Polymerization Chemistry 101

D. Christopher Radford

Gormley Lab Group Meeting

May 22nd, 2024

Learning Objectives

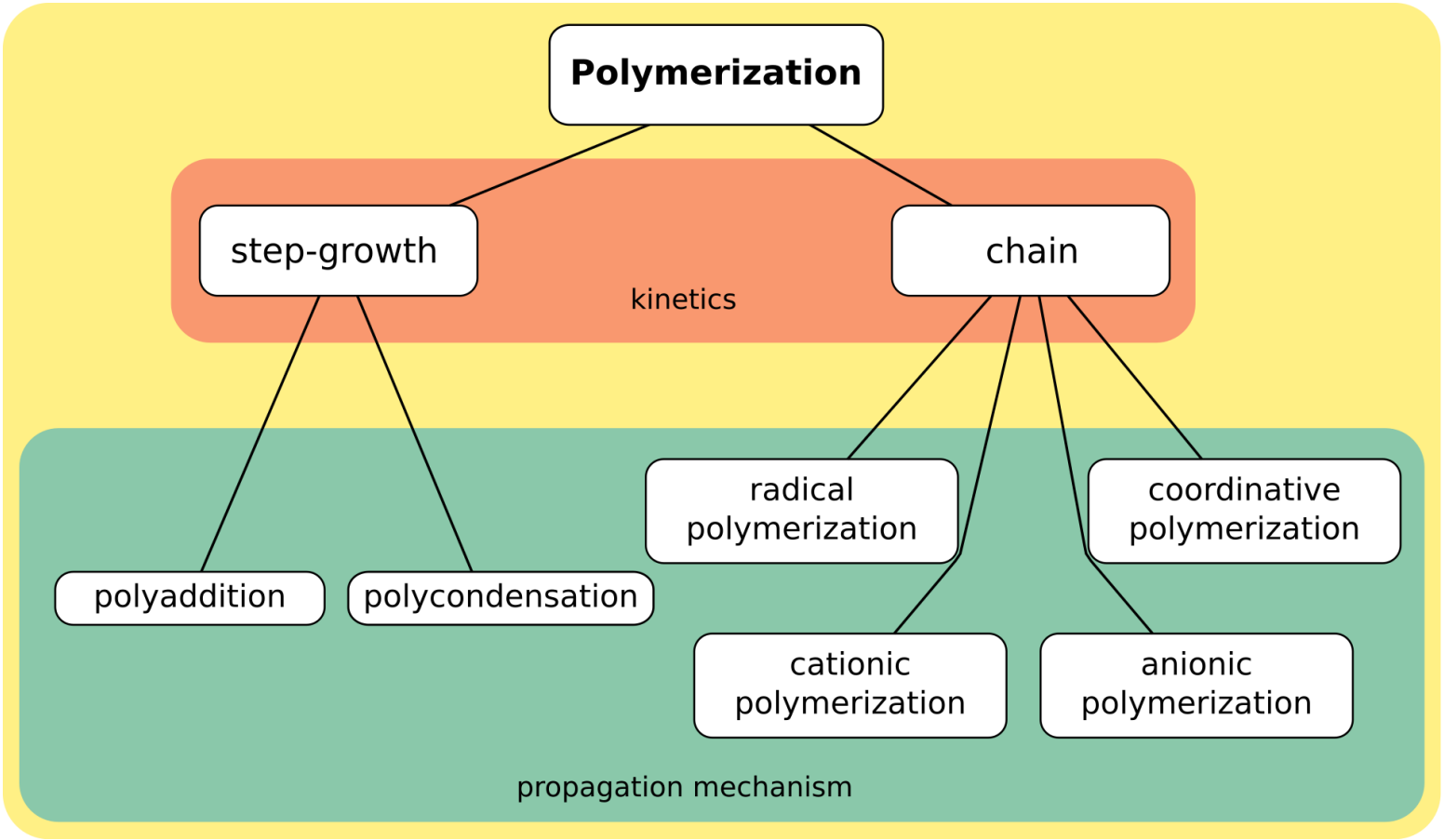
- Develop foundational organic chemistry literacy
- Establish a conceptual framework for visualizing and understanding free radical polymerization reaction chemistry
- Understand the roles of various chemical components in RAFT and PET-RAFT
- Understand rationale for selection of components in the reaction (i.e. why use *this* CTA?)

Overview of Today's Presentation

Part 1:
Basics of Free Radical Polymerization, RAFT, and PET-RAFT

Part 2:
Practical Considerations for PET-RAFT Reactions

Categories of Polymerization Reactions



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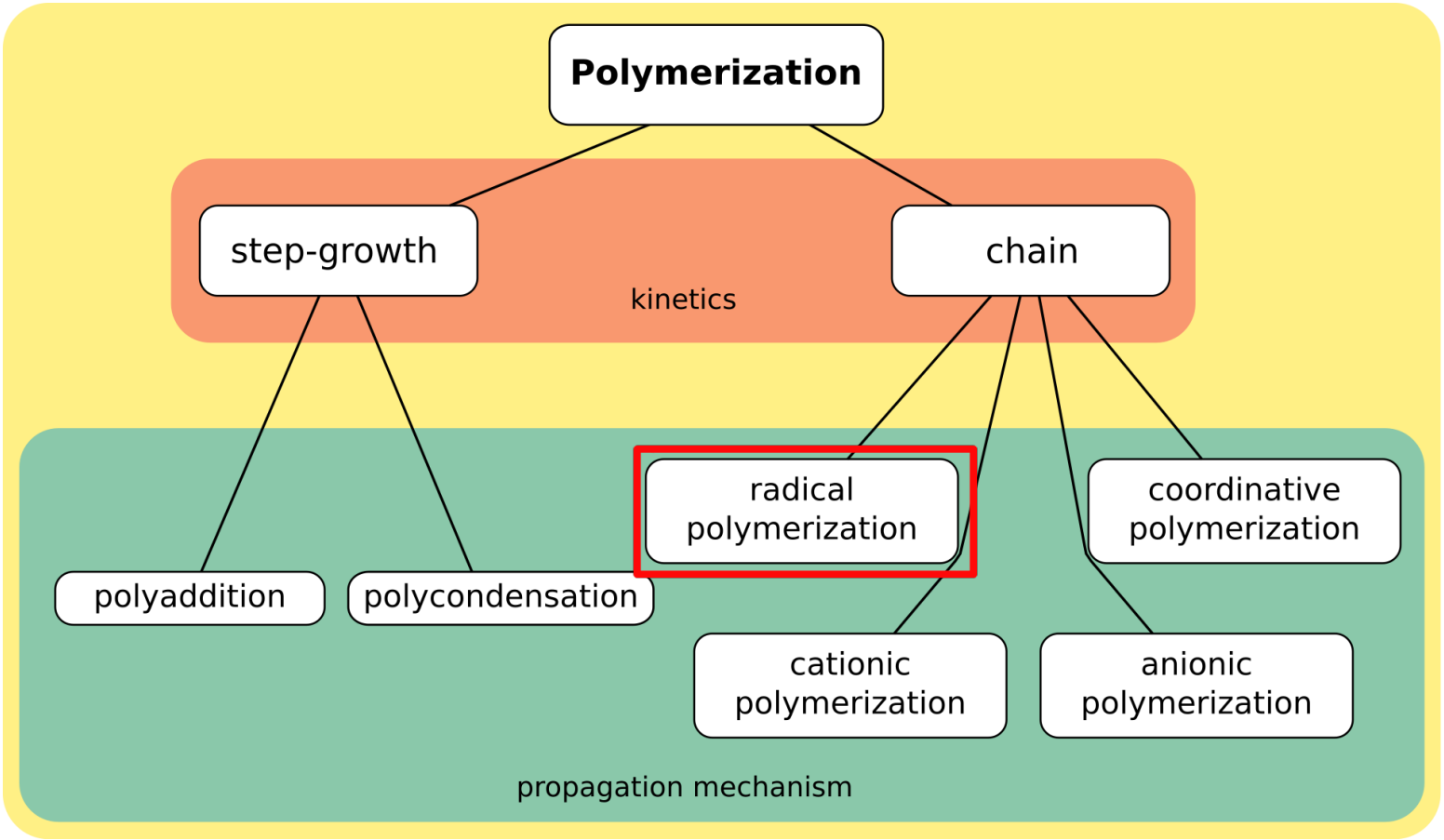
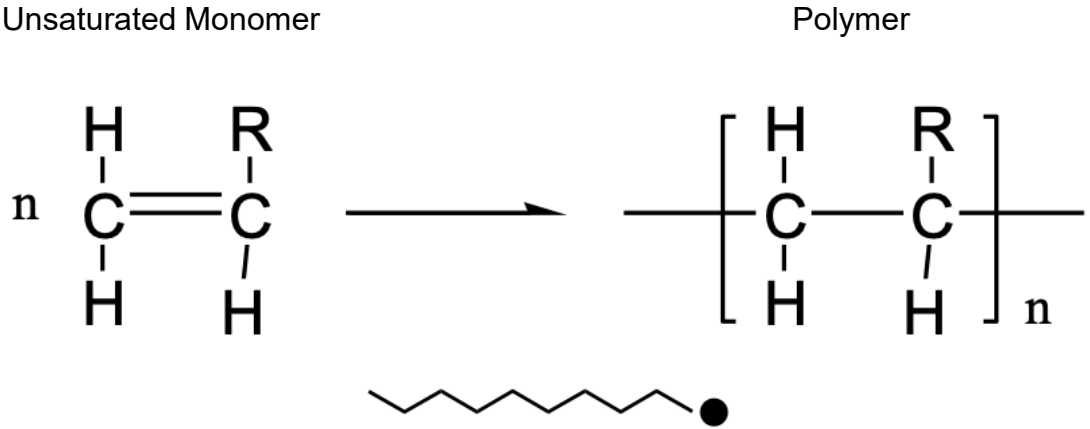


Basics of Free Radical Polymerization

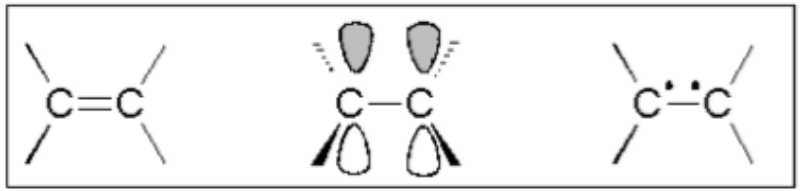


Sidenote: this conversion of vinyl protons to alkyl protons is what we measure for conversion in NMR!

Basics of Free Radical Polymerization (Cont.)

Polymerization arises from rearrangement of electrons to form new chemical bonds

Equivalent views of a carbon-carbon double bond:



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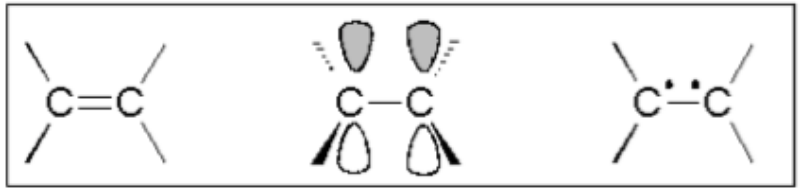
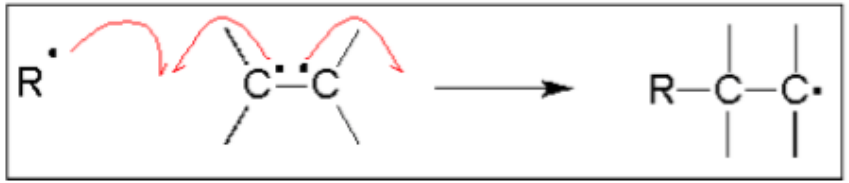


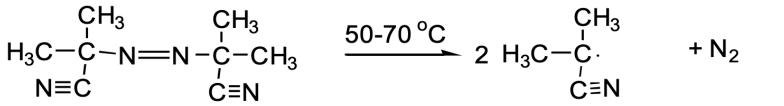
The essence of chain polymerizations:



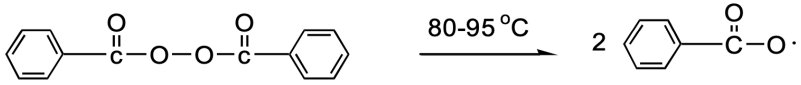
In a free radical polymerization, the growing chain bears an unpaired electron. Addition of each monomer molecule to the chain end involves an attack by the radical site on the unsaturated monomer. Thus, the unpaired electron is transferred to the new chain end at each addition step.

Basics of Free Radical Polymerization (Cont.)

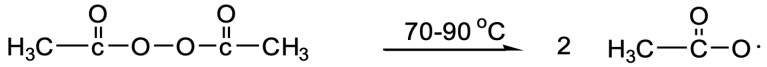
Example of Common Radical Source – “Thermal Initiators”



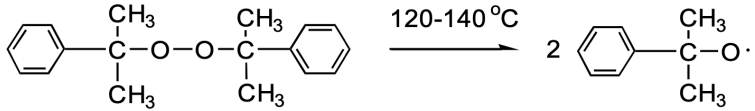
2,2'-azobisisobutyronitrile (AIBN)



bezoyl peroxide



acetyl peroxide



dicumyl peroxide

Basics of Free Radical Polymerization (Cont.)

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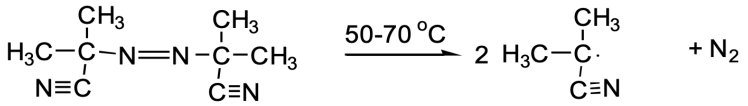

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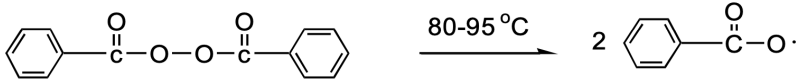

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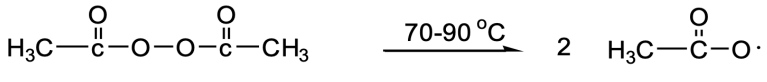

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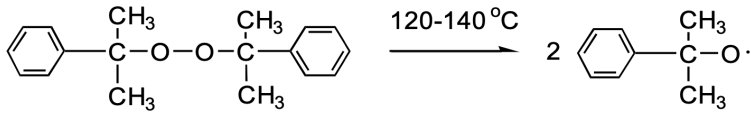
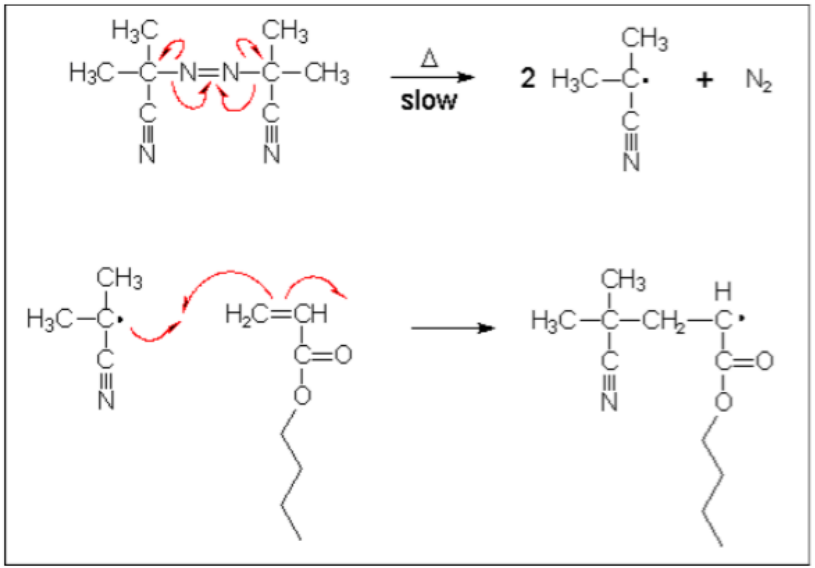


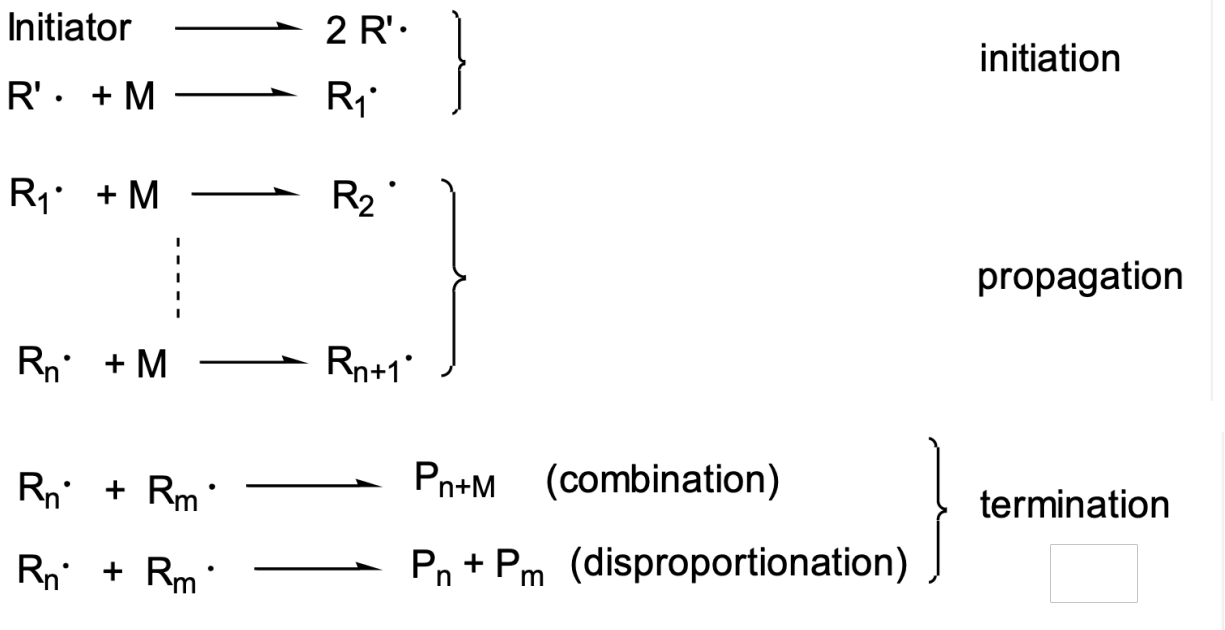
dicumyl peroxide

Polymerization of Butyl Acrylate by AIBN



Basics of Free Radical Polymerization (Cont.)

Overview of Free Radical Mechanism

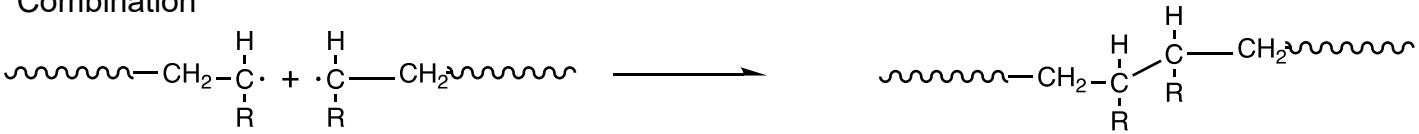


Polymerization reaction (propagation) for each chain continues until it is terminated!

Basics of Free Radical Polymerization (Cont.)

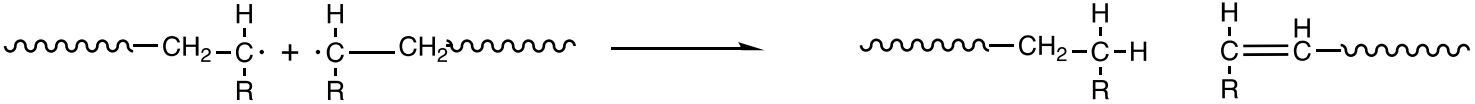
Termination Mechanisms

Combination



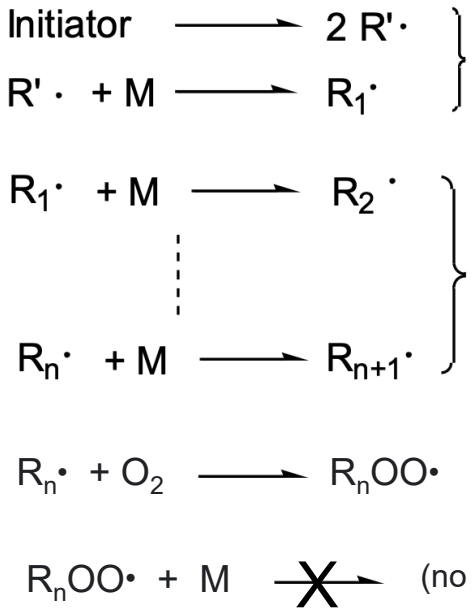
*Note: this doubles polymer chain length!

Disproportionation



Basics of Free Radical Polymerization (Cont.)

Why is Free Radical Polymerization Intolerant to Oxygen?



initiation

propagation

Termination of Reaction by Formation of Peroxy Radical

Zavada, S. R., Battsengel, T. & Scott, T. F. Radical-Mediated Enzymatic Polymerizations. *Int. J. Mol. Sci.* **17**, 195 (2016).

Basics of Free Radical Polymerization (Cont.)

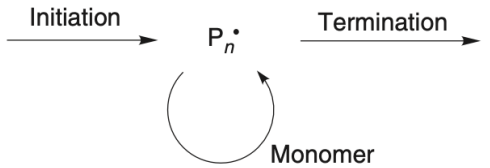
- Disadvantage of “traditional” free radical polymerization
  - Oxygen intolerance
  - Poor control over reaction

RAFT Polymerization

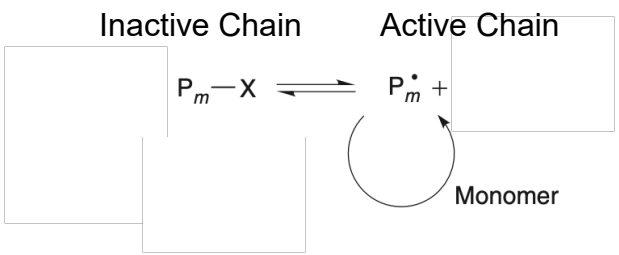
RAFT: Reversable addition fragmentation chain-transfer polymerization

- Key Feature: Chain Transfer
- During polymerization, polymer chain can enter into a temporary, reversable “inactive” state where it is dormant and not continuing to consume monomers
- Upon chain transfer, polymer “reawakens” and continues to grow
- Result is a “living” polymer that is able to repeatedly extended

Traditional Free Radical Polymerization

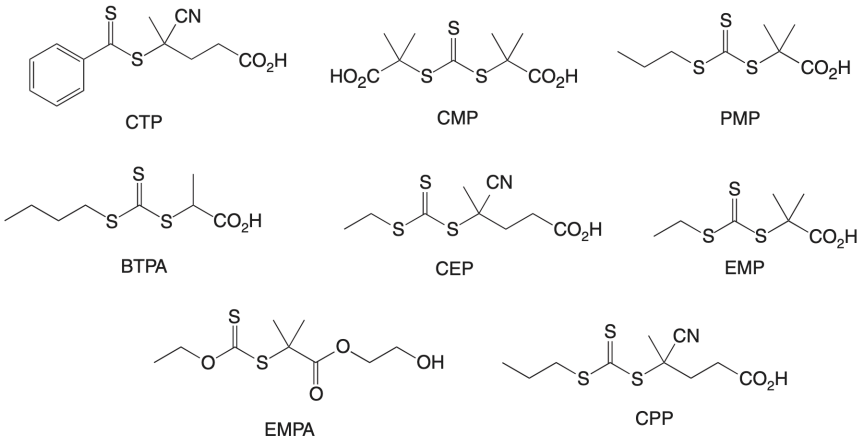


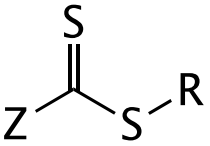
RAFT Polymerization (Simplified)



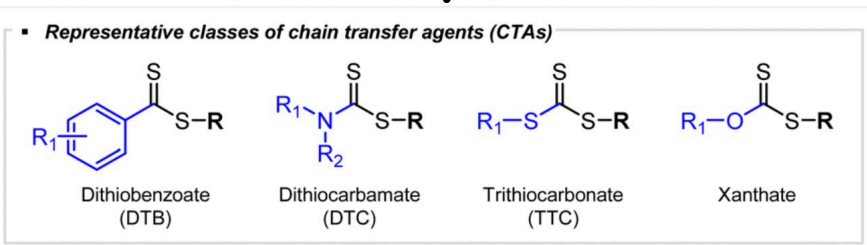
RAFT Polymerization – Role of CTA

Examples of CTAs from Literature





Thiocarbonylthio

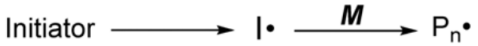


Chain transfer agent (CTA) facilitates RAFT by enabling chain transfer to shuffle chains between active and dormant state

Selection of Z and R groups is important for controlling reaction – will circle back to this later

RAFT Polymerization – General Mechanism

I. ***Initiation and propagation***



Initiator provides initial radical source to kickstart conversion of monomer to polymer (same as traditional free radical mechanism)

Y. Lee, C. Boyer, M.S. Kwon, Photocontrolled RAFT polymerization: past, present, and future, Chem. Soc. Rev. 52 (2023) 3035–3097. https://doi.org/10.1039/d1cs00069a.

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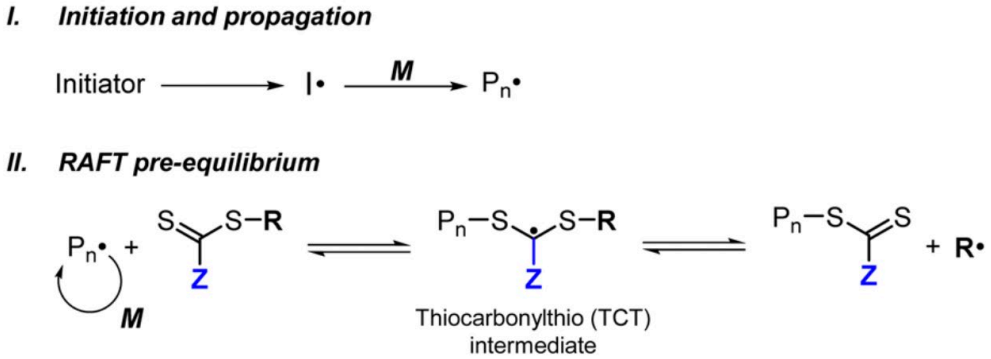

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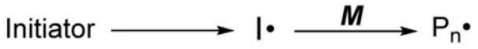
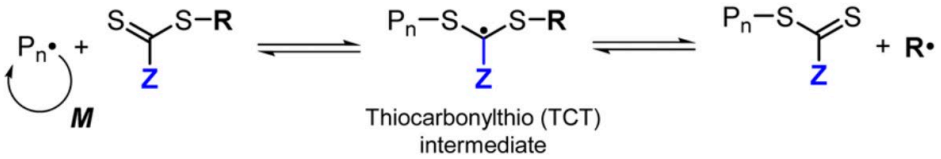
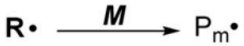


II. *RAFT pre-equilibrium*



III. *Reinitiation and propagation*



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“R” radical propagates new polymer chain via polymerization of monomer

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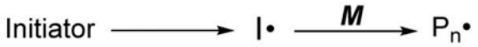

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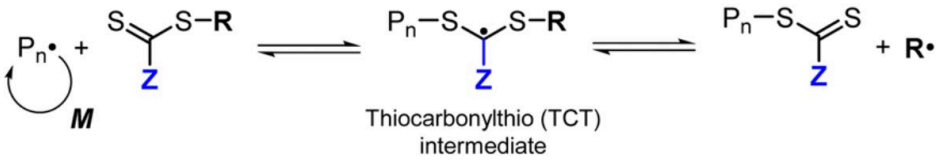

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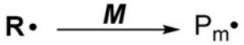

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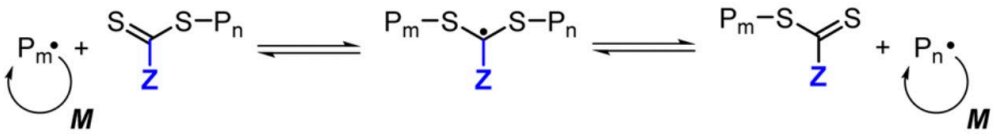
IV. *RAFT main equilibrium*



Growing (active) polymer chain (P_m) attacks dormant polymer bearing thiocarbonylthio group (P_n). After rearrangement, thiocarbonylthio group is transferred, P_n is now dormant and P_m now active.

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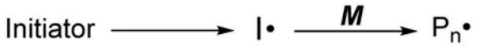

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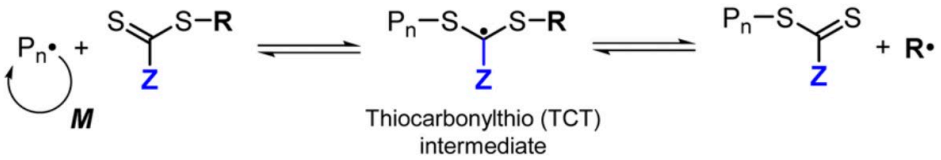

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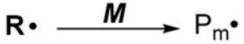

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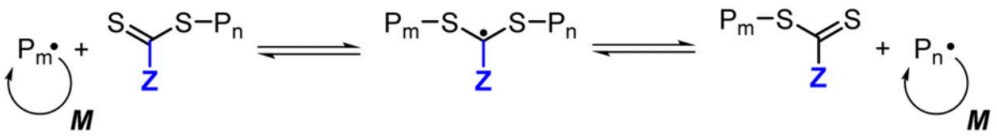

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IV. *Termination*

Termination reactions compete with polymerization and form "dead" chains

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RAFT Polymerization – Chemical End Groups

Question: What do the polymers formed actually look like?

V. Bellotti, R. Simonutti, New Light in Polymer Science: Photoinduced Reversible Addition-Fragmentation Chain Transfer Polymerization (PET-RAFT) as Innovative Strategy for the Synthesis of Advanced Materials, Polymers-Basel 13 (2021) 1119. https://doi.org/10.3390/polym13071119.

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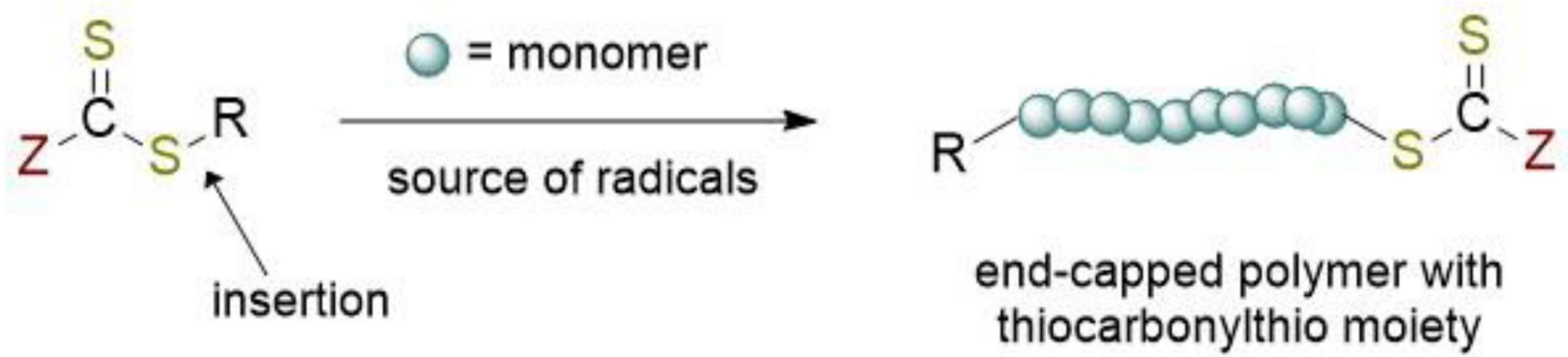

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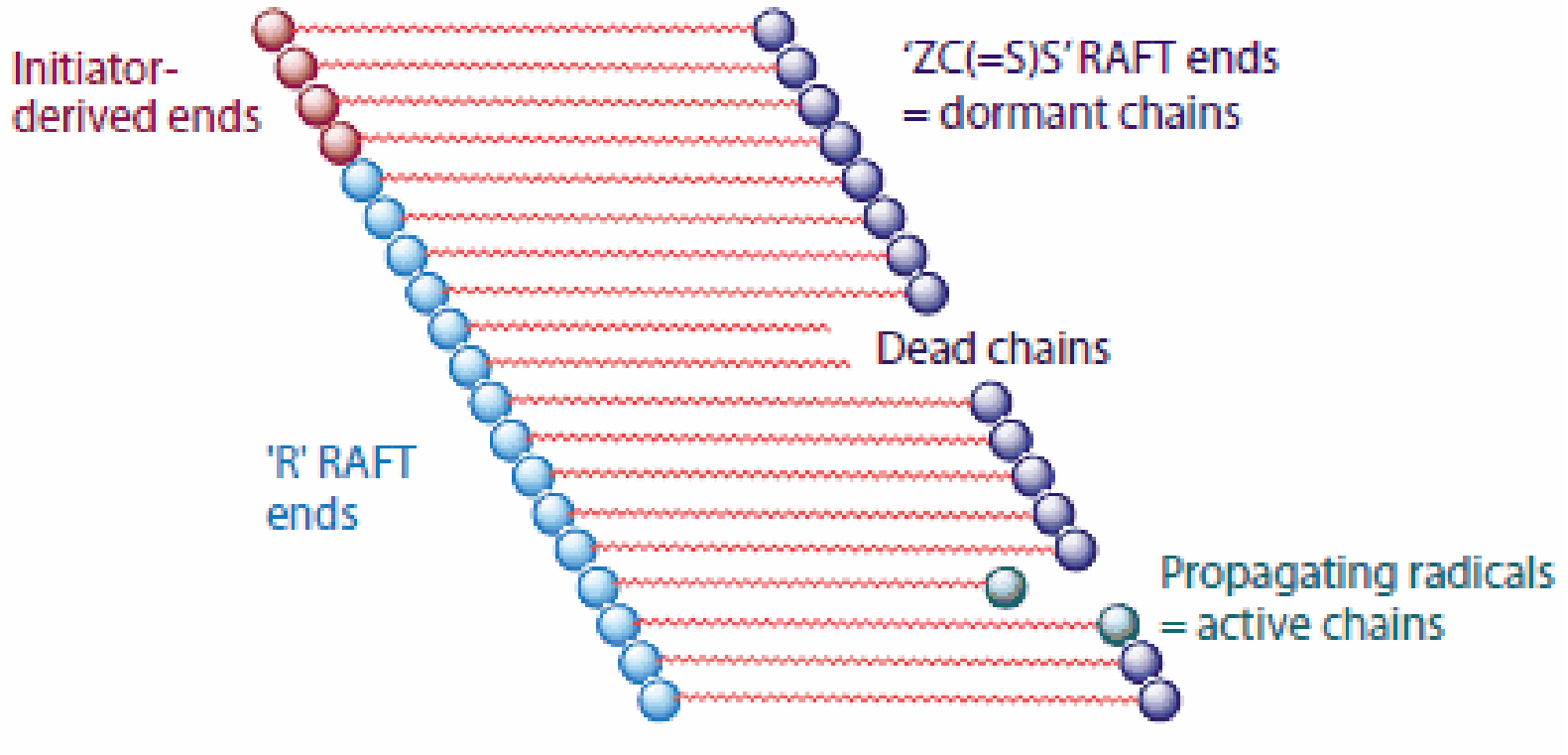
A snapshot from the Middle of RAFT Polymerization



Advantages of RAFT Polymerization over Traditional Free Radical Polymerization

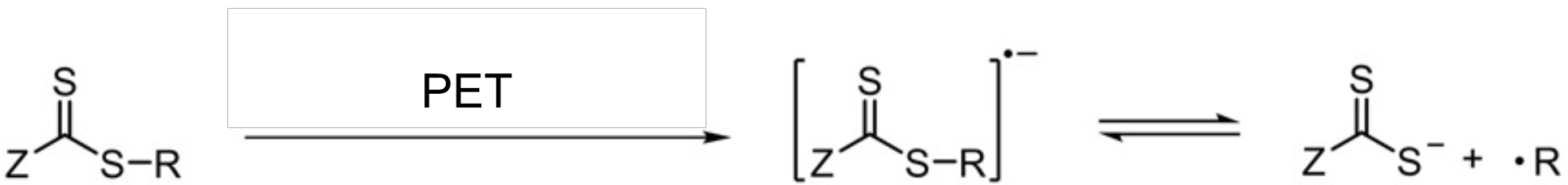
- Greater control over reaction
- Low PDIs (<1.1 routinely achievable)
- Degree of polymerization controlled by ratio of monomer to CTA
- Control over end group functionality
- “Livingness” of end group

However: still not oxygen tolerant!

PET-RAFT Fundamentals

PET-RAFT: Photoinduced electron/energy transfer reversable addition fragmentation chain-transfer polymerization

- All features of RAFT previously discussed also apply to PET-RAFT
- Fundamental difference in PET-RAFT versus RAFT mechanisms is in means of initiation/ radical generation
- CTA is directly split by PET to form “R” radical that propagates polymerization reaction



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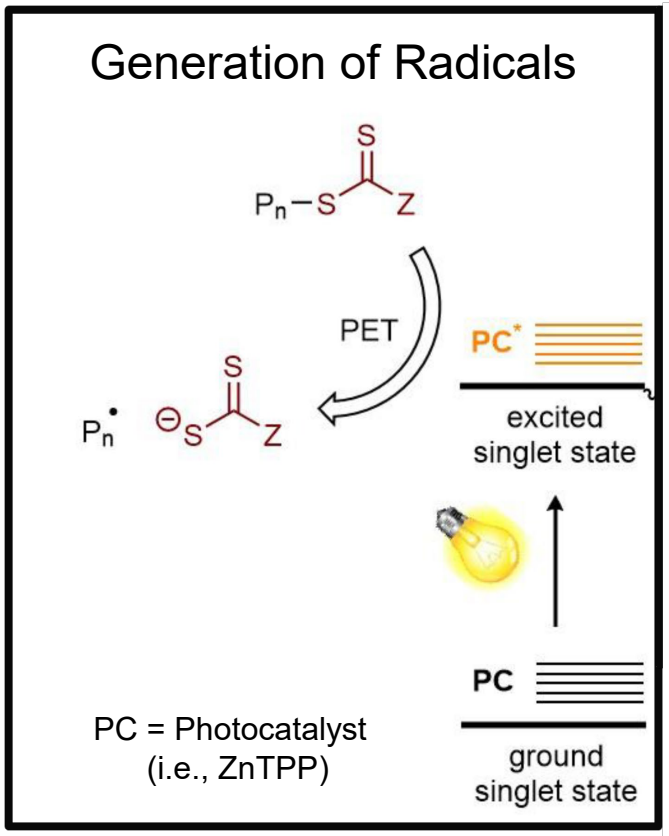
PET Mechanism



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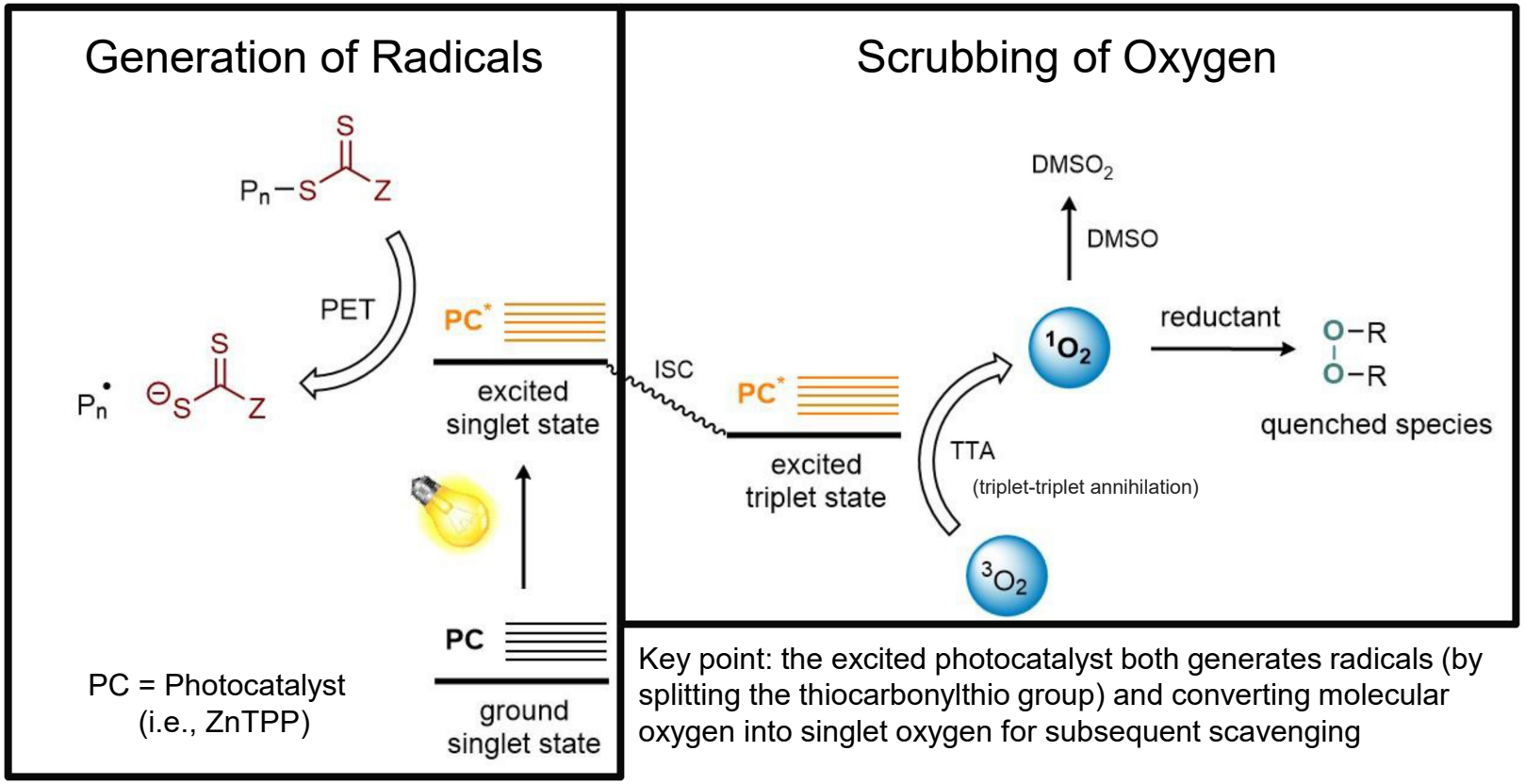
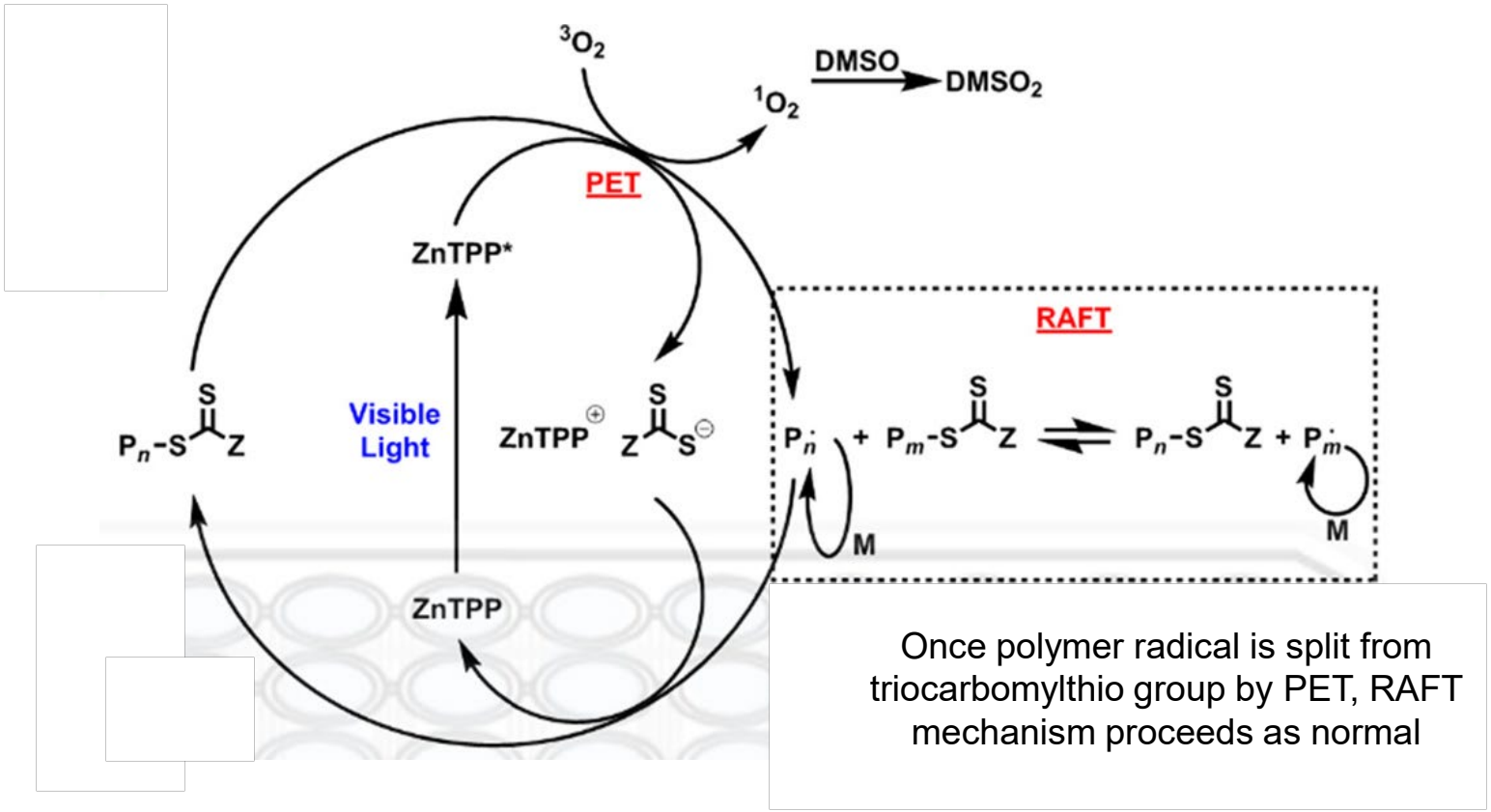


Key point: the excited photocatalyst both generates radicals (by splitting the thiocarbonylthio group) and converting molecular oxygen into singlet oxygen for subsequent scavenging

V. Bellotti, R. Simonutti, New Light in Polymer Science: Photoinduced Reversible Addition-Fragmentation Chain Transfer Polymerization (PET-RAFT) as Innovative Strategy for the Synthesis of Advanced Materials, Polymers-Basel 13 (2021) 1119. https://doi.org/10.3390/polym13071119.

PET-RAFT Mechanism



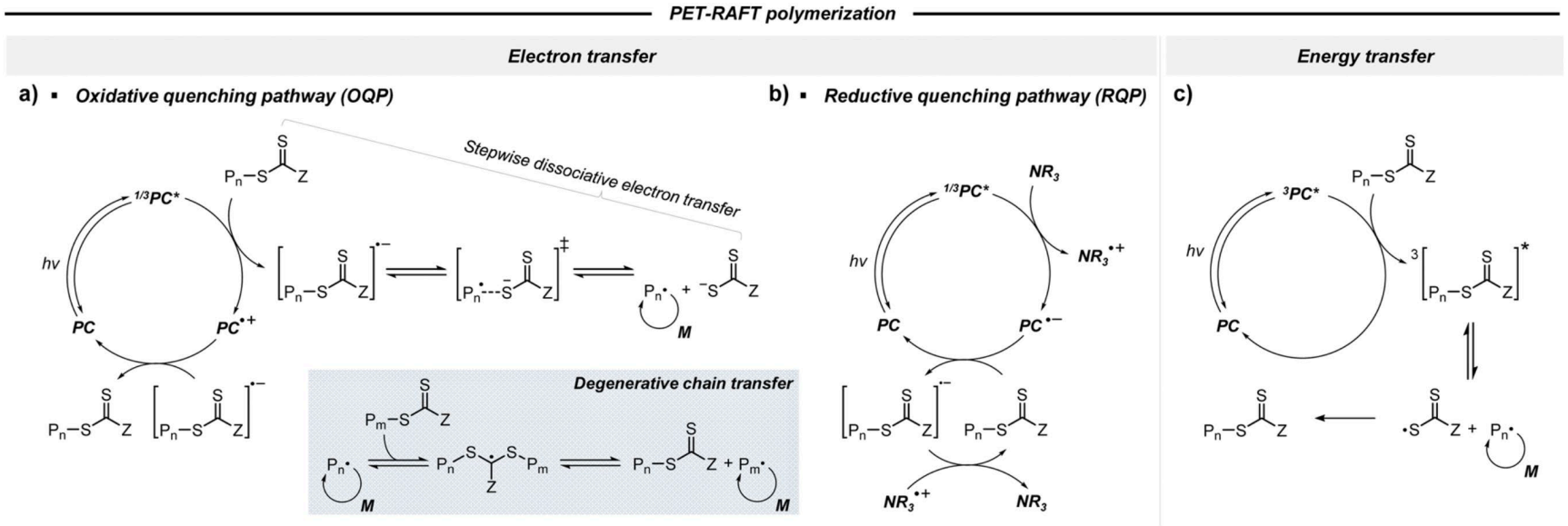
Once polymer radical is split from triocarbomylthio group by PET, RAFT mechanism proceeds as normal

Judzewitsch, P. R., Zhao, L., Wong, E. H. H. & Boyer, C. High-Throughput Synthesis of Antimicrobial Copolymers and Rapid Evaluation of Their Bioactivity. *Macromolecules* **52**, 3975–3986 (2019).

Types of PET-RAFT

Types of PET-RAFT

Types of PET-RAFT (Cont.)

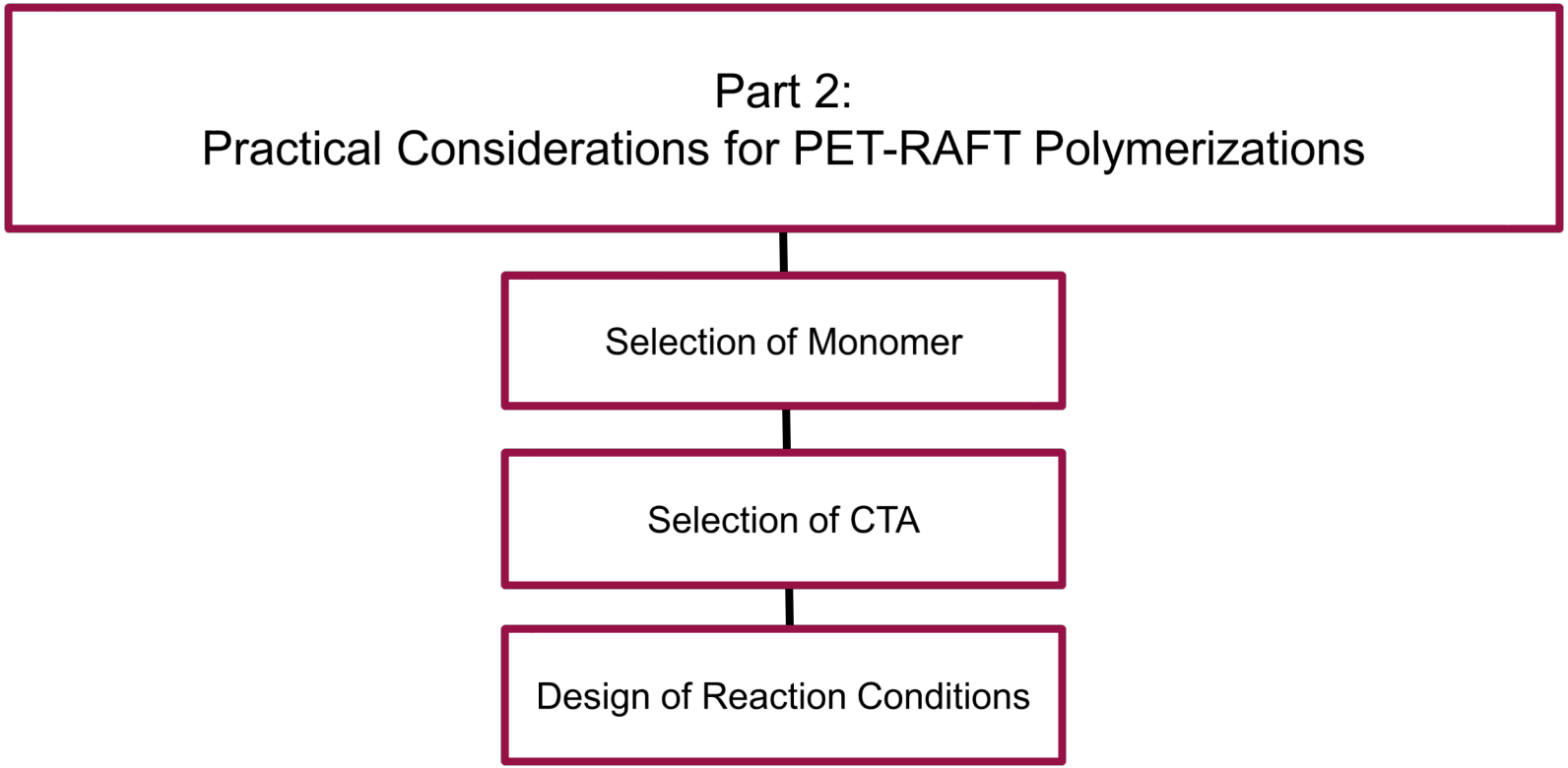


Y. Lee, C. Boyer, M.S. Kwon, Photocontrolled RAFT polymerization: past, present, and future, Chem. Soc. Rev. 52 (2023) 3035–3097. https://doi.org/10.1039/d1cs00069a.

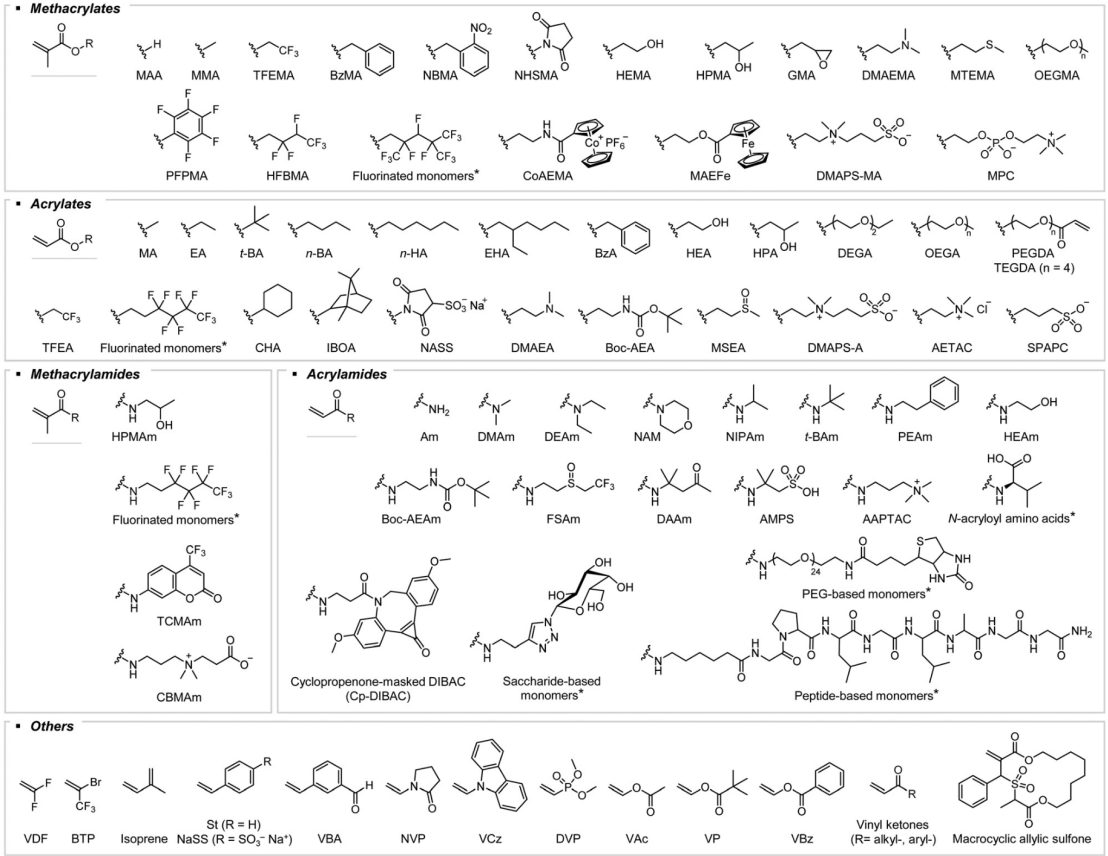
Summary of Polymerization Techniques Covered

- Radical polymerization provides the basis for RAFT and PET-RAFT. In all of these reactions, free radicals “drive” the reaction forward
- RAFT polymerization includes a CTA which is capable of modulating the free radical addition reaction, creating a well-controlled “living” reaction
- PET-RAFT builds on RAFT by utilizing a photoinitiator capable of generating free radicals by directly lysing the triocarbonylthio group, either on the CTA or dormant polymer chains
  - The photoinitiator also acts to scrub oxygen, creating an “oxygen-tolerant” chemistry

Overview of Today's Presentation



Selection of Monomer

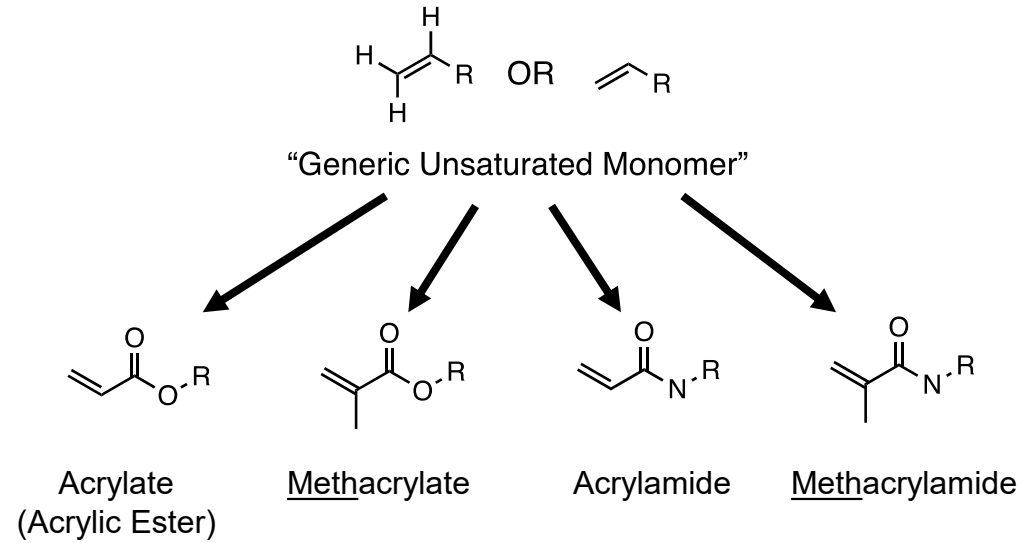


Compilation of All Monomers Reported in PET-RAFT Polymerizations

Lots of Chemical Diversity Available to Us for Synthesis!

Y. Lee, C. Boyer, M.S. Kwon, Photocontrolled RAFT polymerization: past, present, and future, Chem. Soc. Rev. 52 (2023) 3035–3097. https://doi.org/10.1039/d1cs00069a.

Anatomy of a Monomer



Acrylate (Acrylic Ester)

Methacrylate

Acrylamide

Methacrylamide

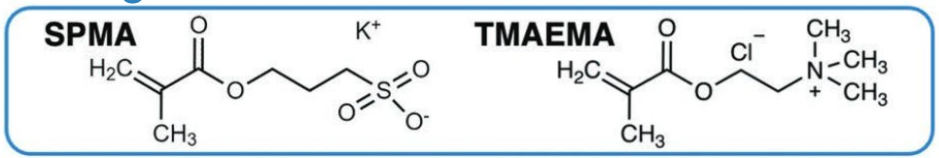
Also vinyl monomers and styrene (not pictured)

Methacrylates/methacrylamides indicate an allylic methyl group

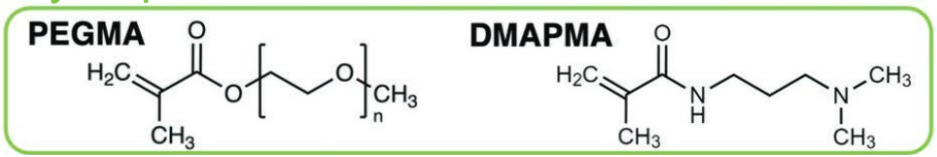
Monomer names refer to the chemical identity of the "R" group. For example, methyl acrylate has a methyl (CH_3) for the R.

Monomer Physiochemical Properties

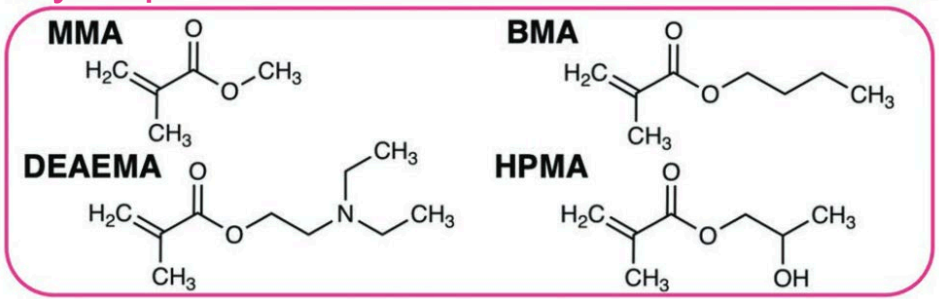
Charged



Hydrophilic



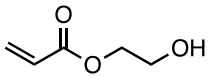
Hydrophobic



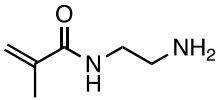
- Monomer hydrophilicity/ hydrophobicity is largely determined by sidechains
- Increasing length of carbon chain increases hydrophobicity
- Prescence of hydrogen donors and acceptors (N and O's) increases hydrophilicity
- Methacrylates/ methacrylamides tend to be more hydrophobic than their acrylate/acrylamide counterparts

M.J. Tamasi, R.A. Patel, C.H. Borca, S. Kosuri, H. Mugnier, R. Upadhya, N.S. Murthy, M.A. Webb, A.J. Gormley, Machine Learning on a Robotic Platform for the Design of Polymer–Protein Hybrids, Adv Mater (2022) e2201809. https://doi.org/10.1002/adma.202201809.

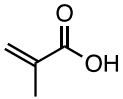
Monomer Physiochemical Properties (Cont.)



2-hydroxyethyl acrylate



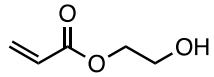
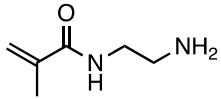
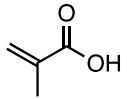
2-aminoethyl methacrylamide



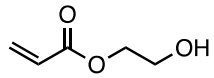
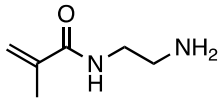
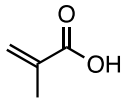
methacrylic acid

Question: Which of these monomers are charged?

Monomer Physiochemical Properties (Cont.)

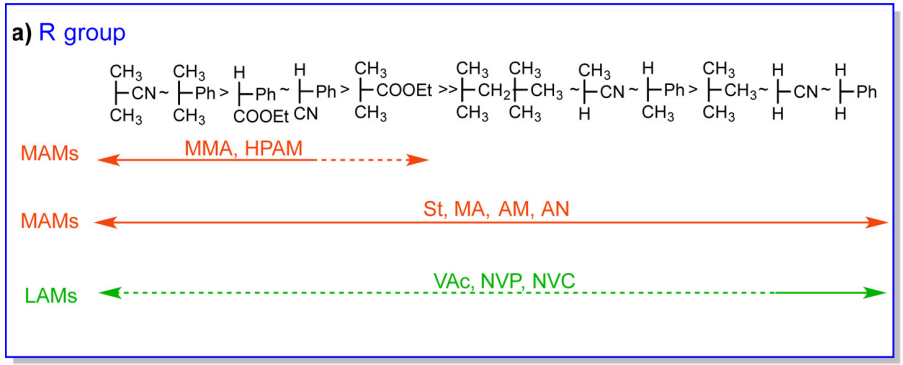
		Monomer Charged At?		
	Sidechain pKa	pH 5	pH 7	pH 9
 2-hydroxyethyl acrylate	~-3			
 2-aminoethyl methacrylamide	~8.8			
 methacrylic acid	~4.7			

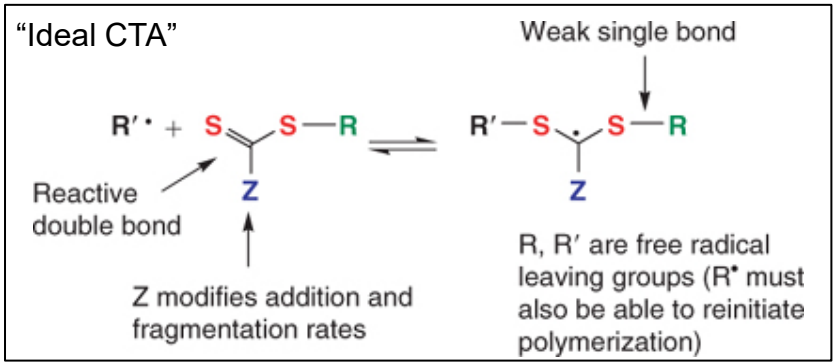
Monomer Physiochemical Properties (Cont.)

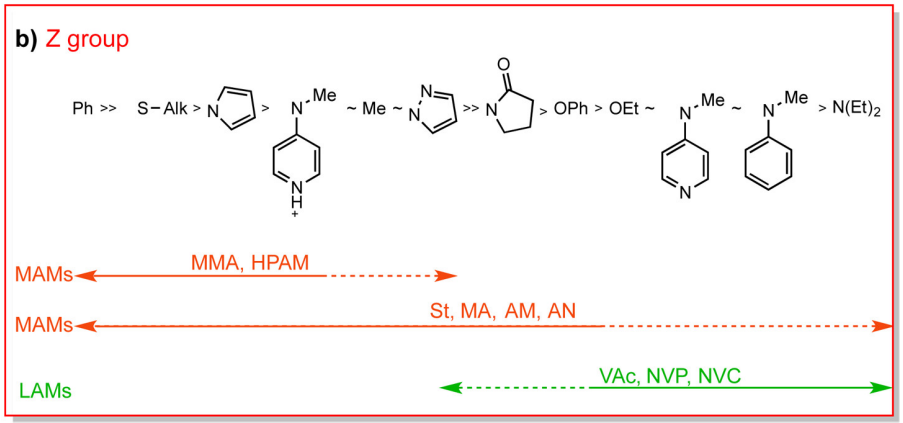
		Monomer Charged At?		
	Sidechain pKa	pH 5	pH 7	pH 9
 2-hydroxyethyl acrylate	~-3			
 2-aminoethyl methacrylamide	~8.8			
 methacrylic acid	~4.7			

Ionizability ≠ “Charged”

Selection of CTA – Role of R and Z Groups







R Group: Transfer coefficients decrease from left to right. Fragmentation rates also decrease from left to right. A dashed line indicates partial control (i.e.,control of molar mass but poor control over dispersity or substantial retardation in the case of VAc, NVC, or NVP).

Z Group: Addition rates decrease and fragmentation rates increase from left to right. A dashed line indicates partial control (i.e., control of molar mass but poor control over dispersity or substantial retardation in the case of LAMs such as VAc or NVP).

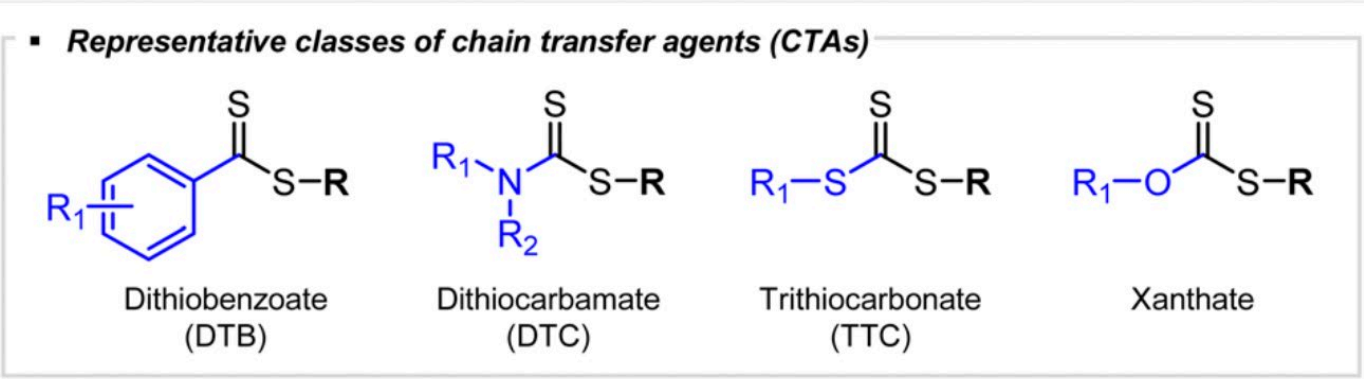
Abbreviations: MMA = methyl methacrylate, HPMAM = N-(2-hydroxypropyl)methacrylamide, St = styrene, MA = methyl acrylate, AM = acrylamide, AN = acrylonitrile, VAc = vinyl acetate, NVP =N-vinylpyrrolidone, and NVC = N-vinylcarbazole.

S. Perrier, 50th Anniversary Perspective: RAFT Polymerization–A User Guide, Macromolecules 50 (2017) 7433–7447. https://doi.org/10.1021/acs.macromol.7b00767.

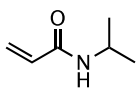
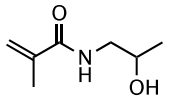
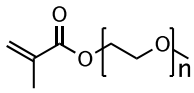
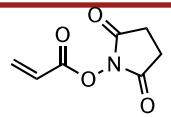
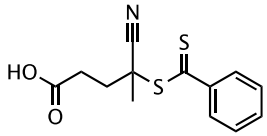
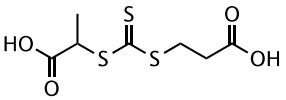
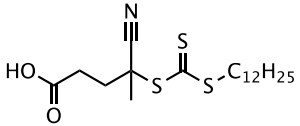
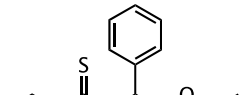
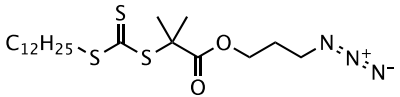
Selection of CTA – A More Practical Guide

"Rule of thumb" for the Gormley Lab CTA library:

- Trithiocarbonate CTAs tend to work well for acrylates and acrylamides
  - Some are also versatile and work with methacrylates and methacrylamides
- Dithiobenzoate CTAs tend to work well for methacrylates and methacrylamides



CTA Quiz

Selection of CTA – The Sacred Text

CTA	Acrylates	Methacrylates	Acrylamides	Methacrylamides	Additional
1	+++	-	+++	-	
2	++	+++	++	+++	
3	+	+++	+	+++	Styrenes
4	++	+++	++	+++	Styrenes
5	+++	+	+++	+	Azide functional
6	+++	+	+++	+	
7	+	+++	+	+++	
8	+	+++	+	+++	
9					3-arm
10					4-arm
11	++	-	++	-	Styrenes
12	-	-	-	-	Vinyl esters/amides
13	+++	++	+++	++	Supposedly versatile but not very suitable

Considerations for PET-RAFT Reaction Conditions

"The Old Ways"

(1) Polymer Synthesis

DP	Monomer Volume (2 M)	CTA Volume (50 mM)	ZnTPP Volume (2 mM)	DMSO Volume	Total Volume
100	100 µL	40 µL	20 µL	40 µL	200 µL
200	100 µL	20 µL	10 µL	70 µL	200 µL
400	100 µL	10 µL	5 µL	85 µL	200 µL

Depending on whether you want to incorporate NHS, this may change
-Dilute NHS into DMSO w/ acetic acid (1 mol equiv)

A good rule of thumb is to allow polymers to polymerize for at least about 10 hours using the timer (~16 hours for methacrylates/methacrylamides)

Considerations for PET-RAFT Reaction Conditions (Cont.)

"Principles, Not Rules"

- Monomer should be high enough concentration to ensure good polymerization kinetics, but not too high to create viscosity challenges (of monomer or expected polymer product)
- Target degree of polymerization is defined by ratio of monomer to CTA concentrations
- Photocatalyst needs to be at sufficiently high concentration to efficiently scrub oxygen from reaction solution and produce radicals to drive polymerization reaction
- Reaction time should be sufficient to reach target conversion, but not so long as to cause over-polymerization resulting in higher PDIs
- Choose a reaction vessel to ensure oxygen flux into solution does not overwhelm scrubbing ability of photocatalyst
  - " 'Oxygen-tolerant' is not 'oxygen-immune' " – Dr. Matthew Tamasi

Learning Objectives

- Develop foundational organic chemistry literacy
- Establish a conceptual framework for visualizing and understanding free radical polymerization reaction chemistry
- Understand the roles of various chemical components in RAFT and PET-RAFT
- Understand rationale for selection of components in the reaction (i.e. why use *this* CTA?)