxyethyl) disulfide ($(\text{MAOE})_2\text{S}_2$), a disulfide-based dimethacrylate crosslinker (**Scheme 1.14**).^[65] Highly branched poly(cyanoacrylates) are of special interest due to unique characteristics like enhanced solubility and reduced viscosity in comparison to their linear analogues with the same molecular weight.

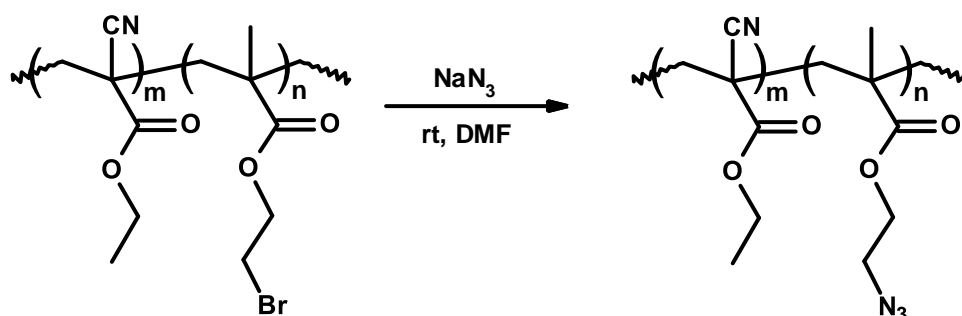


Scheme 1.14. Preparation of disulfide-containing branched ECA-based copolymers.

AIBN was used as initiator at 65 °C, $\text{CF}_3\text{CO}_2\text{H}$ as anionic inhibitor and CBr_4 was employed as a chain transfer agent to limit the polymer chain growth, inhibit gelation and provide bromide functionality to the chain ends. Typical relative ratios were $[\text{AIBN}]_0: [\text{CBr}_4]_0: [\text{ECA}]_0: [\text{HaloEMA}]_0: [(\text{MAOE})_2\text{S}_2]_0 = 1: 200: 500: 300: 100$ and by varying the amount of chain-transfer agent, crosslinker and comonomer, the point of gelation could be modified for different conversions and reaction times. The resulting highly branched polymers could be selectively degraded by treatment with Bu_3P to reductively cleave the disulfide bridges.

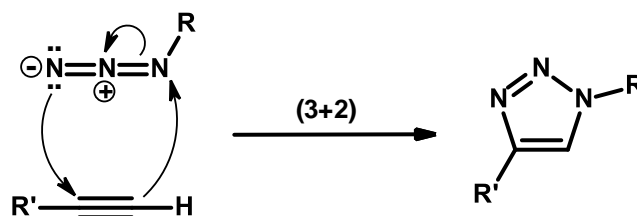
In the same study, Tang et al. synthesized linear random copolymers of ECA with chloroethyl and bromoethyl methacrylate.^[65] It was demonstrated that the pendant alkyl bromide groups present on the haloethyl methacrylate polymer units could be successfully exchanged to give pendent azide groups through a

nucleophilic substitution reaction with NaN_3 in DMF at ambient temperatures (Scheme 1.15).



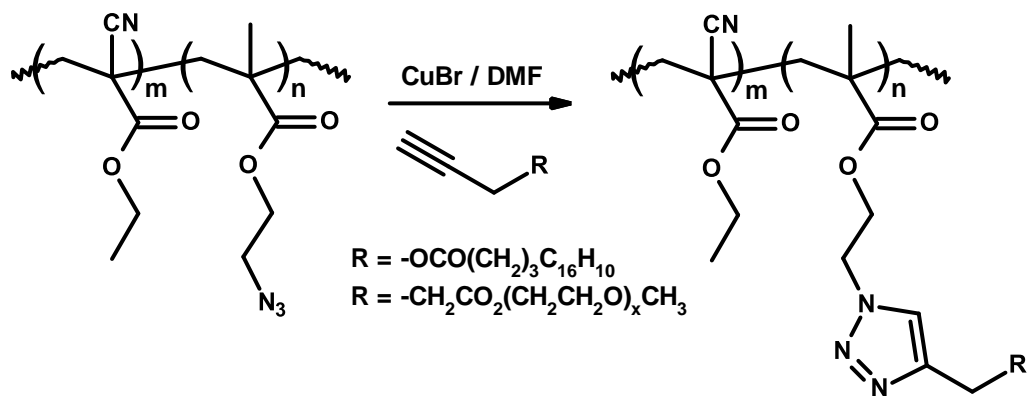
Scheme 1.15. Nucleophilic substitution with sodium azide.

Polymers containing azide groups are attractive as macromolecular precursors since the functionality can be directly reacted with alkynes in the presence of a copper catalyst in a Copper(I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC), a variant of the Huisgen 1,3-dipolar cycloaddition (Scheme 1.16). In this cycloaddition reaction a 1,3-dipole (azide) reacts with a dipolarophile (alkyne) to quantitatively yield a 5-membered heterocycle, a 1,2,3-triazole, in a so-called “click” chemistry type-reaction.^[116]



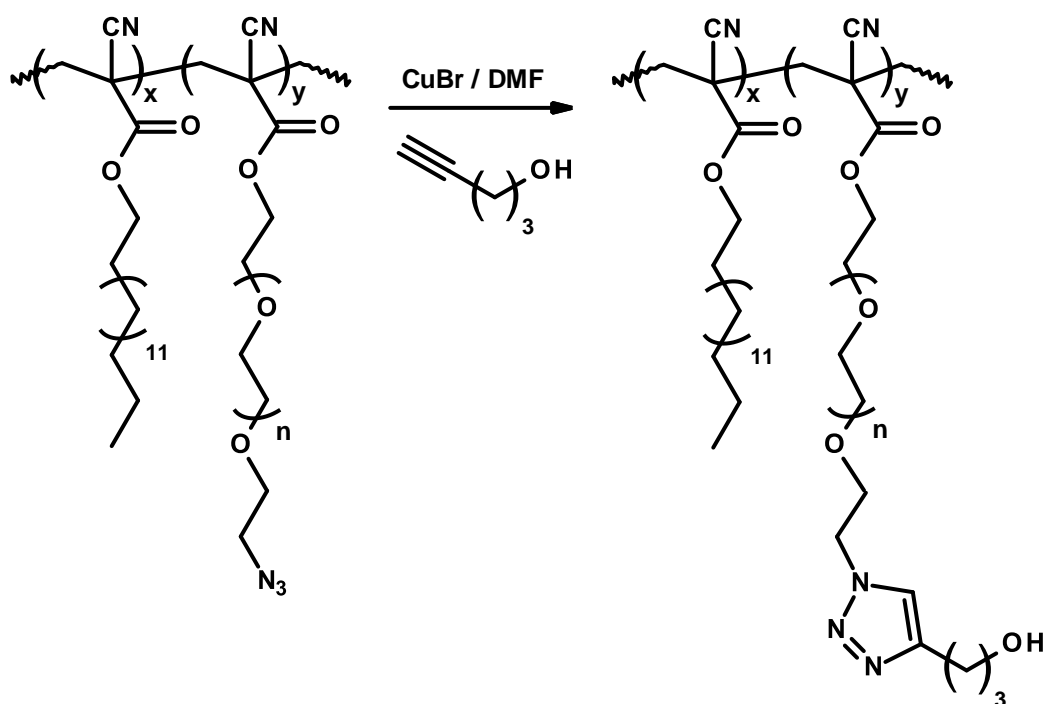
Scheme 1.16. 1,3-dipolar cycloaddition mechanism.

Tang et al. utilized the azide-alkyne cycloaddition to further modify the previously functionalized azide containing poly(ECA) random copolymers by reaction with propargyl pyrenebutyrate and poly(ethylene oxide) monomethylether 4-pentynoate to generate polymers with fluorescence and improved hydrophilicity respectively (Scheme 1.17).



Scheme 1.17. Cycloaddition of pendant azide group with functional alkynes.

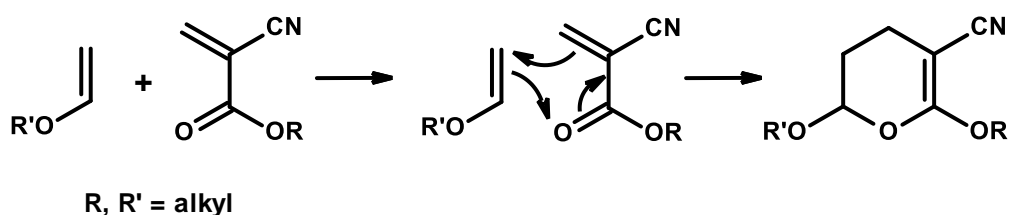
Polymer functionalization using “click” chemistry reactions has been reported by Nicolas et al. using poly[(hexadecyl cyanoacrylate)-*co*-azidopoly(ethylene glycol) cyanoacrylate] random copolymers.^[117] The cycloaddition reaction of the azide groups at the extremity of the PEG pendant chains with 4-pentyn-1-ol (**Scheme 1.18**) was found to proceed quantitatively using IR spectroscopic analysis, showing a total disappearance of the characteristic azide signal at 2103 cm^{-1} in the final copolymer, and ^1H NMR showing the expected peaks associated with the formed triazole ring.



Scheme 1.18. “Click” addition reactions with poly[(hexadecyl cyanoacrylate)-*co*-azidopoly(ethylene glycol) cyanoacrylate].

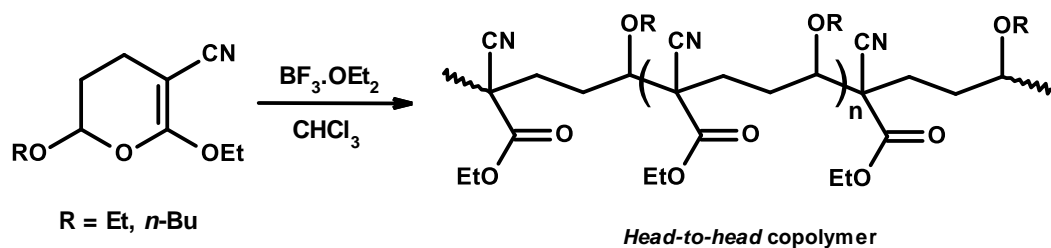
1.3.6 Alternatives to Radical Copolymerization

Cho and Lee have reported *head-to-head* alternating copolymers of cyanoacrylates with electron-rich monomers having markedly lower T_g and greater susceptibility to thermal degradation, as measured by differential scanning calorimetry (DSC), than their chemically equivalent *head-to-tail* copolymers derived from conventional radical copolymerization (**Scheme 1.11**). *Head-to-head* copolymers were derived from a spontaneous concerted [4 + 2] cycloaddition that gave dihydro-2H-pyran adducts when cyanoacrylates were added to alkyl vinyl ethers (**Scheme 1.19**).^[96-99]

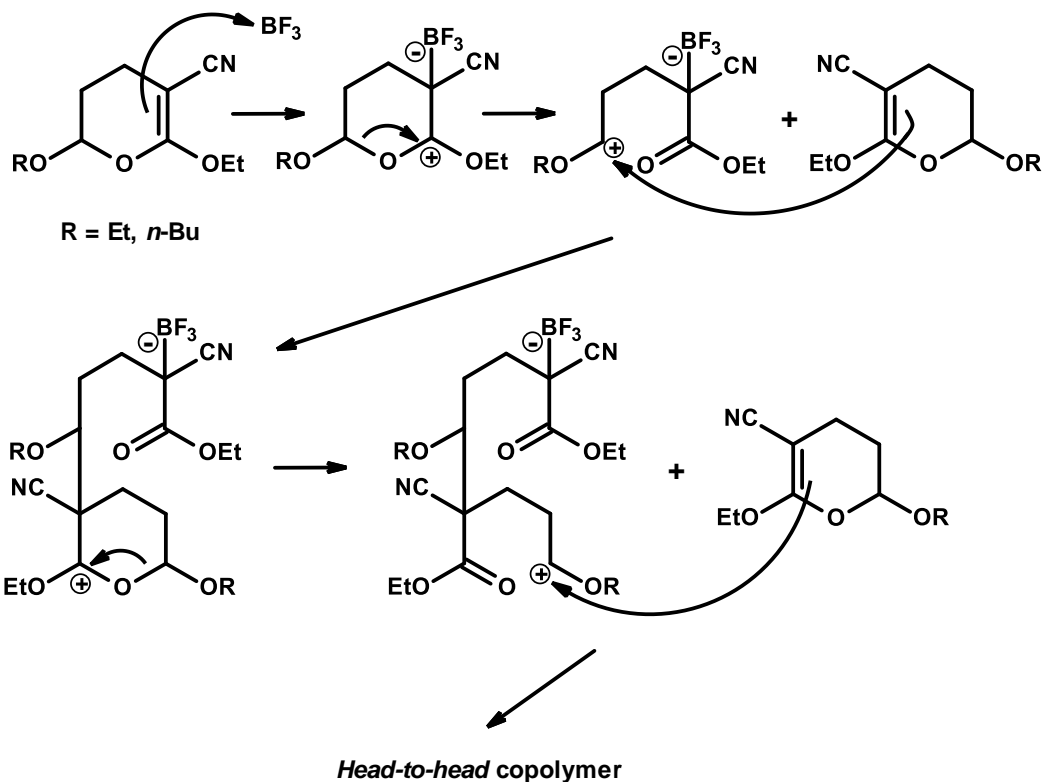


Scheme 1.19. Cycloaddition of cyanoacrylate onto ethyl vinyl ether.

The formed adducts can undergo a cationic ring-opening polymerization using $\text{BF}_3 \cdot \text{OEt}_2$ in CHCl_3 to give *head-to-head* alternating copolymers (**Scheme 1.20**).^[97] Similar *head-to-head* copolymers of vinyl ketones, β -bromostyrene and 2,3-dihydrofuran were reported by cycloaddition reactions with cyanoacrylates.^[118-120]

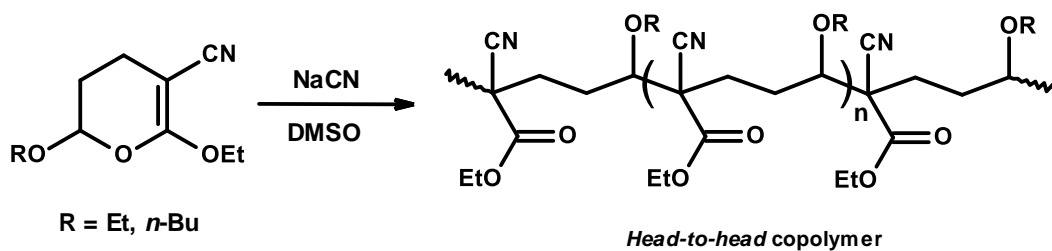


Mechanism:

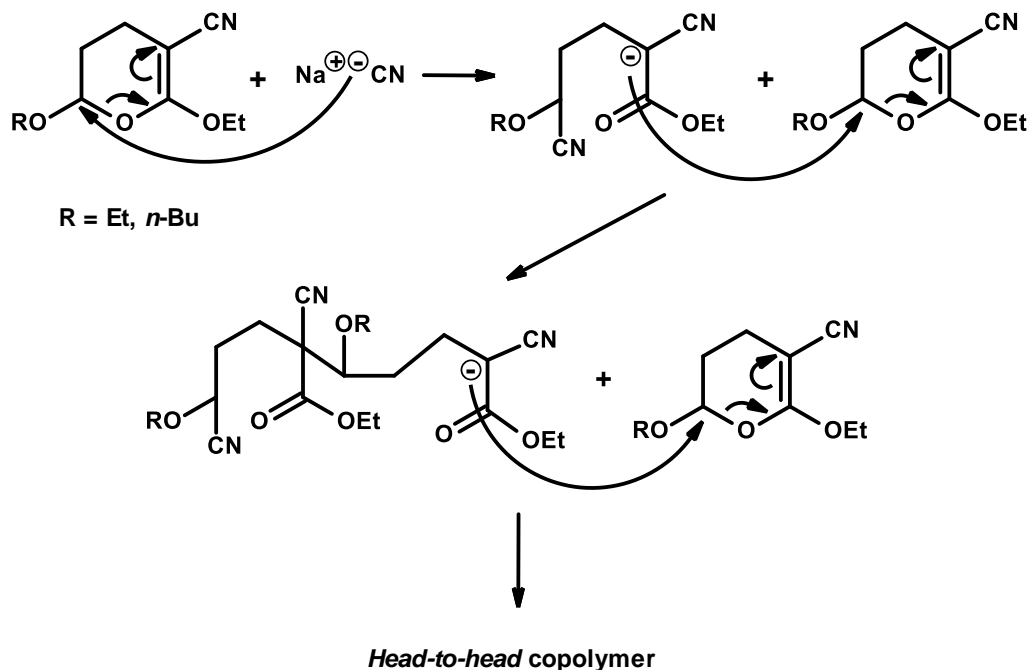


Scheme 1.20. Cationic ring-opening polymerization of the cycloadducts of cyanoacrylate and alkyl vinyl ethers.

NaCN in DMSO was employed as an alternative initiator in the anionic ring-opening polymerization of the same pyrans shown in **Scheme 1.21** to provide an alternative approach to *head-to-head* copolymers.



Mechanism:



Scheme 1.21. Anionic ring-opening polymerization of the cycloadducts of cyanoacrylate and alkyl vinyl ethers.

1.3.7 Nanoparticles

Colloidal nanosystems for drug delivery have been found to alter the pharmacokinetics of numerous drugs which, can often improve their therapeutic indexes.^[121] These colloids are usually spherical, submicron size, stable in bodily fluids, biodegradable, and have no systematic toxicity or immune response. Ideally, these nanoparticles can be loaded with various drugs and targeted to a specific location in the body, allowing drugs to be delivered to certain organs or cells but not to others. Site-specific targeting gives increased drug concentration to infected

or abnormal cells and low concentration to normal cells thus decreasing drug toxicity and undesirable side effects.^[122]

Many synthetic polymers such as poly(lactic acid), poly(caprolactone) and importantly poly(cyanoacrylate) have found utility in the preparation of various drug nanocarriers. Since their introduction almost 40 years ago, nanoparticles based on biodegradable poly(cyanoacrylate) polymers have been developed as drug delivery vehicles for a wide range of medicines in the treatment of various diseases and have become an established technology for colloidal nanomedicine.^[23]

Nanoparticle is a collective name for two different types of colloidal objects that can be separately obtained depending on their method of preparation, namely nanospheres and nanocapsules. Nanospheres are matrix systems constituted of polymer, in which the drug is dispersed or adsorbed, whereas nanocapsules are vesicular systems in which the drug is solubilized in a liquid core of either water or oil surrounded by a thin polymer layer (**Figure 1.5**).

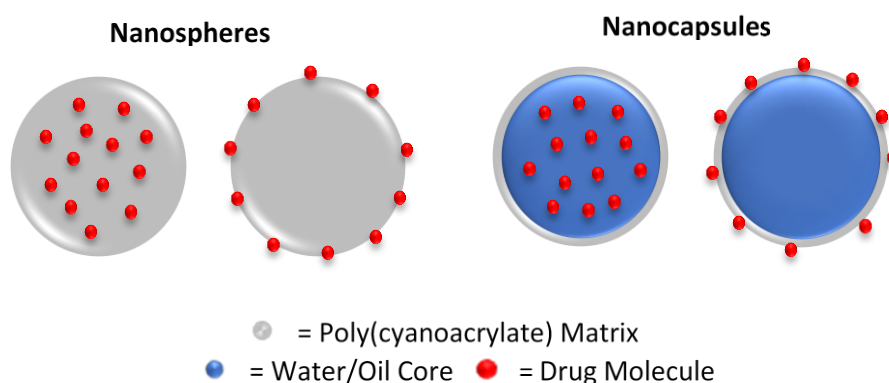
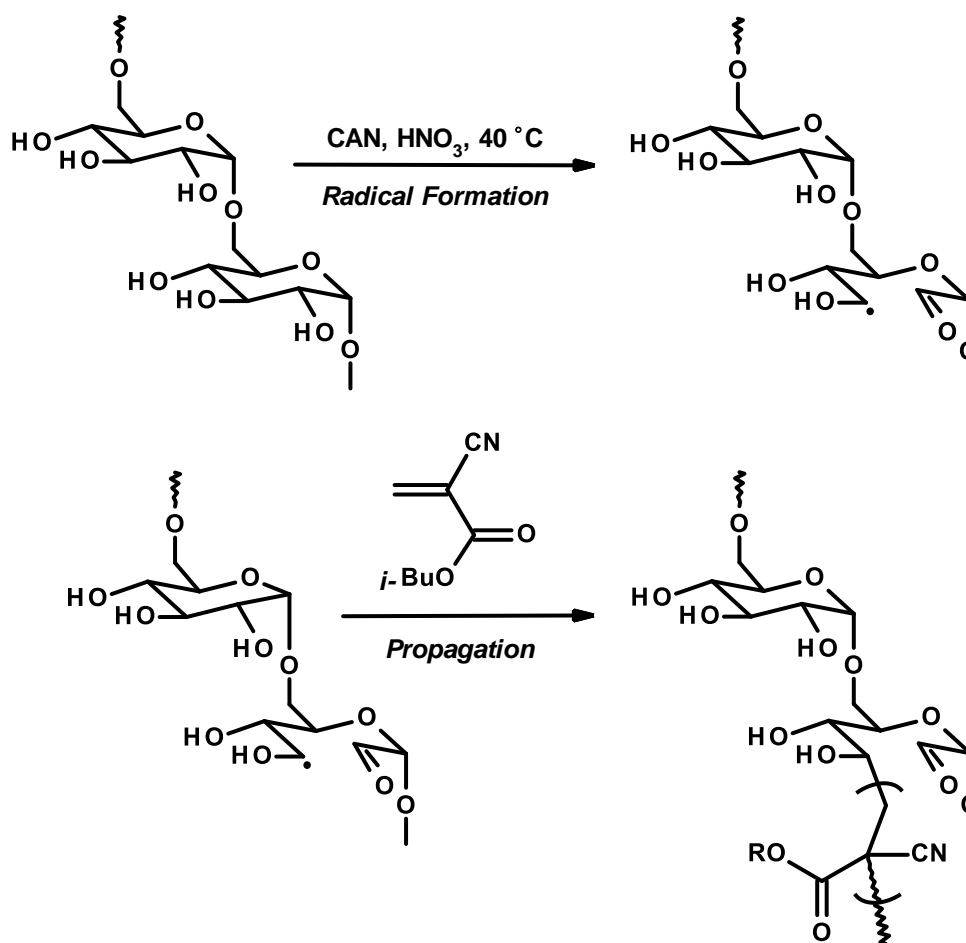


Figure 1.5. Type of nanoparticles

Poly(cyanoacrylate) nanospheres are classically prepared by anionic emulsion or miniemulsion polymerizations of the monomer in an acid aqueous medium, typically of $\text{pH} \approx 3$, containing a surfactant as colloidal stabilizing agent. Since this relatively simple process was first reported by Couvreur et al. in 1979,^[123] numerous studies have investigated the polymerization parameters and kinetics.^[124-126] Alternatively, poly(cyanoacrylate) nanospheres can be produced by

radical polymerization using traditional radical initiators such as AIBN, though at very low pH of close to 1.^[127] Radical polymerization has the advantage of achieving high molecular weight poly(cyanoacrylates), whereas in the case of anionic polymerization, the molecular weight is strongly dependent on the pH of the media and typically results in polymers below 8,000 g.mol⁻¹.^[128]

Chauvierre et al. employed redox radical polymerization using cerium ammonium nitrate, (NH₄)₂Ce(NO₃)₆, (abbreviated as CAN) in HNO₃ to initiate cyanoacrylate polymerization in the presence of various polysaccharides such as dextran, heparin or chitosan.^[129] Initiation and propagation of isobutylcyanoacrylate (*i*-BuCA) occurred as the monomer is added to the polysaccharide and CAN mixture to form the polysaccharide-poly(*i*-BuCA) copolymer (**Scheme 1.22**). The rate of polymerization was found to be rapid, which is due to a fast initiation step whereby all the radicals are produced at the same time by action of the cerium ions and are ready to initiate the cyanoacrylate monomer upon its addition. The fast radical initiation rate at low pH renders any anionic polymerization negligible within the timescale of the reaction and allows radical propagation to predominate. This initiation process has since been applied to emulsion polymerizations in the preparation of poly(cyanoacrylate) based nanospheres with various polysaccharides on the surface.^[129-131]

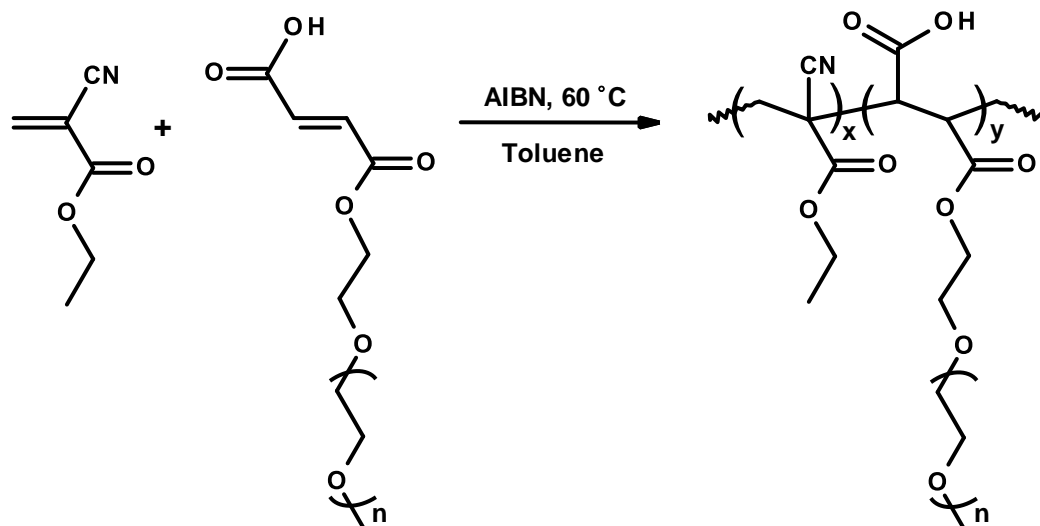


Scheme 1.22. Preparation of nanospheres by radical polymerization of cyanoacrylate onto a polysaccharide (dextran) with cyanoacrylate.

Poly(cyanoacrylate) nanocapsules are typically prepared by anionic interfacial polymerization techniques in water-in-oil or oil-in-water emulsion systems,^[132-134] however, nanocapsules can also be formed by nanoprecipitation. In this method preformed polymers (such as those made by radical polymerization) are dissolved in an organic solvent, typically acetone, and then added dropwise to an aqueous solution of surfactant where they self-assemble to form nanocapsules.^[135]

Using this approach, poly[α -maleic anhydride- ω -methoxypoly(ethylene glycol)-co-ethyl cyanoacrylate] copolymers were prepared by radical solution copolymerization of a PEG macromonomer with ECA at $60\text{ }^\circ\text{C}$ using AIBN (**Scheme 1.23**).^[136] Using the nanoprecipitation method, the formed polymer was added to acetone containing the drug (ibuprofen) and successfully self-assembled upon

addition to water to encapsulate the drug (**Figure 1.6**).^[137] PEGylated particles (also termed “stealth” nanoparticles) are of great significance as they can escape immuno-recognition to give long-circulating drug delivery vehicles.^[138,139]



Scheme 1.23. Polymerization of a PEG macromonomer with ECA.

Nanoparticles based on cyanoacrylates are considered the most promising polymer colloidal drug delivery system and have been significantly developed for cancer therapy with certain formulations having reached Phases III in clinical trials.^[140]

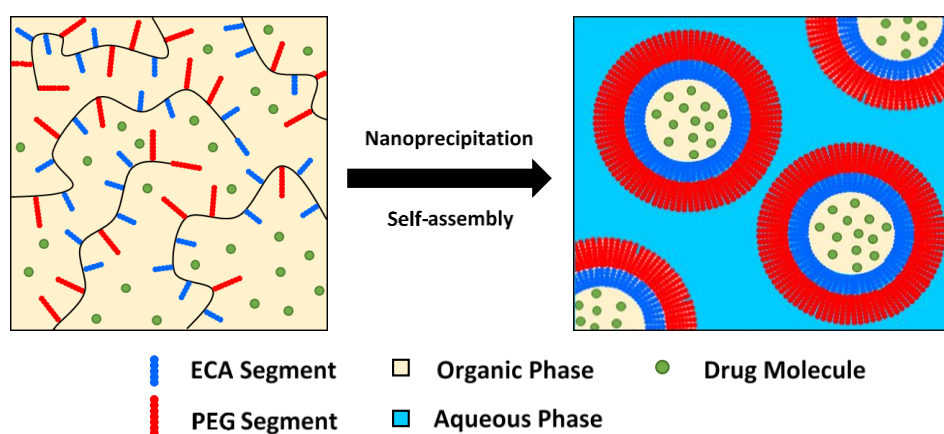


Figure 1.6. Formation of nanocapsules by polymer self-assembly.

CHAPTER 2

INITIAL ATTEMPTS AT RAFT

POLYMERIZATION OF CYANOACRYLATES

2.0 INITIAL ATTEMPTS AT RAFT POLYMERIZATION OF CYANOACRYLATES

2.1 Introduction to Reversible-Deactivation Radical Polymerization (RDRP)

Living polymerization was first described by Szwarc and the current definition can be ascribed to him.^[141] An ideal living system consists of a chain growth process where all polymer chains are initiated at the beginning of the polymerization and continue to propagate without chain breaking reactions (transfer and termination) until all monomer is consumed. Living polymerization techniques allow advanced, complex architectures and well controlled polymer structures. Up to the early 1990s, ionic polymerizations were the only living technique available to synthesize well-defined polymers.

Anionic and cationic living polymerizations are disadvantaged by their requirement for stringent reaction conditions and are limited to a relatively small number of monomer combinations for copolymerization.^[142] Radical polymerization is applicable to a much wider spectrum of monomers (both electron-rich and electron-deficient vinyl monomers). It was realised that living character had to be actualised in the context of the more versatile radical polymerization which ultimately lead to an explosion of academic and industrial research into more controlled radical polymerization. Collectively, such polymerization methods have been called a variety of names such as controlled or living radical polymerizations (CRP or LRP) however, it is the IUPAC recommendation that such techniques be referred to as reversible-deactivation radical polymerization (RDRP) and that the word “control” should be put into context in terms of the specific aspect that is being controlled.^[143] It should be noted that since RDRP methods proceed through a radical mechanism, they are not truly living as defined by Szwarc since some radical-radical termination is inevitable.

In a typical so-called RDRP process, all chains are initiated early in the reaction and are allowed to grow throughout the reaction by establishing equilibrium between active and dormant chains. When active, these chains successively add monomer and termination events are minimized to the point of being negligible. Generally speaking, for a successful RDRP the resulting polymer will have a low dispersity and

predetermined number average molecular weight and can be extended to form block copolymers more efficiently. Ideally, RDRP should feature the criteria of:

➤ *1st order kinetics with respect to monomer*

The logarithmic function of monomer concentration, $\ln([M]_0/[M])$ is linear with respect to time, indicating a constant propagating radical concentration as is the feature of steady-state conditions, typical of conventional radical polymerization. Acceleration on such a plot may be indicative of slow initiation.^[144]

➤ *Linear increase of M_n with monomer conversion*

The degree of polymerization is determined by the consumed monomer to initially introduced initiator molar ratio. Linearity of such a plot indicates only a constant number of all chains (dead and growing).^[144]

➤ *Low polydispersity*

Polydispersity indices should be close to a Poisson distribution of $M_w/M_n \approx 1$. Polydispersities increase with conversion when chain transfer or termination events become significant.^[144]

➤ *Polymer chain end functionality is preserved*

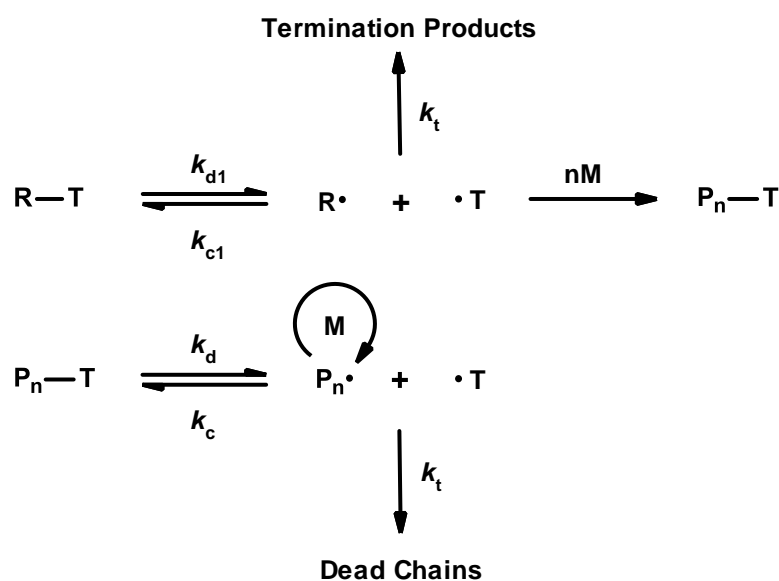
Quantitative α - and ω - functionalization through elimination of irreversible chain transfer and termination enables the possibility for polymer chains to grow after monomer consumption to allow block copolymer synthesis.^[144]

RDRP methods and techniques have revolutionised the field of polymer synthesis over the past 30 years, allowing the design of polymers with carefully controlled chain structures, length, molecular weight distribution, end-group functionalities and architecture through radical mechanisms. Among the different RDRP techniques, nitroxide-mediated polymerization (NMP),^[145] atom-transfer radical polymerization (ATRP),^[146] and reversible addition-fragmentation chain transfer (RAFT) polymerization^[147] remain the most popular. There is a continued effort to obtain well-defined materials from RDRP to give complex polymer architectures

and nanostructures which offer substantial benefits to modern application areas such as electronics and biotechnology.

2.1.1 Nitroxide Mediated Polymerization (NMP)

Nitroxide-mediated polymerization (NMP) is one of the earliest forms of RDRP techniques that allows the design of well-defined, functional and complex macromolecular architectures. IUPAC recommends the term “aminoxyl” as the term “nitroxide” is discouraged in IUPAC nomenclature. Therefore, NMP can be termed aminoxyl mediated radical polymerization (AMRP) however, this terminology has not been widely adopted.^[143] The first real demonstration of NMP for the polymerization of several monomers using nitroxides and alkoxyamines was originally reported by Solomon, Rizzardo and Cacioli in 1986.^[148] The work was carried out at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) in what was then the Division of Applied Organic Chemistry and was described as a method of living radical polymerization. Their patent was derived from previous work by the same group where they employed nitroxides to efficiently trap carbon centred radicals in their studies into free-radical initiation mechanisms.^[149] The 1986 patent disclosed the synthesis of low molecular weight oligomers, primarily acrylates, using nitroxides such as commercial (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (**Figure 2.0**) at polymerization temperatures of 80-100 °C. It wasn't until a report from Georges et al. at Xerox describing the effective use of NMP to synthesize polystyrene with narrow molecular weight distributions that NMP began receiving significant interest.^[150]



Scheme 2.0. Complete mechanism of the NMP process.

The NMP process functions by a reversible termination mechanism with a growing propagating (macro)radical ($\text{P}_n\cdot$) and the controlling agent nitroxide ($\text{T}\cdot$) to predominantly yield a (macro)alkoxyamine ($\text{P}_n\text{-T}$) (**Scheme 2.0**). This dormant, functionalized chain dissociates back to the propagating radical by a thermally induced homolytic cleavage which is able to then add to more monomer (**M**). When a suitable nitroxide is employed, an activation-deactivation is established between dormant and active species. This equilibrium presents the advantage of being a purely thermal process where no added catalyst is required. The polymerization kinetics is governed by both this activation–deactivation equilibrium (with $K = k_d/k_c$, the activation–deactivation equilibrium constant) and the persistent radical effect (PRE). The PRE is an unusual kinetic phenomenon which is a key feature of the NMP mechanism and was first described by Fischer in 1986 regarding radical reactions, though not in a polymerization context.^[151] The Fischer group have subsequently carried out significant studies dedicated to the PRE in the kinetic description of NMP.^[152,153] The PRE can be explained in the context of NMP as follows: the NMP process starts by decomposition of (**R-T**) to give transient carbon radical (**R**•) and a persistent nitroxide radical (**T**•). In the initial reaction stages, generation of both of these radical species increase linearly with time, as dictated by the decomposition rate coefficient k_{d1} (**Scheme 2.0**). This continues until such time as radical concentration is sufficiently large enough to allow bimolecular reactions, either by

self-termination of ($R\cdot$) or termination with a propagating oligomer, which results in the removal of two initiator derived radicals from the system. The irreversible termination of ($R\cdot$) leads to a decrease in concentration of ($R\cdot$) and consequently the concentration of the persistent nitroxide radical ($T\cdot$) gradually begins to increase as ($T\cdot$) cannot undergo self-termination. The increased concentration of ($T\cdot$) is self-limiting, as a higher concentration leads to more efficient formation of a dormant chain end (P_n-T) and reduced irreversible radical coupling. The PRE then eventually controls the polymerization process. A small fraction of active propagating chains is maintained throughout the polymerization, thus significantly reducing the probability of irreversible termination reactions occurring.

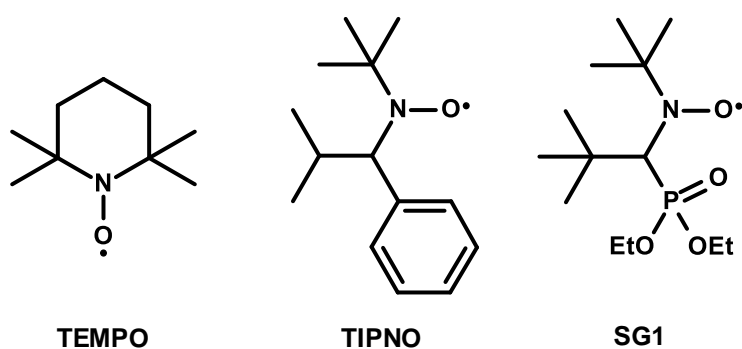
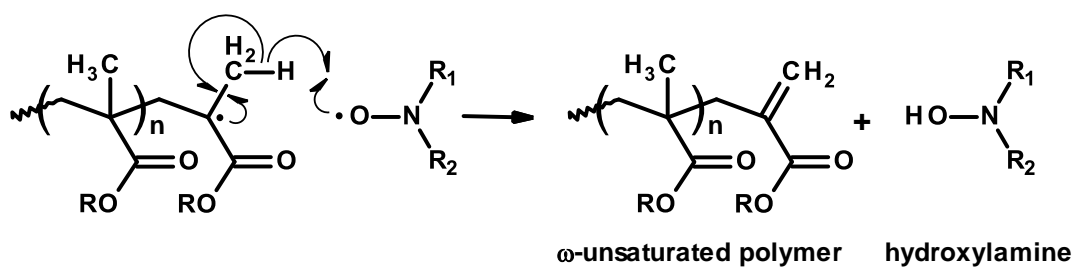


Figure 2.0. Commonly used nitroxides with NMP.

One of the most significant breakthroughs in NMP was the design of non-cyclic nitroxides bearing a hydrogen atom on one of the α -carbons. The two best examples of these next generation nitroxides are *N-tert-butyl-N*-[1-diethylphosphono-(2,2-dimethylpropyl)] nitroxide better known as SG1 developed by Gnanou and Tordo^[154] and 2,2,5-trimethyl-4-phenyl-3-azahexane-3-aminoyl (TIPNO) introduced by Braslau and Hawker et al.^[155] (**Figure 2.0**). These nitroxides act as almost universal initiators, allowing accurate control of polymerization for a wide variety of monomer families such as acrylates, acrylamides, 1,3-dienes, acrylonitriles, whereas cyclic nitroxides can only effectively control the polymerization of styrene.^[156] Disproportionation between the nitroxide and a poly(methacrylate) radical is a particular drawback of NMP, where the hydrogen atom is readily abstracted by the nitroxide from the α -methyl group leading to formation of a hydroxylamine and ω -unsaturated chain terminus (**Scheme 2.1**).^[157]



Scheme 2.1. Disproportionation mechanism of poly(MMA) in NMP to give ω -unsaturation.

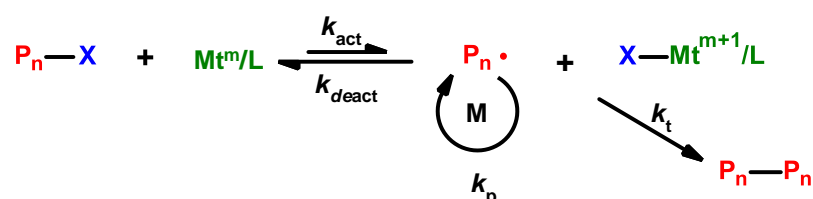
NMP has become a mature technique in RDRP and due to its simple method of implementation continues to be utilized in a variety of emerging new application areas.

2.1.2 Atom Transfer Radical Polymerization (ATRP)

Atom transfer radical polymerization (ATRP) is another type of RDRP, defined by IUPAC as the “controlled reversible-deactivation radical polymerization in which the deactivation of the radicals involves reversible atom transfer or reversible group transfer catalyzed usually, though not exclusively, by transition-metal complexes”,^[143] and was discovered independently by Sawamoto^[158] and Matyjaszewski in 1995.^[159] Since it was initially reported, ATRP has become one of the most researched RDRP techniques with over 14,000 publications as of the beginning of 2014.^[160]

All ATRP processes comprise of three key components: a monomer, an initiator and a catalyst (in the form of a transition metal and suitable ligand). ATRP is based on the redox reaction between an initiating alkyl halide/pseudo-halide or a halogen end-capped polymer chain (P_nX) and a transition metal catalyst (Mt^m/L), where control is achieved by the equilibrium between propagating radicals and dormant species (**Scheme 2.2**). The transition metal catalyst complex (Mt^m/L) in its lower oxidation state (m) behaves as an activator which homolytically cleaves the alkyl (pseudo)halide bond (k_{act}) to form the alkyl radical ($P_n\cdot$) and the deactivator transition metal complex ($X-Mt^{m+1}/L$) in its higher oxidation state ($m+1$). $P_n\cdot$ can then propagate (k_p) with a suitable monomer (M), terminate as in conventional free

radical polymerization by either coupling or disproportionation (k_t), or be reversibly deactivated (k_{deact}) by $X-Mt^{m+1}/L$ to form a dormant end-capped polymer (P_nX) and activator (Mt^m/L). Termination reactions cannot be avoided in ATRP and those that occur in the initial stages of the polymerization will lead to a build-up of deactivator concentration resulting in PRE. The shifting of the equilibrium to the left (i.e. to the side of the dormant species), minimizes termination, enabling a good control over molecular weight and architecture.



Scheme 2.2. General ATRP Mechanism.

ATRP has been successfully utilized for a variety of monomer types, (meth)acrylates, (meth)acrylamides, styrenics, acrylonitrile and carried out in various reaction condition, in bulk, in a heterogeneous system (e.g., emulsion, suspension) and in solutions of both polar and non-polar solvents.^[161]

The most important component in ATRP is the transition metal catalyst, usually in the form of a salt of chlorine, bromine or iodine, as it determines the equilibrium between the active and dormant species. Overwhelmingly the most used catalyst is copper due to its versatility in ATRP and relatively low cost,^[162] however a number of other metals have been employed such as iron,^[163] ruthenium,^[164] nickel,^[165] molybdenum,^[166] rhenium,^[167] rhodium,^[168] and palladium.^[169] Several different types of ligand have been used in conjunction with the transition metals and are an important feature of ATRP. The ligands help to solubilize the transition metal salt in the polymerization media and can adjust the redox characteristics of the final metal complex. Copper is usually ligated with multidentate nitrogen based ligands such as bidentate 2,2'-bipyridine (Bpy),^[159] tridentate pentamethyldiethylenetriamine (PMDETA)^[170] and tetradentate tris(2-(dimethylamino)ethyl)amine (Me6-TREN).^[171] Iron is usually ligated by phosphine ligands whereas phosphorous ligands are often

used to complex with other metal catalysts like rhenium, rhodium, nickel and palladium.

Initiators for ATRP have the primary function of determining the number of growing polymer chains and therefore the initiator concentration determines the molecular weight of the resulting polymer. Initiators are typically alkyl halides and commonly the initiator is chosen so that the generated radical is structurally analogous to the propagating radical of the monomer to be polymerized. For example, compounds such as ethyl 2-bromopropionate and ethyl 2-bromoisobutyrate are routinely used for acrylates and methacrylates respectively,^[172] whereas (1-bromoethyl)benzene is usually used for polymerizing styrene and styrene derivatives.^[173] The structures of these common ATRP initiators are shown in **Figure 2.1**. Another important class of initiator are sulfonyl halides, reported by Percec et al. as universal initiators in ATRP.^[174] Conventional radical initiators such as AIBN can be used to initiate ATRP with the metal catalyst in its higher oxidation state in what is termed “Reverse ATRP”.^[175] The initiator radical adds to monomer and creates a propagating chain to which the metal catalyst efficiently transfers a halogen, thereby reducing the metal complex and deactivating the growing chain.

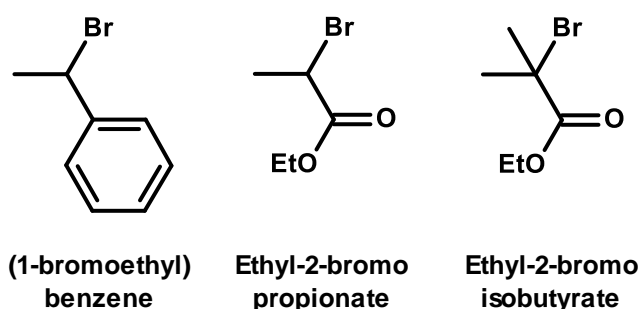


Figure 2.1. Commonly used initiators in ATRP.

One key limitation of the ATRP process is the large amounts of metal catalyst required to sufficiently control polymerizations and the subsequent removal from the polymer product, however, modern developments in ATRP have led to significant improvements in this area. Newer methods such as addition of a reducing agent as is done in the continuous Activator (Re)generation by Electron-Transfer (ARGET),^[176] and addition of an external radical initiator, as is done in

Initiators for Continuous Activator (Re)generation (ICAR) ATRP^[176] have allowed low metal catalyst loadings to be used.

ATRP is more versatile than NMP in terms of the range of polymerizable monomers, although the less reactive monomers such as ethylene, vinyl acetate or vinyl chloride have proven more difficult to control and require more reactive ATRP activators which can bring unwanted complications to the polymerization. A further limitation of ATRP is its low tolerance to acid protons which means monomers such as acrylic acid and methacrylic acids can only be polymerized in their carboxylate salt form.^[177]

2.1.3 Reversible Addition-Fragmentation Chain-Transfer Polymerization (RAFT)

Unlike NMP and ATRP that rely on PRE and exchange reactions and can be considered reversible termination of propagating radicals, RAFT operates on the principle of degenerative chain transfer whereby radicals exchange with dormant species in a reversible transfer process. The equilibrium between active and dormant chains is achieved in RAFT by employing thiocarbonylthio compounds (**Scheme 2.3, 1**) that function as reversible addition-fragmentation chain transfer (RAFT) agents, and was first reported by Rizzardo, Moad, and Thang in 1998.^[178]

In a degenerative chain transfer system, there is no change in the overall number of radicals during the activation-deactivation process, and an external source of radicals is required, typically a radical initiator.

RAFT has become a powerful tool for polymer synthesis and arguably the most robust and versatile method of RDRP.^[179,180] RAFT can be used to control the polymerization of a vast array of vinyl monomers such as (meth)acrylates, (meth)acrylamides, styrenics, vinyl esters and vinyl amides. It is highly tolerant of polymerization temperature, solvents, pressure and a wide range of functionalities (e.g. -OH, -NR₃, -SO₃H, -COOH, -CONR₂).^[181]

an equal probability for all chains to grow, which results in the formation of polymers with narrow molecular weight distributions (MWDs). Radical-radical termination is not directly prevented by the RAFT process, therefore termination and irreversible chain transfer events are inevitable with the number of dead chains depending on initiator concentration. Their significance however, is suppressed since the number of dormant RAFT chains is typically much greater than the number of initiator derived chains. The number of dead chains is equal to the number of chains generated from the initiator, and the theoretical number fraction of living chains (L , “livingness”) can be calculated according to equation 3.

$$L = \frac{[RAFT]_0}{[RAFT]_0 + 2f[I]_0(1 - e^{-k_d t}) \left(1 - \frac{f_c}{2}\right)} \quad (3)$$

Where $[RAFT]_0$ and $[I]_0$ are the respective initial concentrations of RAFT agent and initiator (of dissociation coefficient k_d). The value “2” means that one molecule of initiator gives two primary radicals with an efficiency f (assumed to be 0.5). The term $(1-f_c/2)$ represents the number of chains produced in a radical-radical termination event with the coupling factor f_c assumed to be zero.^[182,183]

After the polymerization is complete (or stopped), the vast majority of chains retain the thiocarbonylthio end-group and can be isolated as stable materials.

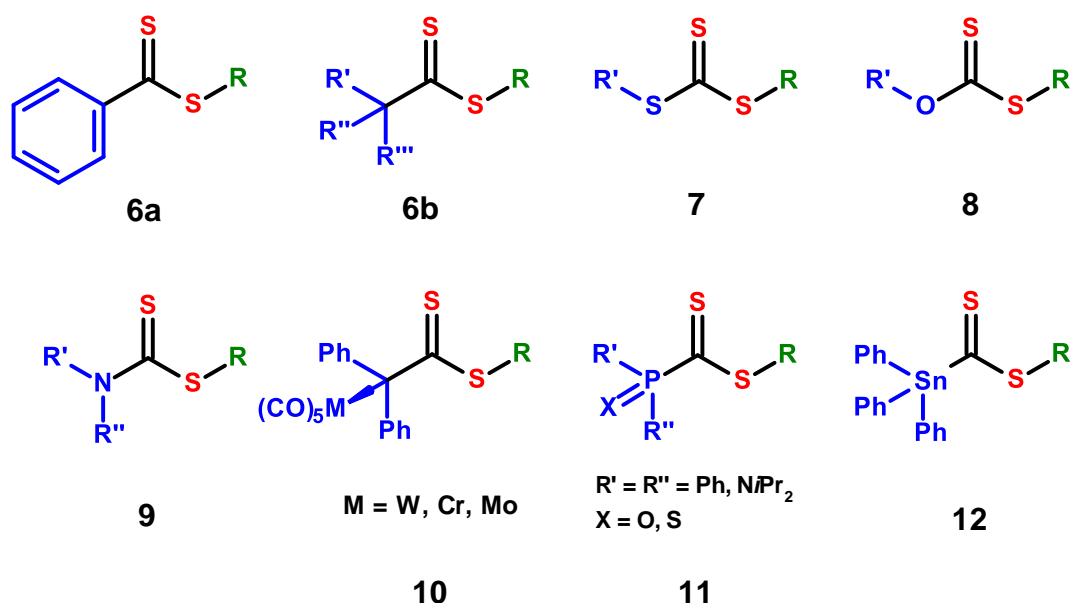


Figure 2.2. Types of RAFT agents.

The Z and R substituents of RAFT agents will have a significant impact on the efficiency of the RAFT agents control over the polymerization and this will be related to the structure of the monomer being polymerized. The Z group serves to activate or deactivate the thiocarbonyl group radical addition and the R group must be a good leaving group that is capable of reinitiating polymerization. Therefore a RAFT agent must be carefully selected based on the monomer to be polymerized. **Table 2.0** shows the compatibility of monomer families with some commercially available RAFT agents.

There now exist many different RAFT agents, but they generally fall into five main classes (**Figure 2.2**) which include: aromatic **6a** and aliphatic **6b** dithioesters, trithiocarbonates **7**, dithiocarbonates (xanthates) **8**, dithiocarbamates **9**, and in the last number of years a new class of organometallic RAFT agents (so-called M-RAFT agents) **10** have been developed.^[185] There are a wide variety of other RAFT agents which fall outside these classes, the majority of which have sulfonyl, phosphonate, or phosphine moieties as their Z-group. Two recent publications have reported two further distinct types of RAFT agent: phosphinoyl and thiophosphinoylcarbodithioates^[186] **11** and triphenylstannylcarbodithioates (Sn-RAFT)^[187] **12**, the latter reportedly possessing similar reactivity to dithiobenzoates.

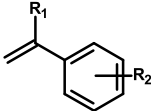
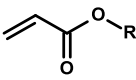
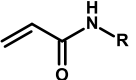
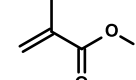
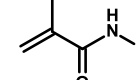
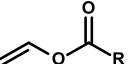
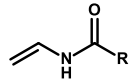
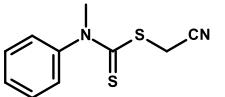
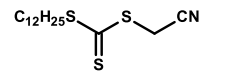
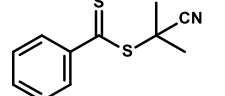
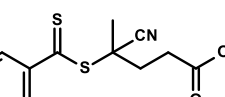
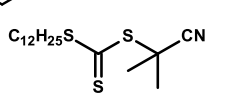
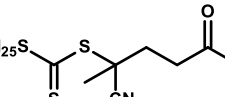
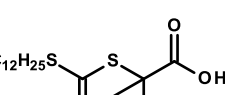
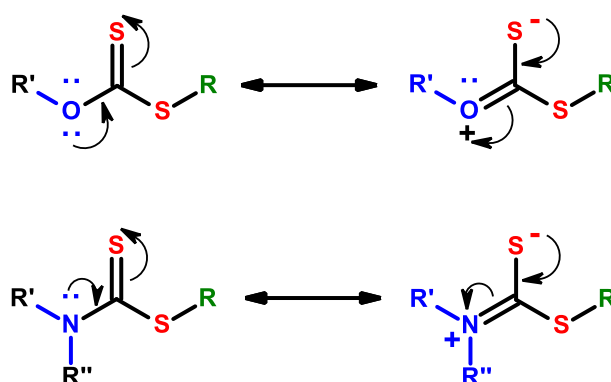
							
	styrenes	acrylates	acrylamides	methacrylates	methacrylamides	vinyl esters	vinyl amides
	—	—	—	—	—	+++	+++
	+++	+++	+++	—	—	—	—
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Table 2.0. RAFT agent compatibility table.^[184]

The R group of the RAFT agent must be a good homolytic leaving group relative to the incoming propagating monomer ($P_n\cdot$) and favour forward fragmentation of **2** to rapidly give a dormant macroRAFT **3** and $R\cdot$. The expelled radical $R\cdot$ must also be able to efficiently add to the monomer to reinitiate polymerization so that $k_{Ri} \gg k_p$. It is not sufficient for R to be a monomeric analogue of the propagating radical, for example the R group of 2-ethylpropionate ($C(CH_3)_2CO_2Et$), a monomeric analogue of poly(MMA), is a poor R group for controlling the polymerization of MMA as R is a poor homolytic leaving group with respect to the poly(MMA) propagating radical.^[188] Radical stability is important in determining fragmentation rates. Control over the polymerization of 1,1-disubstituted monomers which result in a tertiary $P_n\cdot$ usually requires R to be tertiary however, polymerization of monomers with high k_p are best controlled with RAFT agents having primary or secondary R groups. Polar effects are also extremely important in determining fragmentation rates as electron-withdrawing groups on R both decrease rates of addition to the thiocarbonyl group and increase rates of fragmentation.



Scheme 2.4. Zwitterionic canonical forms of dithiocarbonates and dithiocarbamates.

The Z-group acts to activate (or deactivate) the thiocarbonyl group of **1** or **3** toward addition of the propagating radical $P_n\cdot$, while also modifying the rate of fragmentation of intermediate radicals **2** and **4**. The reactivity of a RAFT agent can be effectively altered by changing the Z-group. RAFT agents that have a carbon or sulfur atom adjacent to the thiocarbonylthio such as dithioesters (**6a** and **6b**) and trithiocarbonates **7** respectively, are more active toward radical addition whereas RAFT agents that have an oxygen or nitrogen such as dithiocarbonates **8** or

dithiocarbamates **9** for example, are significantly less reactive toward radical addition.^[189] This lower reactivity can be attributed to the contribution of their zwitterionic canonical forms (**Scheme 2.4**) which reduces the doublebond character of the thiocarbonyl group due to the lone pair of electrons on the oxygen or nitrogen heteroatom.

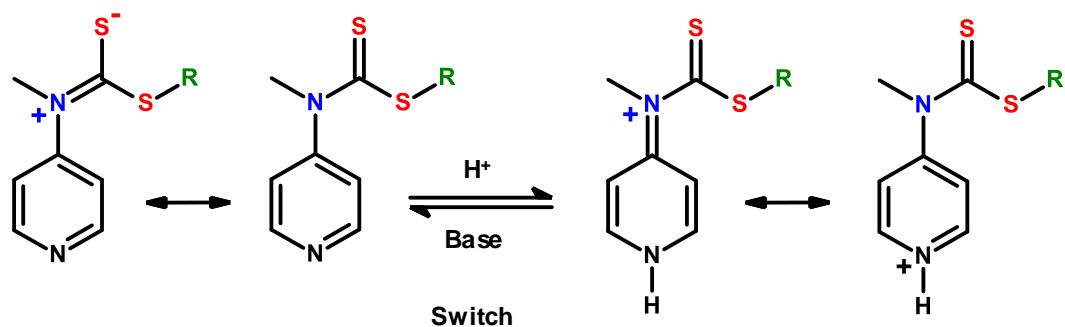
Polymers formed by RAFT can be chain extended to form block copolymers whereby the first block acts as a macroRAFT in the polymerization of the second monomer. The RAFT agent for the first monomer must therefore also be suitable for the polymerization of the second monomer. For example, in the case of a methacrylate-acrylate block copolymer, the methacrylate must be the first monomer polymerized as the R-group of a polyacrylate macroRAFT would not be an efficient leaving group relative to a propagating methacrylate radical.

Moad et al. proposed the naming of radically polymerizable monomers as “more activated monomers” (MAMs) and “less-activated monomers” (LAMs),^[190] although recently a further type has been referred to, IAMs or “intermediate activity monomers,^[191] which lie in between these two classifications. MAMs have vinyl groups that are conjugated to an aromatic ring (i.e. styrenes) or a carbonyl group (i.e. (meth)acrylates, (meth)acrylamides) for example, whereas LAMs often have vinyl groups that are adjacent to an oxygen or nitrogen lone pair (i.e. vinyl esters, vinyl amides) however, other monomers can also be considered LAMs, such as ethylene.^[192] Parallels of these classifications can be drawn with the ionic polymerizations of substituted vinyl monomers. Cationic polymerization is essentially limited to those monomers with electron-donating substituents, whereas anionic polymerization takes place with monomers possessing electron-withdrawing groups. As such, cyanoacrylates would be expected to fall under the MAM classification. Modes of polymerization for common vinyl monomers are shown in **Table 2.1**.

Monomer	Radical	Anionic	Cationic
Ethyl Vinyl Ether	+	—	+
Styrene	+	+	+
Methyl Methacrylate	+	+	—
Acrylonitrile	+	+	—
Ethyl Cyanoacrylate	+	+	—

Table 2.1. Modes of polymerization for common vinyl monomers.

When creating block copolymers, the more active RAFT agents allow for the preparation of poly(MAM)-*b*-poly(MAM) and less active RAFT agents allow for the preparation of poly(LAM)-*b*-poly(LAM), however, incorporating segments of both MAMs and LAMs using conventional RAFT agents is considerably difficult. To address this issue the CSIRO developed new “switchable” RAFT agents based on *N*-(4-pyridinyl)-*N*-methyldithiocarbamates, which can offer control of the polymerization of both LAMs and MAMs and allow for the synthesis of poly(MAM)-*b*-poly(LAM) block copolymers.^[190] In their non-switched or neutral form, the RAFT agents provide good control over LAM polymerization however, by simple addition of a strong protic or Lewis acid the protonated or switched forms are very efficient at controlling the polymerization of MAMs (**Scheme 2.5**). Recently, switchable *N*-aryl-*N*-(4-pyridinyl) dithiocarbamates (**Figure 2.3**) have been described in the literature which are reportedly more efficient than their *N*-(4-pyridinyl)-*N*-methyldithiocarbamate analogues.^[193] The apparent chain transfer coefficient values for the RAFT agents were found to increase as the electron density on the dithiocarbamate nitrogen decreased as a consequence of stronger electron withdrawing substituents (OMe, F, CN) at the 4-position of the aryl ring.



Scheme 2.5. Switchable RAFT agents.

Experimentally, RAFT is carried out under conditions almost identical to those of conventional radical polymerization (with the exception of the RAFT agent addition) and therefore has the advantages and versatility of conventional radical polymerization.

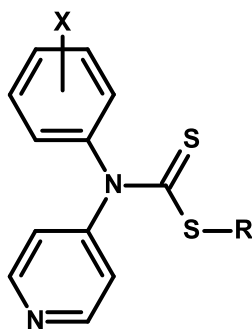


Figure 2.3. General structure of *N*-aryl-*N*-(4-pyridinyl) dithiocarbamates.

2.2 Thesis Aims and Objectives

1. To establish the first controlled/living radical polymerizations of cyanoacrylates through the reversible addition and fragmentation by chain transfer (RAFT) polymerization process.
2. To prepare the first block copolymers containing cyanoacrylates.
3. To assess control/living character during polymerizations using advanced Gel Permeation Chromatography (GPC) techniques.

2.3 Chapter Aims and Objectives

RAFT was deemed as the most suitable RDRP due to the unsuitability of both NMP and ATRP because of the basicity of the respective aminoxyl functionality and amine ligands used, which would initiate unwanted anionic polymerizations of cyanoacrylates. In this chapter, we attempt to utilize various small molecule RAFT agents to achieve control/living polymerization of the most common cyanoacrylate, ECA.

2.3.1 Precautions

Stringent acidification is required to prevent inadvertent anionic polymerization of alkyl CAs; glassware used for polymerizations was soaked in dilute sulfuric acid, rinsed with acetone, and oven-dried prior to use. Prior to polymerization, 1,3-propanesultone was added as an anionic stabilizer^[80] at a level of 0.01% w/w. Commonly used anionic stabilizers such as acetic and chloroacetic acids were avoided as these can act as chain transfer agents.^[37] After precipitation in polar non-solvents, degradation of poly(CA)s prepared by radical polymerization is reported to be less than if prepared through anionic polymerization.^[52,53] Nevertheless, the poly(CA)s in the present work were precipitated in cold methanol containing 0.05% w/v MSA as a precaution to prevent degradation of the isolated polymer while also inhibiting the anionic polymerization of any residual monomer.

2.3.2 Experimental

2.3.2.1 Materials

Anhydrous toluene (99.8%, Alfa Aesar), cyanoisopropyl dithiobenzoate (CPDB) (>97%, Strem Chemicals Inc.), 4-cyano-4-[(dodecylsulfanylthiocarbonyl) sulfanyl] pentanoic acid (CDSPA) (>97%, Aldrich), 4-Cyano-4-(phenylcarbonothioylthio)pentanoic acid (CTPA) (>97%, Aldrich), 1,3-propanesultone (98%, Aldrich), and methanesulfonic acid (MSA) ($\geq 99.5\%$, Aldrich) were all used as received. Methyl (ethoxycarbonothioyl)sulfanyl acetate (MESA) was prepared as previously described.^[194] Ethyl cyanoacrylate (ECA, 99%) was received from Henkel Ireland, and vacuum distilled prior to use to remove inhibitors. 2,2'-azobis(2-methylpropionitrile) (AIBN) (97%, VWR Ireland) and 1,1'-azobis(cyclohexanenitrile) (ACN) (98%, Aldrich) were recrystallized from methanol and dried under vacuum. Polymerization solutions were purged with nitrogen and immersed in an oil bath at the required temperature for the prescribed time, then quenched by placing the opened reactions on an ice bath. Viscous polymerization mixes were dissolved in a minimum of acetone prior to precipitation by dropwise addition into tenfold excess of cold methanol containing 0.05% w/v MSA for cyanoacrylate polymerizations. After purification, polymers were dried under vacuum to a constant weight, and conversions were measured gravimetrically.

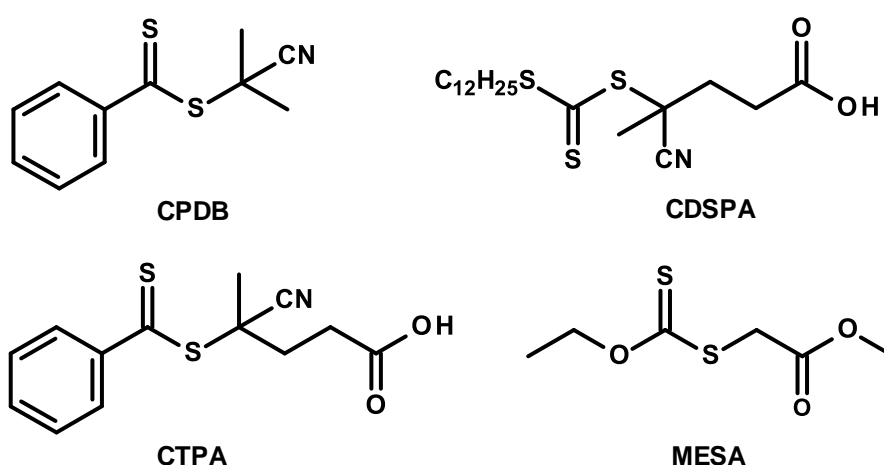


Figure 2.4. RAFT agents used.

2.3.2.2 Instrumentation and Measurements

Gel Permeation Chromatography (GPC): Molecular weight distributions were recorded using size exclusion chromatography (SEC) at 30 °C using an Agilent 1260 Infinity Series GPC/SEC system equipped with Agilent PLGel 5 µm guard column (7.5 × 50 mm) and two Agilent PLGel 5 µm MIXED-D columns (molecular weight range of 450,000 – 500 g.mol⁻¹) with a differential refractive index detector (Agilent 1260 Infinity Refractive Index Detector) and an ultraviolet detector (Agilent 1260 Infinity Variable Wavelength Detector). Dichloromethane was used as the eluent at a flow rate of 1 mL min⁻¹. The SEC system was calibrated using seven poly(MMA) standards in the range of 330,000 to 1850 g.mol⁻¹. Theoretical molecular weight ($M_{n,th}$) was calculated according to equation 4:

$$M_{n,th} = \frac{[Monomer]_0}{[RAFT]_0} \times M_{Monomer} \times c + M_{RAFT} \quad (4)$$

where $M_{Monomer}$ and M_{RAFT} correspond to the molecular weight of the monomer and RAFT agent respectively and c is the fractional conversion.

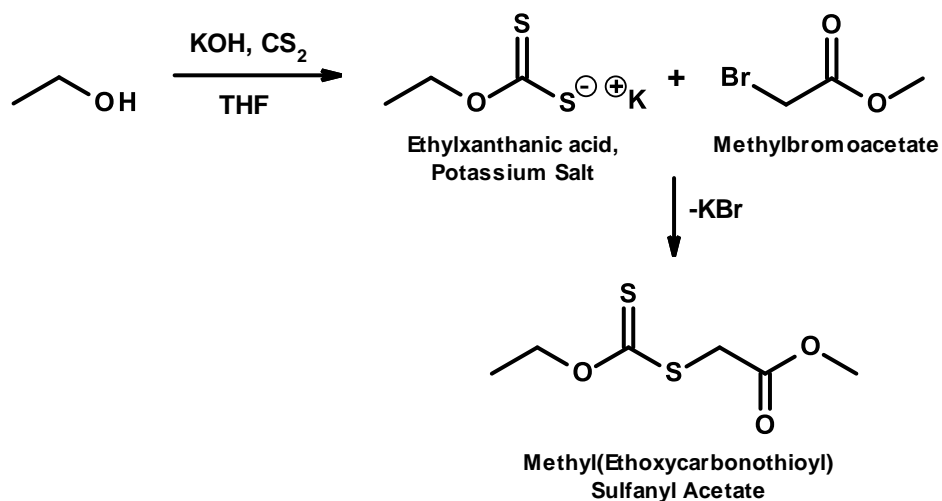
Nuclear Magnetic Resonance (NMR) Spectroscopy: ¹H NMR spectra were recorded using a Bruker Ultrashield 500 MHz instrument. Samples were run in CDCl₃.

2.3.2.3 Synthesis of Methyl (ethoxycarbonothioyl)sulfanyl acetate (MESA)

This dithiocarbonate RAFT agent was prepared as described by Stenzel et al (**Scheme 2.6**).^[194] Potassium hydroxide (2.8 g, 0.05 mol) was added to 20 mL (0.3425 mol) of ethanol. This was stirred at room temperature until the potassium dissolved to give a cloudy solution. Carbon disulfide (10 mL, 12.61 g, 0.1656 mol) was added slowly. A salt precipitate was formed instantaneously and 50 mL of THF was added to help dissolve the salt. The reaction was stirred for 4 hours. Methyl bromoacetate (7.6485 g, 4.724 mL, 0.05 mol) was then added and the reaction was stirred overnight. The formed precipitate was then filtered and the filtrate was condensed by vacuum. Crude Yield obtained was 76.53% [7.434 g, (0.03826 mol)]. The crude product was purified by washing over basic aluminium oxide with diethyl

ether. The solvent was removed by vacuum condensation to yield the pure product as a slightly yellow liquid, 39% [3.788 g (0.0195 mol)].

$^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 1.42$ (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 3.77 (3H, s, OCH_3), 3.94 (2H, s, SCH_2), 4.64 (2H, q, $J = 7.1$ Hz, OCH_2CH_3) (**Figure 2.5**).



Scheme 2.6. Synthesis of methyl(ethoxycarbonothioyl) sulfanyl acetate (MESA).

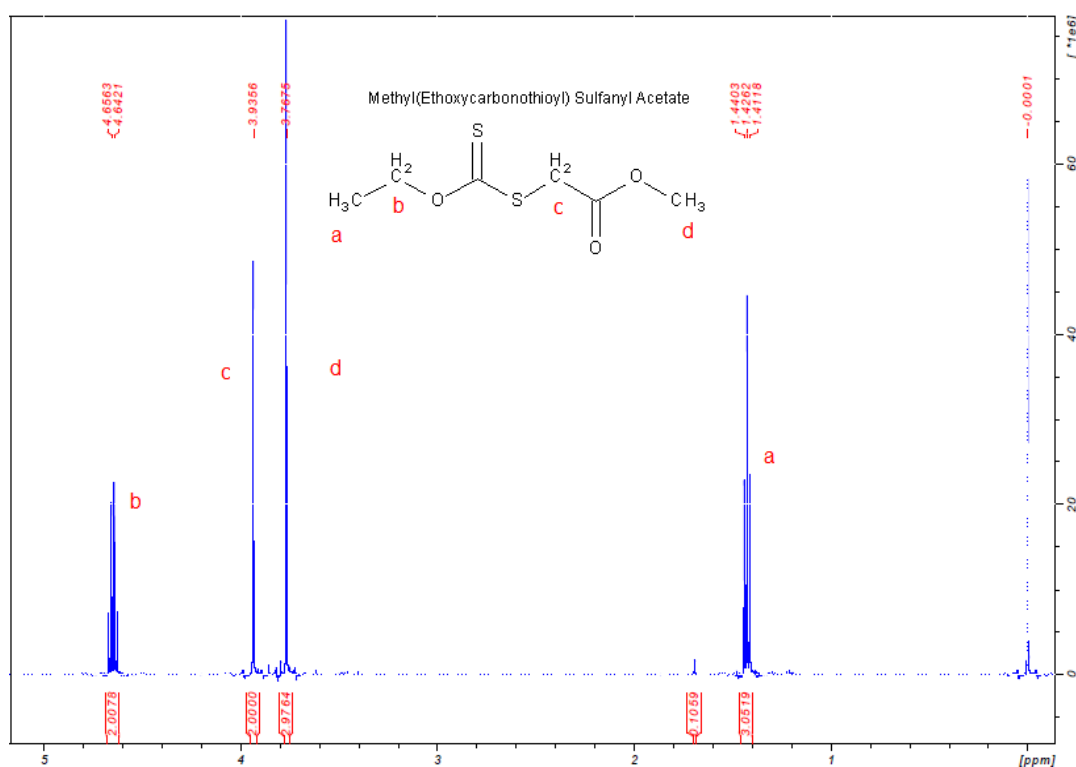


Figure 2.5. $^1\text{H NMR}$ spectrum of MESA.

2.3.2.4 RAFT Polymerization of ECA using 4-cyano-4-[(dodecylsulfanylthiocarbonyl) sulfanyl] pentanoic acid (CDSPA)

ECA (15 g, 0.12 mol), AIBN (19.7 mg, 0.12 mmol), CDSPA (0.484 g, 1.2 mmol) and 1,3-propanesultone (3 mg, 0.0246 mmol) in toluene (17.25 mL) were heated at 60 °C for various times up to 4 hrs.

2.3.2.5 RAFT Polymerization of ECA using Cyanoisopropyl Dithiobenzoate (CPDB)

ECA (5 g, 0.040 mol), AIBN (3.3 mg, 0.020 mmol), CPDB (22.3 mg, 0.100 mmol) and 1,3-propanesultone (1 mg, 0.0082 mmol) in toluene (5.8 mL) were heated at 60 °C for various times up to 4 hrs.

2.3.2.6 RAFT Polymerization of ECA using Methyl (ethoxycarbonothioyl)sulfanyl acetate (MESA)

ECA (10 g, 0.080 mol), AIBN (3.97 mg, 0.024 mmol), MESA (91.89 mg, 0.473 mmol) and 1,3-propanesultone (2 mg, 0.0164 mmol) in toluene (11.5 mL) were heated at 60 °C for various times up to 7 hrs.

2.4 Results and Discussion

2.4.1 RAFT Polymerization of ECA using 4-Cyano-4-[(dodecylsulfanylthiocarbonyl) sulfanyl] pentanoic acid (CDSPA)

The trithiocarbonate, CDSPA, has been reported previously as an effective RAFT agent in the polymerization of MMA.^[195] Polymerizations of ECA initiated by AIBN at 60 °C in toluene in the presence of CDSPA at a ratio of $[ECA]_0/[CDSPA]_0 = 100$ proceeded to intermediate conversion (32%) after 4 hours (**Figure 2.6**). A rapid increase in molecular weight (MW) was observed at low conversion with no significant shift of the MWD to higher MW occurring at higher conversion (**Figure 2.7 and 2.8**). The observation of an initially high MW that gradually approaches the

theoretical number average molecular weight ($M_{n,th}$) with increasing conversion is similar to a phenomenon sometimes seen in RAFT polymerizations known as “hybrid behaviour” and is caused by a low transfer constant of the initial RAFT agent.^[196] A low transfer constant can be a consequence of a slow rate of addition of the monomer to the RAFT agent or the partitioning of the intermediate radical adduct in favour of starting materials.^[197]

MWDs are noticeably broad with M_w/M_n in the range of 1.4 - 1.6. MWs did not increase linearly with conversion as would be expected in a controlled RAFT polymerization and were vastly greater than the expected $M_{n,th}$ values. Overall, the results from this polymerization showed little evidence of controlled/living character.

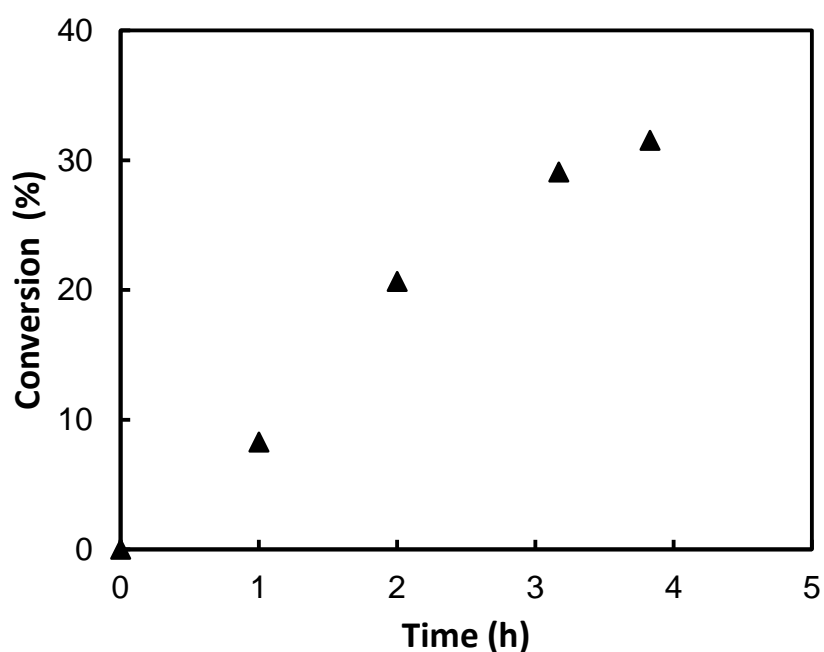


Figure 2.6. Conversion versus time plot for RAFT polymerizations of ECA at 60 °C in toluene using CSDPA RAFT agent, where $[RAFT]_0/[AIBN]_0 = 10$ and $[ECA]_0/[RAFT]_0 = 100$.

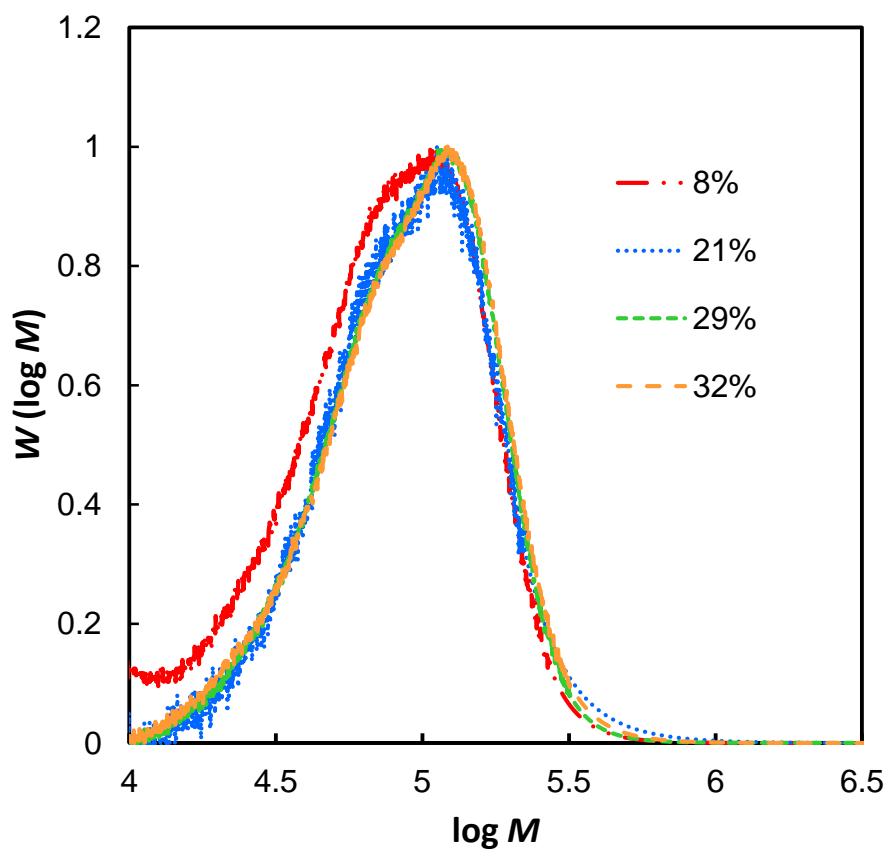


Figure 2.7. MWDs for RAFT polymerizations of ECA at 60 °C in toluene using CSDPA RAFT agent, where $[\text{RAFT}]_0/[\text{AIBN}]_0 = 10$ and $[\text{ECA}]_0/[\text{RAFT}]_0 = 100$.

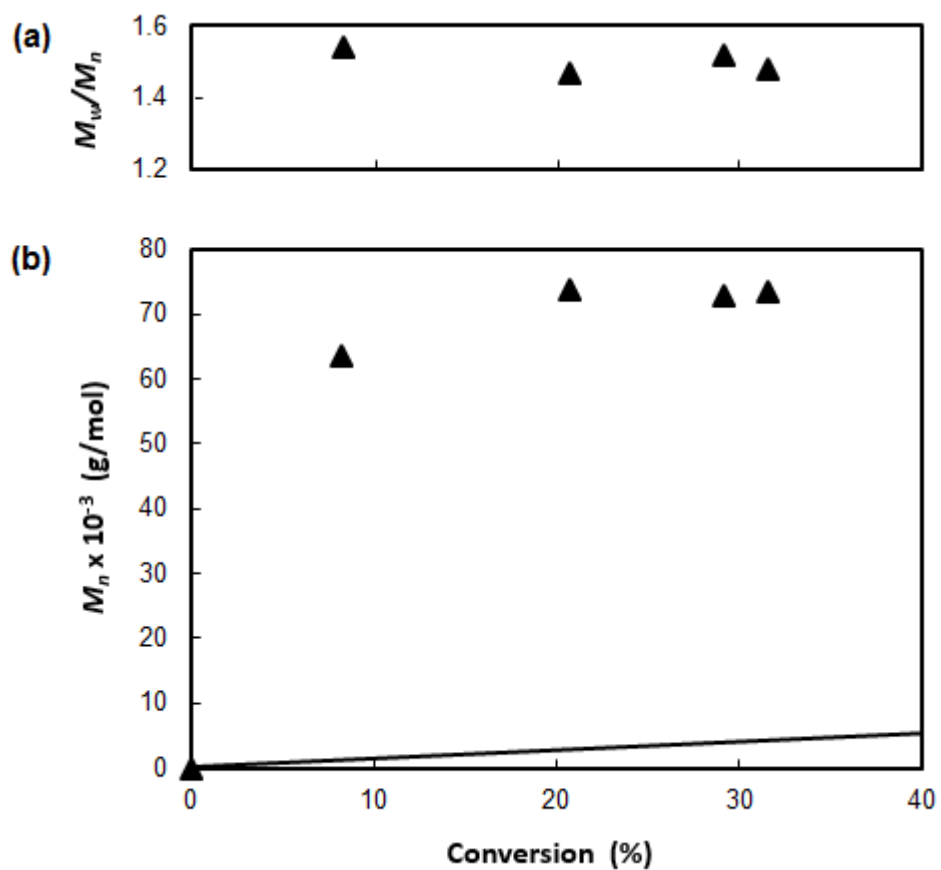


Figure 2.8. (a) M_w/M_n and (b) M_n versus conversion for polymerizations of ECA at 60 °C in toluene using CSDPA RAFT agent, where $[RAFT]_0/[AIBN]_0 = 10$ and $[ECA]_0/[RAFT]_0 = 100$ with $M_{n,th}$ represented by a continuous line.

2.4.2 RAFT Polymerization of ECA using Cyanoisopropyl Dithiobenzoate (CPDB)

Dithiobenzoates are amongst the most active RAFT agents and are known to have a good general utility in the polymerization of MAMs.^[198] CPDB was selected as its R group is identical to that of an AIBN initiating cyanoisopropyl radical. Polymerizations of ECA initiated by AIBN at 60 °C in toluene in the presence of CPDB at a ratio of $[ECA]_0/[CPDB]_0 = 400$ proceeded to intermediate conversion (32%) after 4 hours (**Figure 2.9**). MW rapidly increased at low conversion with behaviour similar to that observed with the use of CDSPA as RAFT agent. Besides an initial shift in MWD to higher MW between 6 and 11% conversion points there was no discernible shift to higher MW thereafter (**Figure 2.10(a) and 2.11**). MWDs are noticeably broad with M_w/M_n in the range of 1.4 - 1.6 and MWs did not increase linearly with conversion. Observed M_n were significantly greater than $M_{n,th}$ indicating limited control.

The polymerization of ECA in the presence of CPDB was repeated, this time the reaction was carried out at 80 °C in toluene to increase the rate of fragmentation. At this higher temperature, ACN was employed as initiator and the concentration of the RAFT agent was increased to a ratio of $[ECA]_0/[CPDB]_0 = 100$. The polymerization proceeded to 42% after 4 hours (**Figure 2.9**). As with the previous polymerization, there is a larger increase in MW at low conversion. There is an increase in MW of ~13,500 between 6 and 11% but after which there is little increase in M_n with respect to conversion (**Figure 2.10(b) and 2.11**). M_n is larger than the theoretical values with M_w/M_n in the range of 1.4 - 1.6. Although controlled/living character was not achieved by comparing the two polymerizations with differing concentrations of CPDB, it can be seen that by increasing the concentration of RAFT agent from $[ECA]_0/[CPDB]_0 = 400$ to 100 there is almost a threefold reduction in final polymer M_n . This is indicative that some degree of control in M_n is being achieved by using CPDB albeit limited control.

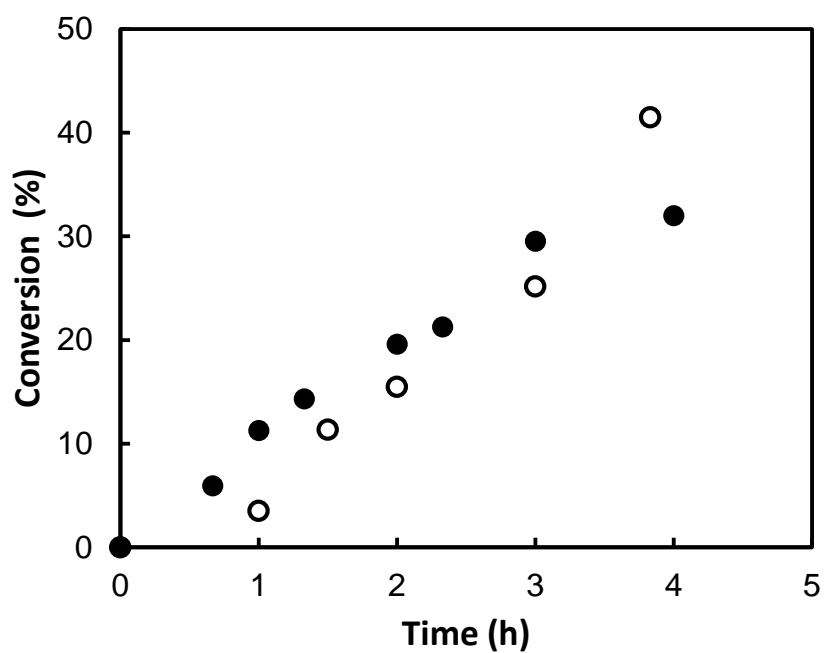


Figure 2.9. Conversion versus time plot for RAFT polymerizations of ECA in toluene using CPDB RAFT agent, where $[\text{RAFT}]_0/[\text{AIBN}]_0 = 5$ and $[\text{ECA}]_0/[\text{RAFT}]_0 = 400$ at 60 °C (closed symbols) and $[\text{RAFT}]_0/[\text{ACN}]_0 = 5$ and $[\text{ECA}]_0/[\text{RAFT}]_0 = 100$ at 80 °C (open symbols).

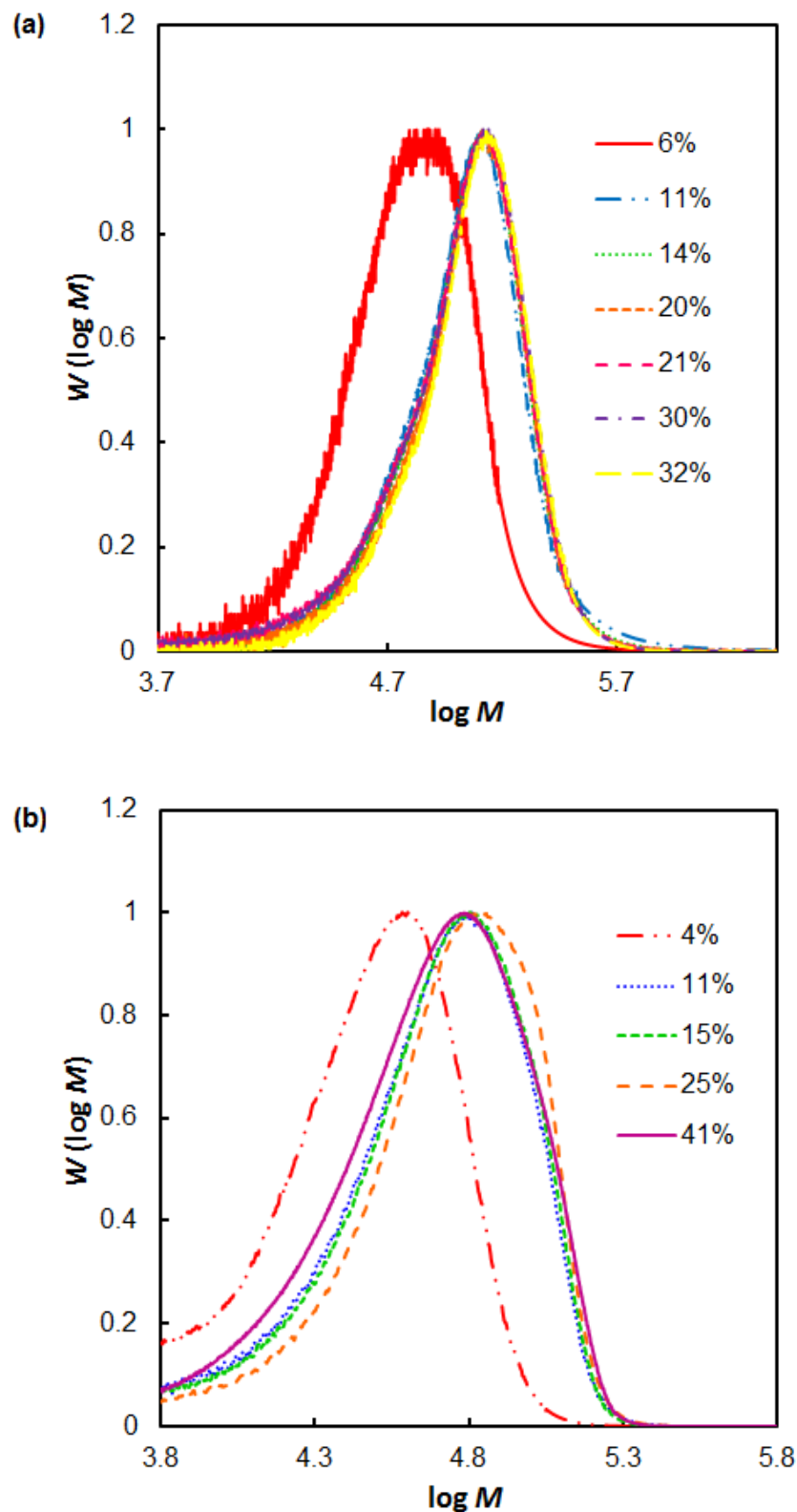


Figure 2.10. MWDs for RAFT polymerizations of ECA in toluene using CPDB RAFT agent, where **(a)** $[\text{RAFT}]_0/[\text{AIBN}]_0 = 5$ and $[\text{ECA}]_0/[\text{RAFT}]_0 = 400$ at 60 °C and **(b)** $[\text{RAFT}]_0/[\text{ACN}]_0 = 5$ and $[\text{ECA}]_0/[\text{RAFT}]_0 = 100$ at 80 °C.

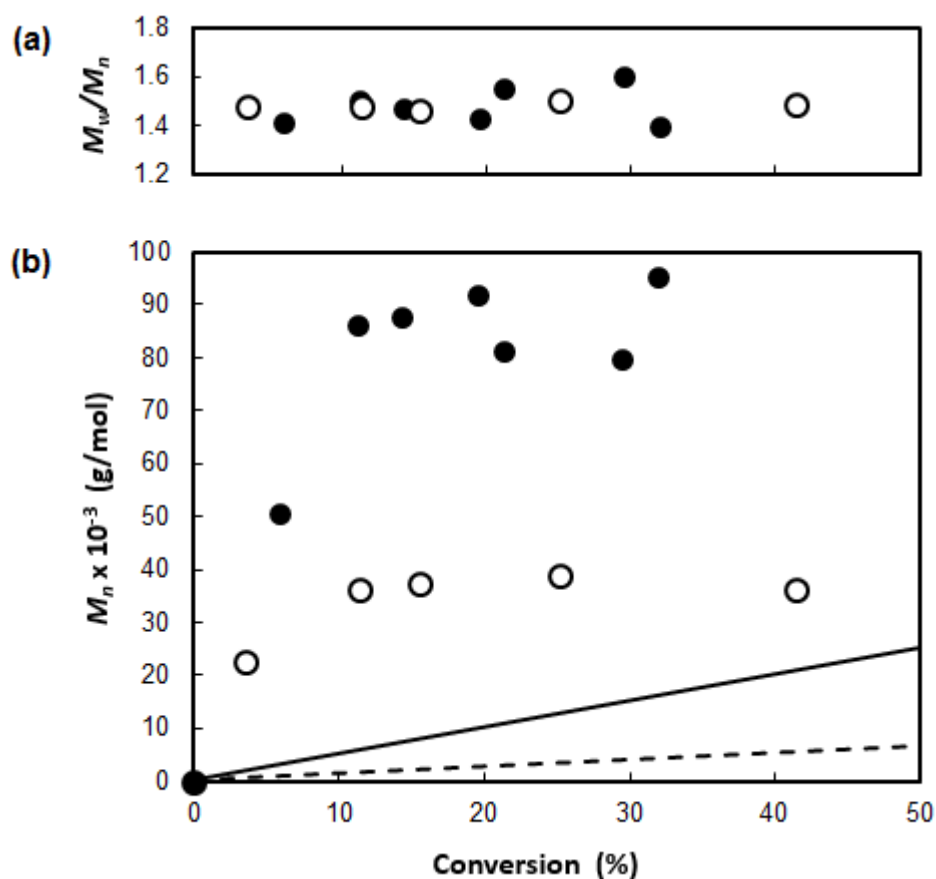


Figure 2.11. (a) M_w/M_n and (b) M_n versus conversion for RAFT polymerizations of ECA in toluene using CPDB RAFT agent, where $[RAFT]_0/[AIBN]_0 = 5$; $[ECA]_0/[RAFT]_0 = 400$ at 60 °C (closed symbols) with $M_{n,th}$ continuous line and $[RAFT]_0/[ACN]_0 = 5$; $[ECA]_0/[RAFT]_0 = 100$ at 80 °C (open symbols) with $M_{n,th}$ dashed line.

2.4.3 RAFT Polymerization of ECA using Methyl (ethoxycarbonothioyl)sulfanyl acetate (MESA)

Synthesis:

Synthesis of MESA was carried out as previously described by Stenzel.^[194] The initial step involves the reaction of ethanol with potassium hydroxide to give potassium ethoxide. The metal alkoxide is reacted with carbon disulfide to form the potassium salt of ethylxanthanic acid and THF was added to keep the salt in solution. Through nucleophilic substitution of the methylbromoacetate alkyl halide with the dithiocarboxylate salt and subsequent elimination of potassium bromide, the desired xanthate is formed (76.53%). The product was further purified by washing over basic aluminium with diethyl ether. ¹H NMR peaks corresponded to those reported (**Figure 2.5**).

Polymerization:

Dithiocarbonates (xanthates) are reported to be effective controlling agents for the polymerization of high k_p LAMs such as vinyl acetate. MESA was selected to observe if any control could be imparted on the polymerization of ECA. Polymerizations were initiated by AIBN at 60 °C in toluene using the same conditions as those employed by Stenzel et al. in their controlled polymerization of vinyl acetate with $[\text{RAFT}]_0/[\text{AIBN}]_0 = 20$ and $[\text{ECA}]_0/[\text{RAFT}]_0 = 169$. Polymerizations proceeded to intermediate conversion (33%) after almost 7 hours (**Figure 2.12**) and much slower than what was required to achieve similar conversion for the other RAFT agents tested. A rapid increase in molecular weight (MW) was observed at low conversion with no significant shift of the MWD to higher MW occurring at higher conversion (**Figure 2.13 and 2.14**). MWDs are noticeably broad with M_w/M_n in the range of 1.6 - 1.85. MWs did not increase linearly with conversion and were the highest observed for the polymerizations of the other tested RAFT agents and much greater than $M_{n,th}$. The use of a dithiocarbonate did not result in any improved control in the polymerization of ECA.

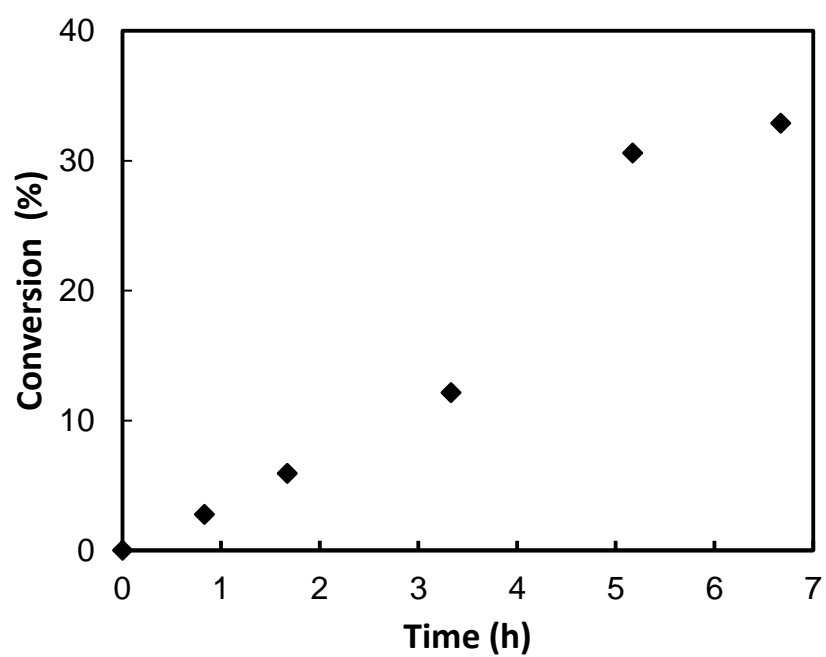


Figure 2.12. Conversion versus time plot for RAFT polymerizations of ECA at 60 °C in toluene using MESA RAFT agent, where $[\text{RAFT}]_0/[\text{AIBN}]_0 = 20$ and $[\text{ECA}]_0/[\text{RAFT}]_0 = 169$.

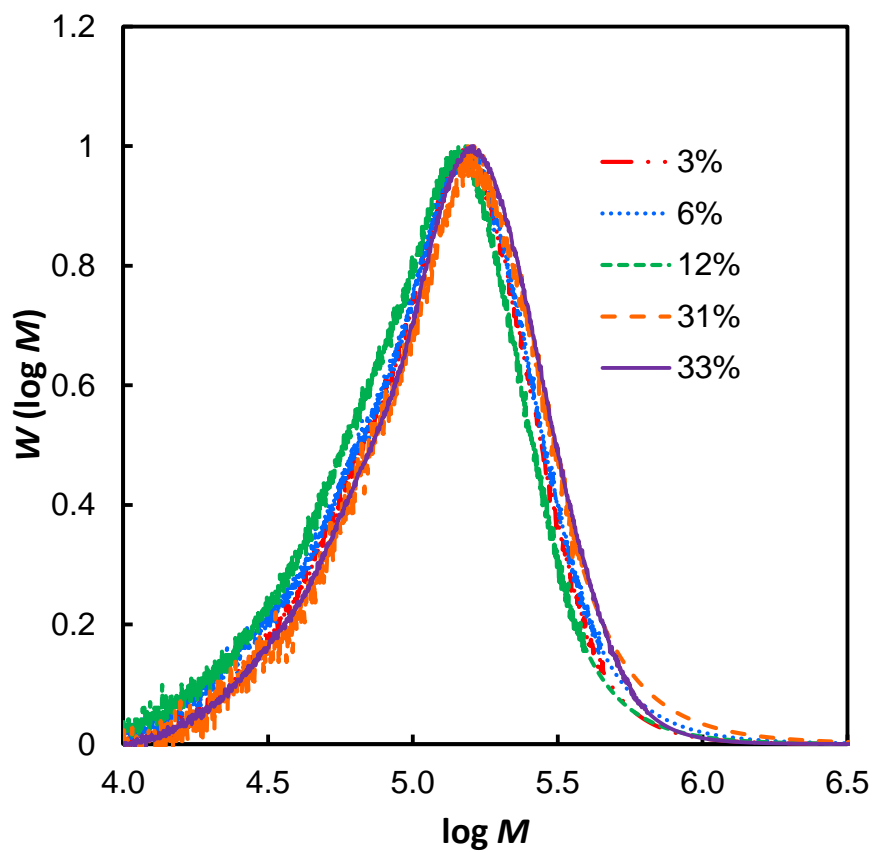


Figure 2.13. MWDs for RAFT polymerizations of ECA at 60 °C in toluene using MESA RAFT agent, where $[\text{RAFT}]_0/[\text{AIBN}]_0 = 20$ and $[\text{ECA}]_0/[\text{RAFT}]_0 = 169$.

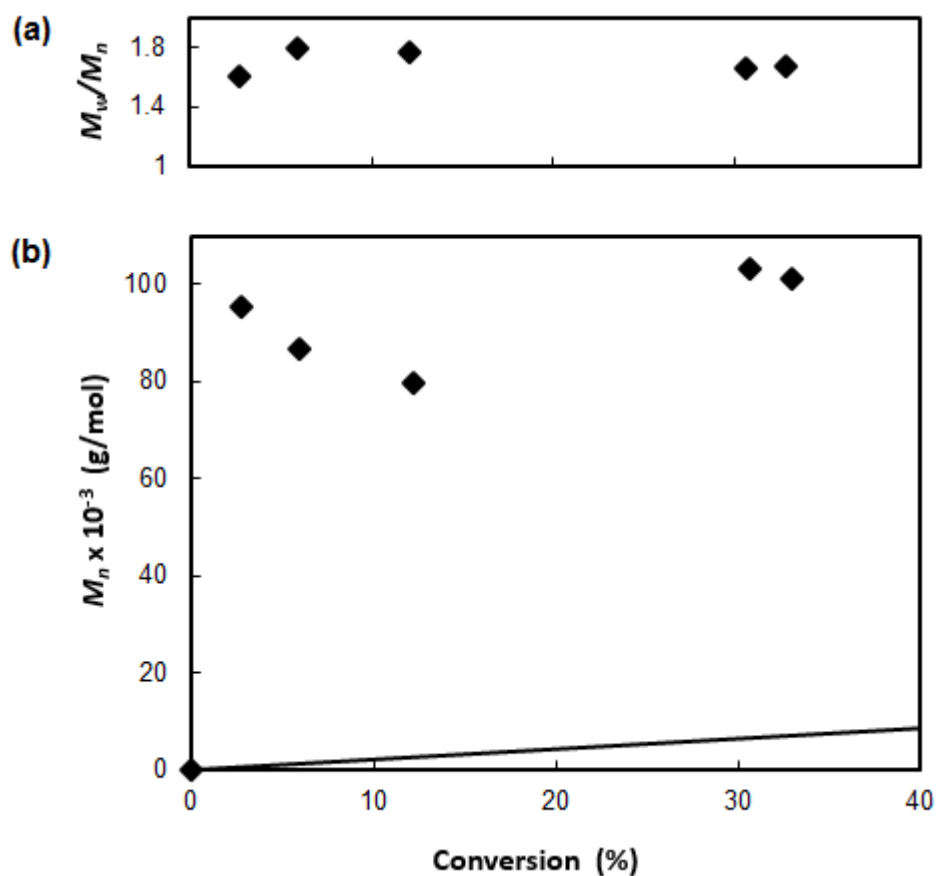


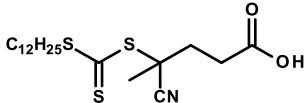
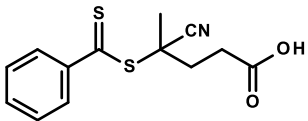
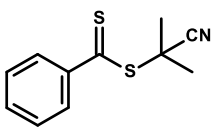
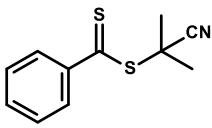
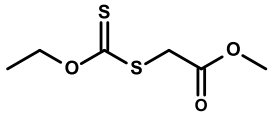
Figure 2.14. (a) M_w/M_n and (b) M_n versus conversion for RAFT polymerizations of ECA at 60 °C in toluene using MESA RAFT agent, where $[RAFT]_0/[AIBN]_0 = 20$ and $[ECA]_0/[RAFT]_0 = 169$ with $M_{n,th}$ represented by a continuous line.

2.5 Conclusions

Our preliminary investigation utilized the commercial RAFT agents 4-cyano-4-[(dodecylsulfanylthiocarbonyl) sulfanyl]pentanoic acid (CDSPA), 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (CTPA) and cyanoisopropyl dithiobenzoate (CPDB), which are typically used to control the polymerization of methacrylates and methacrylamides. Methyl (ethoxycarbonothioyl)sulfanyl acetate (MESA), which is often used to control the polymerization of vinyl acetate^[199,200] was also examined. In all these cases, controlled/living character was not achieved (**Table 2.2**) with M_n being vastly greater than $M_{n,th}$ and M_w/M_n relatively high. MESA, a dithiocarbonate, was chosen since dithiocarbamates caused inadvertent anionic polymerization of the CA.

The use of MESA did not result in any improvement with an even larger discrepancy between M_n and $M_{n,th}$ and higher dispersity ($M_w/M_n = 1.67$).

Given polymerization of CAs involves a conjugated tertiary propagating radical, it seemed plausible that a reasonably bulky macroRAFT agent with a leaving group ability greater than or at least comparable to that of the poly(CA) radical is required and is discussed further in the Chapter 3. Although the dispersities in **Table 2.2** are relatively high for all of the RAFT agents evaluated, there is greater discrepancy between M_n and $M_{n,th}$ for CDSPA and MESA than for the dithiobenzoates CTPA and CPDB.

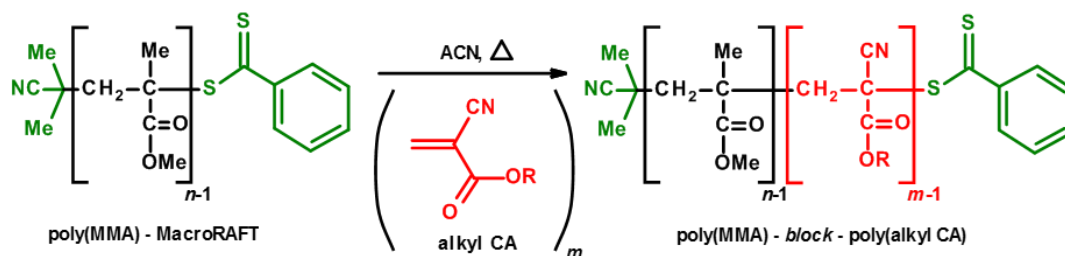
RAFT Agent	Temp.	[AIBN]/[RAFT]/[ECA]	Conv. (%)	M_n	$M_{n,th}$	M_w/M_n
	60 °C	1 / 10 / 1000	32	72750	4400	1.52
	60 °C	1 / 5 / 1000	41	72150	10550	1.35
	60 °C	1 / 5 / 2000	32	95250	16250	1.40
	80 °C ^a	1 / 5 / 500	41	36050	5350	1.49
	60 °C	1 / 19.5 / 3300	33	101150	7150	1.67

[ECA] = [3.82M] in toluene. ^a Polymerization used ACN as initiator.

Table 2.2. Summary of low molecular weight RAFT agent polymerizations with ECA.

CHAPTER 3

RAFT POLYMERIZATION OF CYANOACRYLATES USING A MACRORRAFT AGENT



3.0 RAFT POLYMERIZATION OF CYANOACRYLATES USING A MACRORAFT AGENT

3.1 Introduction

The polymerizations of ECA using various common RAFT agents exhibited limited evidence of control in terms of linear M_n growth with respect to monomer conversion, or low M_w/M_n , as described in Chapter 2. This was thought to be attributed to a low transfer constant of the initial RAFT agent giving so-called “hybrid behaviour”, whereby an initially high MW is observed that gradually approaches the $M_{n,th}$ with increasing conversion.^[196] A low transfer constant can be a result of a slow rate of addition of the monomer to the RAFT agent, or the partitioning of the intermediate radical adduct in favour of starting materials, but in the case of ECA it would seem that the latter would be more likely. In order to improve upon the limited control observed in the polymerizations of ECA, it seemed plausible that a reasonably bulky R-group of a macroRAFT agent would aid the leaving group ability of the intermediate radical adduct relative to that of the incoming tertiary poly(CA) radical and favour forward fragmentation. Therefore, as the next step, a macroRAFT agent was chosen based on poly(MMA) derived from CPDB ($M_n \approx 6000 \text{ g.mol}^{-1}$ and $M_w/M_n \approx 1.10$). The polymerization temperature was increased to 90 °C to ensure sufficiently rapid fragmentation of the intermediate polymeric RAFT adducts.

The use of a macroRAFT agent facilitates access to a wide variety of unique block copolymers which could be utilized as additives in cyanoacrylate formulations. Given that poly(cyanoacrylates) are typically soluble in their respective monomers, these block copolymers would have increased compatibility and solubility with cyanoacrylate monomers and could help to achieve desirable enhanced adhesive properties such as improved toughness, thermal stability or moisture resistance. Additionally, block copolymers based on cyanoacrylates would be attractive precursors in the synthesis of nanoparticles for drug delivery applications.

3.2 Chapter Aims and Objectives

In this chapter, a macroRAFT agent based on poly(MMA) was utilized in an attempt to improve on the small molecule RAFT polymerizations previously reported in Chapter 2 to achieve control/living polymerization of cyanoacrylates. RAFT polymerizations carried out with a poly(MMA) macroRAFT initially focussed on ECA before the longer chain *n*-BuCA and solid monomer, PECA, were examined.

To test the livingness of the formed poly(MMA)-*b*-poly(CA)-RAFT, further extension with MMA was carried out to give a triblock copolymer with analysis of the polymerizations carried out by RI-GPC.

3.2.1 Precautions

Precautions were carried out as per Chapter 2.

3.2.2 Experimental

3.2.2.1 Materials

Methyl methacrylate (MMA) (99%, Aldrich) was used after removal of monomethyl ether hydroquinone (MEHQ) radical stabilizer by passing through columns pre-packed with inhibitor removers (Aldrich). Anhydrous toluene (99.8%, Alfa Aesar), cyanoisopropyl dithiobenzoate (CPDB) (>97%, Strem Chemicals Inc.), 1,3-propanesultone (98%, Aldrich) and methanesulfonic acid (MSA) (\geq 99.5%, Aldrich) were all used as received. Ethyl cyanoacrylate (ECA, 99%), *n*-butyl cyanoacrylate (*n*-BuCA, 98%) and phenylethyl cyanoacrylate (PECA, 99%) were received from Henkel Ireland, and vacuum distilled prior to use to remove inhibitors. 2,2'-azobis(2-methylpropionitrile) (AIBN) (97%, VWR Ireland) and 1,1'-azobis(cyclohexanenitrile) (ACN) (98%, Aldrich) were recrystallized from methanol and dried under vacuum. Polymerization solutions were purged with nitrogen and immersed in an oil bath at the required temperature for the prescribed time, then quenched by placing the

opened reactions on an ice bath. Viscous polymerization mixes were dissolved in a minimum of acetone prior to precipitation by dropwise addition into tenfold excess of cold methanol containing 0.05% w/v MSA for CA polymerizations (and without MSA for macroRAFT and triblock polymerizations). After purification polymers were dried under vacuum to a constant weight, and conversions were measured gravimetrically.

3.2.2.2 Instrumentation and Measurements

Molecular weight distributions were recorded using size exclusion chromatography (SEC) at 30 °C using an Agilent 1260 Infinity Series GPC/SEC system as described in Chapter 2. Theoretical molecular weight ($M_{n,th}$) was calculated according to equation 4.

3.2.2.3 Representative synthesis of poly(MMA) MacroRAFT agent

MMA (75 g, 0.749 mol), AIBN (0.492 g, 3.0 mmol) and CPDB (3.315 g, 15 mmol) in toluene (80 mL) were heated at 65 °C. After 6.5 h, 41.80 g of dried polymer was isolated with $M_n = 6,600$ and $M_w/M_n = 1.10$. The M_n of the macroRAFT used in the diblock synthesis varied.

3.2.2.4 Representative example of the synthesis of the diblocks

ECA (22 g, 0.176 mol), ACN (9.5 mg, 0.039 mmol), poly(MMA)-RAFT (11.605 g, 1.758 mmol) and 1,3-propanesultone (11 mg, 0.090 mmol) in toluene (58 mL) was divided into equal parts, and heated at 95 °C for various times.

3.2.2.5 Representative example of the synthesis of the triblocks

MMA (11.060 g, 0.110 mol), ACN (9 mg, 0.037 mmol) and poly(MMA)-*b*-poly(ECA)-RAFT (2.100 g, 0.184 mmol) were heated at 90 °C for 2.5 h.

3.3 Results and Discussion

3.3.1 Synthesis of poly(MMA) MacroRAFT agent

CPDB is known to be an effective RAFT agent for the polymerization of MMA.^[198] Polymerizations of MMA initiated by AIBN at 60 °C in toluene in the presence of CPDB at a ratio of $[MMA]_0/[CPDB]_0 = 50$ proceeded to high conversion (75%) after 9 hours (**Figure 3.0**). MW increased linearly with conversion (**Figure 3.2**) although slightly higher than the $M_{n,th}$ (thought to be due to the high initiator concentration of $[CPDB]_0/[AIBN]_0 = 50$). There is a gradual shift of the MWD to higher MW as conversion increased (**Figure 3.1**) and are noticeably narrow with M_w/M_n in the range of 1.10 – 1.14 indicating good control of the polymerization.

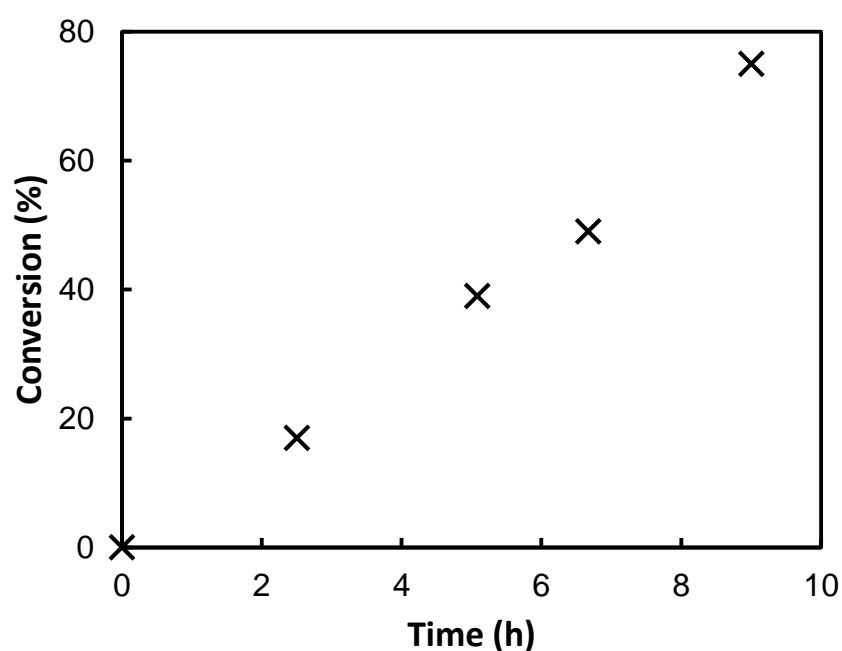


Figure 3.0. Conversion versus time plot for the RAFT polymerization of MMA in toluene in the presence of CPDB RAFT agent at 60 °C; $[MMA=8.67M]_0/[CPDB]_0/[AIBN]_0 = 250/5/1$ (X).

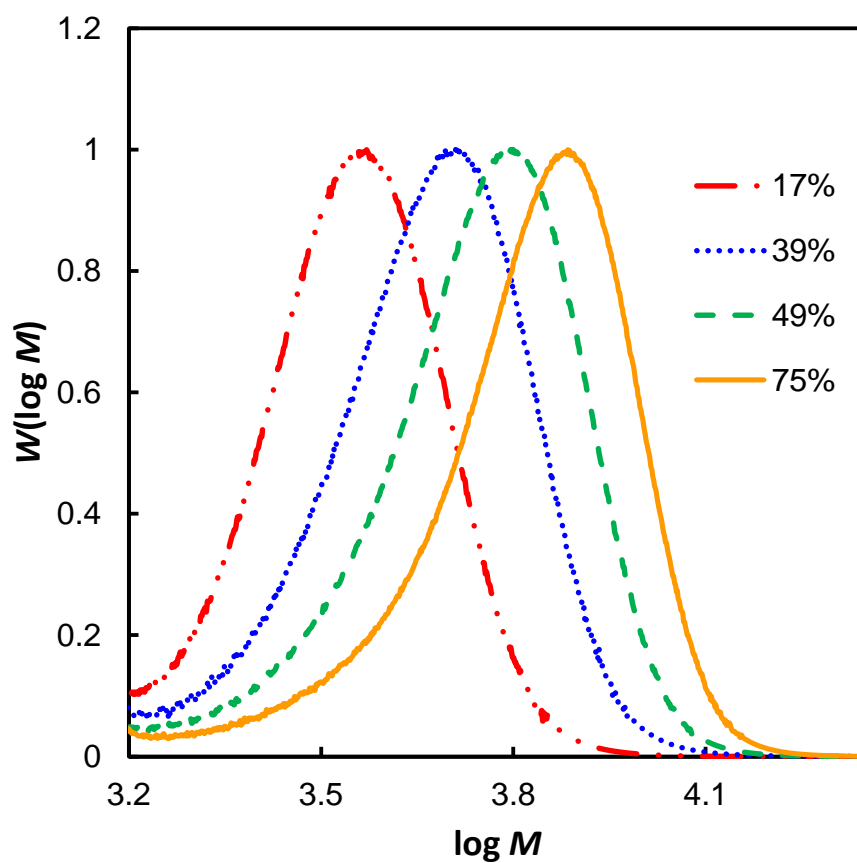


Figure 3.1. MWDs for the RAFT polymerization of MMA in toluene in the presence of CPDB RAFT agent at 60 °C; $[MMA=8.67M]_0/[CPDB]_0/[AIBN]_0 = 250/5/1$.

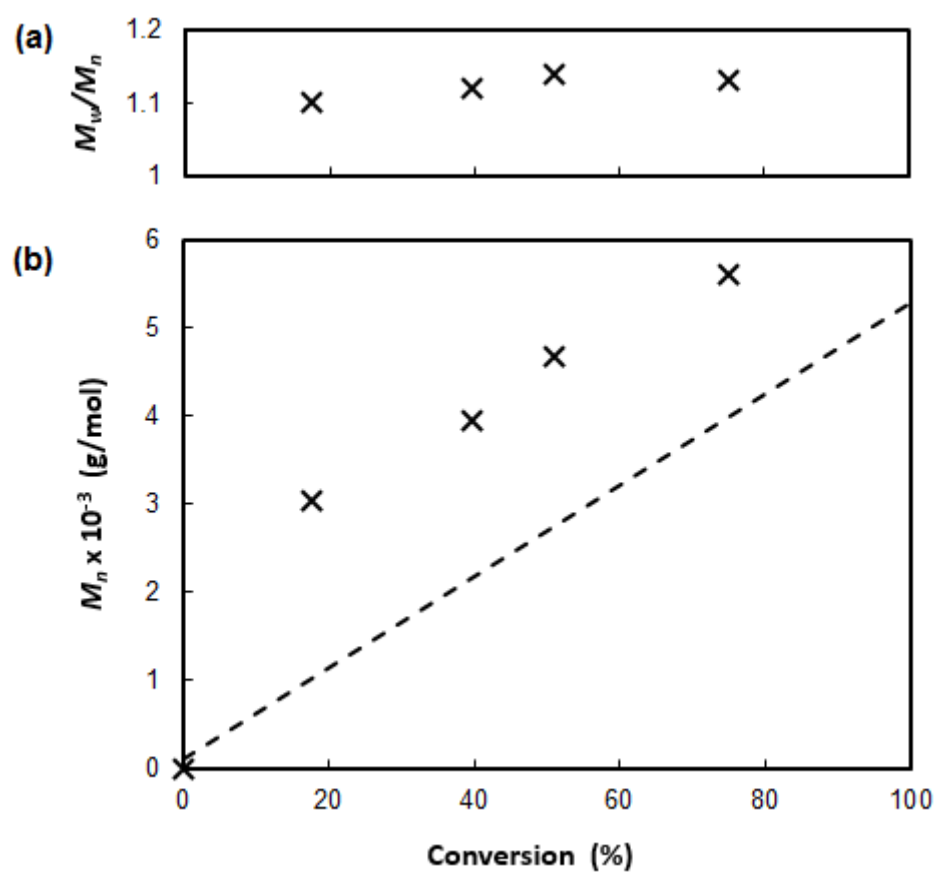


Figure 3.2. RAFT polymerization of MMA in toluene in the presence of CPDB RAFT agent at 60 °C. **(a)** M_w/M_n and **(b)** M_n versus conversion. Polymerizations used $[MMA=8.67M]_0/[CPDB]_0/[AIBN]_0 = 250/5/1$ with $M_{n,th}$ short dashed line.

3.3.2 RAFT Polymerization of ECA using poly(MMA) MacroRAFT agent

Polymerizations of ECA were carried out using ACN as initiator and $[\text{macroRAFT}]_0/[\text{ACN}]_0 = 5$ with two different $[\text{ECA}]_0/[\text{macroRAFT}]_0$ ratios of 45 and 90. Polymerizations proceeded to high conversions of 65 ($[\text{ECA}]_0/[\text{macroRAFT}]_0 = 45$) and 85% ($[\text{ECA}]_0/[\text{macroRAFT}]_0 = 90$) within 2.5 h (**Figure 3.3**). The MWDs were relatively narrow and monomodal for both $[\text{ECA}]_0/[\text{macroRAFT}]_0$ ratios ($M_w/M_n = 1.12\text{--}1.15$ and $1.26\text{--}1.29$), shifting to higher molecular weights with increasing conversion, indicating controlled/living character (**Figure 3.4**). M_n increased with conversion but deviated somewhat from $M_{n,\text{th}}$ (**Figure 3.5**). It must be pointed out that the molecular weights are relative to linear poly(MMA) standards, which invariably introduces a level of error.

In an attempt to further improve the control/livingness, the initiator concentration was lowered from $[\text{macroRAFT}]_0/[\text{ACN}]_0 = 5$ (for the above ECA polymerizations) to 20 and 45 at 90 °C and 95 °C respectively, for $[\text{ECA}]_0/[\text{macroRAFT}]_0 = 100$. In RAFT polymerization, the number of dead chains via bimolecular termination is equal to the number of radicals generated from the initiator that initiate polymer chains (if termination occurs exclusively via disproportionation, half that number of dead chains are generated compared to the case of combination only).^[182] The two polymerizations using the higher $[\text{macroRAFT}]_0/[\text{ACN}]_0$ ratios proceeded at a similar rate to high conversions (**Figure 3.3**) with molecular weights increasing gradually with conversion (**Figure 3.6**), but tended to deviate toward M_n values lower than $M_{n,\text{th}}$ (**Figure 3.7**). Surprisingly, the lower initiator concentration resulted in lower M_n at a given conversion, which may partly originate in the higher temperature (resulting in a greater number of chains due to more initiator decomposition) with this 95 °C polymerization also being marginally faster. The MWDs remained narrow throughout ($M_w/M_n = 1.12\text{--}1.25$ and $1.13\text{--}1.21$ for $[\text{macroRAFT}]_0/[\text{ACN}]_0 = 20$ and 45), although there is some high molecular weight broadening at intermediate to high conversion (**Figure 3.7**).

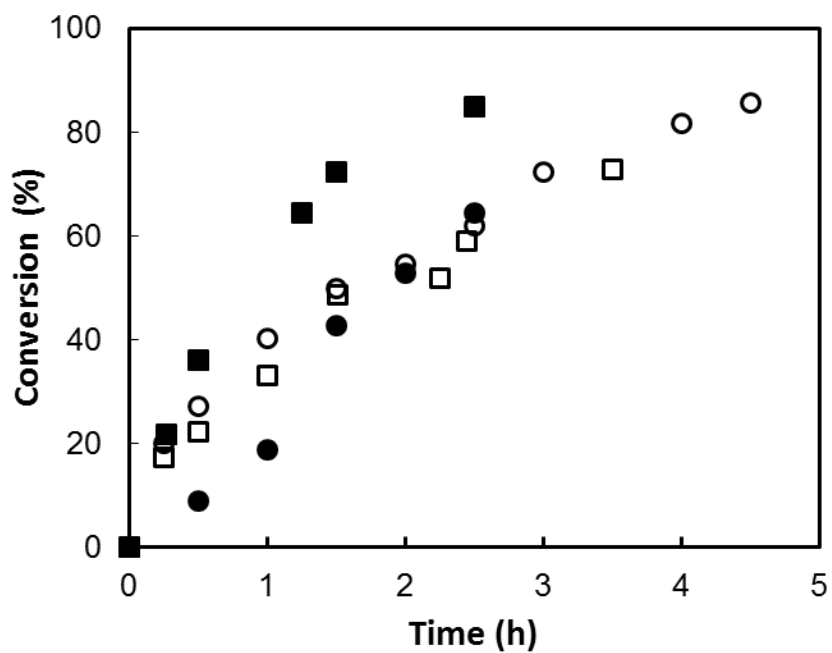


Figure 3.3. Conversion versus time plot for the RAFT polymerization of ECA in toluene in the presence of poly(MMA)-RAFT (macroRAFT) at 90 °C unless otherwise stated.

[ECA=1.11M]₀/[macroRAFT]₀/[ACN]₀ = 225/5/1 (●);

[ECA=2.23M]₀/[macroRAFT]₀/[ACN]₀ = 450/5/1 (■);

[ECA=2.23M]₀/[macroRAFT]₀/[ACN]₀ = 2000/20/1 (□);

[ECA=2.23M]₀/[macroRAFT]₀/[ACN]₀ = 4500/45/1 (○) at 95 °C

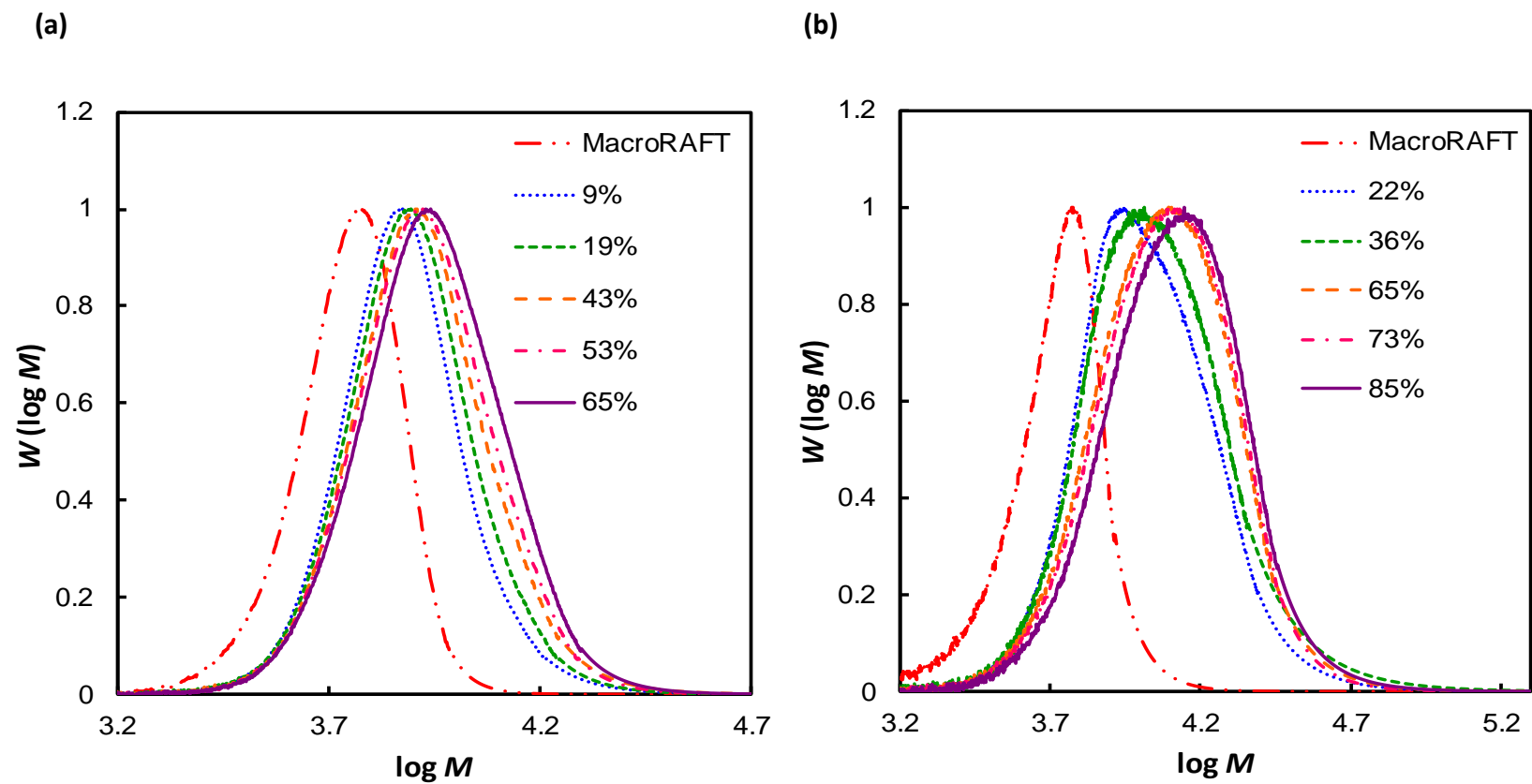


Figure 3.4. MWDs for the RAFT polymerization of ECA in toluene in the presence of poly(MMA)-RAFT (macroRAFT). Polymerizations at 90 °C using (a) $[ECA]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ (b) $[ECA]_0/[macroRAFT]_0/[ACN]_0 = 450/5/1$.

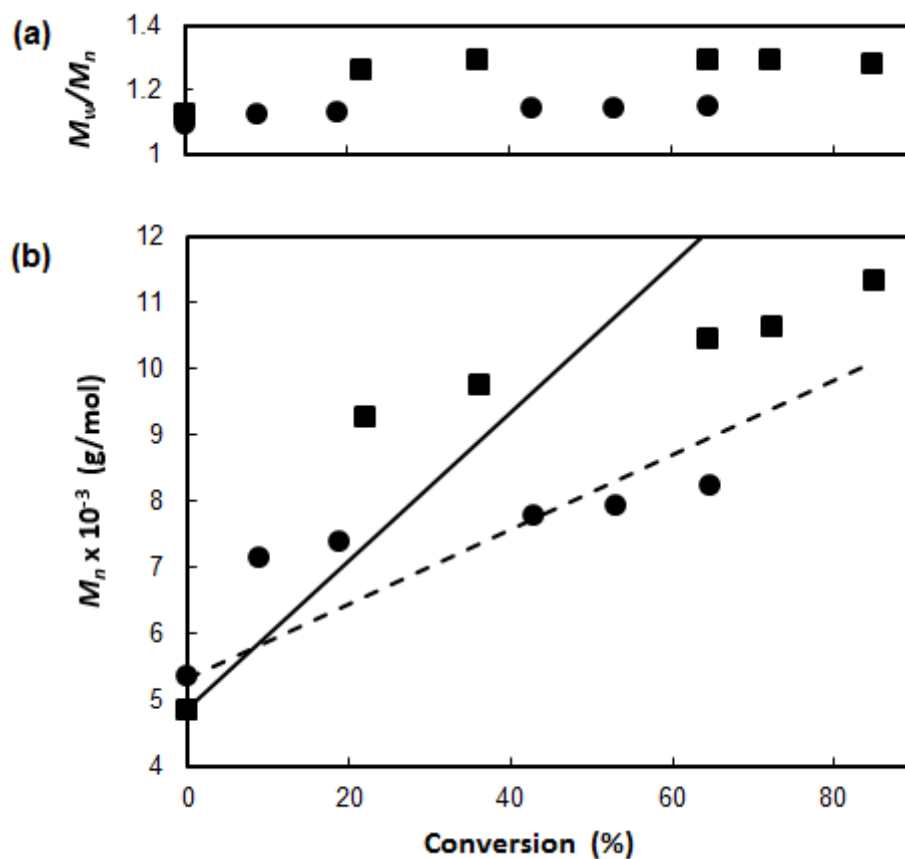


Figure 3.5. RAFT polymerization of ECA in toluene in the presence of poly(MMA)-RAFT (macroRAFT) at 90 °C **(a)** M_w/M_n and **(b)** M_n versus conversion. Polymerizations used $[ECA]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ (●) with $M_{n,th}$ short dashed line and $[ECA]_0/[macroRAFT]_0/[ACN]_0 = 450/5/1$ (■) with $M_{n,th}$ continuous line.

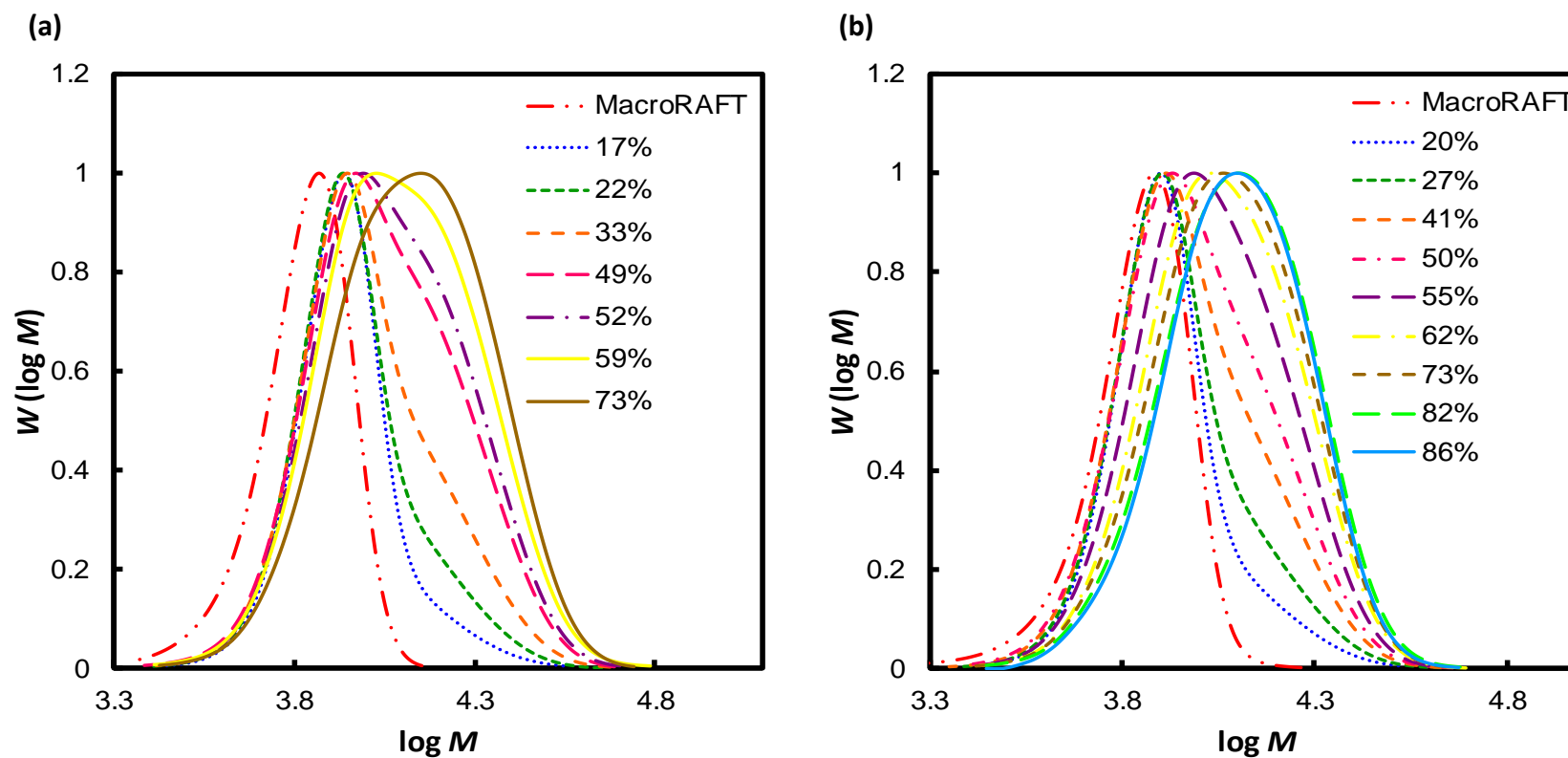


Figure 3.6. MWDs for the RAFT polymerization of ECA in toluene in the presence of poly(MMA)-RAFT (macroRAFT). Polymerizations using lower initiator concentrations with **(a)** $[ECA]_0/[macroRAFT]_0/[ACN]_0 = 2000/20/1$ at 90 °C **(b)** $[ECA]_0/[macroRAFT]_0/[ACN]_0 = 4500/45/1$ at 95 °C.

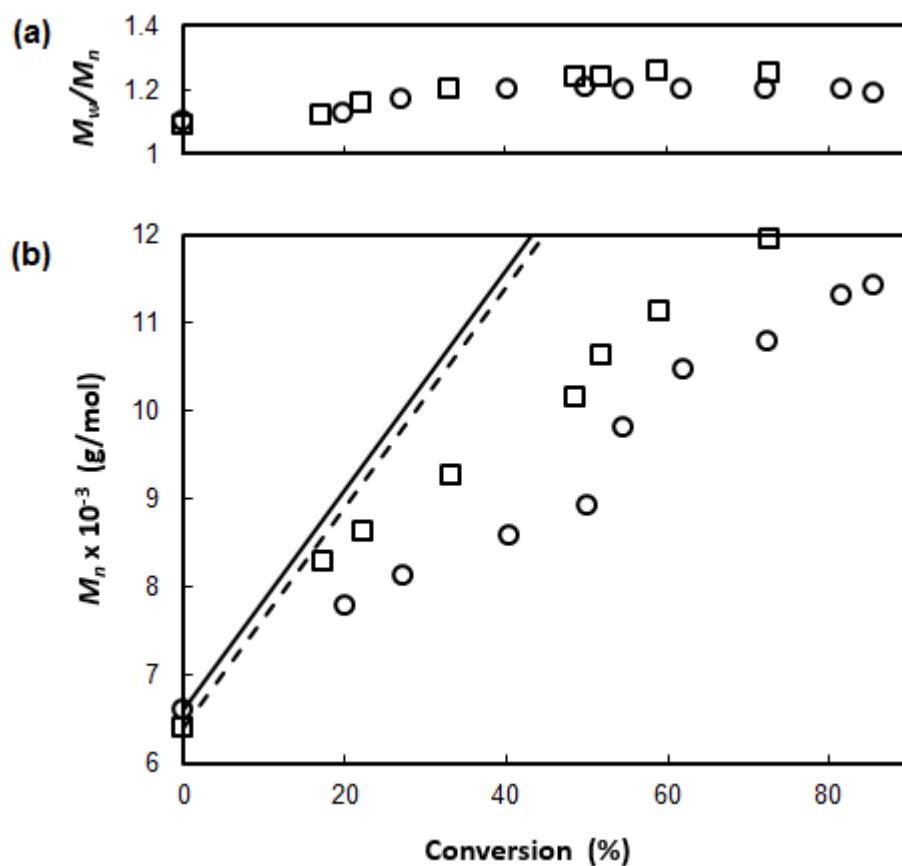


Figure 3.7. RAFT polymerization of ECA in toluene in the presence of poly(MMA)-RAFT (macroRAFT) **(a)** M_w/M_n and **(b)** M_n versus conversion. Polymerizations used $[ECA]_0/[macroRAFT]_0/[ACN]_0 = 2000/20/1$ (\square) with $M_{n,th}$ short dashed line and at 95 °C $[ECA]_0/[macroRAFT]_0/[ACN]_0 = 4500/45/1$ (\circ) with $M_{n,th}$ continuous line using at 90 °C a macroRAFT of $M_n = 6,400$ and 6,600 respectively.

3.3.3 RAFT polymerization of *n*-BuCA and PECA using MacroRAFT agent

RAFT polymerizations of alternative CA monomers were also investigated; *n*-BuCA was polymerized at 90 °C with $[n\text{-BuCA}]_0/[\text{macroRAFT}]_0 = 45$ and 90, and $[\text{macroRAFT}]_0/[\text{ACN}]_0 = 5$ and 10 respectively. Polymerizations proceeded to 69 and 86% conversions in 5–6 h (**Figure 3.8**), the somewhat lower rate presumably caused by the lower k_p of *n*-BuCA compared to that of ECA.^[81,86] In both cases, the MWDs were monomodal and narrow ($M_w/M_n = 1.13\text{--}1.16$ and $1.15\text{--}1.24$ for $[n\text{-BuCA}]_0/[\text{macroRAFT}]_0 = 45$ and 90, respectively) throughout, and shifting to higher molecular weight with increasing conversion (**Figure 3.9**). The linear evolution of M_n with conversion for $[n\text{-BuCA}]_0/[\text{macroRAFT}]_0 = 90$ with molecular weights almost double those using $[n\text{-BuCA}]_0/[\text{macroRAFT}]_0 = 45$ is consistent with good control/livingness (**Figure 3.10**).

RAFT polymerization of the solid CA monomer PECA was examined using 0.72 M solutions in toluene. Polymerization at 90 °C using $[\text{PECA}]_0/[\text{macroRAFT}]_0 = 45$ and $[\text{macroRAFT}]_0/[\text{ACN}]_0 = 5$ reached 83% conversion in 18 h. The polymerization was slower due to the use of dilute solutions in toluene (**Figure 3.11**). The MWDs remained narrow and monomodal ($M_w/M_n = 1.08\text{--}1.18$) throughout (**Figure 3.12(a)**), with M_n increasing with conversion (**Figure 3.13**). In order to increase the rate, the polymerization was also carried out at a higher temperature of 110 °C, resulting in a three-fold increase in rate to reach 92% conversion in 8 h (**Figure 3.11**). Molecular weights grew linearly with conversion with M_w/M_n remaining low ($1.10\text{--}1.25$; **Figure 3.12(b)**). However, at both temperatures, the M_n values were significantly lower than $M_{n,\text{th}}$ at conversions beyond ~20%.

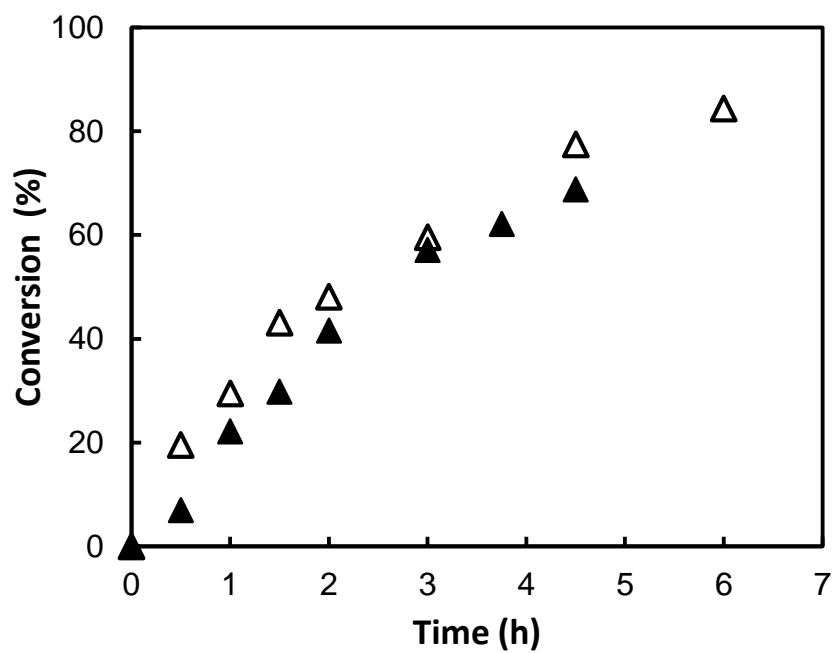


Figure 3.8. Conversion versus time plot for the RAFT polymerization of *n*-BuCA in toluene in the presence of poly(MMA)-RAFT (macroRAFT) at 90 °C:

$[n\text{-BuCA}]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ (▲);

$[n\text{-BuCA}]_0/[macroRAFT]_0/[ACN]_0 = 900/10/1$ (△).

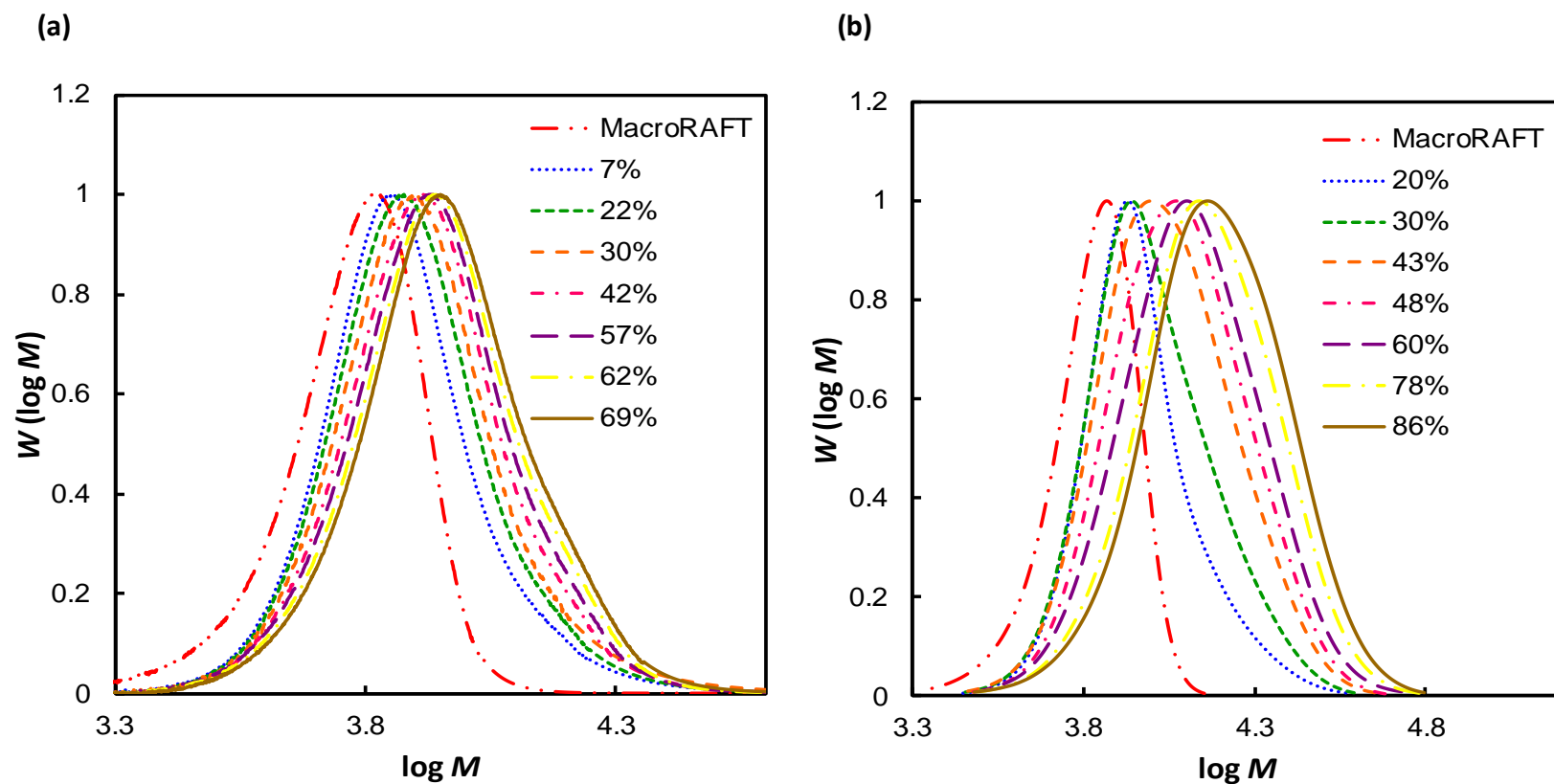


Figure 3.9. MWDs for the RAFT polymerization in the presence of poly(MMA)-RAFT (macroRAFT) of *n*-BuCA in toluene at 90 °C **(a)** $[n\text{-BuCA}]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$; **(b)** $[n\text{-BuCA}]_0/[macroRAFT]_0/[ACN]_0 = 900/10/1$.

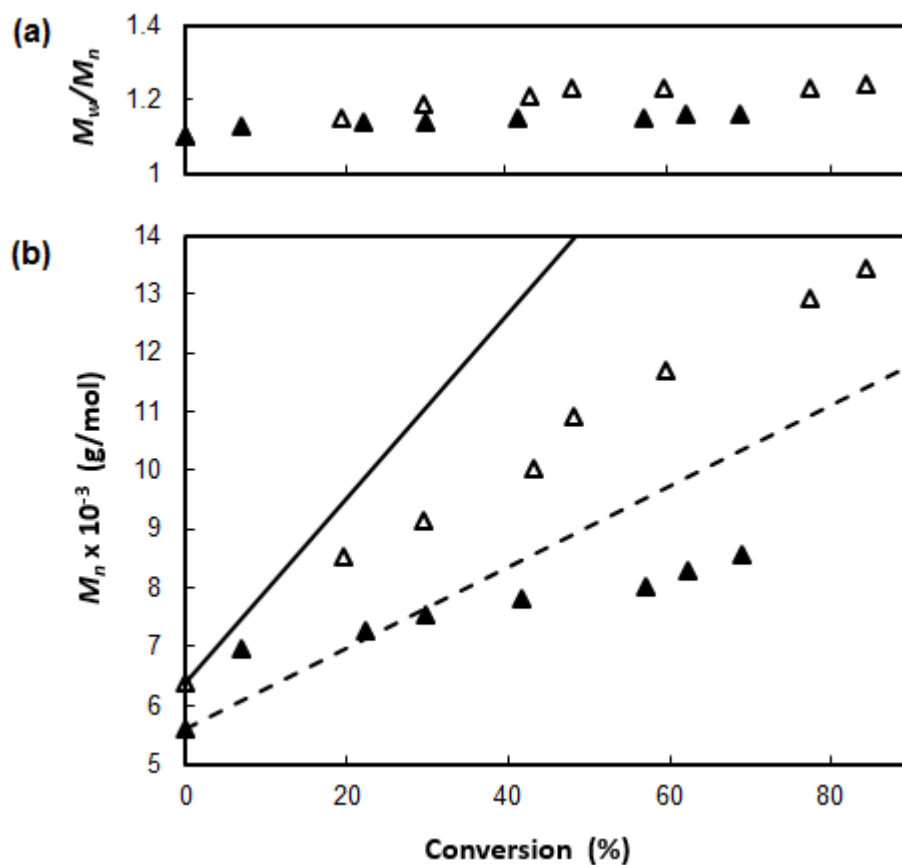


Figure 3.10. RAFT polymerization in the presence of poly(MMA)-RAFT (macroRAFT) of *n*-BuCA in toluene at 90 °C **(a)** M_w/M_n and **(b)** M_n versus conversion. Polymerizations used $[n\text{-BuCA}]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ (▲) with $M_{n,th}$ short dashed line and $[n\text{-BuCA}]_0/[macroRAFT]_0/[ACN]_0 = 900/10/1$ (△) with $M_{n,th}$ continuous line.

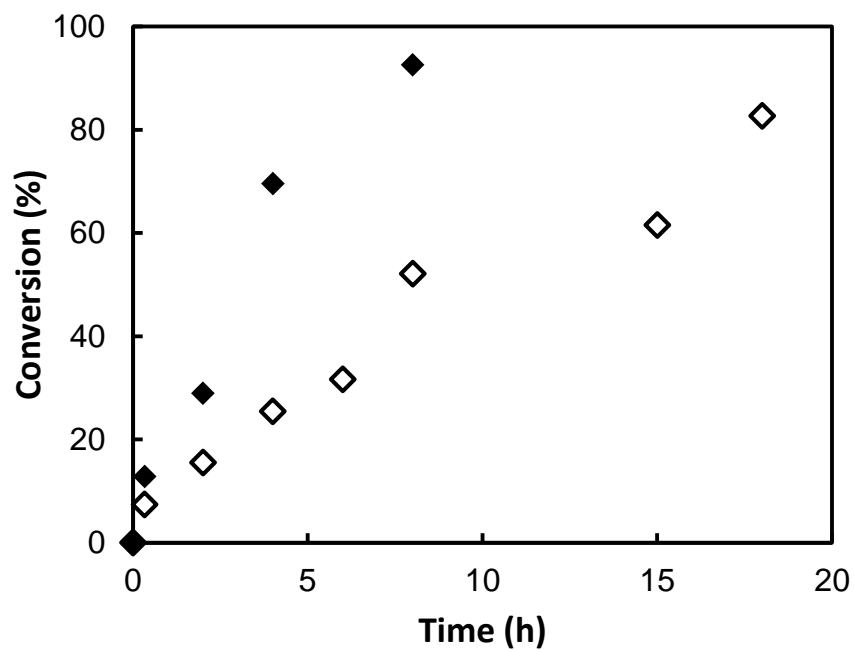


Figure 3.11. Conversion versus time plot for the RAFT polymerization of PECA in toluene in the presence of poly(MMA)-RAFT (macroRAFT):
 $[PECA]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ (◇) at 90 °C;
 $[PECA]_0/[macroRAFT]_0/[ACN]_0 = 900/20/1$ (◆) at 110 °C.

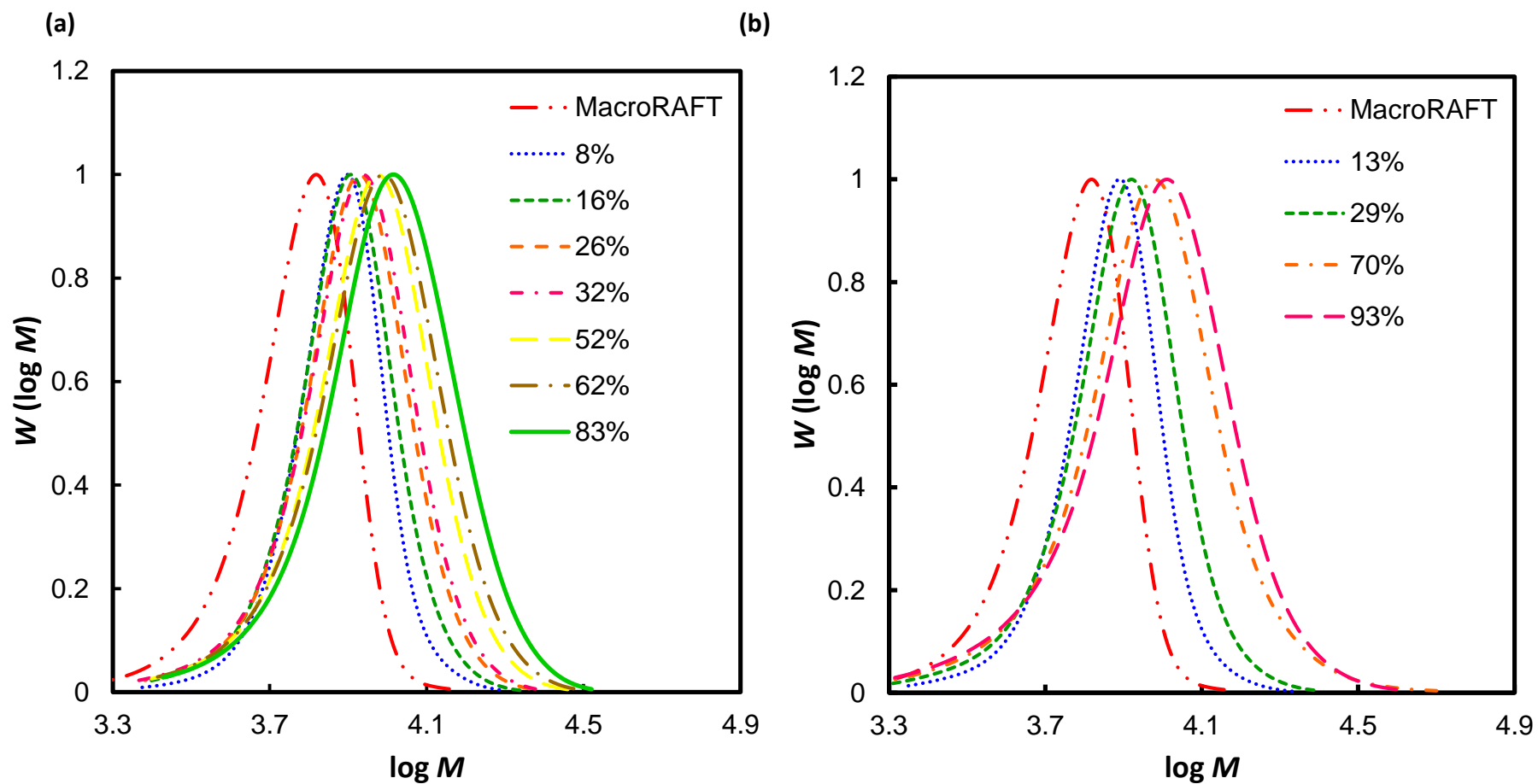


Figure 3.12. MWDs for the RAFT polymerization in the presence of poly(MMA)-RAFT (macroRAFT) of PECA in toluene **(a)** $[PECA]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ at $90\text{ }^\circ\text{C}$; **(b)** $[PECA]_0/[macroRAFT]_0/[ACN]_0 = 900/20/1$ at $110\text{ }^\circ\text{C}$.

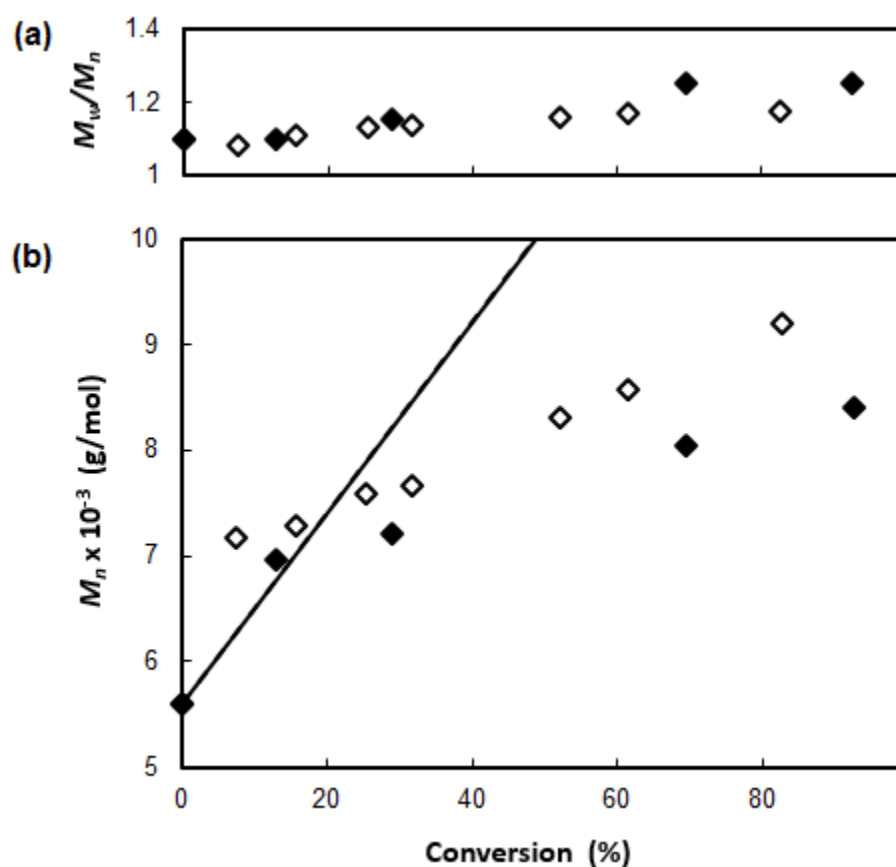


Figure 3.13. RAFT polymerization in the presence of poly(MMA)-RAFT (macroRAFT) with (a) M_w/M_n and (b) M_n versus conversion. Polymerizations used $[PECA]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ (\diamond) at 90 °C and $[PECA]_0/[macroRAFT]_0/[ACN]_0 = 900/20/1$ (\blacklozenge) at 110 °C with $M_{n,th}$ continuous line.

3.3.4 Chain Extension of poly(MMA)-*b*-poly(CA)-RAFT with MMA

A key feature of RAFT polymerization is the retention of the RAFT functionality on the polymer chain which can then act as a macroRAFT agent in the polymerization of a suitable monomer to form di, tri or multiblock copolymers. Isolated ECA, *n*-BuCA and PECA poly(MMA)-*b*-poly(CA)-RAFT diblocks were chain extended with MMA in order to examine the livingness of the diblock copolymers. Chain extensions of the poly(MMA)-*b*-poly(CA)-RAFT diblock copolymers with MMA were carried out in bulk at 90 °C using $[MMA]_0/[diblock]_0 = 600$ and $[diblock]_0/[ACN]_0 = 5$ (**Figure. 3.14**). In all three cases, the resulting RI-GPC MWDs clearly show generation of triblock copolymer poly(MMA)-*b*-poly(CA)-*b*-poly(MMA)-RAFT, but a significant portion of the original diblock copolymers are not chain extended indicating non-living polymer chains. This bimodality in chain extensions was further analysed using UV-GPC and are discussed in the next chapter.

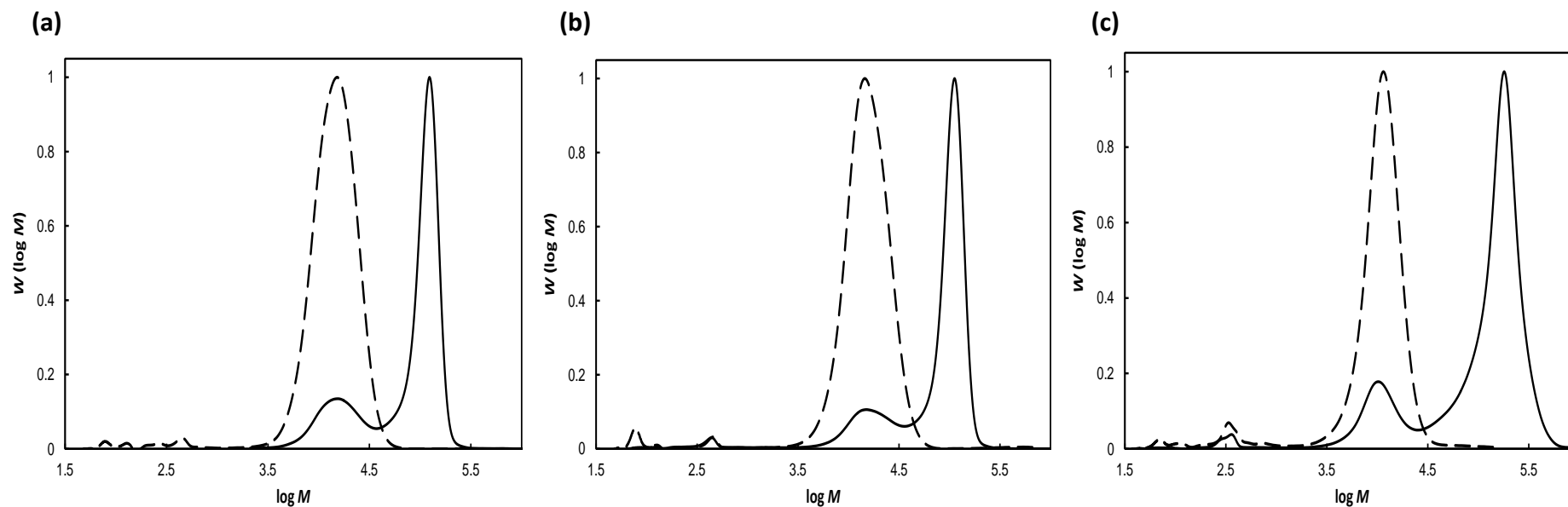


Figure 3.14. RI GPC/SEC distributions for the chain extensions of poly(MMA)-*b*-poly(CA)-RAFT (dashed line), which is then extended with MMA in bulk at 90 °C, where $[MMA]_0/[diblock]_0 = 600$ and $[diblock]_0/[ACN]_0 = 5$ to give the triblock (continuous line) **(a)** Extension of ECA containing diblock (from **Figure 3.6 (b)**) at 86% conversion) at 47% conversion. **(b)** Extension of *n*-BuCA containing diblock (from **Figure 3.9 (b)**) at 86% conversion) at 51% conversion. **(c)** Extension of PECA containing diblock (from **Figure 3.12(a)**) at 83% conversion) at 69% conversion.

3.4 Conclusion

The use of poly(MMA) macroRAFT agents has allowed control in the polymerization of cyanoacrylates, which was absent in the presence of small molecular RAFT agents. The large initial increase in MW at low conversion or “hybrid behaviour” appears to be significantly diminished. This supports the notion that changing the RAFT R-group to a sterically bulkier poly(MMA) group favoured the forward fragmentation of the intermediate adduct radical.

Decreasing the concentration of initiator and increasing the temperature further improved control by reducing the number of chains generated throughout the polymerization, thus a higher proportion of chains are derived from the RAFT agent.

In all cases, MWDs can be observed shifting to higher MW with increasing conversion while maintaining a low M_w/M_n (<1.3). M_n increases with increasing conversion and values are closer to $M_{n,th}$ than previously observed with the small molecular RAFT agents.

Although improved, the RAFT polymerization of cyanoacrylates using a macroRAFT agent is not ideal as M_n deviates significantly from $M_{n,th}$ (with due consideration to errors in using linear poly(MMA) standards for GPC calibration). Further limitations of the cyanoacrylate RAFT polymerization were highlighted when poly(MMA)-*b*-poly(CA)-RAFT diblocks were chain extended with MMA and RI-GPC analysis revealed a significant portion of chains did not extend, and thus were non-living. The UV-detector functionality of the GPC was utilized to allow a greater understanding of the nature of these non-living chains and attest to their formation. This work is discussed in more detail in Chapter 4.

CHAPTER 4
UV-ANALYSIS OF LIVINGNESS IN THE
RAFT POLYMERIZATION OF
CYANOACRYLATES USING A MACRORRAFT
AGENT

4.0 UV-ANALYSIS OF LIVINGNESS IN THE RAFT POLYMERIZATION OF CYANOACRYLATES USING A MACRORRAFT AGENT

4.1 Introduction

GPC UV-detection is an especially useful analytical tool for RAFT polymerizations as it allows for end group analysis due to the thiocarbonyl groups absorbing in the UV-Vis range, which accounts for the yellow, orange or reddish colour of RAFT derived polymers. Variable wavelength detectors can be specifically tuned to the absorbance maxima of particular RAFT functionalities and is a convenient way to test for the RAFT end-groups retention of polymer chains. Whereas RI detector response is proportional to polymer mass, UV detector response is proportional to the number of chains and as a result, shorter chains appear more strongly in UV distributions compared to RI. By comparing RI and UV distributions, a more comprehensive visualization of an overall polymerization can be obtained.

4.2 Chapter Aims and Objectives

In the previous chapter, GPC-RI analysis of the chain extensions of poly(MMA)-*b*-poly(CA)-RAFT diblock copolymers demonstrated that a significant proportion of the diblock did not extend and were therefore non-living. The aim of this chapter was to utilize GPC UV-detection to assess the livingness of the poly(MMA)-*b*-poly(CA)-RAFT diblock copolymers and better understand what might be occurring in the RAFT polymerization of cyanoacrylates.

4.2.1 Experimental

4.2.1.1 Instrumentation and Measurements

Molecular weight distributions were recorded using size exclusion chromatography (SEC) at 30 °C using an Agilent 1260 Infinity Series GPC/SEC system as described in Chapter 2. Theoretical molecular weight ($M_{n,th}$) was calculated according to equation 4.

Mass spectrometry was carried out at the Mass Spectrometry Facility, School of Chemistry, University College Dublin (Ireland) using the GCT premier on chemical ionization mode (CI⁺).

4.3 Results and discussion

4.3.1 RAFT Polymerization of ECA using poly(MMA) MacroRAFT agent

In order to examine the livingness (RAFT end-group retention), the ECA, *n*-BuCA and PECA poly(MMA)-*b*-poly(CA)-RAFT diblocks copolymers were analysed by GPC UV-detection at 304 nm (**Figure. 4.0**, **Figure 4.1** and **Figure 4.2** respectively). At this wavelength, the detector response corresponds to the $\pi \rightarrow \pi^*$ transition of the C=S bond of the dithioester functionality^[201,202] and poly(MMA) and poly(CA) repeating units do not absorb. The UV-GPC traces have been normalized to the height of the polymer peak in each case (**Figure. 4.0–4.2**). The polymer peak remains narrow and shifts to higher molecular weight with increasing conversion. There are however, several low molecular weight peaks in the UV-GPC traces that are absent in the RI data, which increase in relative intensity with increasing conversion. Moreover, these low molecular weight peaks are very similar for the three monomers examined (ECA, *n*-BuCA and PECA) (**Figure. 4.0–4.2**). It can be inferred that the number of living chains in the polymer peak (around $\log M \approx 4$) is decreasing during the polymerization.

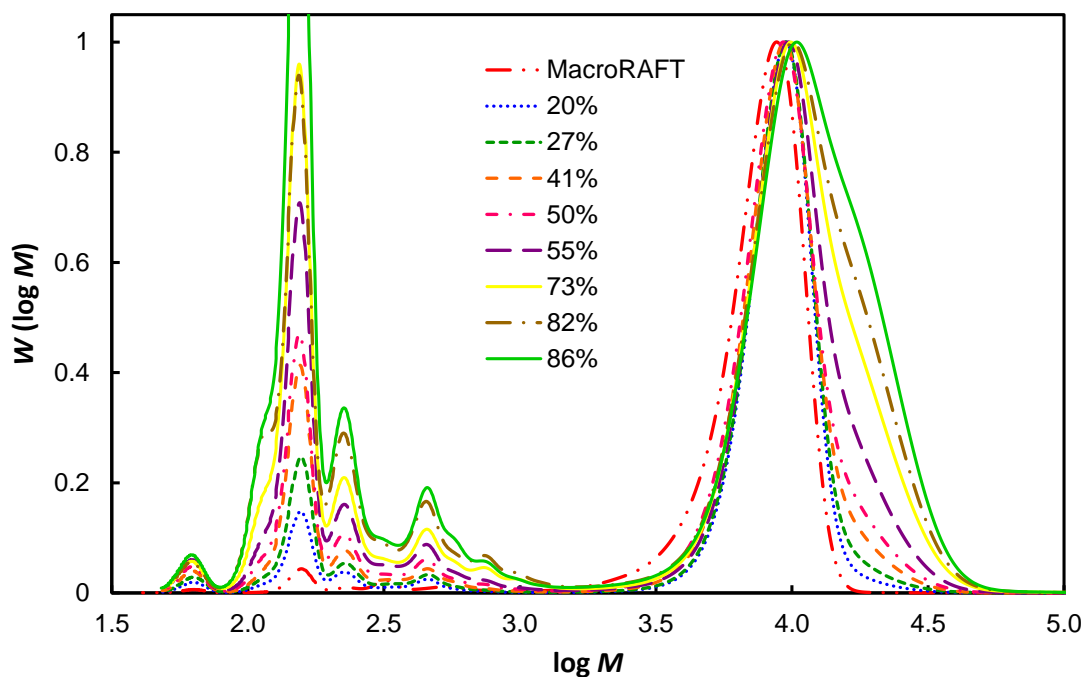


Figure 4.0. UV MWDs at 304 nm for the RAFT polymerization of CA in toluene in the presence of poly(MMA)-RAFT (macroRAFT) (conversions as indicated). Polymerization using $[ECA]_0/[macroRAFT]_0/[ACN]_0 = 4500/45/1$ at 95 °C.

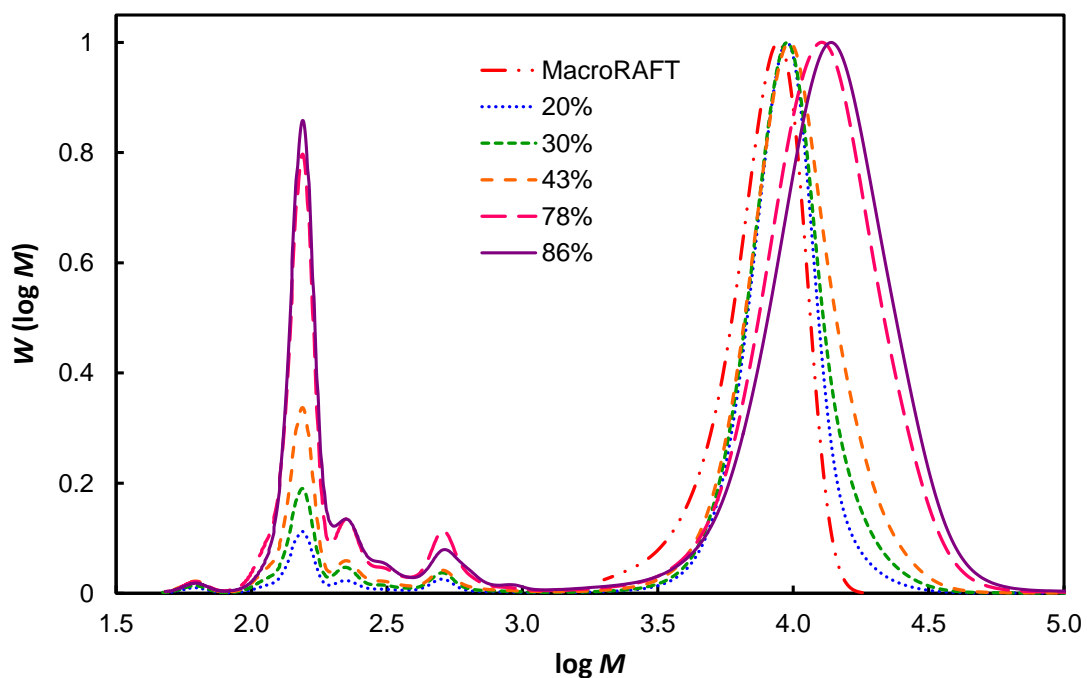


Figure 4.1. UV MWDs at 304 nm for the RAFT polymerization of CA in toluene in the presence of poly(MMA)-RAFT (macroRAFT) (conversions as indicated). Polymerization using $[n-BuCA]_0/[macroRAFT]_0/[ACN] = 900/10/1$ at 90 °C.

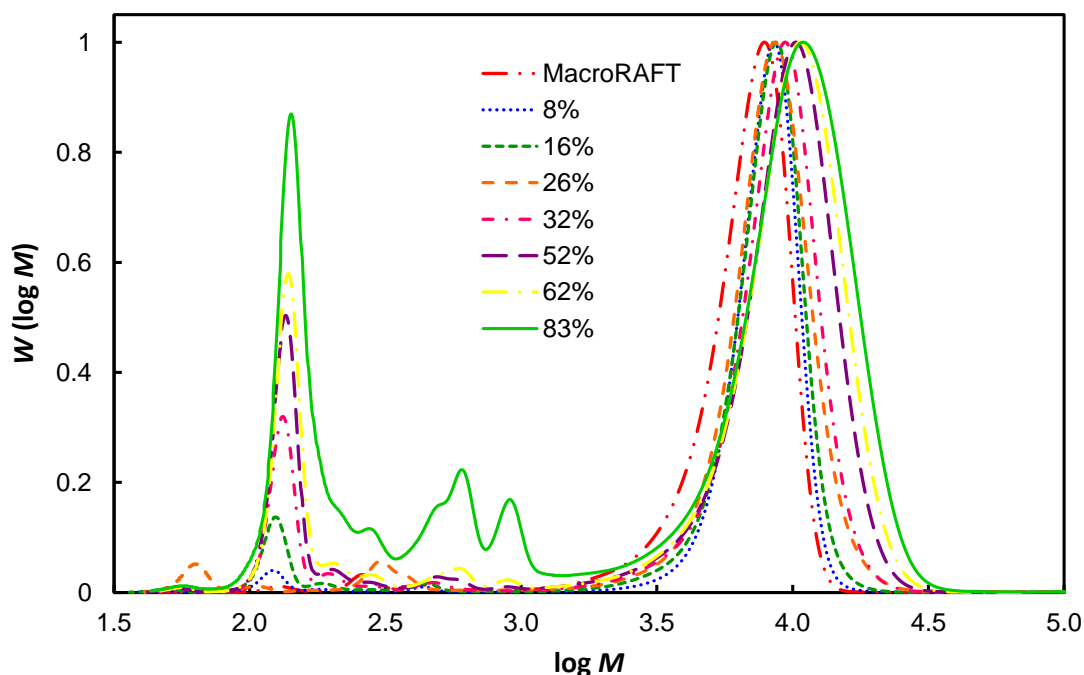


Figure 4.2. UV MWDs at 304 nm for the RAFT polymerization of CA in toluene in the presence of poly(MMA)-RAFT (macroRAFT) (conversions as indicated). Polymerization using $[PECA]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ at 90 °C.

The loss of RAFT end groups was quantified by monitoring the area of the polymer peak in the UV detector response versus time (based on a constant injection volume of GPC samples of fixed wt% polymer, and correcting for the increase in polymer mass relative to the number of end groups with conversion). The resulting normalized UV response (area under the curve), which is proportional to the number of RAFT end groups, was plotted versus time (**Figure. 4.3**) and conversion (**Figure. 4.4**). For all three monomers, the loss of livingness is at least 70% at the end of the polymerization. The plots of UV response versus conversion all follow a very similar trend.

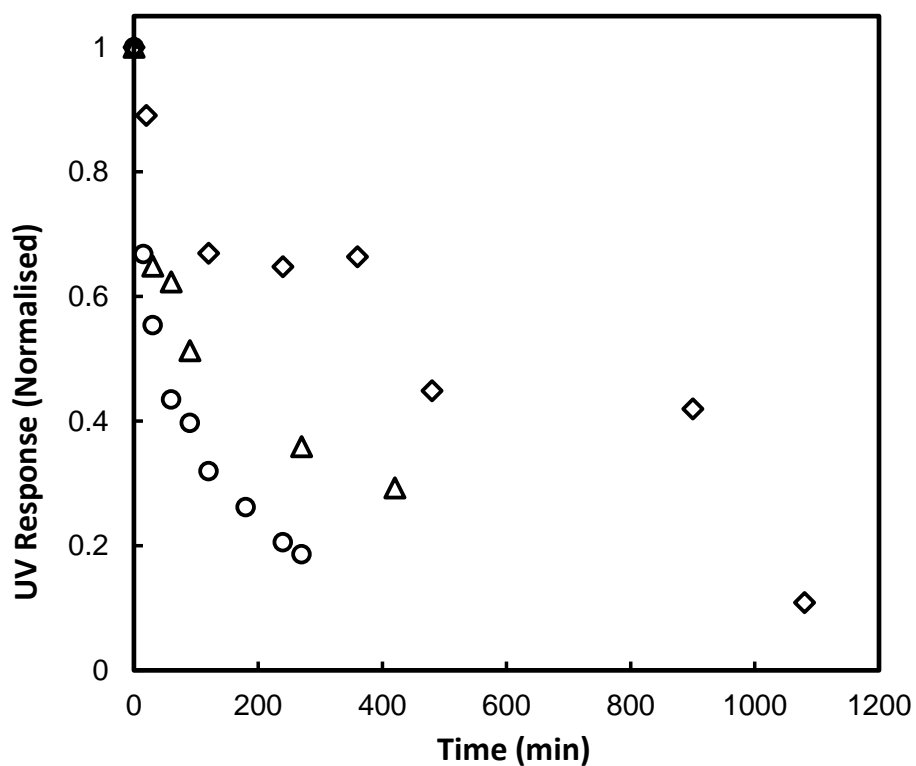


Figure 4.3. Total UV Response from UV-GPC of the polymer peaks versus time for $[ECA=2.23M]_0/[macroRAFT]_0/[ACN]_0 = 4500/45/1$ (o) at 95 °C, $[n-BuCA=0.98M]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ (Δ) at 90 °C and $[PECA=0.72M]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ (\diamond) at 90 °C.

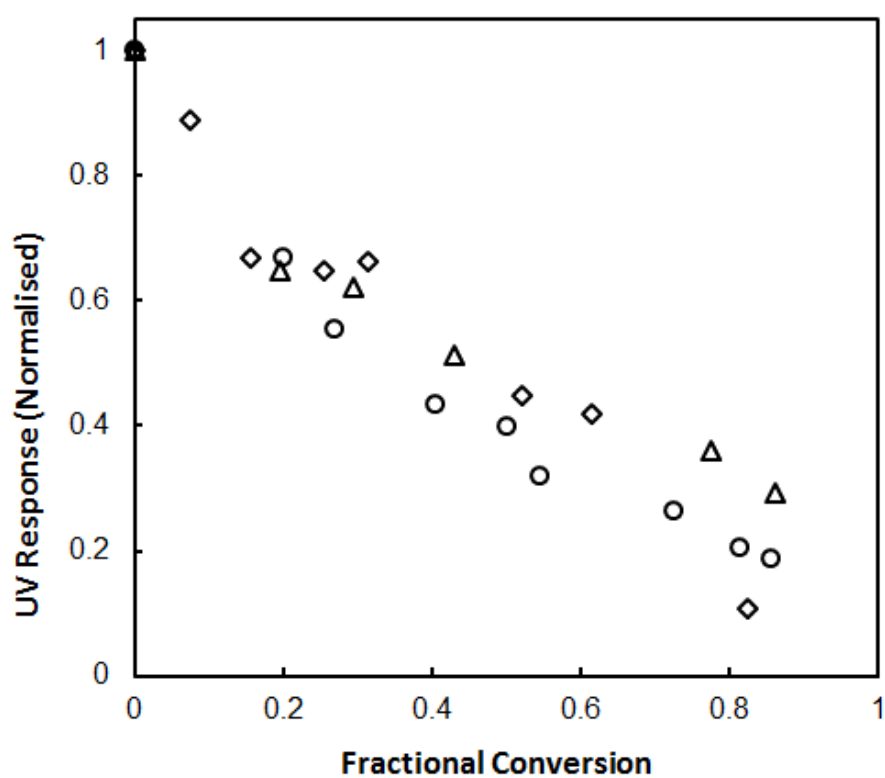


Figure 4.4. Total UV Response from UV-GPC of the polymer peaks versus fractional conversion for $[ECA=2.23M]_0/[macroRAFT]_0/[ACN]_0 = 4500/45/1$ (o) at 95 °C, $[n-BuCA=0.98M]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ (Δ) at 90 °C and $[PECA=0.72M]_0/[macroRAFT]_0/[ACN]_0 = 225/5/1$ (\diamond) at 90 °C.

Further evidence of the poly(MMA)-*b*-poly(CA)-RAFT inherent instability was demonstrated when a sample of poly(MMA)-*b*-poly(ECA)-RAFT was dissolved in toluene and heated at the typical polymerization temperature of 90 °C for a number of hours with aliquots withdrawn periodically for UV-GPC analysis (**Figure 4.5**) using the same methodology as **Figure 4.3** and **4.4**. A steady decrease in the number of polymer RAFT end groups was observed.

Dithioester RAFT agents are particularly susceptible to hydrolysis reactions which eliminate the active end group. This is typically observed in basic media with an increased rate of hydrolysis as pH increases, and can manifest itself as $M_n > M_{n,th.}$ ^[203,204] Given that the reaction media of the polymerizations reported herein are moderately acidic, the effect of such hydrolysis would be expected to be negligible.

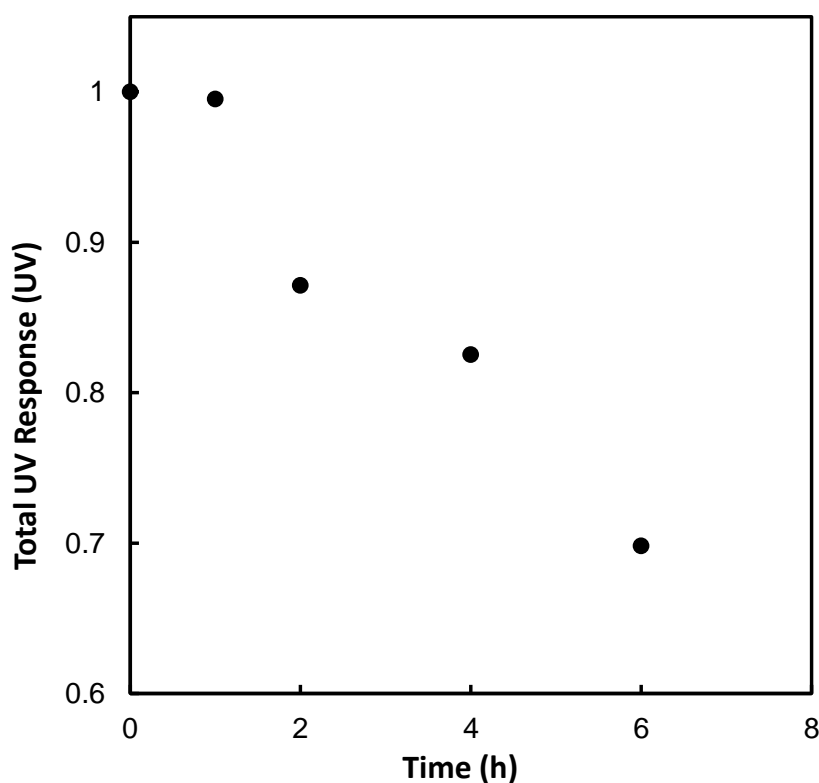
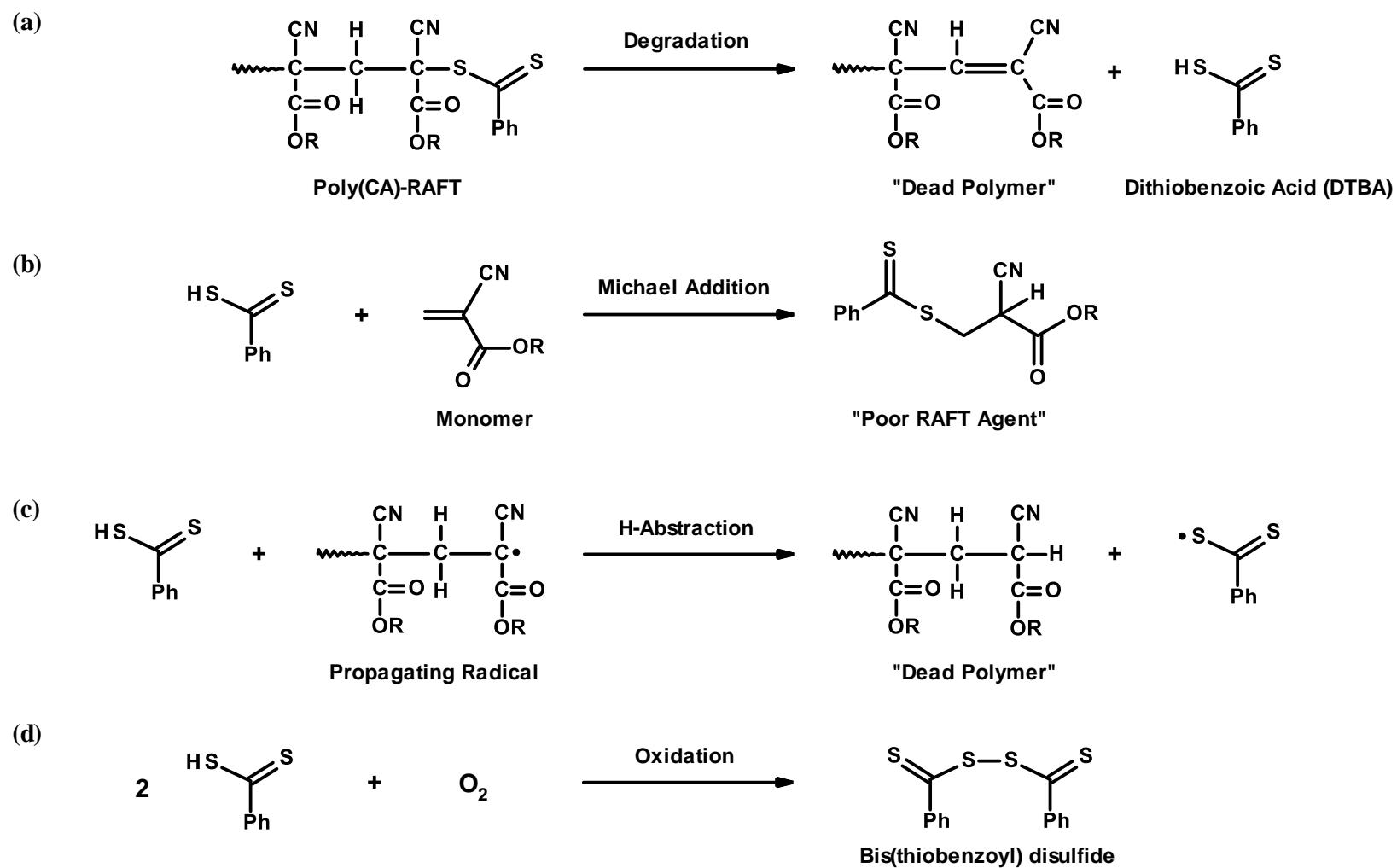


Figure 4.5. Total UV Response of polymer peaks versus time from UV-GPC of poly(MMA)-*b*-poly(ECA)-RAFT heated in toluene at 90 °C.

An alternative degradation pathway is proposed for these poly(MMA)-*b*-poly(CA)-RAFT polymers via an elimination mechanism to generate dithiobenzoic acid (DTBA) and polymer with an unsaturated end group (**Scheme 4.0**) analogous to the degradation of poly(MMA)-RAFT polymers.^[205-207] The prominent low molecular weight peak in the UV-GPC spectra (**Figure. 4.0–4.2**) has a peak value of 155 g.mol⁻¹, which coincides with the molar mass of DTBA.

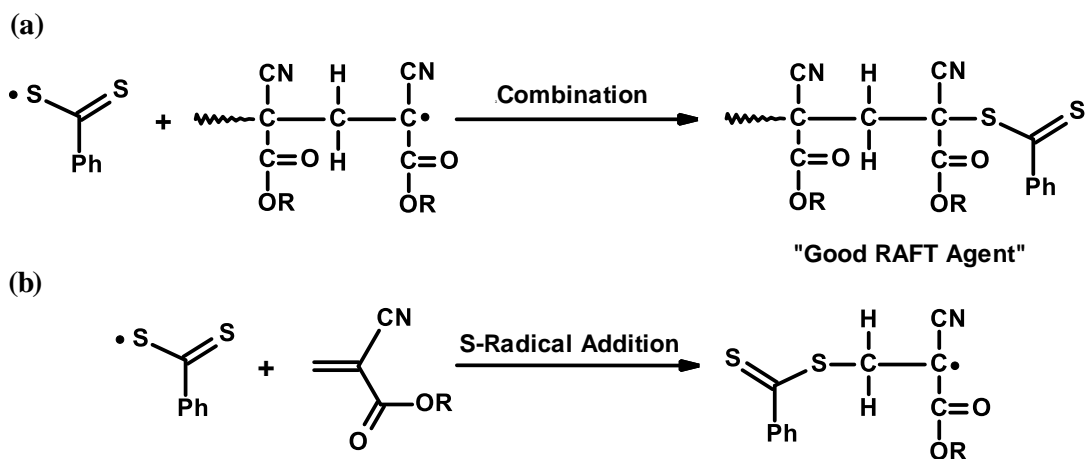
However, this value is obviously prone to significant error given that it is based on poly(MMA) standards and also falls outside the calibrated range of the GPC. Mass spectra of these diblock copolymer mixtures confirmed the presence of DTBA with a sharp peak at m/z 153 and 154 g.mol⁻¹.^[202]

It is worth mentioning that the presence of DTBA is also indicated by a strong red colour^[208] with all CA polymerization mixtures changing from the characteristic RAFT pink colour to a red colour with time/conversion. The acidity of the methylene at the chain terminus is expected to be enhanced by the inductively electron withdrawing nitrile and ester functionalities, leading to formation of an unsaturated end group. The latter is difficult to detect by conventional techniques (such as NMR) due to its quaternary nature or full substitution (with CN and COOR).



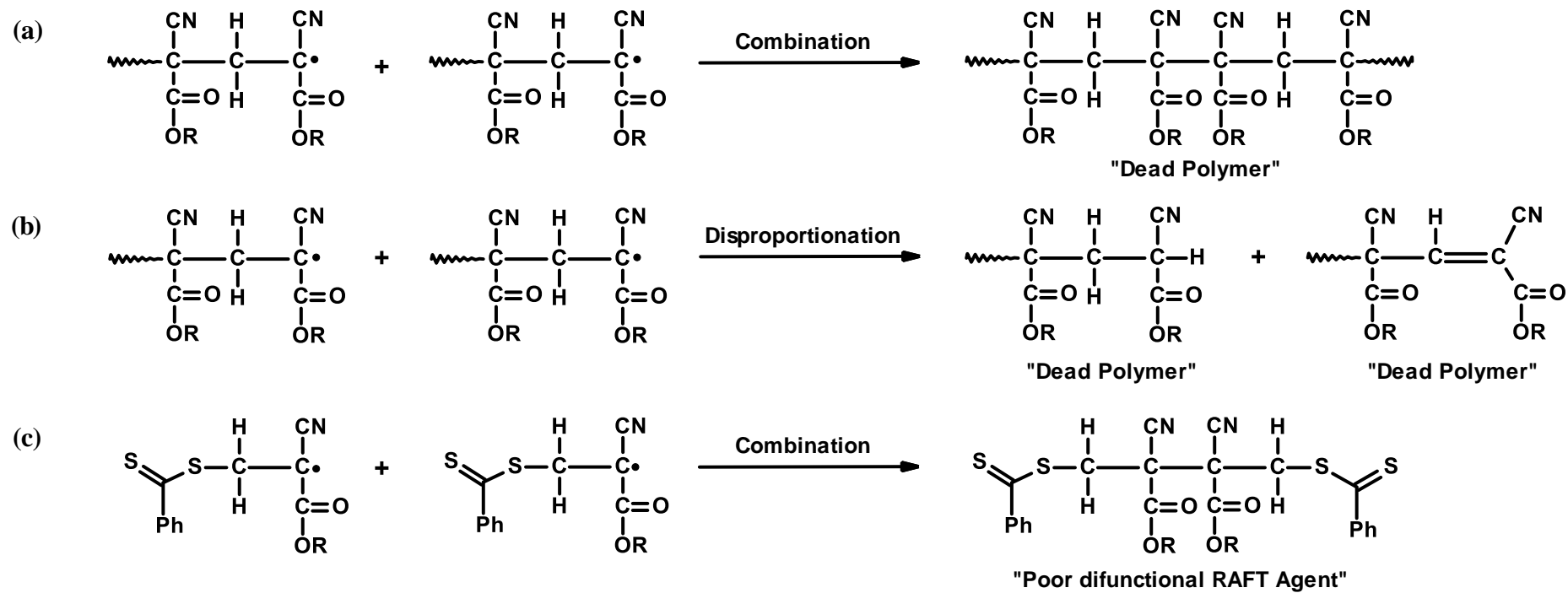
Scheme 4.0. Degradation of poly(CA) macroRAFT and reactivity of DTBA.

The DTBA formed via RAFT end group decomposition can add to a CA monomer via a Michael addition reaction as reported for acrylates and MMA (**Scheme 4.0(b)**).^[209] This would generate an ineffective RAFT agent with a poor primary leaving group and would be slow to fragment in the RAFT process. However, it cannot be excluded that the formation of low molecular weight species detected in UV-GPC traces could be to some extent attributable to species derived from the chain transfer via the Michael adduct. More importantly, the DTBA can itself act as a chain transfer agent through the radical abstraction by a propagating radical of the labile-H from the thiol moiety to give a hydrogen terminated dead polymer chain and the reactive Ph-C(=S)-S• radical species (**Scheme 4.0(c)**). This S-radical can then combine with a propagating radical to give a dithioester with a tertiary polymeric leaving group and thereby generate a “good” RAFT agent (**Scheme 4.1(a)**), as proposed for controlled/living RAFT polymerizations of MMA using DTBA as mediator,^[209-211] or alternatively the DTBA radical can add to a CA monomer (**Scheme 4.1(b)**). This might seem unlikely given the expected electrophilic nature of the DTBA radical and the electron deficient double-bond of the CA monomer however, dithiocarbamates are known iniferters for MMA polymerization^[212] and similarly electrophilic radical fragments of benzoyl peroxide are known to add to CA monomer.^[80] Despite this, addition to monomer will be slow as the transfer constant is predicted to be low and even with an addition of a single monomer unit (or a few monomer units) there is a high probability that termination with other radicals in the system will occur rather than extensive propagation.^[213] Such termination reactions would generate “poor” difunctional (combination) and mono-functional RAFT agents (disproportionation) that may in turn participate in further reactions (**Scheme 4.2**).



Scheme 4.1. Reactions of DTBA radical derived from end-group decomposition.

The set of reactions outlined in **Scheme 4.2** have the net effect of transforming a polymer chain with a RAFT end group to a dead polymer chain and a low molecular weight species (DTBA; **Scheme 4.0(a)**), which is proposed to ultimately lead to an increase in the number of chains via the reaction pathways starting with the generation of DTBA. This exchange of polymer RAFT end groups to give non-living polymers and newly formed living polymers increases the number of chains, this in turn causes a steady increase in M_w/M_n with conversion, which is what is experimentally observed (**Figures 3.5, 3.7, 3.10** and **3.13**). This is in contrast to the typical decrease in M_w/M_n with increasing conversion that would be expected in a standard RAFT polymerization.^[147] Furthermore, the increase in the number of chains accounts for the 2-3 fold deviation of M_n below $M_{n,th}$ observed in these RAFT mediated alkyl CA polymerizations.



Scheme 4.2. Propagating radical termination reactions.

4.3.2 Chain Extension of poly(MMA)-*b*-poly(CA)-RAFT with MMA

Formation of non-living polymer chains was further evidenced by chain extensions of the poly(MMA)-*b*-poly(CA)-RAFT diblock copolymers with MMA in bulk at 90 °C using $[MMA]_0/[diblock]_0 = 600$ and $[diblock]_0/[ACN]_0 = 5$ (**Figure 4.6**). As discussed in Chapter 3, the RI-GPC distributions for each poly(MMA)-*b*-poly(CA)-RAFT diblock clearly show chain extension with MMA to form the triblock copolymer, but a significant portion of the original diblock copolymers are not chain extended. GPC with UV detection revealed that these non-extended chains not only comprised dead chains as a result of loss of RAFT end groups (**Scheme 4.0**), but also consisted of chains that possessed the thiocarbonyl functionality, consistent with the formation of “poor” RAFT agents (**Scheme 4.0 and 4.2**). UV detection also showed essentially negligible amounts of low molecular weight material (unlike the CA polymerizations, **Figures 4.0–4.2**) for the chain extensions of the ECA and *n*-BuCA blocks (save for PECA, but still substantially less than for the CA polymerizations). This data thus support the notion that RAFT end group decomposition occurs at a markedly higher rate for CA polymers than for poly(MMA).

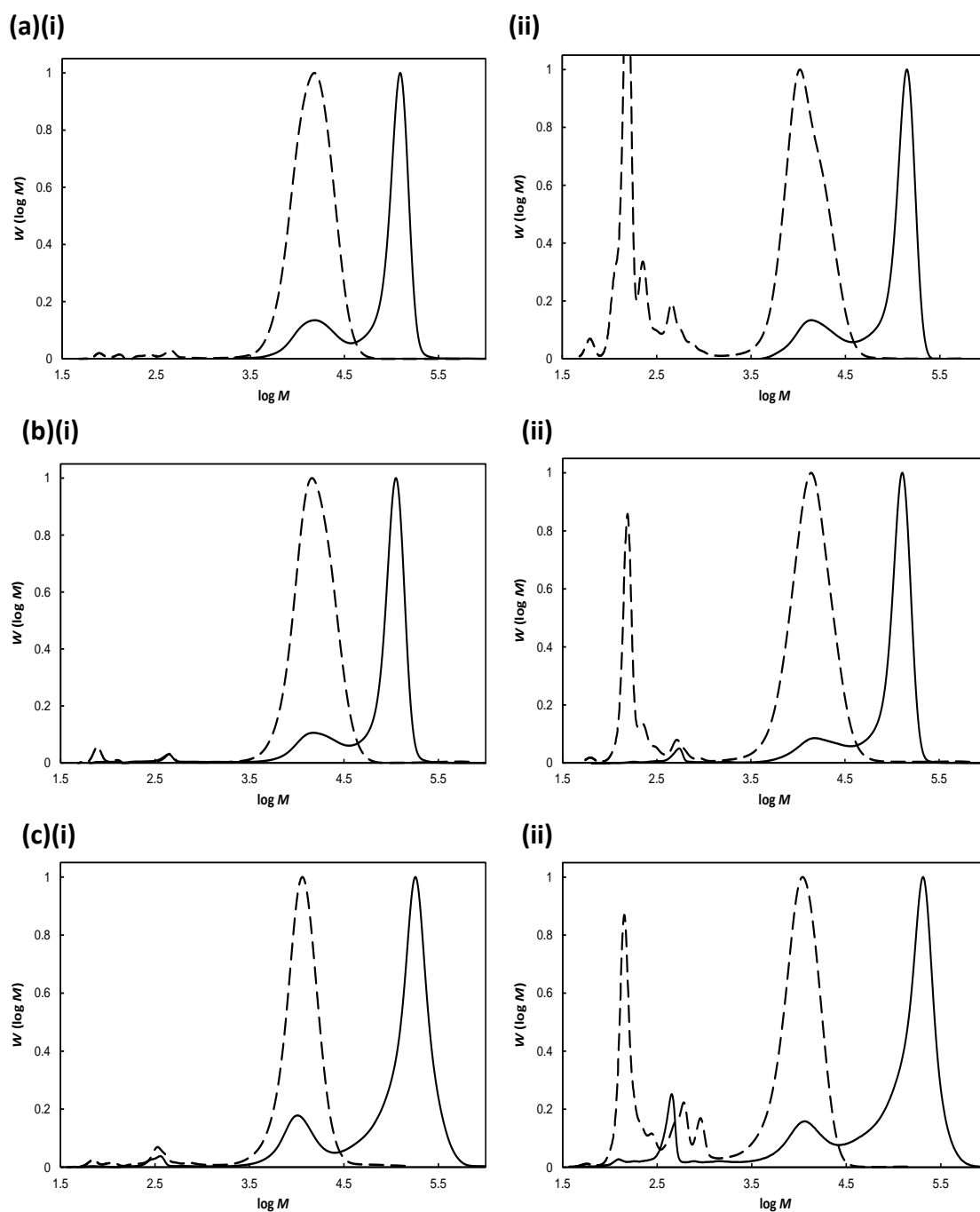


Figure 4.6. (i) RI and (ii) UV GPC/SEC distributions for the chain extensions of poly(MMA)-*b*-poly(CA)-RAFT (dashed line), which is then extended with MMA in bulk at 90 °C, where $[MMA]_0/[diblock]_0 = 600$ and $[diblock]_0/[ACN]_0 = 5$ to give the triblock (continuous line) (a) Extension of ECA containing diblock (from **Figure 3.6 (b)**) at 86% conversion) at 47% conversion. (b) Extension of *n*-BuCA containing diblock (from **Figure 3.9 (b)**) at 86% conversion) at 51% conversion. (c) Extension of PECA containing diblock (from **Figure 3.12(a)**) at 83% conversion) at 69%.

4.4 Conclusion

The first study of controlled/living character for polymerization of cyanoacrylates is reported using a poly(MMA) macroRAFT. The synthesis of diblock (and triblock) copolymers of this challenging monomer class by radical polymerization has not previously been reported. Control was however, far from ideal, as molecular weights tended to deviate towards values lower than $M_{n,th}$, which was attributed to degradation of the formed polymer during polymerization. UV-analysis has revealed that poly(MMA)-*b*-poly(CA)-RAFT formed appears to be inherently unstable with self-elimination of the RAFT end group occurring rapidly as the polymer is formed to generate DTBA. This degradation was not apparent by RI detection but was evident for all three cyanoacrylate monomers polymerized. The polymerization process is thought to be further complicated by combination and disproportionation reactions of radicals due to elimination of the RAFT end-group.

4.5 Future Work

RI-detection in GPC analysis is standard and when combined with a viscometer and light-scattering in a triple detection GPC configuration, has the benefit of obtaining a wealth of characteristic information about the polymer being analysed. However, for future work carried out in the RAFT polymerization of cyanoacrylates, it cannot be over-stated that UV-detection in the polymer analysis is of paramount importance. The data presented in Chapter 4 shows that when RI is contrasted to UV-detection, a much clearer picture of the polymerization is realised that could have otherwise been overlooked.

An issue that was encountered in the initial small molecule RAFT polymerizations of ECA was a rapid increase in MW at low conversion and was attributed to poor transfer to RAFT agent due to poorly favoured forward fragmentation of the intermediate radical adduct. The poly(ECA) tertiary propagating radical is stabilized by a nitrile and ester functionality and therefore a proficient RAFT agent should have an R-group of greater radical stability and thus a better leaving group to ensure forward fragmentation. Such an R-group would be expected to be tertiary in nature with two strongly electron withdrawing substituents, however, no such RAFT agents have yet appeared in literature, likely owing to the difficulty in their preparation. If such a RAFT agent could be synthesized, it would potentially be an effective RAFT agent for the polymerization of cyanoacrylates provided the R-group was able to efficiently reinitiate polymerization on fragmentation. However, the problem of poly(CA)-RAFT instability may still persist.

To circumvent the poor rate of transfer in RAFT, we employed a macroRAFT agent in cyanoacrylate polymerization to increase the rate of transfer by using a sterically bulky poly(MMA) R-group to favour forward fragmentation of the intermediate radical adduct. The macroRAFT that was primarily used in this study was based on poly(MMA) derived from CPDB ($M_n \approx 6000 \text{ g.mol}^{-1}$ and $M_w/M_n \approx 1.10$) and macroRAFT agents derived from other small molecule RAFT agents were not extensively studied. It would be interesting to examine the effects of varying the Z-group of the macroRAFT agent in the polymerization of cyanoacrylate by preparing similar MW poly(MMA)macroRAFTs derived from different families of RAFT agents

like trithiocarbonates or aliphatic dithioesters. Furthermore, it may even be of interest to check the effect of varying the Z-group size of trithiocarbonate macroRAFT agents by comparing CDSPA to a shorter Z-group trithiocarbonate like that of 4-(((2-carboxyethyl)thio)carbonothioyl)thio)-4-cyanopentanoic acid (CCC) for example (**Figure 4.7**). CCC is currently employed in the RAFT of methacrylate monomers.^[214]

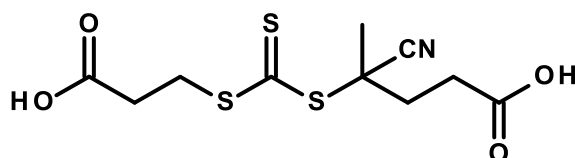


Figure 4.7. Structure of CCC.

Trithiocarbonates have the advantage of being more hydrolytically stable than dithiobenzoates and can be successfully utilized as RAFT agents under strongly acidic conditions.^[215,216] This would be beneficial for the acidic polymerization conditions required for cyanoacrylates with the polymer end-group exhibiting a better resistance to degradation than macroRAFTs based on CPDB.

A trithiocarbonate macroRAFT based on a more hydrophilic methacrylate starting block, like the commercially available poly(hydroxyethyl methacrylate) derived from 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (DDMAT) (**Figure 4.8.**), could be chain extended with cyanoacrylates to form amphiphilic diblock copolymers. Post polymerization, such copolymers would be able to self-assemble upon introduction to an aqueous medium to form structures of various conformations. The presence of the strongly hydrophobic dodecyl moiety on the RAFT ω -end group may significantly impact the polymer morphology as observed by Chalmers et al. in their preparation of CO₂-responsive polyacrylamide copolymers leading to complex ABA' self-assembled vesicles.^[216] Nano-objects based on self-assembled polymers are of particular interest for various biomedical applications including drug delivery.

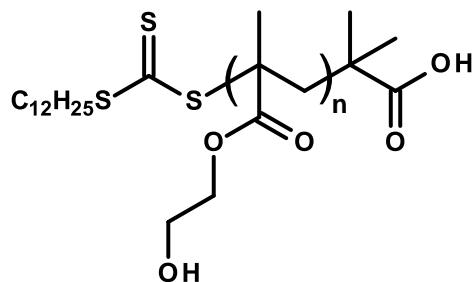


Figure 4.8. Poly(hydroxyethyl methacrylate) macroRAFT based on DDMAT.

As described in Chapter 2, switchable RAFTs can be used in the polymerization of both LAMS and MAMs depending on the agents' neutral or protonated form. In their protonated form they have been described as very effective RAFT agents for MAM polymerization. Intuitively, these switchable RAFT agents would not be considered compatible with cyanoacrylates as the dithiocarbamate nitrogen would likely cause unwanted anionic polymerization, however, in their protonated form (**Figure 4.9**) and in an acidic medium, they may potentially be suitable RAFT agents for cyanoacrylate polymerization as the electron density of the nitrogen is reduced. A number of differing switchable RAFT agents are currently commercially available such as 2-cyanopropan-2-yl *N*-methyl-*N*-(pyridin-4-yl)carbamodithioate (CPMPC) (**Figure 4.9**).

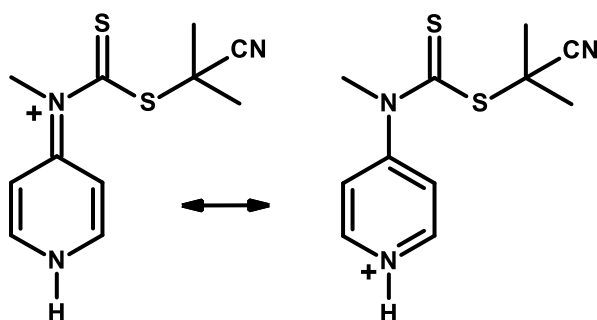


Figure 4.9. Protonated resonance structures of CPMPC.

REFERENCES

- [1] Klemarczyk, P.; Guthrie, J. "Advances in anaerobic and cyanoacrylate adhesives": *Advances in Structural Adhesive Bonding*, Woodhead Publishing Limited, Cambridge, **2010**, 96–131.
- [2] Shantha, K. L.; Thennarasu, S.; Krishnamurti, N. Developments and applications of cyanoacrylate adhesives. *J. Adhes. Sci. Technol.*, **1989**, 3, 237–260.
- [3] Fink, J. K. "Chapter 13 Cyanoacrylates": *Reactive Polymers Fundamentals and Applications*, Elsevier, **2013**, 317–330.
- [4] Burns, B. "Polycyanoacrylates": *Encyclopedia of Polymer Science and Technology*. John Wiley & Sons, Inc., **2016**, 4, 1–27.
- [5] O'Connor, J. T. "Acrylic Ester Polymers, 2-Cyanoacrylic Ester Polymers" in *Kirk-Othmer Encyclopedia of Chemical Technology*. John Wiley & Sons, Inc., **2000**, 1–7.
- [6] Woods, J. "Polycyanoacrylates": *Encyclopedia of Polymer Science and Technology*. John Wiley & Sons, Inc., **2001**, 3, 643–652.
- [7] Singer, A. J.; Thode Jr, H. C. A review of the literature on octylcyanoacrylate tissue adhesive. *Am. J. Surg.*, **2004**, 187, 238–248.
- [8] Singer A. J.; Quinn J. V.; Hollander J. E. The cyanoacrylate topical skin adhesives. *Am. J. Emerg. Med.*, **2008**, 26, 490–496.
- [9] Shivamurthy, D. M.; Singh, S.; Reddy, S. Comparison of octyl-2-cyanoacrylate and conventional sutures in facial skin closure. *Natl. J. Maxillofac. Surg.*, **2010**, 1(1), 15–19.
- [10] Ruthinéia Diógenes Alves Uchôa et al. Use of cyanoacrylate in the coaptation of edges of surgical wounds. *An Bras Dermatol.*, **2012**, 87(6), 871–876.
- [11] Sameena, T.; Sethy, S. P.; Patil, P.; Shailaja, K.; Ashraf, O. Cyanoacrylate: A Bio Adhesive for Sutureless Surgery: A Review. *Asian J. Research Chem.*, **2014**, 7(3), 349–354.

- [12] García Cerdá, D.; Ballester, A. M.; Aliena-Valero, A.; Carabén-Redaño, A.; Lloris, J. M. Use of cyanoacrylate adhesives in general surgery. *Surg. Today*, **2015**, 45, 939–956.
- [13] Hynes, S. J. Biomedical Applications of 2-Cyanoacrylates. *Irish Chem. News*, **2009**, 25, 24–28.
- [14] Murthy, R. S. R.; Harivardhan Reddy, L. “Chapter 15: Poly(Alkyl Cyanoacrylate) Nanoparticles for Delivery of Anti-Cancer Drugs”: *Nanotechnology for Cancer Therapy*, Amiji, M. M., **2006**, 251–288.
- [15] Nicolas, J.; Couvreur, P. Synthesis of poly(alkyl cyanoacrylate)-based colloidal nanomedicines. *Wiley Interdiscipl. Rev. Nanomed. Nanobiotechnol.*, **2009**, 1, 111–127.
- [16] Graf, A.; McDowell, A.; Rades, T. Poly(alkylcyanoacrylate) nanoparticles for enhanced delivery of therapeutics – is there real potential? *Expert Opin. Drug Deliv.*, **2009**, 6(4), 371–387.
- [17] Pawar, R. P.; Jadhav, A. E.; Tathe, S. B.; Khade, B. C.; Domb, A. J. “Chapter 12: Medicinal Applications of Cyanoacrylates”: *Biodegradable Polymers in Clinical Use and Clinical Development*, John Wiley & Sons, Inc., **2011**, 417–459.
- [18] Nicolas, J.; Vauthier, C. “Poly(Alkyl Cyanoacrylate) Nanosystems”: *Intracellular Delivery: Fundamentals and Applications*, Prokop, A., Springer, **2011**, 5, 225–250.
- [19] Yordanov, G. Poly(alkyl cyanoacrylate) nanoparticles as drug carriers: 33 years later. *Bulg. J. Chem.*, **2012**, 1, 61–73.
- [20] Arias, J. L.; Gallardo, V.; Ruiz, M. A. “Chapter 4: Multifunctional Anticancer Nanomedicine Based on a Magnetically Responsive Cyanoacrylate Polymer”: *Methods in Enzymology*, Elsevier, **2012**, 61–88.
- [21] Stewart, V.; Deacon, P.; Farrugia, K. J. A review of one-step fluorescent cyanoacrylate techniques. *Fingerprint Whorld*, **2016**, 41 (162), 1–24.
- [22] McArdle, C.; Xiao, E. S.; Van Wijk, K.; Zhao, L.; Schneider, A.; Hansjoerg, A.; Petrick, P.; Domanski, R.; Schafer, V.; Schafer, S. *Patent WO2013174430A1*, (2013).

- [23] Gololobov, Y. G.; Krylova, T. O. 2-Cyanoacrylates as Reagents in Heteroatomic Synthesis (A Review). *Heteroatom Chem.*, **1995**, *6*, 271–280.
- [24] Quirce, S.; Baeza, M.L.; Tornero, P.; Blasco, A.; Barranco, R.; Sastre, J. Occupational asthma caused by exposure to cyanoacrylate. *Allergy*, **2001**, *56*, 446–449.
- [25] Leggat, P. A.; Kedjarune, U.; Smith, D. R. Toxicity of Cyanoacrylate Adhesives and Their Occupational Impacts for Dental Staff. *Industrial Health*, **2004**, *42*, 207–211.
- [26] Leggat, P. A.; Smith, D. R.; Kedjarune, U. Surgical Applications Of Cyanoacrylate Adhesives: A Review Of Toxicity. *ANZ Journal of Surgery*, **2007**, *77*, 209–213.
- [27] Millet, G. H. in Hartshorn, S. R. ed., "Cyanoacrylate Adhesive": *Structural Adhesives, Chemistry and Technology*, Plenum Press, New York, **1986**, 249–307.
- [28] Dossi, M.; Storti, G.; Moscatelli, D. Synthesis of Poly(Alkyl Cyanoacrylates) as Biodegradable Polymers for Drug Delivery Applications. *Macromol. Symp.*, **2010**, *289*, 124–128.
- [29] Eromosele, I. C.; Pepper, D. C. Anionic polymerizations of butyl cyanoacrylate by tetrabutylammonium salts, 2. *Makromol. Chem.*, **1989**, *190*, 3095–3103.
- [30] Johnston, D. S.; Pepper, D. C. Polymerisation via macrozwitterions, 1. Ethyl and butyl cyanoacrylates polymerised by triethyl and triphenylphosphines. *Makromol. Chem.*, **1981**, *182*, 393–406.
- [31] Eromosele, I. C.; Pepper, D. C. Anionic polymerization of butyl cyanoacrylate by tetrabutylammonium salts, 1. Initiation processes. *Makromol. Chem.*, **1989**, *190*, 3085–3094.
- [32] Johnston, D. S.; Pepper, D. C. Polymerisation via macrozwitterions, 2. Ethyl and butyl cyanoacrylates polymerised by pyridine and polyvinylpyridine. *Makromol. Chem.*, **1981**, *182*, 407–420.
- [33] Johnston, D. S.; Pepper, D. C. Polymerisation via macrozwitterions, 3. Ethyl and Butyl Cyanoacrylates Polymerised by Benzyldimethyl, Triethyl and Tribenzylamines. *Makromol. Chem.*, **1981**, *182*, 421–435.

- [34] Donnelly, E. F.; Johnston, D. S.; Pepper, D. C. Ionic and zwitterionic polymerization of n-alkyl 2-cyanoacrylates. *Polym. Lett. Ed.*, **1977**, 15, 399–405.
- [35] Pepper, D. C.; Ryan, B. Initiation Processes in Polymerizations of Alkyl Cyanoacrylates by Tertiary Amines: Inhibition by Strong Acids. *Makromol. Chem.*, **1983**, 184, 383–394.
- [36] Pepper, D. C.; Ryan, B. Kinetics of polymerization of alkyl cyanoacrylates by tertiary amines and phosphines. *Makromol. Chem.*, **1983**, 184, 395–410.
- [37] Pepper, D. C. Transfer by weak acids in the slow-initiation-no-termination (SINT) polymerization of butyl cyanoacrylate. *Makromol. Chem.*, **1987**, 188, 527–536.
- [38] Cronin, J. P.; Pepper, D. C. Zwitterionic polymerization of butyl cyanoacrylate by triphenylphosphine and pyridine. *Makromol. Chem.*, **1988**, 189, 85–102.
- [39] Pepper, D. C. Kinetics and Mechanisms of Zwitterionic Polymerizations of Alkyl Cyanoacrylates. *Polymer Journal*, **1980**, 12, 629–637.
- [40] Baskaran, D.; Müller, A. H. E. Kinetic Investigation on Metal Free Anionic Polymerization of Methyl Methacrylate Using Tetraphenylphosphonium as the Counterion in Tetrahydrofuran. *Macromolecules*, **1997**, 30, 1869–1874.
- [41] Quirk, R. P.; Ocampo, M. Anionic Polymerization. *Material Matters*, **2006**, 1, 10–11.
- [42] Kulkarni, R. K.; Porter, H. J.; Leonard, F. Glass transition temperatures of poly(alkyl α -cyanoacrylates). *J. Appl. Polym. Sci.*, **1973**, 17, 3509–3514.
- [43] Cheung, K.; Guthrie, J.; Otterburn, M.; Rooney, J. The dynamic mechanical properties of poly(alkyl 2-cyanoacrylates). *Makromol. Chem.*, **1987**, 188(12), 3041–3046.
- [44] Bykova, T. A.; Kiparisova, Y. G.; Lebedev, B. V.; Mager, K. A.; Golobov, Y. G. A calorimetric study of ethyl- α -cyanoacrylate and its polymerization and a study of polyethyl- α -cyanoacrylate at 13–450 K and normal pressure. *Polym. Sci.*, **1991**, 33, 537–543.

- [45] Guthrie, J.; Otterburn, M. S.; Rooney, J. M.; Tsang, C. N. The effect of heat on the molecular weight of poly(ethyl 2-cyanoacrylate) adhesive. *J. Appl. Polym. Sci.*, **1985**, 30, 2863–2867.
- [46] Busfield, W. K. in H. H. G. Jellinek ed., “Ceiling Temperatures”: *Aspects of Degradation and Stabilization of Polymers*, Elsevier, Amsterdam, **1978**, 39–78.
- [47] Chorbadjiev, K. G.; Novakov, P. C. Study of the thermal degradation of poly(alkyl α -cyanoacrylate)s. *Eur. Polym. J.*, **1991**, 27, 1009–1015.
- [48] Birkinshaw, C.; Pepper, D. C. The thermal degradation of polymers of *n*-butylcyanoacrylate prepared using tertiary phosphine and amine initiators. *Polym. Degrad. Stab.*, **1986**, 16, 241–259.
- [49] Hickey, A.; Leahy, J. J.; Birkinshaw, C. End-Group Identity and Its Effect on the Thermal Degradation of Poly(butyl cyanoacrylate). *Macromol. Rapid Commun.*, **2001**, 22, 1158–62.
- [50] Leonard, F.; Kulkarni, R.K.; Brandes, G.; Nelson, J.; Cameron, J.J. Synthesis and degradation of poly (alkyl α -cyanoacrylates). *J. Appl. Polym. Sci.*, **1966**, 10, 259–72.
- [51] Barkan, Y.; Levinman, M.; Veprinsky-Zuzuliya, I.; Tsach, T.; Merqioul, E.; Blum, G.; Domb, A. J.; Basu, A. Comparative evaluation of polycyanoacrylates. *Acta Biomater.*, **2017**, 48, 390–400.
- [52] Ryan, B.; McCann, G.; Novel sub-ceiling temperature rapid depolymerization-repolymerization reactions of cyanoacrylate polymers. *Macromol. Rapid Commun.*, **1996**, 17, 217–227.
- [53] Robello, D. R.; Eldridge, T. D.; Swanson, M. T. Degradation and stabilization of polycyanoacrylates. *J. Polym. Sci. A: Polym. Chem.*, **1999**, 37, 4570–4581.
- [54] Han, G. H.; Kim, S.; Liu, S. X. Synthesis and degradation behavior of poly(ethyl cyanoacrylate) *Polym. Degrad. Stab.*, **2008**, 93, 1243–1251.
- [55] Vicart, N.; Goré, J.; Cazes, B. Palladium-catalyzed substitution of acrolein acetals by β -dicarbonyl nucleophiles. *Tetrahedron*, **1998**, 54, 11063–11078.
- [56] Vianello, R.; Maksić, Z. B. The Acidity of Brønsted CH Acids in DMSO – The Extreme Acidity of Nonacyanocyclononatetraene. *Eur. J. Org. Chem.*, **2004**, 24, 5003–5010.

- [57] Coover, H. W.; Shearer, N. H. Adhesive compositions containing alkyl esters of cyanoacrylic acid. *U.S. Patent 2,794,788* (1957).
- [58] Ito, K.; Kondo, K. Stabilized alpha-cyanoacrylate adhesive compositions. *U.S. Patent 3,557,185* (1971).
- [59] Kawamura, S.; Kondo, K.; Ito, K.; Suzuki, H.; Yasui, E.; Kobayashi, T. Stabilized alpha-cyanoacrylate adhesive compositions. *U.S. Patent 3,652,635* (1968).
- [60] Coover, H. W.; Wicker, T. H. Stabilized cyanoacrylate adhesives. *U.S. Patent 3,355,482* (1967).
- [61] Schoenberg, J. E. Anionic polymerization inhibitor for cyanoacrylate adhesives. *U.S. Patent 4,182,823* (1980).
- [62] Ardis, A. E. Preparation of monomeric alkyl alpha-cyano-acrylates. *U.S. Patent 2,467,927* (1949).
- [63] Loctite Corp., *Jpn Patent 58,63,771* (1981).
- [64] Population Research Inc., *FRG Patent 156,365* (1982).
- [65] Tang, H.; Tsarevsky, N. V., Preparation and Functionalization of Linear and Reductively Degradable Highly Branched Cyanoacrylate-Based Polymers. *J. Polym. Sci. A: Polym. Chem.*, **2016**, 54, 3683–3693.
- [66] Shering, A. G. *Ger. Patent 2,228,379* (1973).
- [67] Petrie, E. M. "Chapter 8: Cyanoacrylate Adhesives in Surgical Applications": *Progress in Adhesion and Adhesives*, John Wiley & Sons, Inc., Hoboken, NJ, USA., **2015**, 245–298.
- [68] Hawkins, G. F.; McCurry, H. J. Esters of alpha-cyanoacrylic acid and process for the manufacture thereof. *U.S. Patent 3,254,111* (1966).
- [69] Leung, J. C.; Clark, J. G. Biocompatible monomer and polymer compositions. *U.S. Patent 5,328,687* (1994).
- [70] Private communications, Henkel Ireland and Operations Ltd.
- [71] Duffy, C.; Phelan, M.; Zetterlund, P. B.; Aldabbagh, F. Reversible addition–fragmentation chain transfer polymerization of alkyl-2-cyanoacrylates: An assessment of livingness. *J. Polym. Sci. A: Polym. Chem.*, **2017**, 55, 1397–1408.

- [72] Odian, G. "Chapter 3: Radical Chain Polymerization" in *Principles of Polymerization*, Fourth Edition, John Wiley & Sons, Inc., Hoboken, NJ, USA., **2004**, 198–350.
- [73] Magee, C.; Sugihara, Y.; Zetterlund, P. B.; Aldabbagh, F. Chain transfer to solvent in the radical polymerization of structurally diverse acrylamide monomers using straight-chain and branched alcohols as solvents. *Polym. Chem.*, **2014**, 5, 2259–2265.
- [74] Fuhrman, N.; Mesrobian, R. B. Chain Transfer of Vinyl Monomers with Carbon Tetrabromide. *J. Am. Chem. Soc.*, **1954**, 76, 3281–3286.
- [75] Ballard, N.; De la Cal, J. C.; Asua, J. M. The Role of Chain Transfer Agent in Reducing Branching Content in Radical Polymerization of Acrylates. *Macromolecules*, **2015**, 48, 987–993.
- [76] Bevington, J. C.; Jemmett, J. A. L. Polymerization of methyl α -cyanoacrylate. Part 1.—Initiation by benzoyl peroxide *J. Chem. Soc., Faraday Trans. 1*, **1973**, 69, 1866–1871.
- [77] Chappelow, C. C.; Pinzino, C. S.; Byerley, T. J.; Eick, J. D. Tri-n-butylborane Oxide-Initiated Homopolymerization of Vinyl Monomers Containing Cyano or Isocyanato Groups. *J. Appl. Polym. Sci.*, **1995**, 58, 1147–1150.
- [78] Renaud, P.; Beauseigneur, A.; Brecht-Forster, A.; Becattini, B.; Darmency, V.; Kandhasamy, S.; Montermini, F.; Ollivier, C.; Panchaud, P.; Pozzi, D.; Scanlan, E. M.; Schaffner, A.; Weber, V. Boron: A key element in radical reactions. *Pure Appl. Chem.*, **2007**, 79, 223–233.
- [79] Canale, A. J.; Goode, W. E.; Kinsinger, J. B.; Panchak, J. R.; Kelso, R. L.; Graham, R. K. Methyl α -cyanoacrylate. I. Free-radical homopolymerization. *J. Appl. Polym. Sci.*, **1960**, 4(11), 231–236.
- [80] Bevington, J. C.; Jemmett, J. A. L.; Onyon, P. F. Polymerization of methyl α -cyanoacrylate—II: Conditions for radical polymerization *Eur. Polym. J.*, **1976**, 12, 255–257.
- [81] Yamada, B.; Yoshioka, M.; Otsu, T. Determination of Absolute Rate Constants for Radical Polymerization and Copolymerization of Ethyl α -Cyanoacrylate in the Presence of Effective Inhibitors against Anionic Polymerization. *Makromol. Chem.*, **1983**, 184, 1025–1033.

- [82] Van Herk, A. M. Pulsed Initiation Polymerization as a Means of Obtaining Propagation Rate Coefficients in Free-Radical Polymerizations. *J. Macromol. Sci. Polymer Rev.*, **1997**, 37, 633–648.
- [83] Yamada, B.; Hayashi, T.; Otsu, T. Determination of Absolute Rate Constants for Radical Polymerization and Copolymerization of Ethyl α -Chloroacrylate: Effects of Substituents on Reaction Rates of Monomer and Polymer Radical. *J. Macromol. Sci. Part A: Chem.*, **1983**, 7, 1023–1039.
- [84] Kamachi, M.; Liaw, D. J.; Nozakura, S. Solvent Effect on Radical Polymerization of Methyl Methacrylate. *Polym J.*, **1981**, 13, 41–50.
- [85] Değirmenci, I.; Aviyente, V. DFT Study on the Propagation Kinetics of Free-Radical Polymerization of α -Substituted Acrylates. *Macromolecules*, **2009**, 42, 3033–3041.
- [86] Rooney, T. R.; Mavroudakis, E.; Lacík, I.; Hutchinson, R. A.; Moscatelli, D. Pulsed-laser and quantum mechanics study of n-butyl cyanoacrylate and methyl methacrylate free-radical copolymerization. *Polym. Chem.*, **2015**, 6, 1594–1603.
- [87] Beuermann, S.; Buback, M. Rate coefficients of free-radical polymerization deduced from pulsed laser experiments. *Prog. Polym. Sci.*, **2002**, 27, 191–254.
- [88] Yamada, B.; Kontani, T.; Yoshioka, M.; Otsu, T. Determination of absolute rate constants for free radical polymerization of ethyl α -fluoroacrylate and characterization of the polymer *J. Polym. Sci. Polym. Chem. Ed.*, **1984**, 22, 2381–2393.
- [89] Burnett, G. M.; Evans, P.; Melville, H. W. Polymerization of esters of methacrylic acid. Part I.—the polymerization of n-butyl methacrylate. *Trans. Faraday Soc.*, **1953**, 49, 1096–1104.
- [90] Imoto, M.; Kinoshita, M.; Nishigaki, M. Vinyl polymerization. 93. Polar effects in radical polymerization of p-substituted styrenes. *Makromol. Chem.*, **1965**, 86, 217–230.
- [91] Beuermann, S.; Buback, M.; Davis, T. P.; Gilbert, R. G.; Hutchinson, R. A.; Olaj, O. F.; Russell, G. T.; Schweer, J.; Van Herk, A. M. Critically evaluated rate coefficients for free-radical polymerization, 2. Propagation rate

- coefficients for methyl methacrylate. *Macromol. Chem. Phys.*, **1997**, 198, 1545-1560.
- [92] Beuermann, S.; Buback, M. Critically-evaluated propagation rate coefficients in free radical polymerizations II. Alkyl methacrylates. *Pure Appl. Chem.*, **1998**, 70, 1415-1418.
- [93] Junkers, T.; Schneider-Baumann, M.; Koo, S. S. P.; Castignolles, P.; Barner-Kowollik, C. Determination of Propagation Rate Coefficients for Methyl and 2-Ethylhexyl Acrylate via High Frequency PLP-SEC under Consideration of the Impact of Chain Branching. *Macromolecules*, **2010**, 43, 10427-10434.
- [94] Buback, M.; Gilbert, R. G.; Hutchinson, R. A.; Klumperman, B.; Kuchta, F.; Manders, B. G.; O'Driscoll, K. F.; Russell, G. T.; Schweer, J. Critically evaluated rate coefficients for free-radical polymerization, I. Propagation rate coefficient for styrene. *Macromol. Chem. Phys.*, **1995**, 196, 3267-3280.
- [95] Hatada, K.; Kitayama, T.; Masuda, E. Studies on the Radical Polymerization of Methyl Methacrylate in Bulk and in Benzene Using Totally Deuterated Monomer Technique. *Polymer J.*, **1986**, 18, 395-402.
- [96] Cho, I.; Lee, J. Ring-opening polymerization of 2,6-dialkoxy-5-cyano-3,4-dihydro-2H-pyrans: a novel monomer-to-polymer route to head-to-head alternating copolymers. *Macromolecules*, **1983**, 16, 150-152.
- [97] Cho, I.; Lee, J. Ring-opening polymerization of 2,5,6-trisubstituted-3,4-dihydro-2H-pyrans. Syntheses of head-to-head alternating vinyl copolymers and their properties. *Macromolecules*, **1983**, 16, 1245-1250.
- [98] Lee, J.; Cho, I. Synthesis of Alternating Head-to-Head Vinyl Copolymers and Vinyl Terpolymers via Ring-Opening Mechanism. Ring-Opening Polymerization of Substituted-3,4-dihydro-2H-pyrans. *Bull. Korean Chem. Soc.*, **1987**, 8, 96-101.
- [99] Lee, J.; Cho, I. Ring-opening polymerization of 2,3,5,6-tetrasubstituted-3,4-dihydro-2H-pyrans and their copolymerization behaviors. Syntheses of alternating head-to-head vinyl copolymers and their properties. *J. Polym. Sci. A: Polym. Chem.*, **1987**, 25, 3089-3103.
- [100] Alfrey, T.; Price, C. C. Relative reactivities in vinyl copolymerization. *J. Polym. Sci.*, **1947**, 2, 101.

- [101] Otsu, T.; Yamada, B. Determination of Q, e parameters for methyl α -cyanoacrylate. *Makromol. Chem.*, **1967**, 110, 297–299.
- [102] Jenkins, A. Interpretation of reactivity in radical polymerization—Radicals, monomers, and transfer agents: Beyond the Q-e scheme. *J. Polym. Sci. A: Polym. Chem.*, **1999**, 37, 113–126.
- [103] McFarlane, R. C.; Reilly, P. M.; O'Driscoll, K. F. Comparison of the precision of estimation of copolymerization reactivity ratios by current methods. *J. Polym. Sci. Polym. Chem. Ed.*, **1980**, 18, 251–257.
- [104] Greenley, R. Z. "Q and e Values for Free Radical Copolymerizations of Vinyl Monomers and Telogens". Polymer Handbook, 4th edn, Brandup, J.; Immergut, EH.; Grulke, EA, John Wiley and Sons, New York, **1999**, Chapter II, 309–320.
- [105] Kinsinger, J. B.; Panchak, J. R.; Kelso, R. L.; Bartlett, J. S.; Graham, R. K. Methyl α -cyanoacrylate. II. Copolymerization studies. *J. Appl. Polym. Sci.*, **1965**, 9, 429–437.
- [106] Han, G. H.; Kim, S., Controlled degradation of poly(ethyl cyanoacrylate-co-methyl methacrylate)(PECA-co-PMMA) copolymers. *Polymer*, **2009**, 50, 1270–1280.
- [107] Polyakova, A. M.; Suchkova, M. D.; Mager, K. A.; Korshak, V. V. Copolymerization of the ethyl ester of α -cyanoacrylic acid with di(alkyl) and di(fluoroalkyl) methylene malonates. *Polym. Sci., U. S. S. R.* **1984**, 26, 77–82.
- [108] Sperlich, B.; Eisenbach, C. D. Copolymerization of ethyl cyanoacrylate and ethylene in the presence of zinc chloride or trifluoroacetic acid as complexing agent. *Acta Polymer.*, **1996**, 47, 280–284.
- [109] Hirooka, M.; Yabuuchi, H.; Morita, S.; Kawasumi, S.; Nakaguchi, K. Complex copolymerization. I. Novel equimolar copolymers of acrylonitrile and olefins. *J. Polym. Sci. B Polym. Lett.*, **1967**, 5, 47–55.
- [110] Dikov, V. K.; Kotzev, D. L.; Kabaivanov, S. Polymerization of ethyl 2-cyanoacrylate in the presence of poly (butadiene-co-acrylonitrile). *British Polymer Journal*, **1988**, 20, 9–12.

- [111] Ramadan, K. S.; Sameoto, D.; Evoy, S. A review of piezoelectric polymers as functional materials for electromechanical transducers. *Smart Mater. Struct.*, **2014**, 23, 033001.
- [112] Hall, H.K.; Padias, A.B.; Chu, G.; Lee, H.Y.; Kalinin, I.; Sansone, M. Novel cyano-containing copolymers of vinyl esters for piezoelectric materials. *J. Polym. Sci. A: Polym. Chem.*, **1992**, 30, 2341–2347.
- [113] Rasoul, H. A. A.; Hall, H. K. Cycloaddition and polymerization reactions of methyl α -cyanoacrylate with electron-rich olefins. *J. Org. Chem.*, **1982**, 47, 2080–2083.
- [114] Hall, H. K.; Padias, A. B. A paradigm for the mechanisms and products of spontaneous polymerizations. *J. Polym. Sci. A: Polym. Chem.*, **2009**, 47, 6735–6749.
- [115] Otsu, T.; Yamada, B.; Kusayama, S.; Nagao, S. Radical Copolymerization of α -Cyanoacrylic Ester in the Presence of Inhibitor for Anionic Polymerization. *Kobunshi Ronbunshu*, **1979**, 36, 797–802.
- [116] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem. Int. Ed.*, **2001**, 40, 2004–2021.
- [117] Nicolas, J.; Bensaid, F.; Desmaële, D.; Grogna, M.; Detrembleur, C.; Andrieux, K.; Couvreur, P. Synthesis of Highly Functionalized Poly(alkyl cyanoacrylate) Nanoparticles by Means of Click Chemistry. *Macromolecules*, **2008**, 41, 8418–8428.
- [118] Cho, I. Copolymer sequence control by ring-opening polymerization of prestructured cyclic monomers. *Makromol. Chem., Macromol. Symp.*, **1990**, 33, 45–54.
- [119] Lee, J.; Cho, I. Synthesis of Alternating Head-to-Head Copolymer of Methyl α -cyanoacrylate and 2,3-Dihydrofuran. Ring-Opening Polymerization of 3-Methoxy-4-cyano-2,9-dioxabicyclo [4.3.0] non-3-ene. *Bull. Korean Chem. Soc.*, **1988**, 9, 176–179.
- [120] Lee, J.; Cho, I. Synthesis and ring-opening polymerization of 3-methoxy-4-cyano-2,9-dioxabicyclo[4.3.0]non-3-ene: Preparation of alternating head-

- to-head copolymer of methyl α -cyanoacrylate and 2,3-dihydrofuran. *J. Polym. Sci. C: Polym. Lett.*, **1989**, 27, 85–91.
- [121] Parveen, S.; Misra, R.; Sahoo, S. K. Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. *Nanomedicine*, **2012**, 2, 147–166.
- [122] Rezaei, S. J. T.; Nabid, M. R.; Niknejad, H.; Entezami, A. A. Multifunctional and thermoresponsive unimolecular micelles for tumor-targeted delivery and site-specifically release of anticancer drugs. *Polymer*, **2012**, 53, 3485–3497.
- [123] Couvreur, P.; Kante, B.; Roland, M.; Guiot, P.; BAuduin, P.; Speiser, P. Polycyanoacrylate nanocapsules as potential lysosomotropic carriers: preparation, morphological and sorptive properties. *Journal of Pharmacy and Pharmacology*, **1979**, 31, 331–332.
- [124] Douglas, S. J.; Illum, L.; Davis, S. S.; Kreuter, J. Particle-size and size distribution of poly(butyl-2-cyanoacrylate) nanoparticles. 1. Influence of physicochemical factors. *J. Colloid Interface Sci.*, **1984**, 101, 149–158.
- [125] Douglas, S. J.; Illum, L.; Davis, S. S. Particle-size and size distribution of poly(butyl 2-cyanoacrylate) nanoparticles. 2. Influence of stabilizers. *J. Colloid Interface Sci.*, **1985**, 103, 154–163.
- [126] Behan, N.; Birkinshaw, C.; Clarke, N. Poly n-butyl cyanoacrylate nanoparticles: a mechanistic study of polymerisation and particle formation. *Biomaterials*, **2001**, 22, 1335–1344.
- [127] Hansali, F.; Poisson, G.; Wu, M.; Bendedouch, D.; Marie, E. Miniemulsion polymerizations of n-butyl cyanoacrylate via two routes: Towards a control of particle degradation. *Colloids and Surf. B: Biointerfaces*, **2011**, 88, 332–338.
- [128] Wu, M.; Frochot, C.; Dellacherie, E.; Marie, E. Well-Defined Poly(butyl cyanoacrylate) Nanoparticles via Miniemulsion Polymerization. *Macromol. Symp.*, **2009**, 281, 39–46.
- [129] Chauvierre, C.; Labarre, D.; Couvreur, P.; Vauthier, C. Novel Polysaccharide-Decorated Poly(Isobutyl Cyanoacrylate) Nanoparticles. *Pharm. Res.*, **2003**, 11, 1786–1793.

- [130] Bravo-Osuna, I.; Ponchel, G.; Vauthier, C. Tuning of shell and core characteristics of chitosan-decorated acrylic nanoparticles. *Eur. J. Pharm. Sci.*, **2007**, 30, 143–154.
- [131] Bertholon, I.; Lesieur, S.; Labarre, D.; Besnard, M.; Vauthier, C. Characterization of dextran-poly(isobutylcyanoacrylate) copolymers obtained by redox radical and anionic emulsion polymerization. *Macromolecules*, **2006**, 39, 3559–3567.
- [132] Fallouh, N. A.; Roblottreupel, L.; Fessi, H.; Devissaguet, J. P.; Puisieux, F. Development of a new process for the manufacture of polyisobutylcyanoacrylate nanocapsules. *Int. J. Pharm.*, **1986**, 28, 125–132.
- [133] Xiao, J.; Li, X. Z.; Liu, S.; Lei, P. Preparation of oleanolic acid loaded polybutylcyanoacrylate nanocapsules by interfacial polymerization. *Chin. Pharm.*, **2006**, 20, 1551–1554.
- [134] Lambert, G.; Fattal, E.; Pinto-Alphandary, H.; Gulik, A.; Couvreur, P. Polyisobutylcyanoacrylate Nanocapsules Containing an Aqueous Core as a Novel Colloidal Carrier for the Delivery of Oligonucleotides. *Pharm. Res.*, **2000**, 17, 707–714.
- [135] Thioune, O.; Fessi, H.; Devissaguet, J.; Puisieux, F. Preparation of pseudolatex by nanoprecipitation: Influence of the solvent nature on intrinsic viscosity and interaction constant. *Int. J. Pharm.*, **1997**, 146, 233–238.
- [136] Xing, J.; Deng, L.; Li, J.; Dong, A. Amphiphilic poly{[α -maleic anhydride- ω -methoxypoly(ethylene glycol)]-co-(ethyl cyanoacrylate)} graft copolymer nanoparticles as carriers for transdermal drug delivery. *Int. J. Nanomed.*, **2009**, 4, 227–232.
- [137] Deng, L.; Yao, C.; Li, A.; Dong, A. Preparation and characterization of poly{[α -maleic anhydride- ω -methoxy-poly(ethylene glycol)]-co-(ethyl cyanoacrylate)} copolymer nanoparticles. *Polym. Int.*, **2005**, 54, 1007–1013.
- [138] Stolnik, S.; Illum, L.; Davis, S.S. Long circulating microparticulate drug carriers. *Adv. Drug Deliv. Rev.*, **1995**, 16, 195–214.

- [139] Storm, G.; Belliot, S.O.; Daemen, T.; Lasic, D.D. Surface modification of nanoparticles to oppose uptake by the mononuclear phagocyte system. *Adv. Drug Deliv. Rev.*, **1995**, *17*, 31–48.
- [140] Soma, E.; Attali, P.; Merle, P. “Chapter 11: A Clinically Relevant Case Study: The Development of Livatag for the Treatment of Advanced Hepatocellular Carcinoma”: *Nanostructured Biomaterials for Overcoming Biological Barriers*, Alonso, M. J.; Csaba, N. S., **2012**, 591–600.
- [141] Szwarc, M. “Living” Polymers. *Nature*, **1956**, *178*, 1168–1169.
- [142] Zhou, X. Z.; Shea, K. J. Synthesis of Poly(methylene-*b*-styrene) by Sequential Living Polymerization. *Macromolecules*, **2001**, *34*, 3111–3114.
- [143] Jenkins, A. D.; Jones, R. G.; Moad, G. Terminology for reversible-deactivation radical polymerization previously called “controlled” radical or “living” radical polymerization (IUPAC Recommendations 2010). *Pure Appl. Chem.*, **2010**, *82*, 483–491.
- [144] Matyjaszewski, K. “Chapter 8: General Concepts and History of Living Radical Polymerization”: *Handbook of Radical Polymerization*, John Wiley & Sons, Inc., Hoboken, **2002**, 361–406.
- [145] Nicolas, J.; Guillaneuf, Y.; Lefay, C.; Bertin, D.; Gigmes, D.; Charleux, B. Nitroxide-mediated polymerization. *Prog. Polym. Sci.*, **2013**, *38*, 63–235.
- [146] Matyjaszewski, K. Atom Transfer Radical Polymerization (ATRP): Current Status and Future Perspectives. *Macromolecules*, **2012**, *45*, 4015–4039.
- [147] Moad, G. “Chapter 12: RAFT Polymerization – Then and Now”: *Controlled Radical Polymerization: Mechanisms*, American Chemical Society, Washington DC, **2015**, 211–246.
- [148] Solomon, D. H.; Rizzardo, E.; Cacioli, P. Polymerization process and polymers produced thereby. *U.S. Pat. 4,581,429* (1986).
- [149] Solomon D. H.; Genesis of the CSIRO polymer group and the discovery and significance of nitroxide-mediated living radical polymerization. *J. Polym. Sci. A: Polym. Chem.*, **2005**, *43*, 5748–5764.
- [150] Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K. Narrow molecular weight resins by a free-radical polymerization process. *Macromolecules*, **1993**, *26*, 2987–2988.

- [151] Fischer, H. Unusual selectivities of radical reactions by internal suppression of fast modes. *J. Am. Chem. Soc.*, **1986**, 108, 3925–3927.
- [152] Fischer, H. The Persistent Radical Effect In “Living” Radical Polymerization. *Macromolecules*, **1997**, 30, 5666–5672.
- [153] Fischer, H. The Persistent Radical Effect: A Principle for Selective Radical Reactions and Living Radical Polymerizations. *Chem. Rev.*, **2001**, 101, 3581–3610.
- [154] Benoit, D.; Grimaldi, S.; Robin, S.; Finet, J.; Tordo, P.; Gnanou, Y. Kinetics and Mechanism of Controlled Free-Radical Polymerization of Styrene and n-Butyl Acrylate in the Presence of an Acyclic β -Phosphonylated Nitroxide. *J. Am. Chem. Soc.*, **2000**, 122, 5929–5939.
- [155] Benoit, D.; Chaplinski, V.; Braslau, R.; Hawker, C. J. Development of a Universal Alkoxyamine for “Living” Free Radical Polymerizations. *J. Am. Chem. Soc.*, **1999**, 121, 3904–3920.
- [156] Benoit, D.; Harth, E.; Fox, P.; Waymouth, R. M.; Hawker, C. J. Accurate Structural Control and Block Formation in the Living Polymerization of 1,3-Dienes by Nitroxide-Mediated Procedures. *Macromolecules*, **2000**, 33, 363–370.
- [157] McHale, R.; Aldabbagh, F.; Zetterlund, P. B., The role of excess nitroxide in the SG1 (N-tert-butyl-N-[1-diethylphosphono-(2,2-dimethylpropyl)] nitroxide)-mediated polymerization of methyl methacrylate. *J. Polym. Sci. A Polym. Chem.*, **2007**, 45, 2194–2203.
- [158] Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. Polymerization of Methyl Methacrylate with the Carbon Tetrachloride/Dichlorotris-(triphenylphosphine)ruthenium(II)/Methylaluminum Bis(2,6-di-tert-butyl phenoxide) Initiating System: Possibility of Living Radical Polymerization. *Macromolecules*, **1995**, 28, 1721–1723.
- [159] Wang, J-S.; Matyjaszewski, K. Controlled/“living” radical polymerization. atom transfer radical polymerization in the presence of transition-metal complexes. *J. Am. Chem. Soc.*, **1995**, 117, 5614–5615.
- [160] Scholz, C.; Matyjaszewski, K. Advances in Atom Transfer Radical Polymerization. *Polym. Int.*, **2014**, 63, 801–802.

- [161] Matyjaszewski, K.; Xia, J. Atom Transfer Radical Polymerization. *Chem. Rev.*, **2001**, 101, 2921–2990.
- [162] Matyjaszewski, K. Transition Metal Catalysis in Controlled Radical Polymerization: Atom Transfer Radical Polymerization. *Chem. Eur. J.*, **1999**, 5, 3095–3102.
- [163] Kotani, Y.; Kamigaito, M.; Sawamoto, M. Living Radical Polymerization of Styrene by Half-Metallocene Iron Carbonyl Complexes. *Macromolecules*, **2000**, 33, 3543–3549.
- [164] del Rio, I.; van Koten, G.; Lutz, M.; Spek, A. L. Haloalkane C–X Bond Activation by a Ruthenium(II) Complex: X-ray Characterization of a Ruthenium(III) Intermediate Species in the Atom Transfer Radical Polymerization of Methyl Methacrylate. *Organometallics*, **2000**, 19, 361–364.
- [165] Uegaki, H.; Kotani, Y.; Kamigaito, M.; Sawamoto, M. NiBr₂(Pn-Bu₃)₂-Mediated Living Radical Polymerization of Methacrylates and Acrylates and Their Block or Random Copolymerizations *Macromolecules*, **1998**, 31, 6756–6761.
- [166] Maria, S.; Stoffelbach, F.; Mata, J.; Daran, J.; Richard, P.; Poli, R. The Radical Trap in Atom Transfer Radical Polymerization Need Not Be Thermodynamically Stable. A Study of the MoX₃(PMe₃)₃ Catalysts. *J. Am. Chem. Soc.*, **2005**, 127, 5946–5956.
- [167] Kotani, Y.; Kamigaito, M.; Sawamoto, M. Re(V)-Mediated Living Radical Polymerization of Styrene: ¹ReO₂I(PPh₃)₂/R-I Initiating Systems. *Macromolecules*, **1999**, 32, 2420–2424.
- [168] Percec, V.; Barboiu, B.; Neumann, A.; Ronda, J. C.; Zhao, M. Metal-Catalyzed “Living” Radical Polymerization of Styrene Initiated with Arenesulfonyl Chlorides. From Heterogeneous to Homogeneous Catalysis. *Macromolecules*, **1996**, 29, 3665–3668.
- [169] Lecomte, Ph.; Drapier, I.; Dubois, Ph.; Teyssié, Ph.; Jérôme, R. Controlled Radical Polymerization of Methyl Methacrylate in the Presence of Palladium Acetate, Triphenylphosphine, and Carbon Tetrachloride. *Macromolecules*, **1997**, 30, 7631–7633.

- [170] Grimaud, T.; Matyjaszewski, K. Controlled/"Living" Radical Polymerization of Methyl Methacrylate by Atom Transfer Radical Polymerization. *Macromolecules*, **1997**, 30, 2216–2218.
- [171] Queffelec, J.; Gaynor, S. G.; Matyjaszewski, K. Optimization of Atom Transfer Radical Polymerization Using Cu(I)/Tris(2-(dimethylamino)ethyl)amine as a Catalyst. *Macromolecules*, **2000**, 33, 8629–8639.
- [172] Matyjaszewski, K.; Wang, J.; Grimaud, T.; Shipp, D. A.; Controlled/"Living" Atom Transfer Radical Polymerization of Methyl Methacrylate Using Various Initiation Systems. *Macromolecules*, **1998**, 31, 1527–1534.
- [173] Matyjaszewski, K.; Wang, J. Controlled/"Living" Radical Polymerization. Halogen Atom Transfer Radical Polymerization Promoted by a Cu(I)/Cu(II) Redox Process. *Macromolecules*, **1995**, 28, 7901–7910.
- [174] Percec, V.; Kim, J.; Barboiu, B. Scope and Limitations of Functional Sulfonyl Chlorides as Initiators for Metal-Catalyzed "Living" Radical Polymerization of Styrene and Methacrylates. *Macromolecules*, **1997**, 30, 8526–8528.
- [175] Matyjaszewski, K.; Xia, J. Controlled/"Living" Radical Polymerization. Homogeneous Reverse Atom Transfer Radical Polymerization Using AIBN as the Initiator. *Macromolecules*, **1997**, 30, 7692–7696.
- [176] Matyjaszewski, K.; Jakubowski, W.; Min, K.; Tang, W.; Huang, J.; Braunecker, W. A.; Tsarevsky, N. V. Diminishing catalyst concentration in atom transfer radical polymerization with reducing agents. *Proc. Natl. Acad. Sci. U.S.A.*, **2006**, 103, 15309–15314.
- [177] Ashford, E. J.; Naldi, V.; O'Dell, R.; Billingham, N. C.; Armes, S. P. First example of the atom transfer radical polymerisation of an acidic monomer: direct synthesis of methacrylic acid copolymers in aqueous media. *Chem. Commun.*, **1999**, 0, 1285–1286.
- [178] Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. Living Free-Radical Polymerization by Reversible Addition–Fragmentation Chain Transfer: The RAFT Process. *Macromolecules*, **1998**, 31, 5559–5562.

- [179] Hill, M. R.; Carmean, N. R.; Sumerlin, B. S. Expanding the Scope of RAFT Polymerization: Recent Advances and New Horizons. *Macromolecules*, **2015**, *48*, 5459–5469.
- [180] Perrier, S. 50th Anniversary Perspective: RAFT Polymerization—A User Guide. *Macromolecules*, **2017**, *50*, 7433–7447.
- [181] Keddie, D. J. A guide to the synthesis of block copolymers using reversible-addition fragmentation chain transfer (RAFT) polymerization. *Chem. Soc. Rev.*, **2014**, *43*, 496–505.
- [182] Gody, G.; Maschmeyer, T.; Zetterlund, P. B.; Perrier, S. Exploitation of the Degenerative Transfer Mechanism in RAFT Polymerization for Synthesis of Polymer of High Livingness at Full Monomer Conversion. *Macromolecules*, **2014**, *47*, 639–649.
- [183] Gody, G.; Maschmeyer, T.; Zetterlund, P. B.; Perrier, S. Pushing the Limit of the RAFT Process: Multiblock Copolymers by One-Pot Rapid Multiple Chain Extensions at Full Monomer Conversion. *Macromolecules*, **2014**, *47*, 3451–3460.
- [184] Moad, G.; Rizzardo, E.; Thang, S. H. Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization. *Material Matters*, **2010**, *5*, 2–8.
- [185] Geagea, R.; Ladeira, S.; Mazièrers, S.; Destarac, M. Chromium and Molybdenum Pentacarbonyl Complexes of Phosphinocarbodithioates: Synthesis, Molecular Structure and Behaviour in RAFT Polymerisation. *Chem. Eur. J.*, **2011**, *17*, 3718–3725.
- [186] Mazièrers, S.; Kulai, I.; Geagea, R.; Ladeira, S.; Destarac, M. Phosphinoyl and Thiophosphinoylcarbodithioates: Synthesis, Molecular Structure, and Application as New Efficient Mediators for RAFT Polymerization. *Chem. Eur. J.*, **2015**, *21*, 1726–1734.
- [187] Kulai, I.; Brusylovets, O.; Voitenko, Z.; Harrisson, S.; Mazièrers, S.; Destarac, M. RAFT Polymerization with Triphenylstannylcarbodithioates (Sn-RAFT). *ACS Macro. Lett.*, **2015**, *4*, 809–813.
- [188] Chong, Y. K.; Krstina, J.; Le, T. P. T.; Moad, G.; Postma, A.; Rizzardo, E.; Thang, S. H. Thiocarbonylthio Compounds [S=C(Ph)S-R] in Free Radical Polymerization with Reversible Addition-Fragmentation Chain Transfer

- (RAFT Polymerization). Role of the Free-Radical Leaving Group (R). *Macromolecules*, **2003**, 36, 2256–2272.
- [189] Chiefari, J.; Mayadunne, R. T. A.; Moad, C. L.; Moad, G.; Rizzardo, E.; Postma, A.; Skidmore, M. A.; Thang, S. H. Thiocarbonylthio Compounds [S=C(Ph)S–R] in Free Radical Polymerization with Reversible Addition-Fragmentation Chain Transfer (RAFT Polymerization). Effect of Activating group Z. *Macromolecules*, **2003**, 36, 2273–2283.
- [190] Benaglia, M.; Chiefari, J.; Chong, Y. K.; Moad, G.; Rizzardo, E.; Thang, S. H. Universal (Switchable) RAFT Agents. *J. Am. Chem. Soc.*, **2009**, 131, 6914–6915.
- [191] Moad, G.; Keddie, D.; Guerrero-Sanchez, C.; Rizzardo, E.; Thang, S.H. Advances in Switchable RAFT Polymerization. *Macromol. Symp.*, **2015**, 350, 34–42.
- [192] Dommanget, C.; D’Agosto, F.; Monteil, V. Polymerization of Ethylene through Reversible Addition–Fragmentation Chain Transfer (RAFT). *Angew. Chem.*, **2014**, 53, 6683–6686.
- [193] Keddie, D.; Guerrero-Sanchez, C.; Moad, G.; Mulder, R. J.; Rizzardo, E.; Thang, S. H. Chain Transfer Kinetics of Acid/Base Switchable N-Aryl-N-Pyridyl Dithiocarbamate RAFT Agents in Methyl Acrylate, N-Vinylcarbazole and Vinyl Acetate Polymerization. *Macromolecules*, **2012**, 45, 4205–4215.
- [194] Stenzel, M. H.; Cummins, L.; Roberts, G. E.; Davis, T. P.; Vana, P.; Barner-Kowollik, C. Xanthate Mediated Living Polymerization of Vinyl Acetate: A Systematic Variation in MADIX/RAFT Agent Structure. *Macromol. Chem. Phys.*, **2003**, 204, 1160–1168.
- [195] Moad, G.; Chong, Y. K.; Postma, A.; Rizzardo, E.; Thang, S. H. Advances in RAFT polymerization: the synthesis of polymers with defined end-groups. *Polymer*, **2005**, 46, 8458–8468.
- [196] Theis, A.; Feldermann, A.; Charton, N.; Stenzel, M. H.; Davis, T. P.; Barner-Kowollik, C. Access to Chain Length Dependent Termination Rate Coefficients of Methyl Acrylate via Reversible Addition–Fragmentation Chain Transfer Polymerization. *Macromolecules*, **2005**, 38, 2595–2605.

- [197] Moad, G.; Barner-Kowollik, C. "Chapter 3: The Mechanism and Kinetics of the RAFT Process: Overview, Rates, Stabilities, Side Reactions, Product Spectrum and Outstanding Challenges": Handbook of RAFT Polymerization (ed C. Barner-Kowollik), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2008**, 54–104.
- [198] Moad, G.; Rizzardo, E.; Thang, S. H. Living Radical Polymerization by the RAFT Process. *Aust. J. Chem.*, **2005**, 58, 379–410.
- [199] Shanmugam, S.; Xu, J.; Boyer, C. Utilizing the electron transfer mechanism of chlorophyll a under light for controlled radical polymerization. *Chem. Sci.*, **2015**, 6, 1341–1349.
- [200] d'Ayala, G. G.; Malinconico, M.; Laurienzo, P.; Tardy, A.; Guillaeneuf, Y.; Lansalot, M.; D'Agosto, F.; Charleux, B. RAFT/MADIX copolymerization of vinyl acetate and 5,6-benzo-2-methylene-1,3-dioxepane. *J. Polym. Sci. A Polym. Chem.*, **2014**, 52, 104–111.
- [201] Skrabania, K.; Miasnikova, A.; Bivigou-Koumba, A. M.; Zehm, D.; Laschewsky, A. Examining the UV-vis absorption of RAFT chain transfer agents and their use for polymer analysis. *Polym. Chem.*, **2011**, 2, 2074–2083.
- [202] Nejad, E. H.; Castignolles, P.; Gilbert, R. G.; Guillaeneuf, Y. Synthesis of methacrylate derivatives oligomers by dithiobenzoate-RAFT-mediated polymerization. *J. Polym. Sci. A Polym. Chem.*, **2008**, 46, 2277–2289.
- [203] Thomas, D. B.; Convertine, A. J.; Hester, R. D.; Lowe, A. B.; McCormick, C. L. Hydrolytic Susceptibility of Dithioester Chain Transfer Agents and Implications in Aqueous RAFT Polymerizations. *Macromolecules*, **2004**, 37, 1735–1741.
- [204] Albertin, L.; Stenzel, M. H.; Barner-Kowollik, C.; Davis, T. P. Effect of an added base on (4-cyanopentanoic acid)-4-dithiobenzoate mediated RAFT polymerization in water. *Polymer*, **2006**, 47, 1011–1019.
- [205] Zho, Y.; He, J.; Li, C.; Hong, L.; Yang, Y. Dependence of Thermal Stability on Molecular Structure of RAFT/MADIX Agents: A Kinetic and Mechanistic Study. *Macromolecules*, **2011**, 44, 8446–8457.

- [206] Chong, B.; Moad, G.; Rizzardo, E.; Skidmore, M.; Thang, S. H. Thermolysis of RAFT-Synthesized Poly(Methyl Methacrylate). *Aust. J. Chem.*, **2006**, 59, 755–762.
- [207] Xu, J.; He, J.; Fan, D.; Tang, W.; Yang, Y. Thermal Decomposition of Dithioesters and Its Effect on RAFT Polymerization. *Macromolecules*, **2006**, 39, 3753–3759.
- [208] Liu, Y.; He, J.; Xu, J.; Fan, D.; Tang, W.; Yang, Y. Thermal Decomposition of Cumyl Dithiobenzoate. *Macromolecules*, **2005**, 38, 10332–10335.
- [209] Nguyen, D.; Vana, P. On the Mechanism of Radical Polymerization of Methyl Methacrylate with Dithiobenzoic Acid as Mediator. *Aust. J. Chem.*, **2006**, 59, 549–559.
- [210] Vana, P. Kinetic Aspects of RAFT Polymerization. *Macromol. Symp.*, **2007**, 248, 71–81.
- [211] Bai, R.; You, Y.; Pan, C. Study on controlled free-radical polymerization in the presence of dithiobenzoic acid (DTBA). *Polym. Int.*, **2000**, 49, 898–902.
- [212] Otsu, T. J. Iniferter concept and living radical polymerization. *Polym. Sci. A Polym. Chem.*, **2000**, 38, 2121–2136.
- [213] Goh, Y.; Whittaker, M. R.; Monteiro, M. J. Controlled radical polymerization of styrene and methyl acrylate in the presence of reversible addition–fragmentation chain transfer agents, phenylethyl phenyl dithioacetate and phenyldithioacetic acid. *J. Polym. Sci. A Polym. Chem.*, **2005**, 43, 5232–5245.
- [214] Das, D.; Gerboth, D.; Postma, A.; Srinivasan, S.; Kern, H.; Chen, J.; Ratner, D. M.; Statyon, P. S.; Convertine, A. J. Synthesis of zwitterionic, hydrophobic, and amphiphilic polymers via RAFT polymerization induced self-assembly (PISA) in acetic acid. *Polym. Chem.*, **2016**, 7, 6133–6143.
- [215] Chalmers, B. A.; Alzahrani, A.; Hawkins, G.; Aldabbagh, F. Efficient synthesis and RAFT polymerization of the previously elusive N-[(cycloalkylamino)methyl]acrylamide monomer class. *J. Polym. Sci. A Polym. Chem.*, **2017**, 55, 2123–2128.
- [216] Hoff, E. A.; Abel, B. A.; Tretbar, C. A.; McCormick, C. L.; Patton, D. L. Aqueous RAFT at pH zero: enabling controlled polymerization of unprotected acyl hydrazide methacrylamides. *Polym. Chem.*, **2017**, 8, 4978–4982.

- [217] Chalmers, B. A.; Magee, C.; Cheung, D. L.; Zetterlund, P. B.; Aldabbagh, F. CO₂-responsive polyacrylamide copolymer vesicles with acid-sensitive morpholine moieties and large hydrophobic RAFT end-group. *Eur. Polm. J.*, **2017**, 97, 129–137.