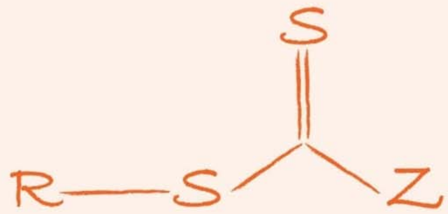


RAFT

RAFT PATENTS: WO9801478/EP0910587 WO9905099/US6512081 WO9931144/US6747111 US6642318 WO05113612/EP1751194 B
WO07100719 WO961515/US6291620/EP0791016B WO9504026/US5830966 WO0177198/US7064151 US6355718/US6355718

RAFT Fundamentals – A History and Recent Developments

CSIRO Manufacturing Flagship

Graeme Moad

MACRO 2016 – Istanbul – 17 July 2016

Reversible Addition Fragmentation Chain Transfer

RAFT

RAFT Polymerization – Description and History

RAFT Application and Development 2011-2015

Conclusions and Outlook

Radical Polymerization

By volume, most commercial polymer production involves radical polymerization

Advantages

- Simple to implement
- Low cost
- Compatible with a wide range of monomers

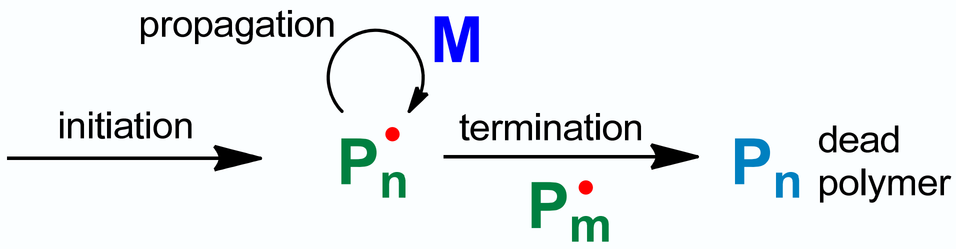
Disadvantages

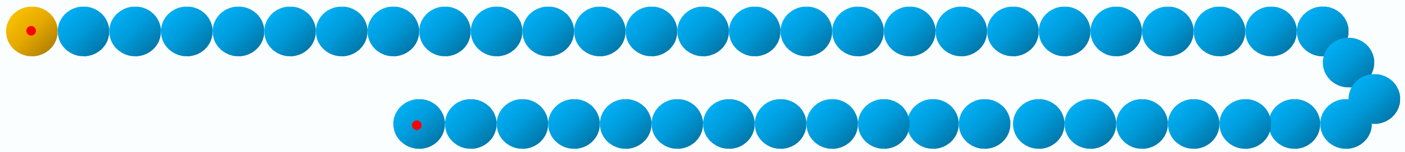
- Relatively broad molecular weight distribution (high dispersity)
- Limited control over polymer architecture & end group functionality

Radical Polymerization

Process involves adding a source of radicals to a monomer (**M**)

Chains are continuously initiated, propagate, and die





Radical Polymerization

Advantages

- Simple to implement
- Low cost
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Disadvantages

- Broad molecular weight distribution (high dispersity)
- Little control over polymer architecture & end group functionality

RAFT Polymerization

The RAFT reviews
Aust. J. Chem. **2005**, *58*, 379-410
Aust. J. Chem. **2006**, *58*, 669-92
Polymer **2008**, *49*, 1079-131
Acc. Chem. Res. **2008**, *41*, 1133-42
Aust. J. Chem. **2009**, *62*, 1402-72
Aust. J. Chem. **2012,** *65*, 985-1076
Chem. Asian J. **2013**, *8*, 1634-1644

Advantages

- Simple to implement
- Low cost
- Compatible with a wide range of monomers
- Narrow molecular weight distribution (low dispersity)
- Intricate control over polymer architecture & end group functionality
- Is a **Reversible Deactivation Radical Polymerization** (**RDRP**)

Disadvantages

- Need to select a RAFT agent for the specific polymerization and process conditions

RAFT Polymerization

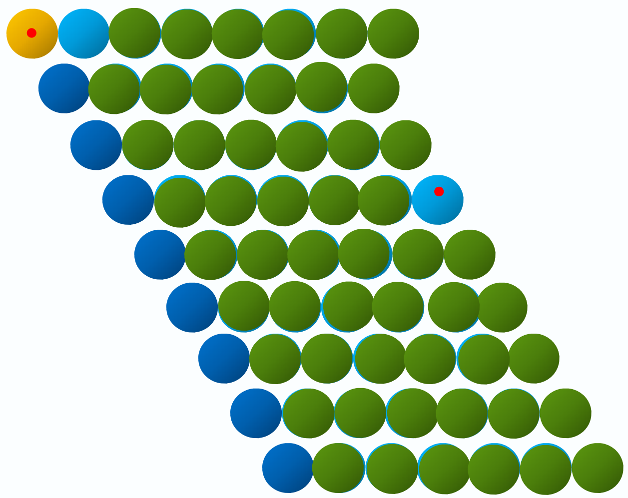
Simply add a source of radicals to a monomer (**M**) and a RAFT agent

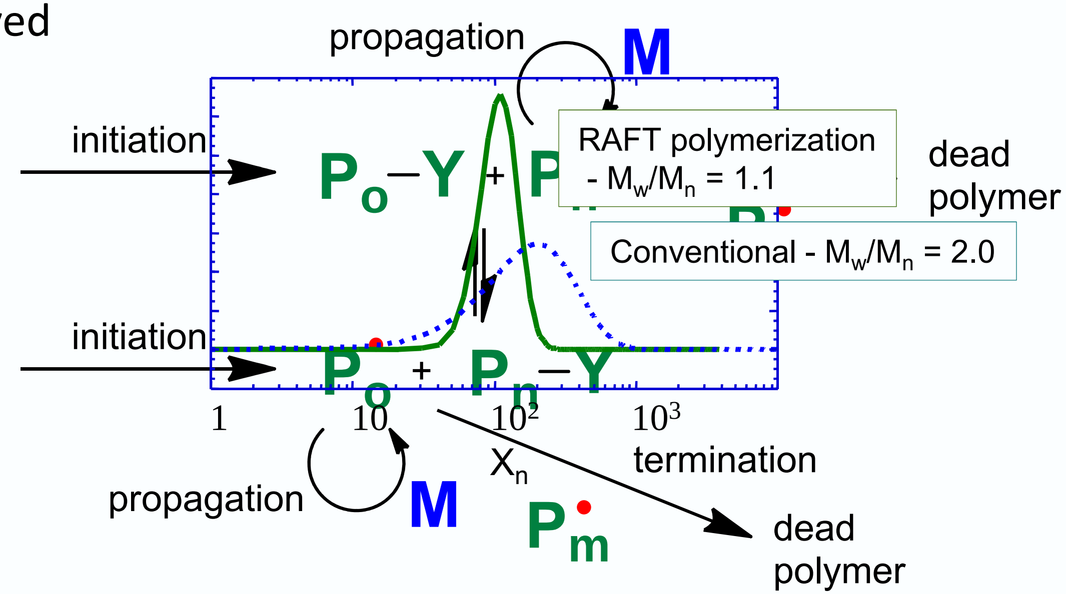
- Chains continuously initiated, propagate, and die (same number as in conventional polymerization)

However,

- More chains (number = moles of RAFT agent)
- On average, all chains grow simultaneously
- Narrow molecular weight distribution
- End-groups , (largely) preserved

Aust. J. Chem. **2005**, *58*, 379-410
Aust. J. Chem. **2006**, *58*, 669-92
Polymer **2008**, *49*, 1079-131
Acc. Chem. Res. **2008**, *41*, 1133-42
Aust. J. Chem. **2009**, *62*, 1402-72
Aust J. Chem. **2012** (in press)

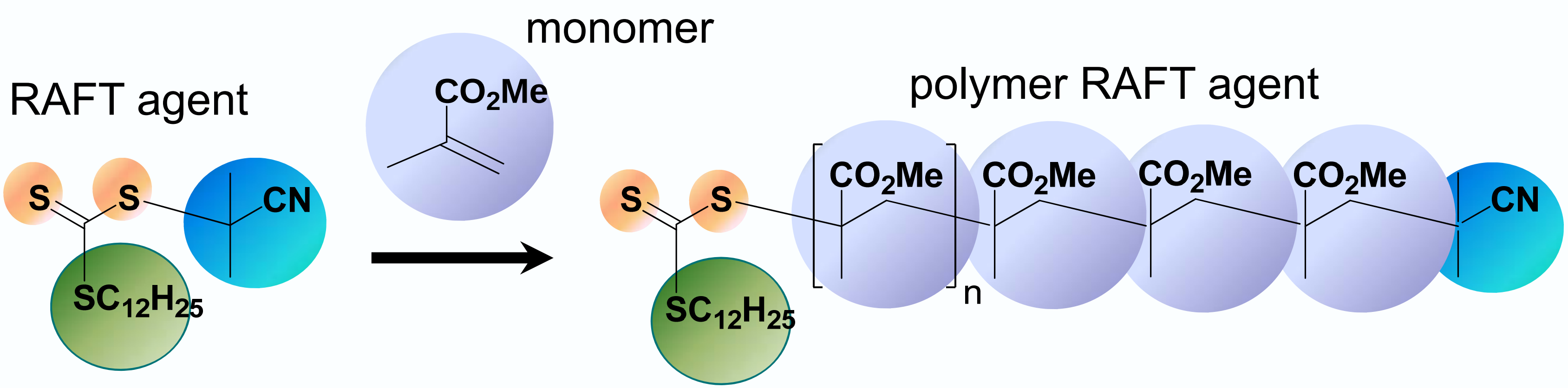




RAFT Agent

- Reacts with radicals by Reversible Addition-Fragmentation chain Transfer
- Determines molar mass

  ~ [monomer consumed]/[RAFT agent]



Chain Transfer

Chain transfer by homolytic substitution

$$R'^{\bullet} + Y\text{—}X\text{—}R \underset{k_{-add}}{\overset{k_{add}}{\rightleftharpoons}} R'\text{—}Y + {}^{\bullet}X\text{—}R$$

Weak single bond

R-X• must also be able to efficiently reinitiate polymerization

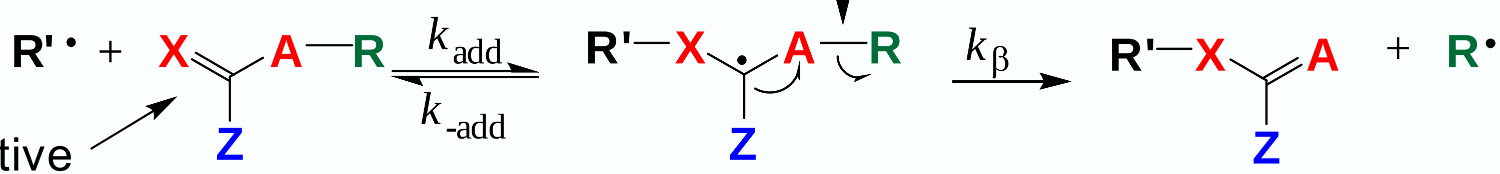
Typical transfer agents

Y—X—R	
H—S—R	thiols
Br—C—R	halocarbons

Chain Transfer

Chain transfer by (irreversible) addition-fragmentation

Weak single bond

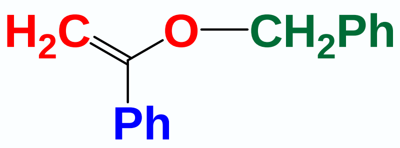


Reactive double bond

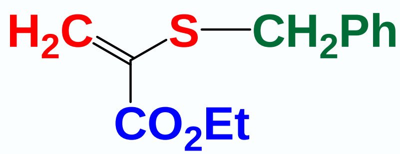
Z modifies addition and fragmentation rates

R is a homolytic leaving group (R• must also be able to reinitiate polymerization)

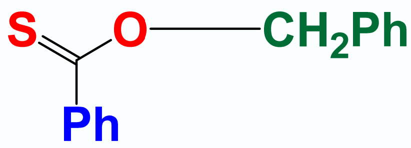
Typical addition fragmentation transfer agents



vinyl ethers



allyl sulfides



thionoesters

Chain Transfer

- Chain transfer does not effect polymerization kinetics.

  (the concentration of radicals is not affected)

- Under ideal conditions the molecular weight dispersity ($Đ = M_w/M_n$) will be 2.0.

- Historically, a transfer constant ($C_{tr}=k_{tr}/k_p$) of 1.0 has been called "ideal" because the ratio of monomer to transfer agent (and thus the molecular weight) remains constant throughout the polymerization.

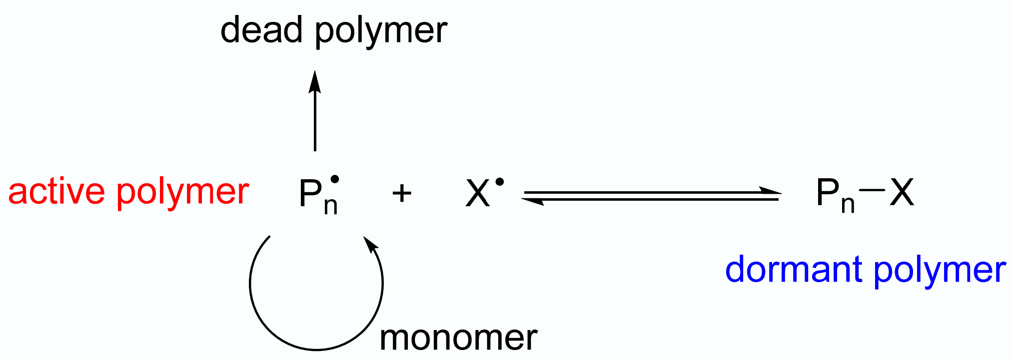
  (many irreversible addition-fragmentation transfer agents have C_{tr}~ 1)

- If the transfer constant is >1.0 the molecular weight will increase linearly with monomer conversion.

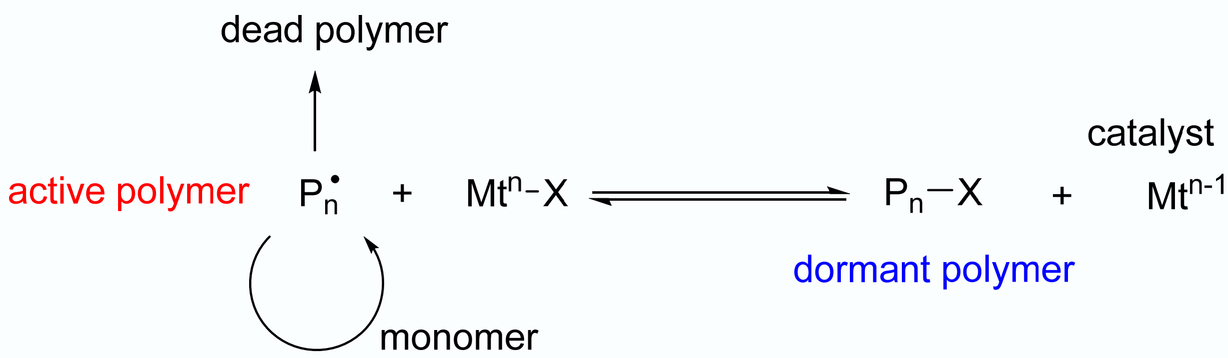
Mechanisms for Reversible Deactivation Radical Polymerization (RDRP)

Stable radical-mediated radical polymerization (SRMP)

e.g., nitroxide-mediated radical polymerization (NMP)



Atom transfer radical polymerization (ATRP)



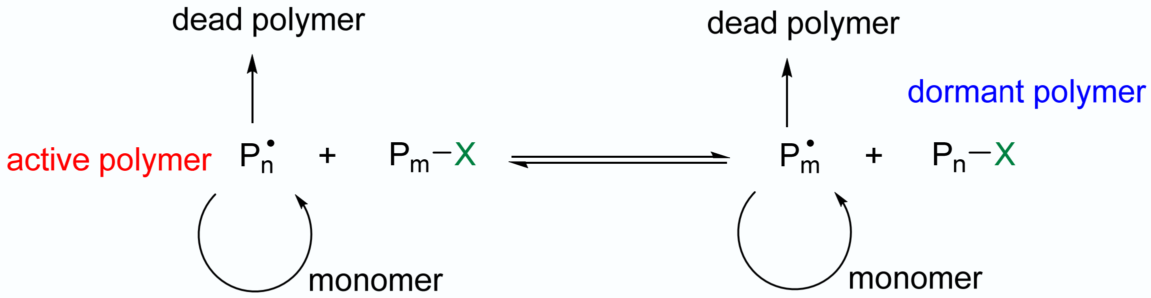
Control through persistent radical effect

RDRP Mechanisms

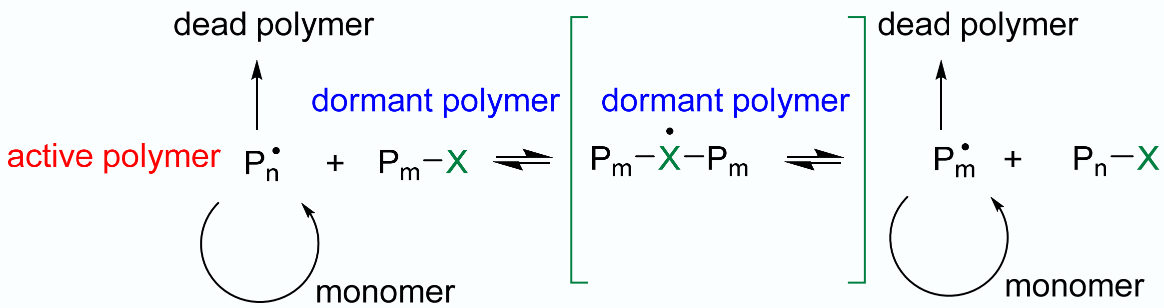
Radical polymerization with degenerate chain transfer

e.g. tellurium mediated polymerization (TERP)

Iodine transfer polymerization (ITP)

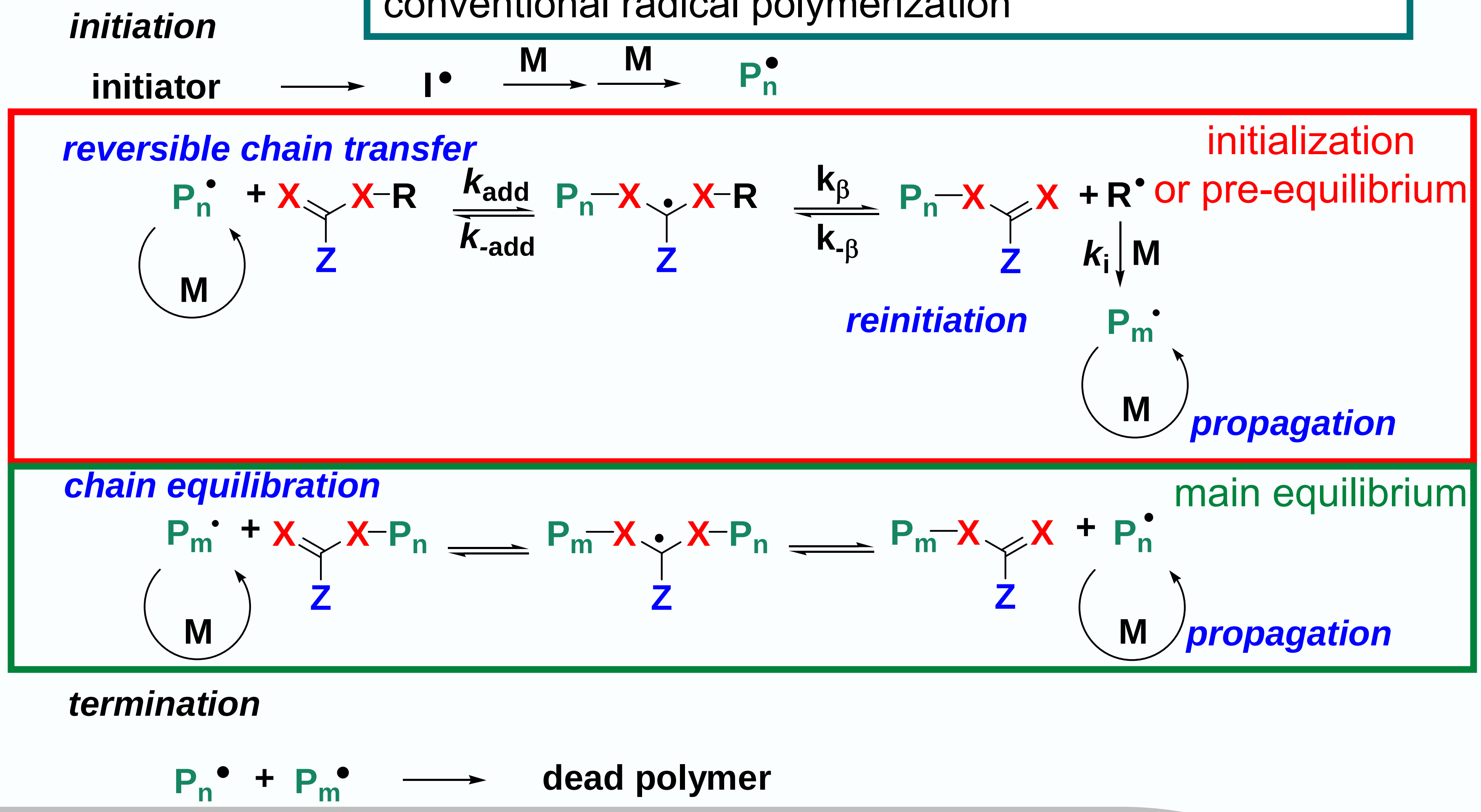


Reversible addition-fragmentation chain transfer (RAFT)

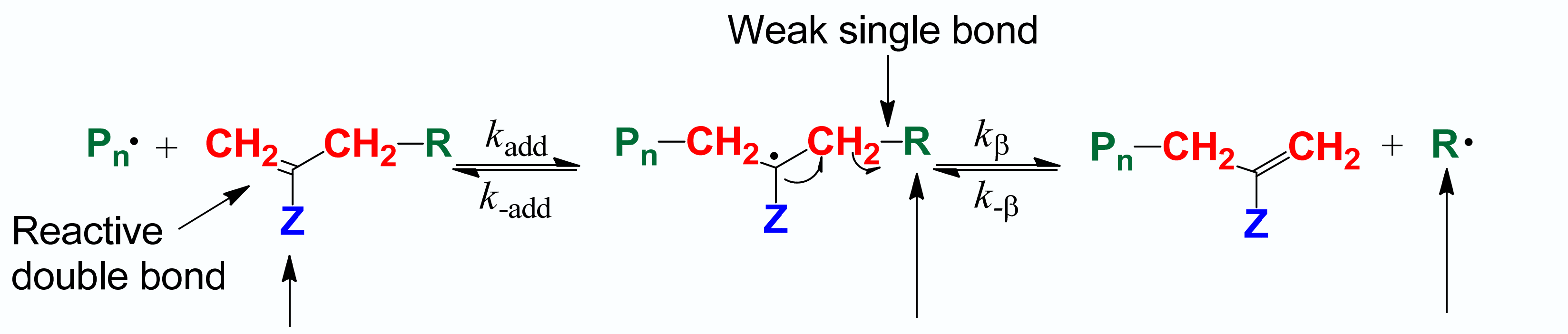


Mechanism of RAFT Polymerisation

The RAFT equilibria are chain transfer reactions. Radicals are neither formed nor destroyed. Ideally the polymerization kinetics are similar to those in conventional radical polymerization



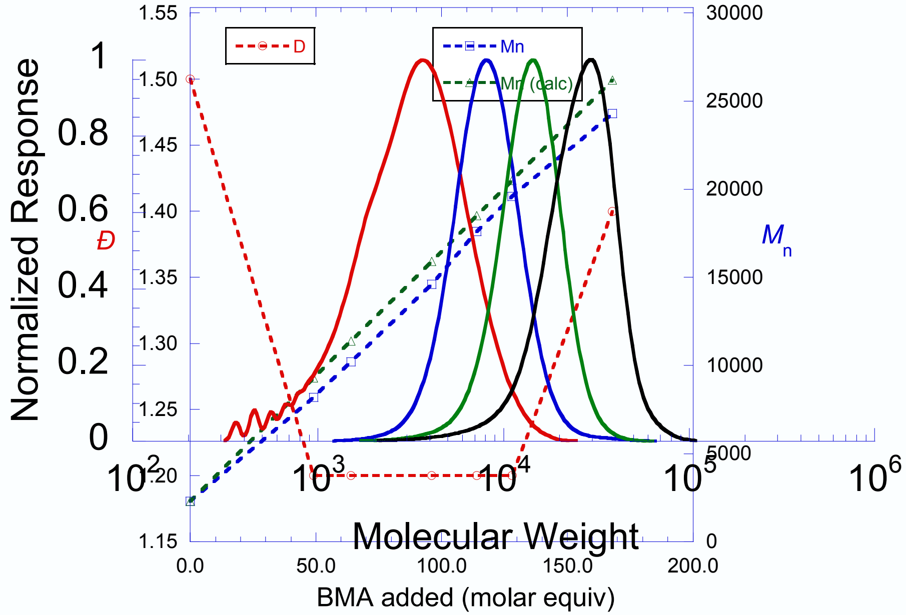
Macromonomer RAFT



PMMA macromonomer RAFT agent (8.5 g, M_n 2300, $Đ$ 1.5, ·····) and for PMMA-*block*-PBMA after additions of 33.6, 59.8, and 88.2 g of BMA

Starved feed emulsion polymerization (instantaneous conversion > 90%)

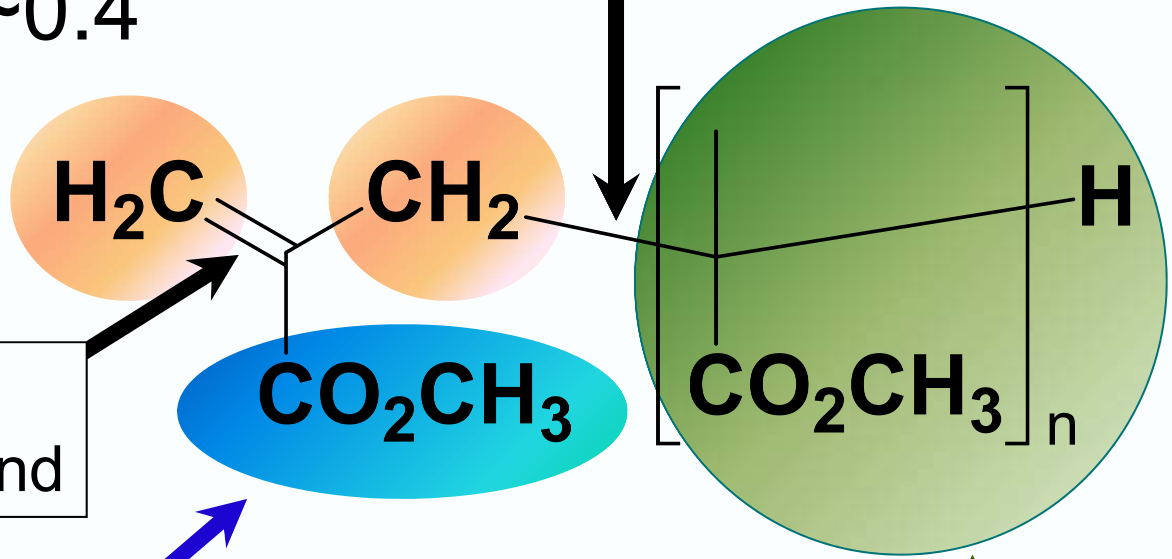
Krstina et al *Macromolecules*, **1995**, *28*, 5381-5385



“Macromonomer” RAFT Agent

C_{tr} (MMA)~0.4

Weak single bond (in intermediate)



Reactive double bond

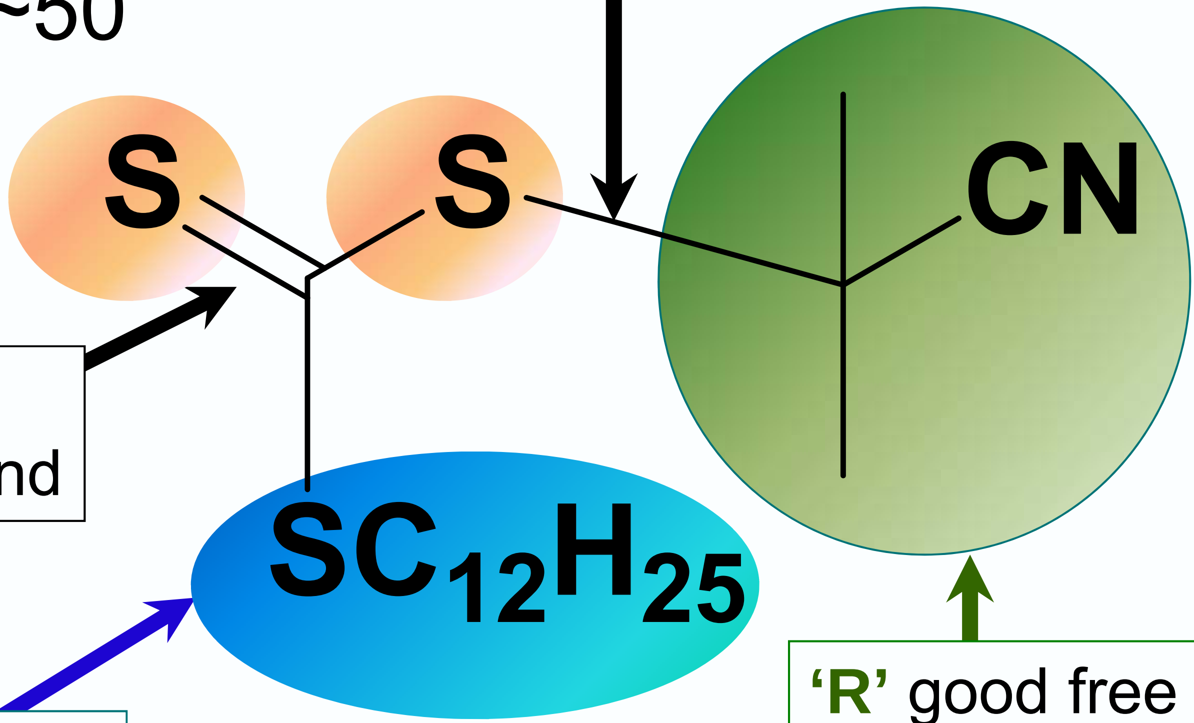
‘Z’ activating group

‘R’ good free radical leaving group, good initiating radical

Trithiocarbonate RAFT Agent

C_{tr} (MMA)~50

Weak single bond (in intermediate)

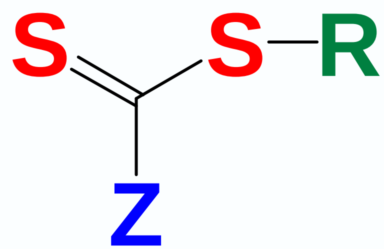


Reactive double bond

'Z' activating group

'R' good free radical leaving group, good initiating radical

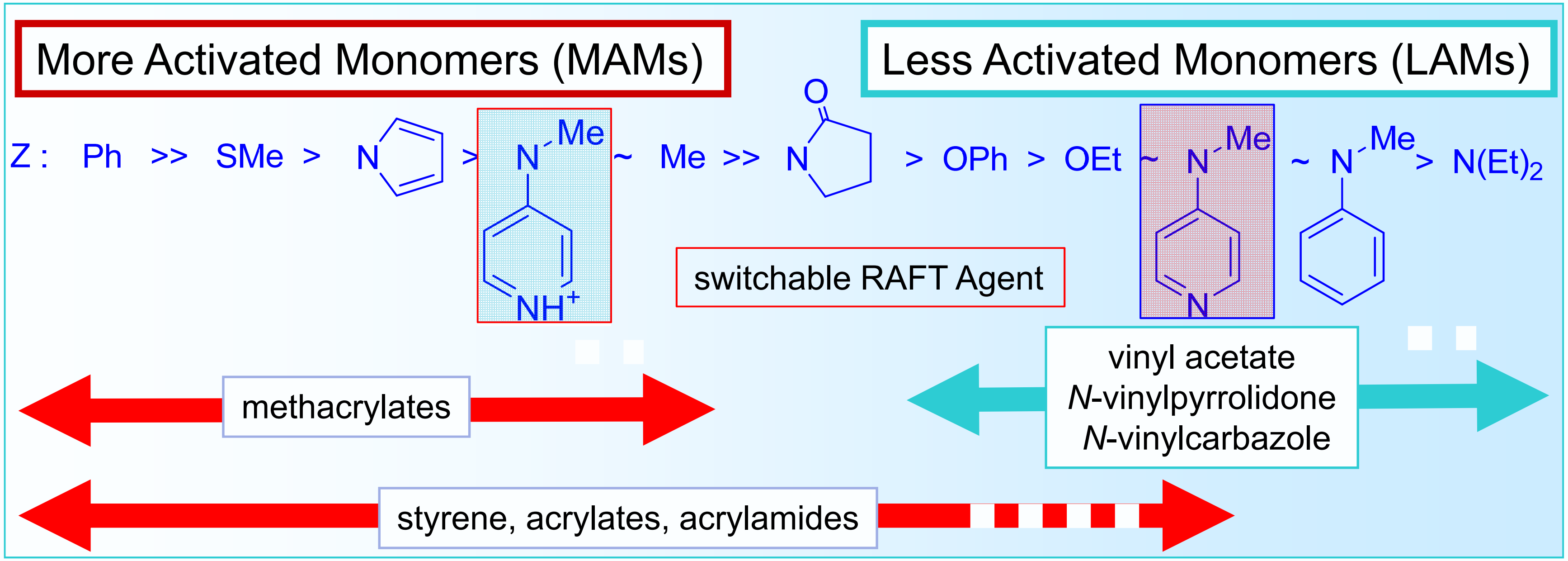
Effectiveness of RAFT Agents



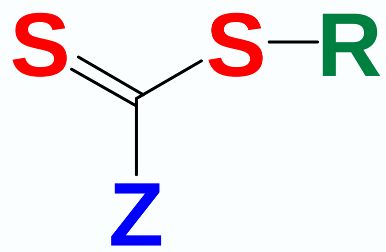
Strong dependence on Z substituent

More active RAFT agents retard or inhibit polymerization of LAMs

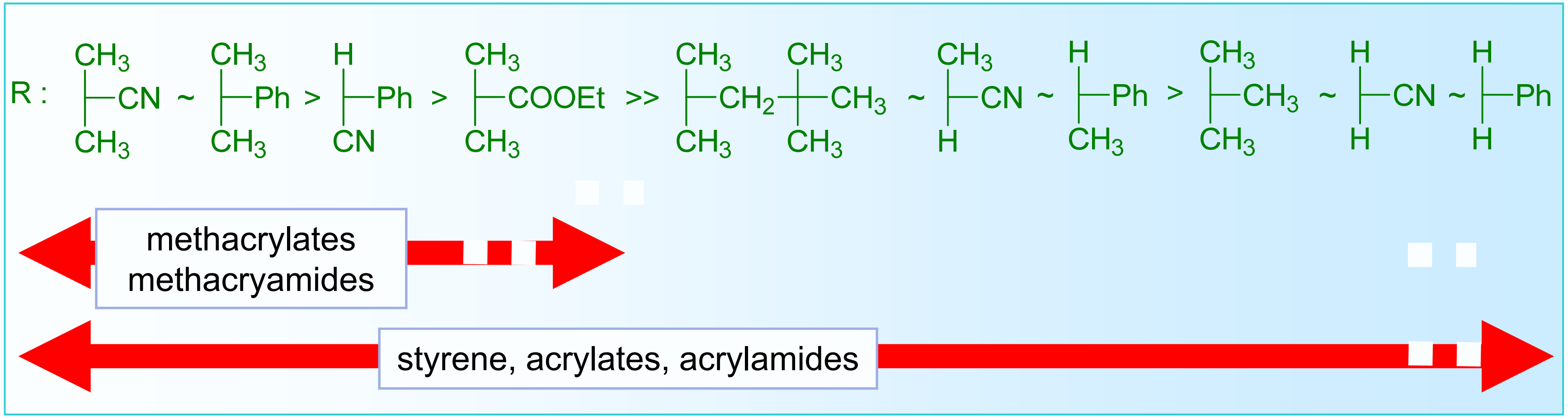
Less active RAFT agents provide little or poor control over the polymerization of MAMs



Effectiveness of RAFT Agents



Strong dependence on R substituent



Transfer constants decrease in the series where homolytic leaving group R is Tertiary >> secondary > primary

where α-substituent on R is CN ~ Ph >> CO_2R >> alkyl

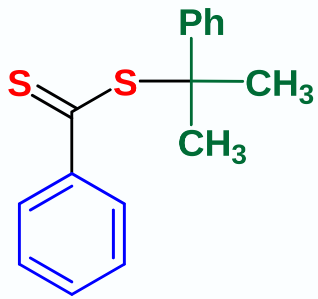
where chain length of R is > 2 >> 1 (significant penultimate unit effect)

Macromolecules **2003**, *36*, 2273-83

Types of RAFT agents

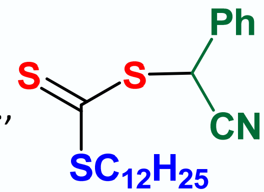
Dithiobenzoates

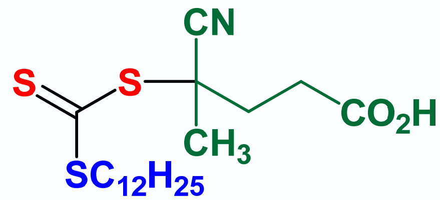
- Very high transfer constants
- Prone to hydrolysis
- May give retardation when used in high concentrations



Trithiocarbonates

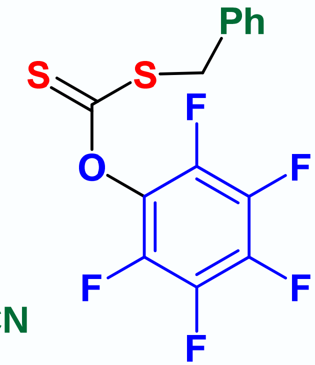
- are readily synthesized
- high transfer constants (effective with activated monomers, e.g., acrylates, styrene)
- give less retardation and are more hydrolytically stable (than dithiobenzoates)





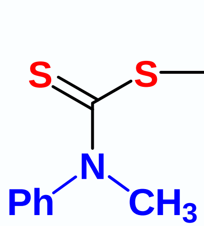
Xanthates

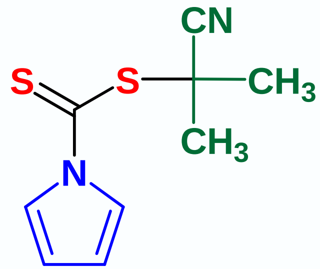
- lower transfer constants
- more effective with less activated monomers, e.g., VAc, NVP
- Made more active by electron-withdrawing substituents



Dithiocarbamates

- Activity determined by substituents on N

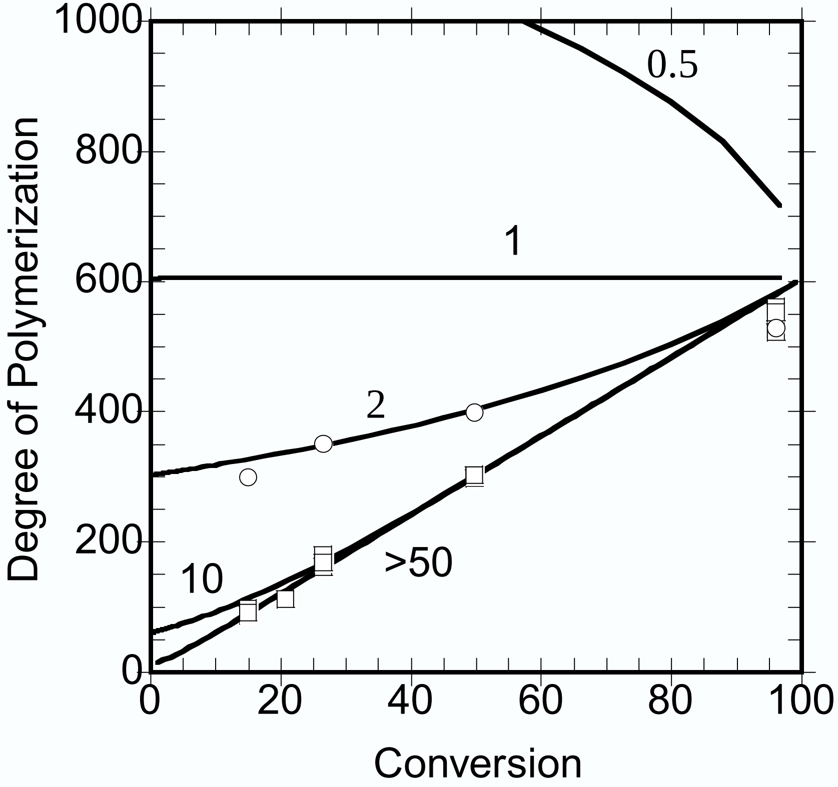




Macromol. Symp. **2007,** 248, 104-116

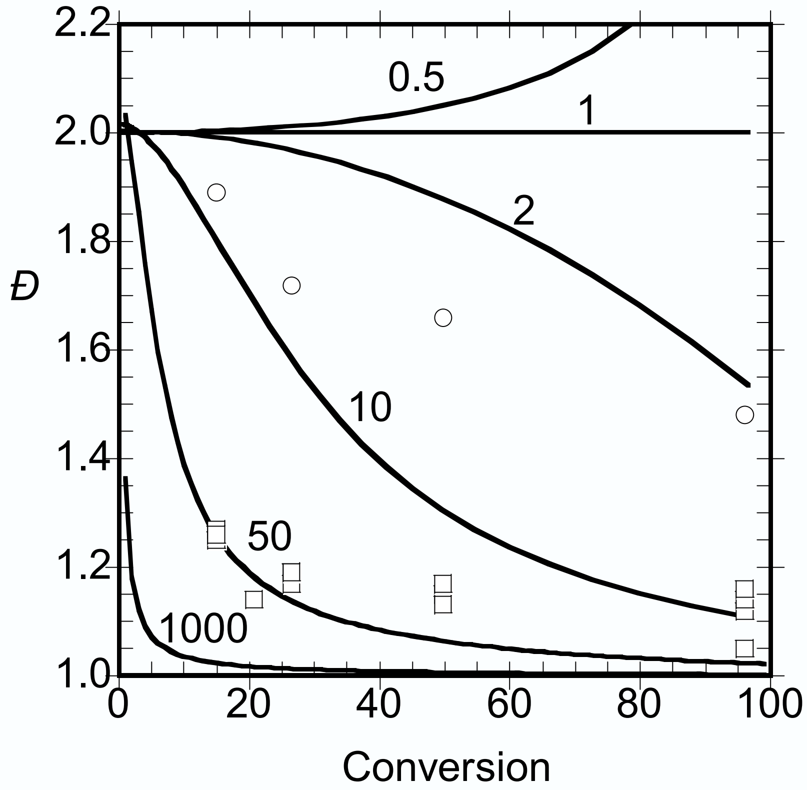
RAFT Polymerization

Dependence of degree of polymerization on transfer constant and monomer conversion



RAFT Polymerization

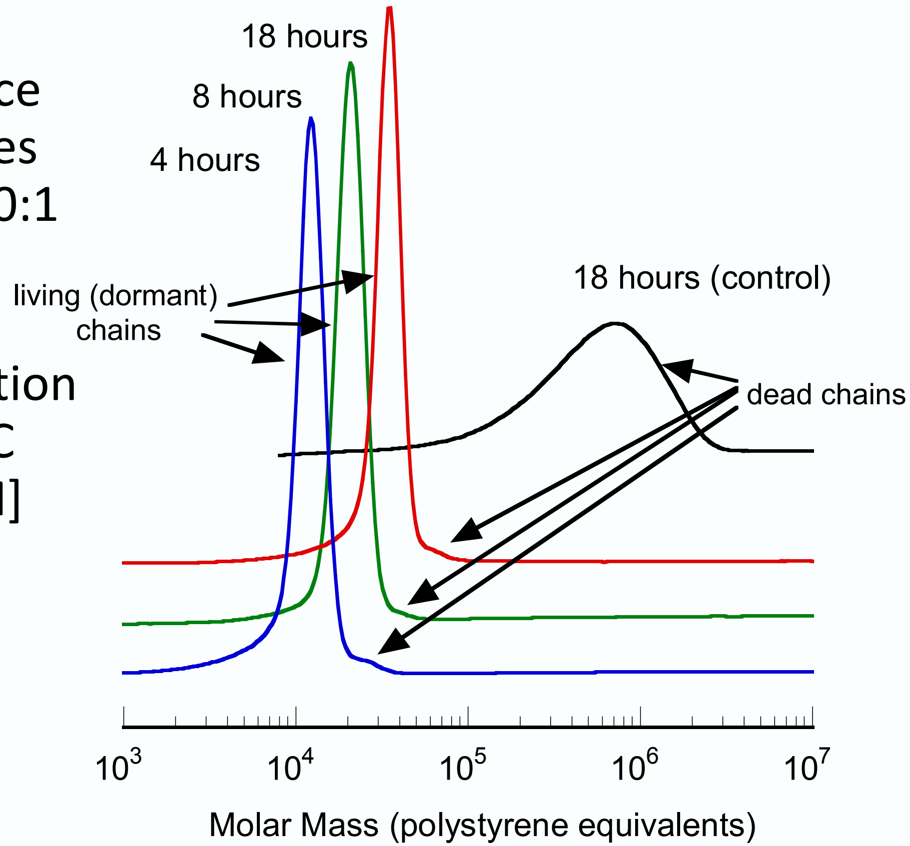
Dependence of dispersity ($Đ = M_w/M_n$) on transfer constant and monomer conversion



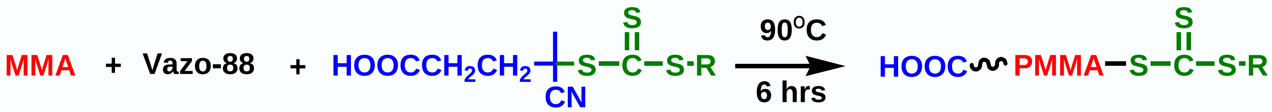
RAFT Polymerization

Ideally, the target molecular weight should be substantially lower that molecular weight seen in the absence of RAFT agent. This usually translates to ratios [RAFT agent]:[initiator] > 10:1

Example is bulk thermal polymerization of styrene and acrylonitrile at 100 °C with cumyl dithiobenzoate [0.123 M]



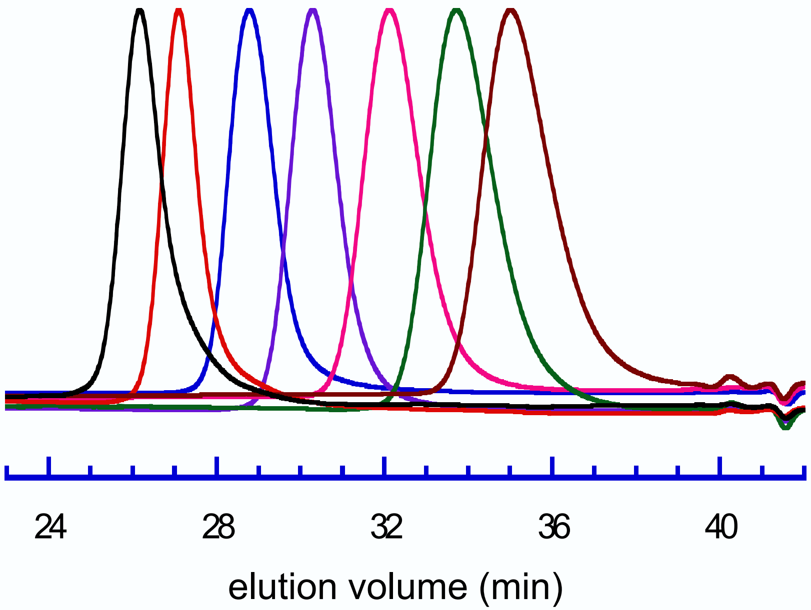
High Conversion
Acid End-functional PMMA



Over ~50-fold range of RAFT agent concentrations

Little retardation

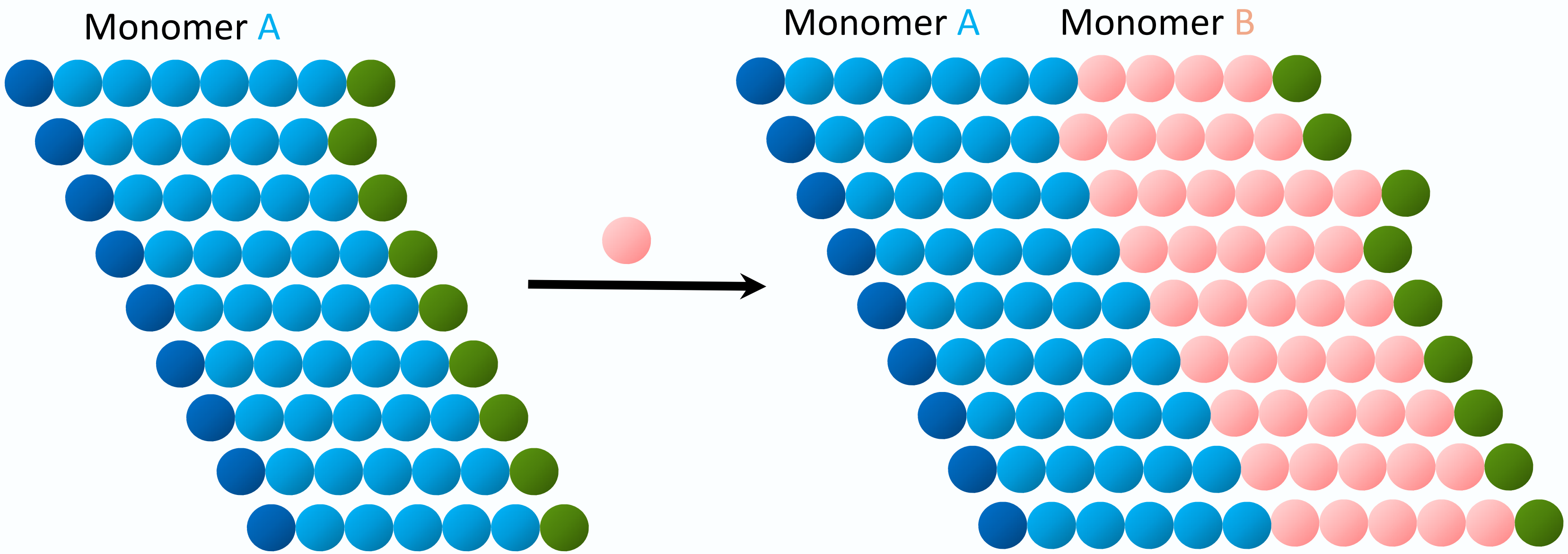
Low dispersities /Monomodal distributions



[RAFT] x 10^2M	M_n	M_w/M_n	% Conv.
19.92	2,600	1.17	80
9.96	4,600	1.15	80
4.95	9,300	1.11	79
2.48	20,600	1.09	91
1.24	39,600	1.09	>99
0.61	84,000	1.11	>99
0.32	125,000	1.16	>99

RAFT Polymerization

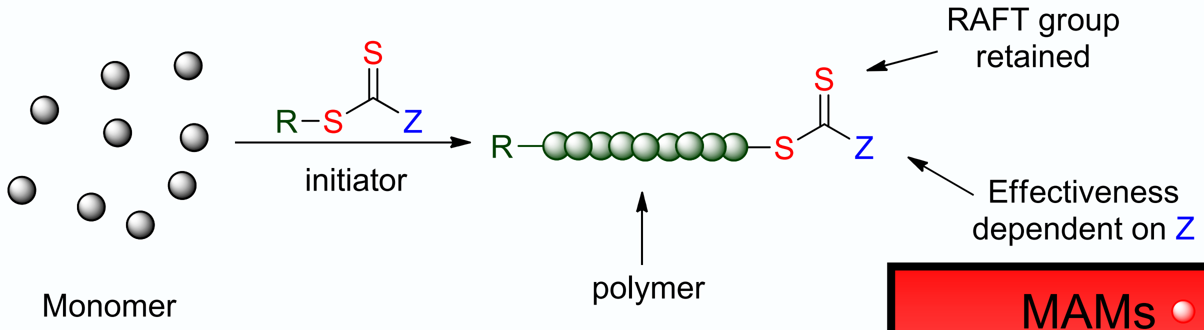
Because RAFT end-groups are (largely) preserved, block copolymers can be prepared by sequential addition of monomers.



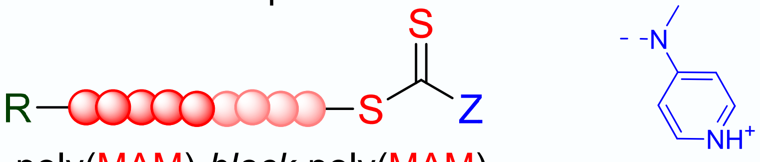
Block copolymers have a wide range of applications as dispersants, surfactants and undergo self-assembly to form nanoreactors and vehicles for delivery of actives in the biomedical, personal care and agrichemical fields. They also allow control of morphology in polymer blends.

Macromolecules **1999**, *32*, 2071-4

Guide to Block Copolymer Synthesis

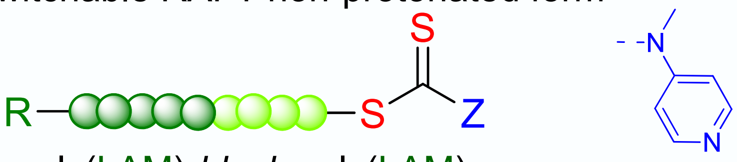


Switchable RAFT protonated form



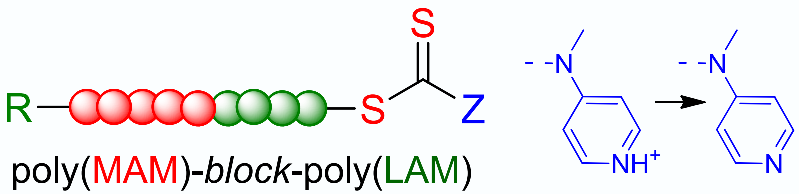
poly(MAM)-*block*-poly(MAM)

Switchable RAFT non-protonated form

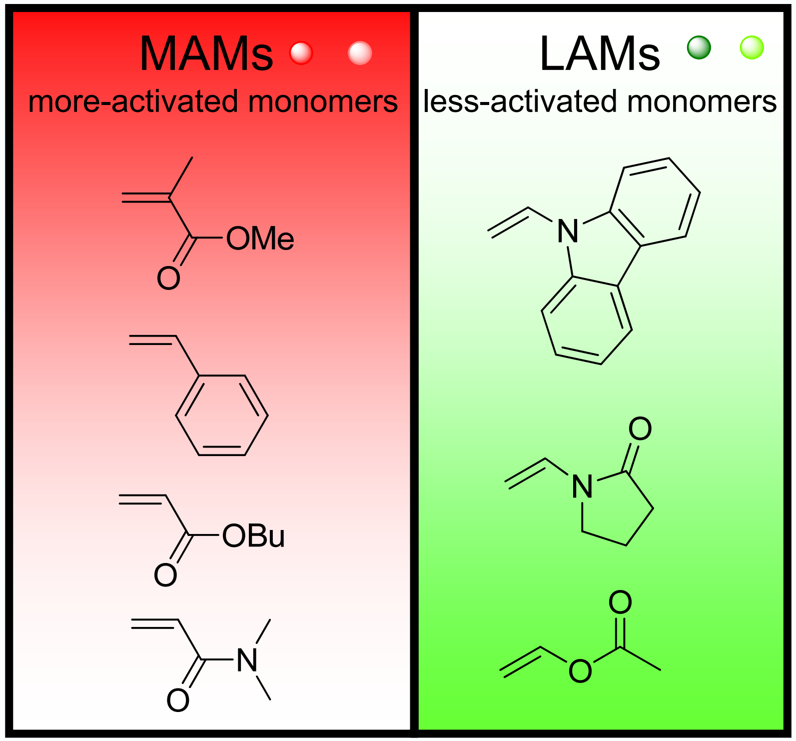


poly(LAM)-*block*-poly(LAM)

Switchable RAFT protonated $\xrightarrow{\text{switch}}$ non protonated form



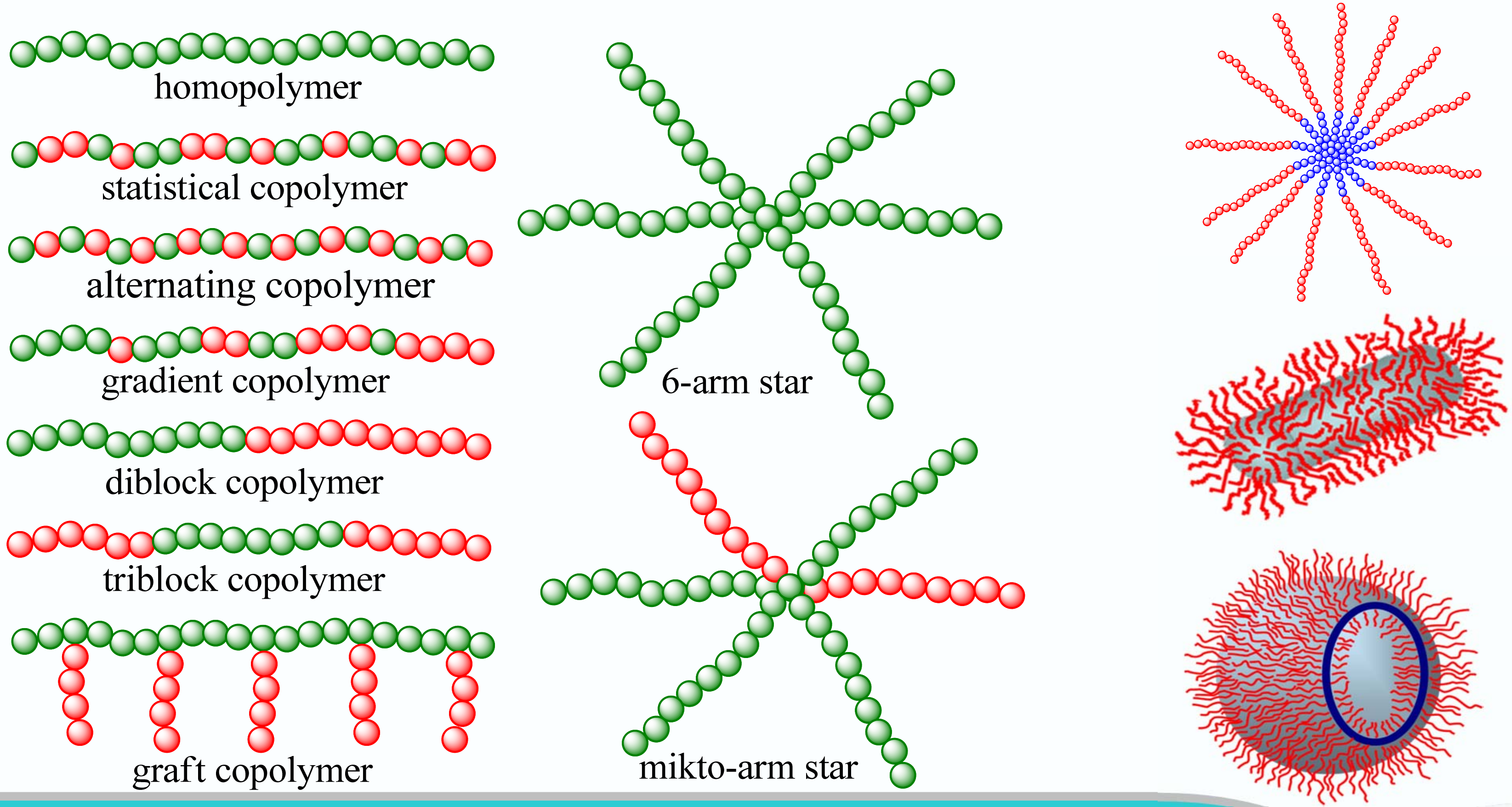
poly(MAM)-*block*-poly(LAM)



J Am Chem Soc **2009**, *131*, 6914-15
Macromolecules **2009**, *42*, 9384-6

RAFT Architectures

A wide range or architectures can be formed by choice of RAFT agent and sequence of monomer additions or by self assembly or …



RAFT Polymerization 2011-2014

Rate of publication on RAFT continues unabated

- >1/3 of publications on RAFT have appeared during 2011-2014. Includes 2500 new journal papers and 350 patents (Scifinder™)

Continued focus on applications

- Biomedical
- Industrial
- Energy

Developments in kinetics, mechanism, new RAFT agents, end group transformation

Commercial availability of RAFT Agents

Polymer therapeutics, biopolymer conjugates, functional particles, delivery, targeting

Functional surfaces

Sequence control

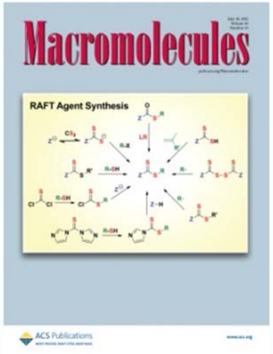
- Precision synthesis
- Multiblock copolymers

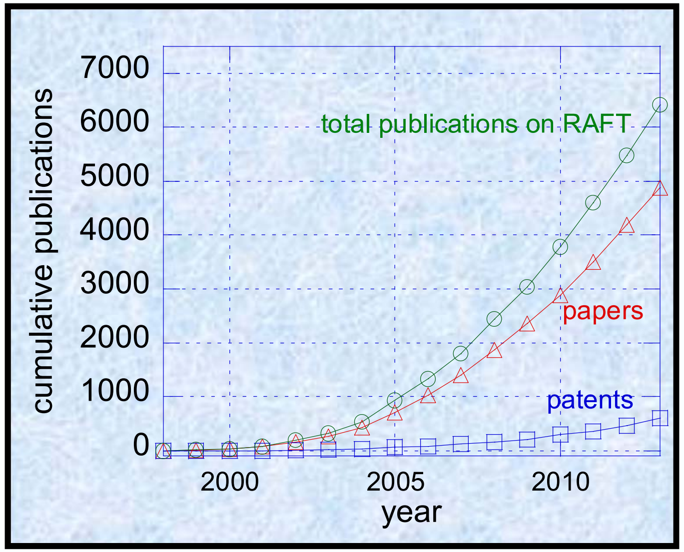
RAFT Crosslinking Polymerization

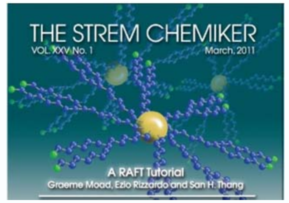
- Porous functional monoliths
- Mikto-arm copolymers

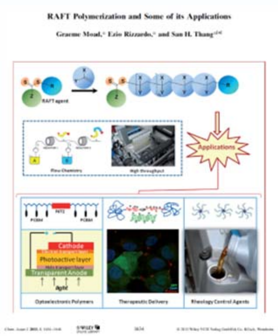
High Throughput RAFT polymerization

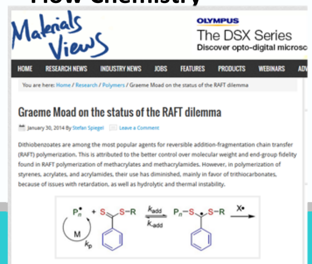
- Automated parallel synthesis
- Flow Chemistry

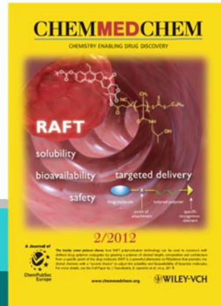


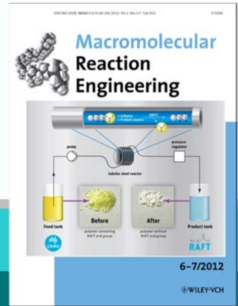


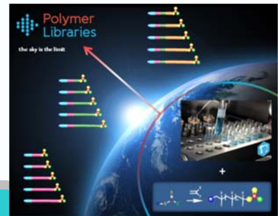












RAFT Polymerization 2011-2014

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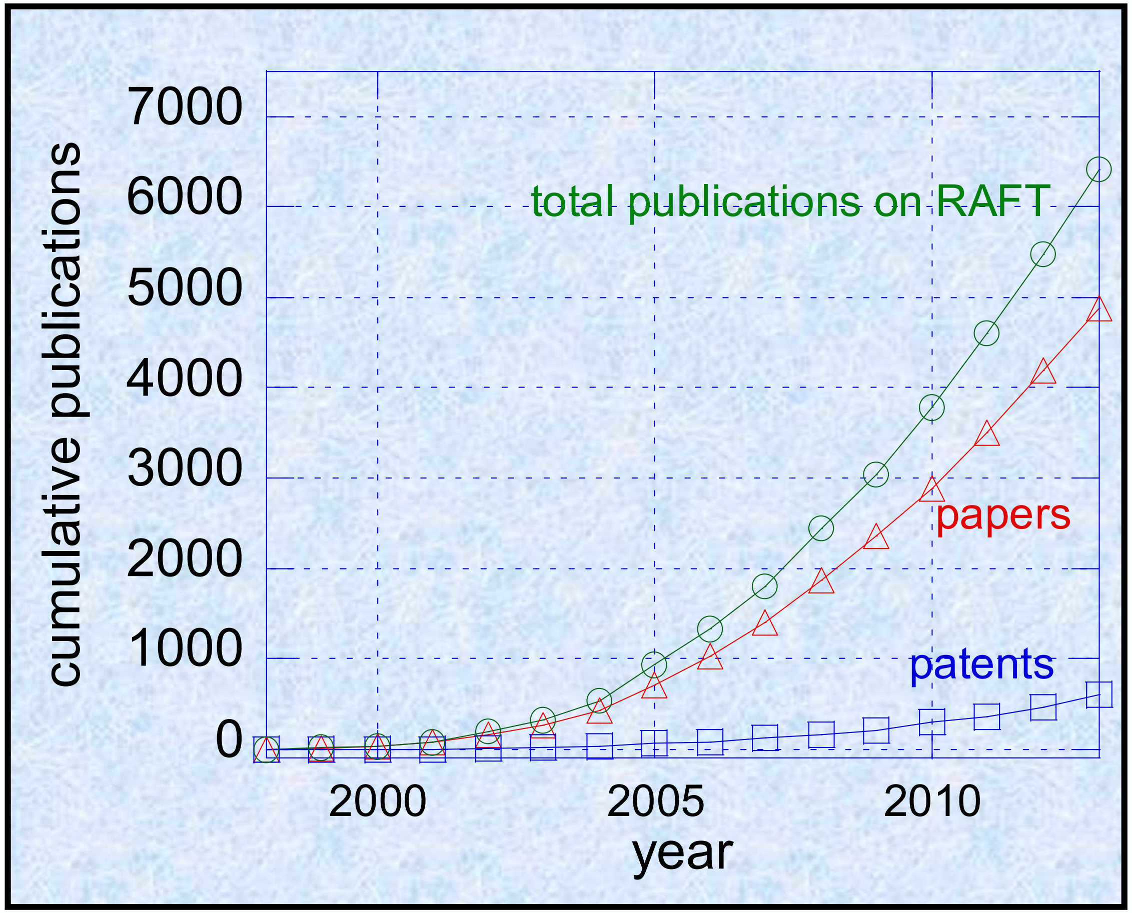
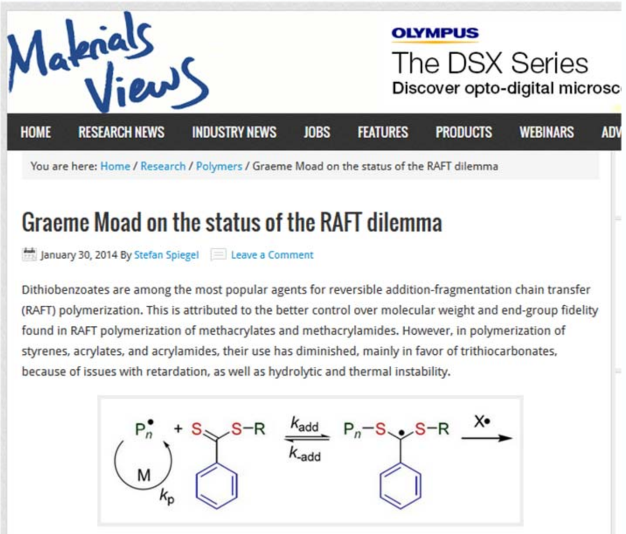
- **2500 new journal papers**
- **350 patents**

(Scifinder^{TM})



RAFT Polymerization 2011-2014

Developments in kinetics, mechanism, new RAFT agents, end-group transformation



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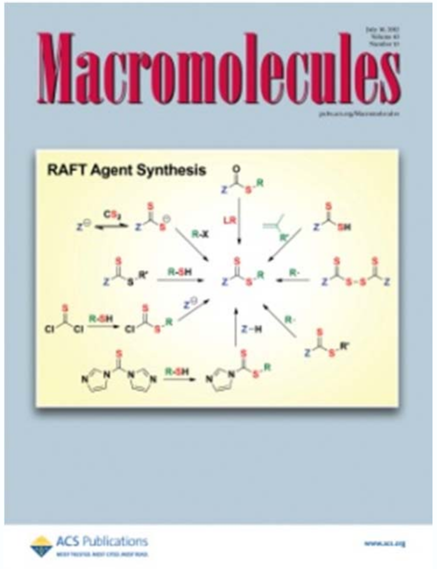
Graeme Moad on the status of the RAFT dilemma

January 30, 2014 By Stefan Spiegel Leave a Comment

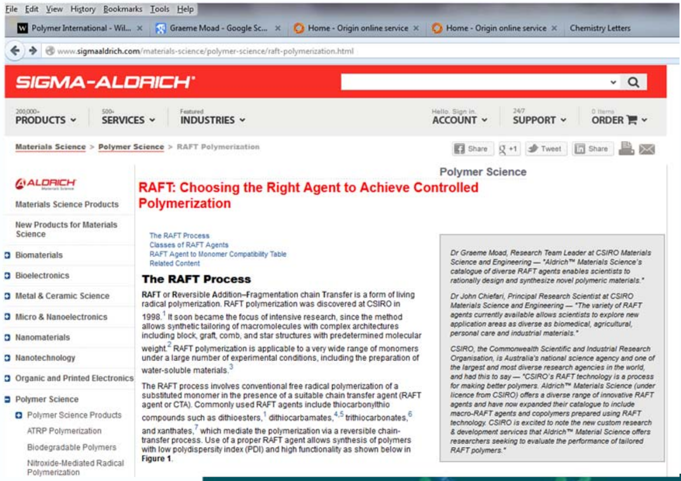
Dithiobenzoates are among the most popular agents for reversible addition-fragmentation chain transfer (RAFT) polymerization. This is attributed to the better control over molecular weight and end-group fidelity found in RAFT polymerization of methacrylates and methacrylamides. However, in polymerization of styrenes, acrylates, and acrylamides, their use has diminished, mainly in favor of trithiocarbonates, because of issues with retardation, as well as hydrolytic and thermal instability.

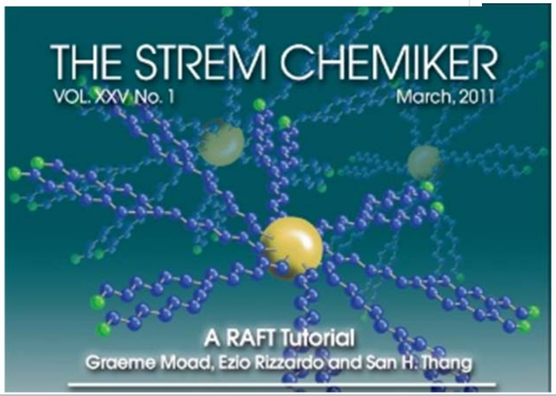


RAFT Polymerization 2011-2014

Commercial availability of RAFT Agents

Research Quantities

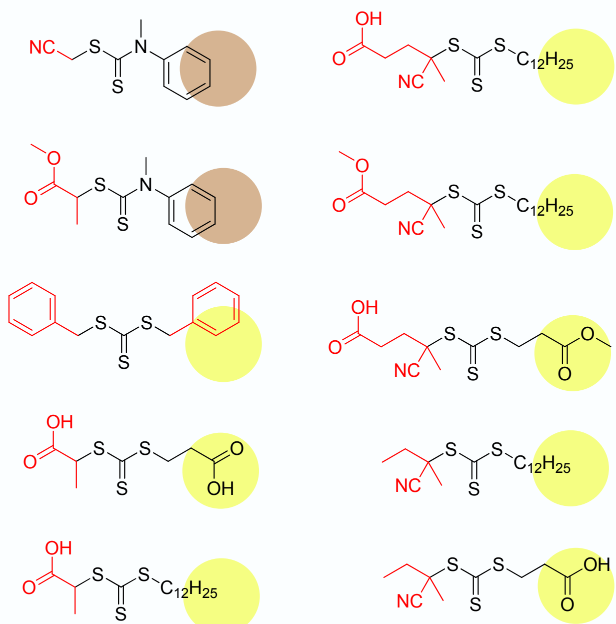




Commercial Quantities

BORON MOLECULAR

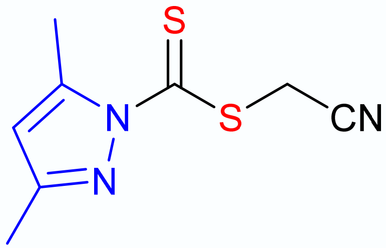
Product Catalogue:

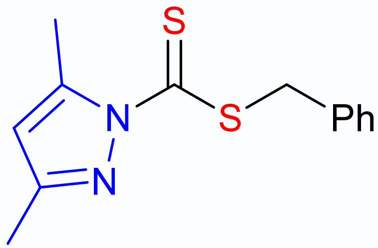


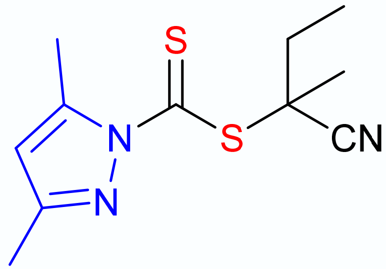
http://www.boronmolecular.com/Products/Raft-Agents

CSIRO

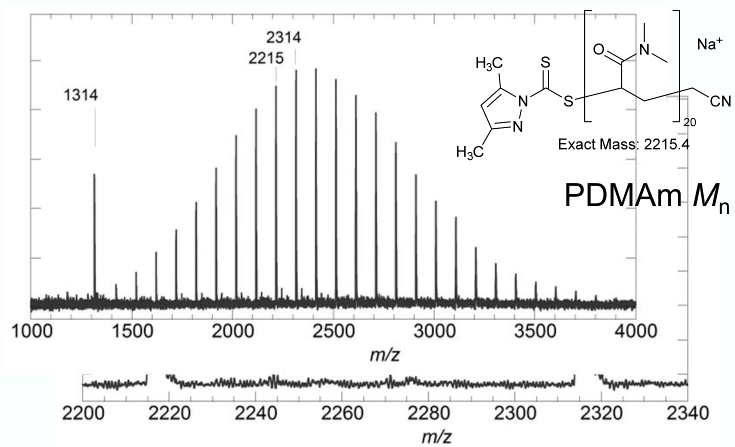
Dithiocarbamate RAFT agents with broad applicability – the 3,5-Dimethyl-1*H*-pyrazole-1-carbodithioates

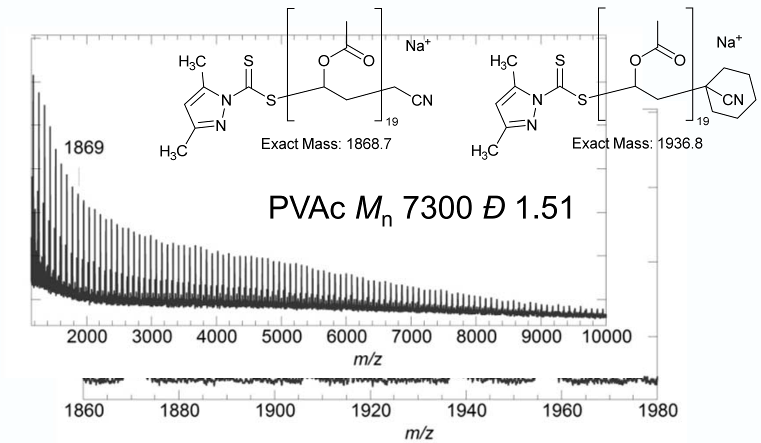






- Readily synthesized (commercially available)
- Similar activity to trithiocarbonates with acrylates, acrylamides
- Good control over vinyl acetate (though some retardation)



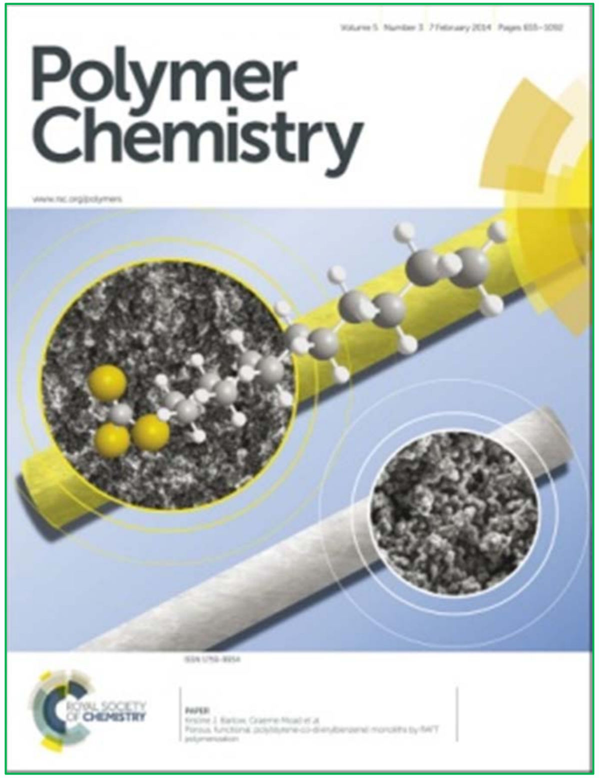


Gardiner et al.. *Polym. Chem.* ***2015***, doi: 10.1039/C5PY01382H.

RAFT Polymerization 2011-2014

RAFT Crosslinking Polymerization

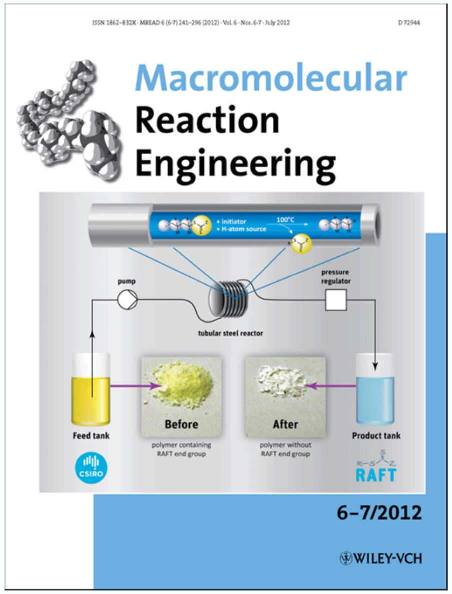
- Porous functional monoliths
- Mikto-arm copolymers

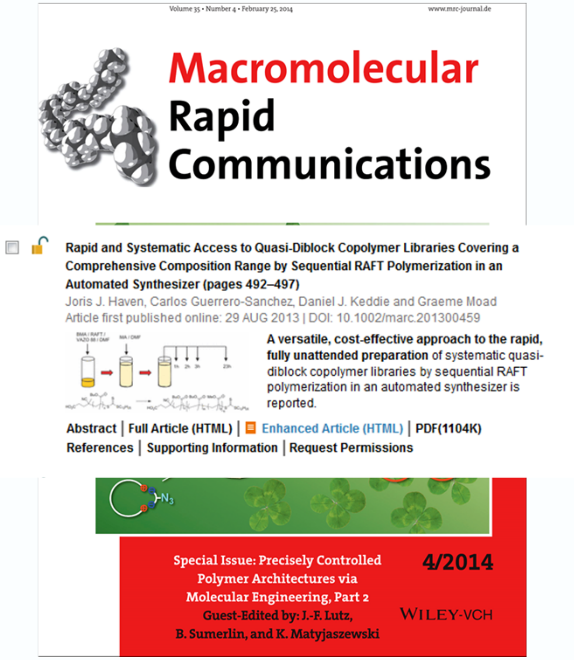


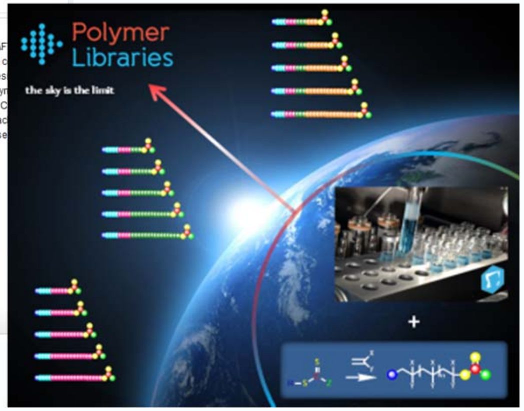
RAFT Polymerization 2011-2014

High Throughput RAFT polymerization

- Automated parallel synthesis
- Flow Chemistry







Continuous Flow Processing at CSIRO

Vapourtec - R2/R4 system

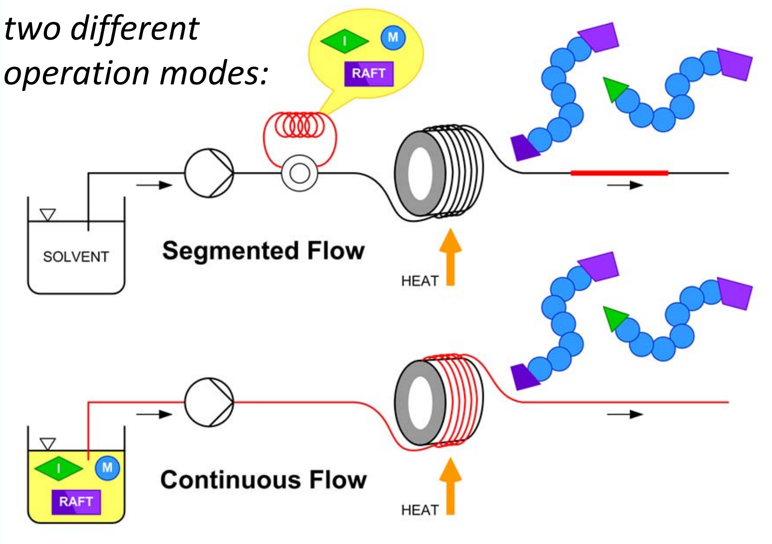
Flow Chemistry techniques enable efficient scale up to access larger quantities of materials

Applying to RAFT technology

- Access RAFT agents
- Polymer synthesis

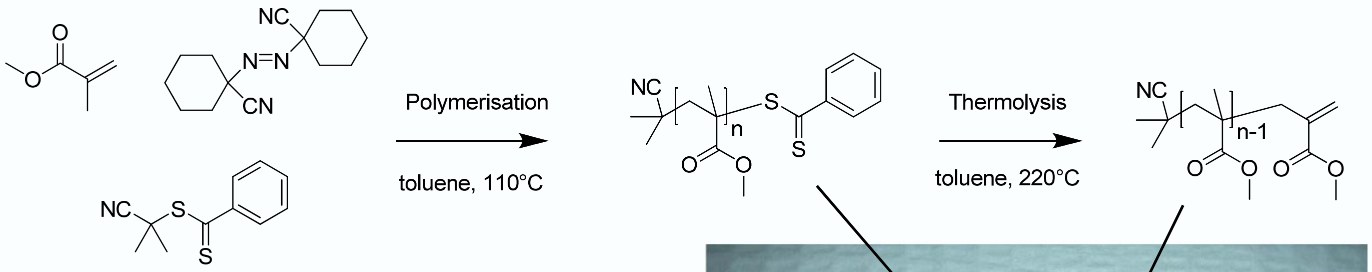
tubular reactor units:

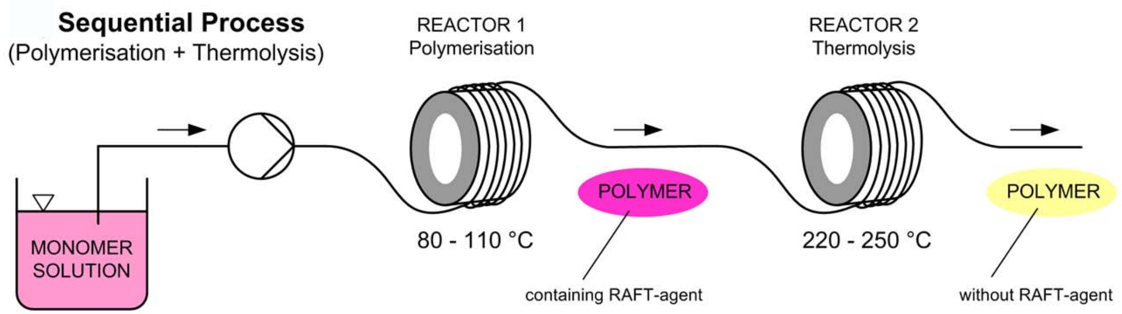
two different operation modes:

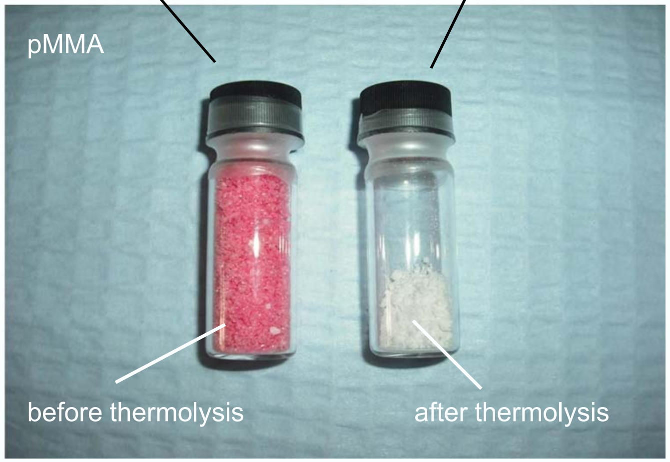


Flow Thermolysis – Two Step Process

Reaction conditions:
SS reactor coil – 10 ml
Reaction time: 60 min
Reaction temperature: 220 – 250 °C





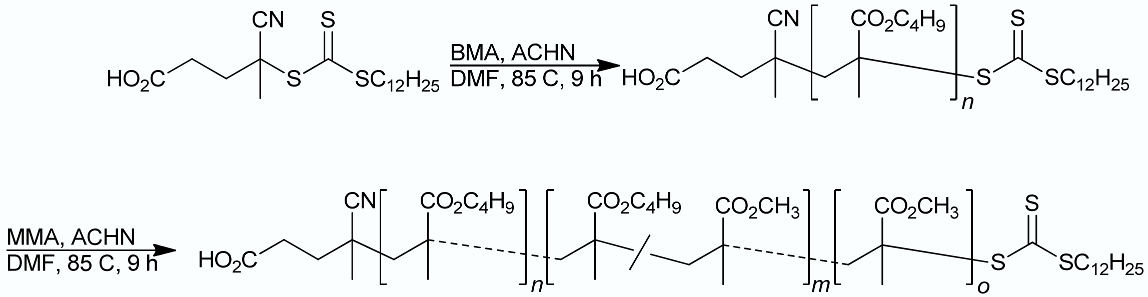


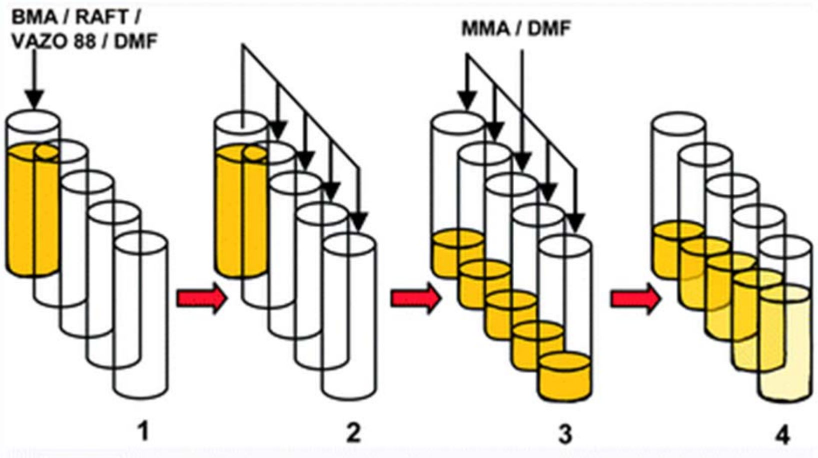
polymer	reactor 1 (polymerisation)	reactor 2 (thermolysis)	molar ratio M/R/I	T [°C]	t [h]	conversion [%]	M_n [g/mol]	Đ [-]
pMA	10 ml	5 ml	100/1.2/0.3	110 / 230	2 / 1	**97** / **85**	7700	1.29
pMA	batch	batch	100/1.2/0.3	110 / 230	2 / 1	**97** / **64**	9200	1.33
pMMA	10 ml	5 ml	100/1.2/0.4	100 / 220	2 / 1	**46** / **~100**	7500	1.19
pMMA	10 ml	5 ml	100/1.2/0.4	110 / 220	2 / 1	**59** / **~100**	7300	1.15
pMMA	2 × 10 ml	5 ml	100/1.2/0.4	110 / 220	4 / 1	**84** / **~100**	8700	1.17

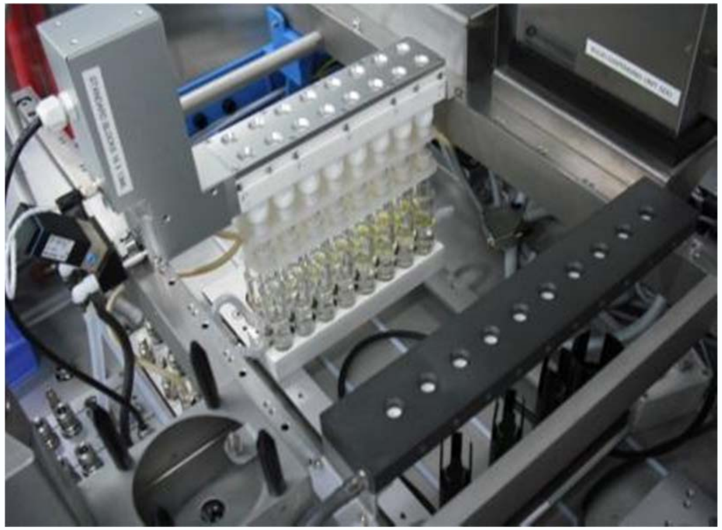
polymerisation   thermolysis

High-Throughput RAFT

Protocol for performing high-throughput RAFT Polymerization have been developed using the Chemspeed™ platform

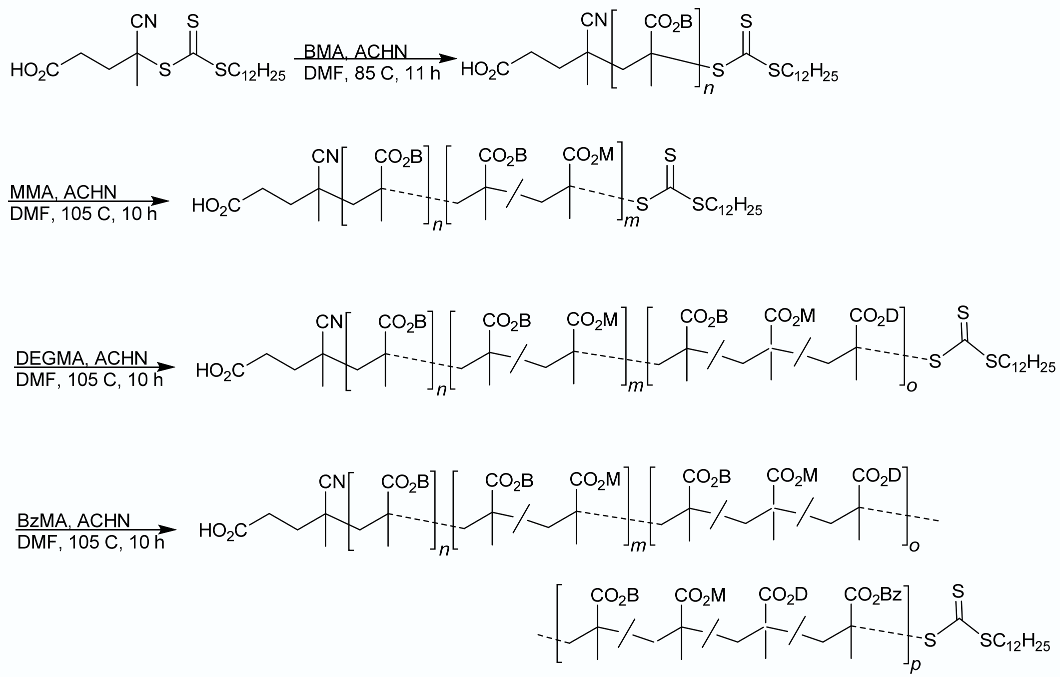




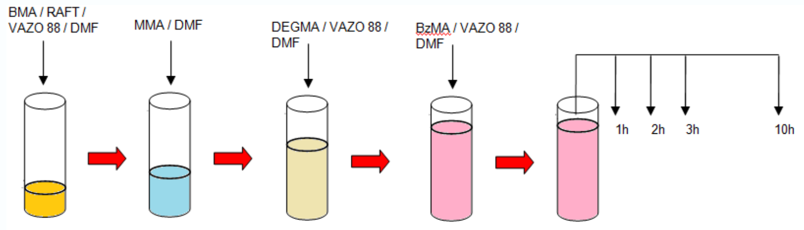


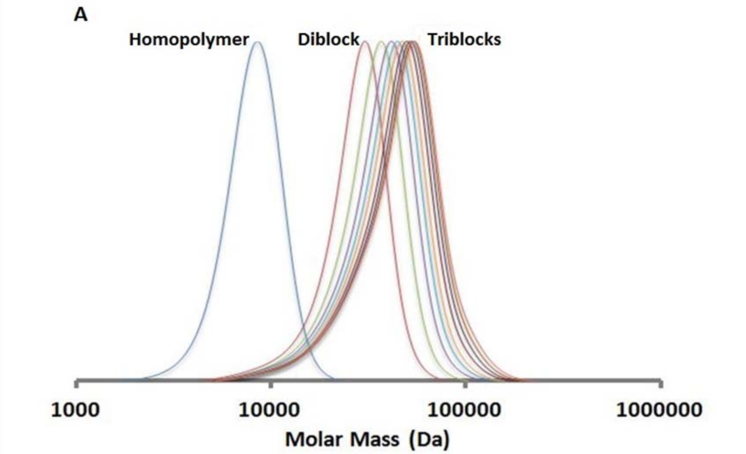
High-Throughput RAFT

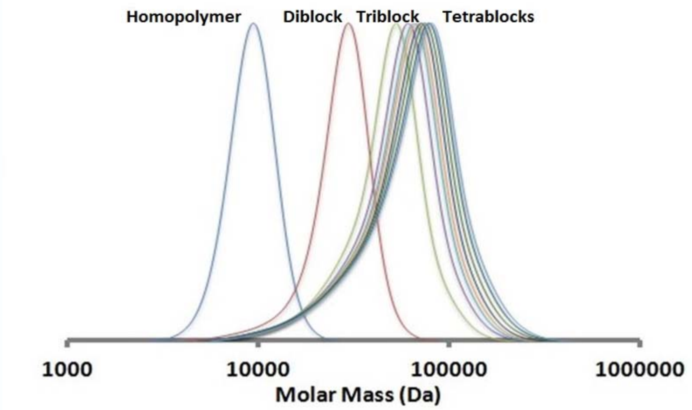
Protocol for performing high-throughput RAFT Polymerization have been developed using the Chemspeed™ platform



PDEGMA-*qb*-PMMA-*qb*-PDEGMA-*qb*-PBzMA



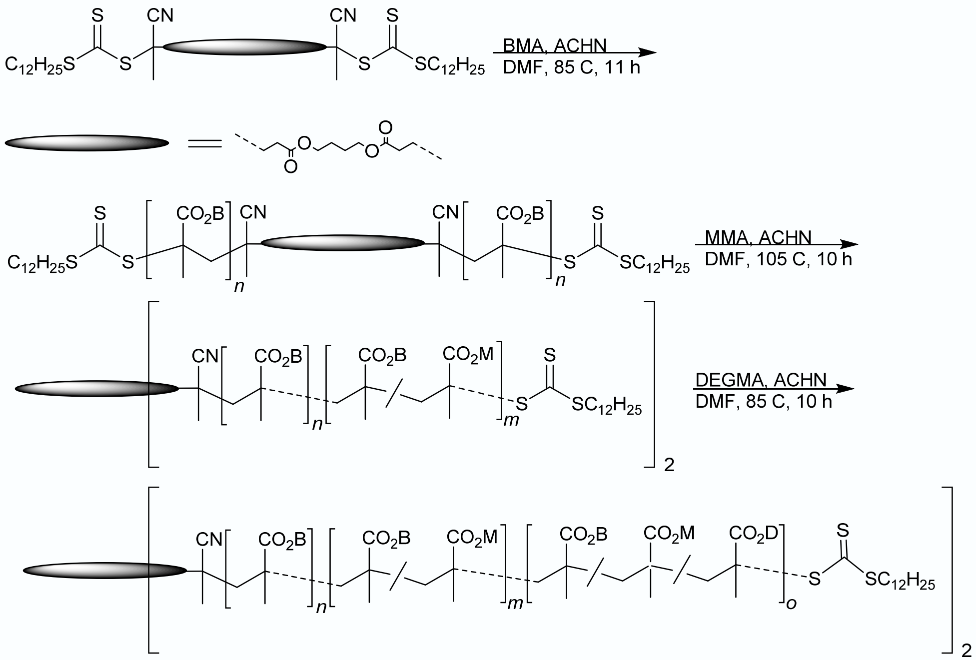


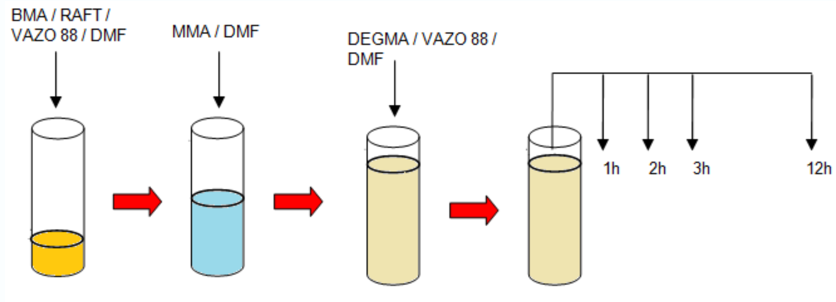


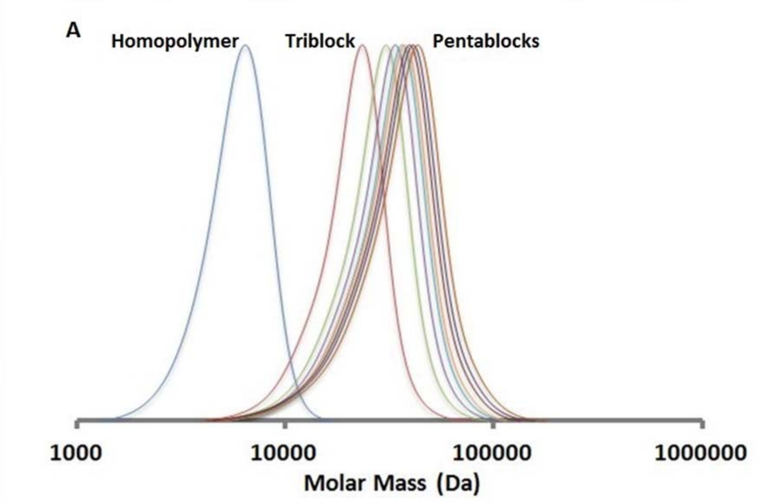
Haven et al. RAFT *Polym. Chem.* **2014,** *doi: 10.1039/C4PY00496E*

High-Throughput RAFT – multiblock synthesis

Protocol for performing high-throughput RAFT Polymerization have been developed using the Chemspeed™ platform







PDEGMA-*qb*-PMMA-*qb*-PBMA-*qb*-PMMA-*qb*-PDEGMA

RAFT:
a process for making better polymers

There are commercial applications in a wide range of industrial and consumer products including polymers for:

- drug delivery
- biomaterials
- personal care
- agrichemicals
- industrial lubricants
- adhesives and dispersants
- paints
- electronics

RAFT Polymerization 2011-2014

Continued focus on applications

- Biomedical
- Industrial
- Energy

REVIEW www.rsc.org/polymers | Polymer Chemistry

Functional polymers for optoelectronic applications by RAFT polymerization

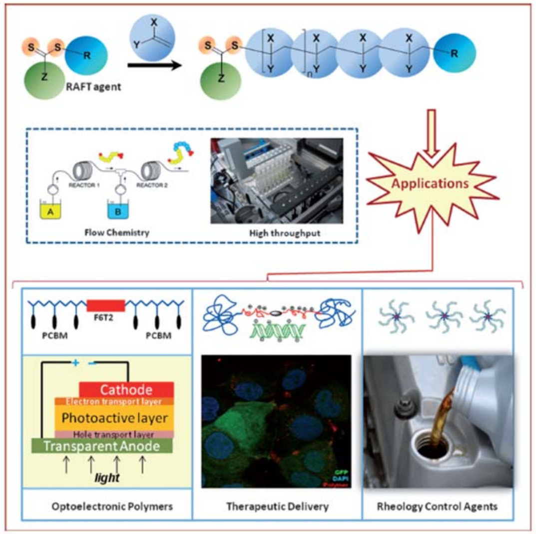
Graeme Moad,* Ming Chen, Matthias Häussler, Almar Postma, Ezio Rizzardo and San H. Thang

Received 11th June 2010, Accepted 13th July 2010
DOI: 10.1039/c0py00179a

This review focuses on the approaches to the synthesis of functional polymers for optoelectronic applications that make use of radical polymerization with reversible addition–fragmentation chain transfer (RAFT) polymerization. Optoelectronic applications include hole/electron transport in photovoltaics (OPVs), light emitting diodes (OLEDs and PLEDs), thin-film transistors (TFTs), sensors, light-harvesting and related applications. In this context we consider metallopolymers (polymers that incorporate a metal or possess metal ligating functionality as a pendant group to the backbone, as an end-group or as a connecting group), organic semiconductors (polymers with an organic semiconductor moiety either as a block or as a pendant group), and various surfaces, nanoparticles and quantum dots that are formed by RAFT polymerization or where a RAFT-synthesized polymer forms an integral part of the process or structure.

RAFT Polymerization and Some of its Applications

Graeme Moad,* Ezio Rizzardo,* and San H. Thang*[a]



Chem. Asian J. 2013, 8, 1634–1644 WILEY ONLINE LIBRARY 1634

Organic & Biomolecular Chemistry
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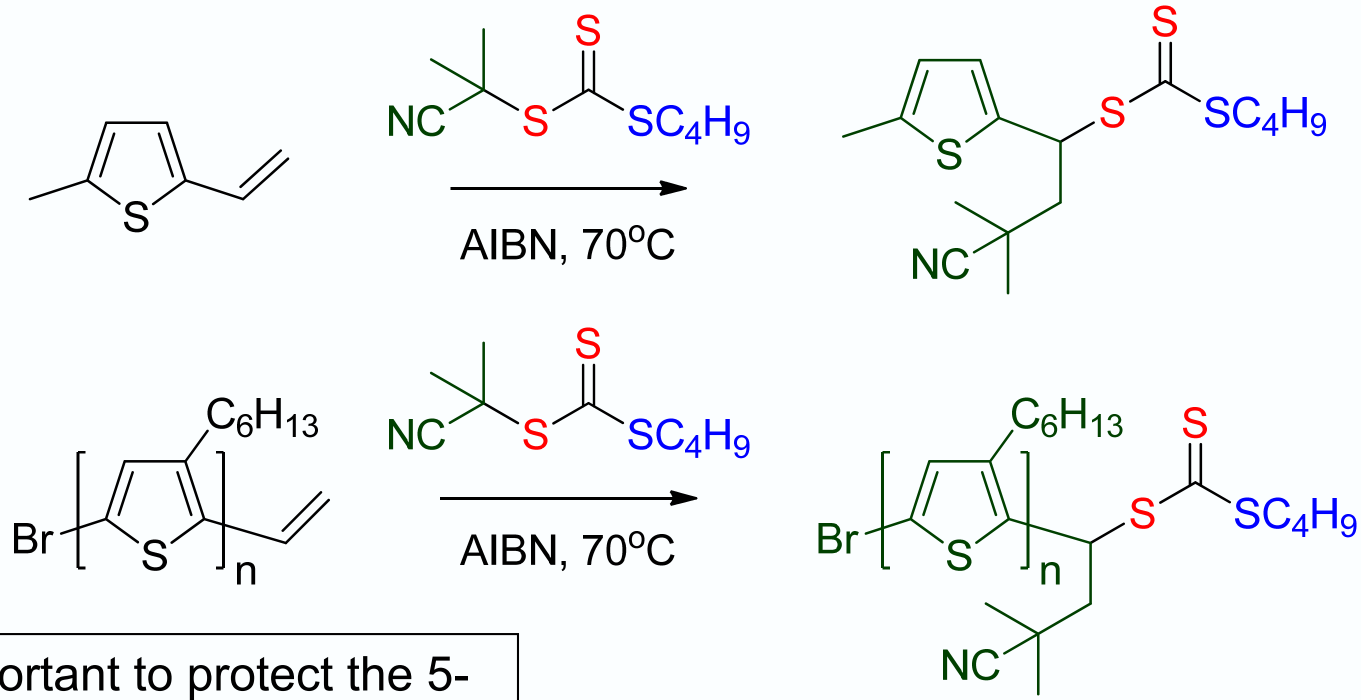
Cite this: Org. Biomol. Chem., 2011, 9, 6111
www.rsc.org/obc PAPER

Block copolymers containing organic semiconductor segments by RAFT polymerization†‡

Ming Chen,* Matthias Häussler,* Graeme Moad* and Ezio Rizzardo

Received 21st February 2011, Accepted 9th June 2011
DOI: 10.1039/c1ob05276d

Polythiophene based Macro-RAFT Agents



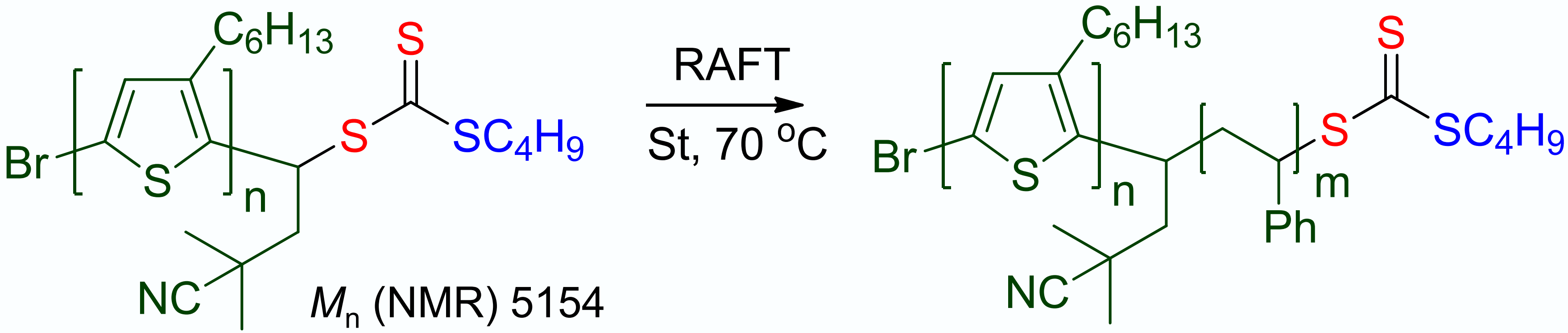
Important to protect the 5-position of the thiophene ring to avoid side reactions

Chen, M.; Haeussler, M.; Moad, G.; Rizzardo, E., Block Polymers Containing Organic Semiconductor Segments by RAFT Polymerization. *Org. Biomolecular Chem.* **2011,** *9*, 6111-6119.

CSIRO

Poly(3-hexylthiophene)-*block*-polystyrene

Bulk styrene polymerization at 70 ºC

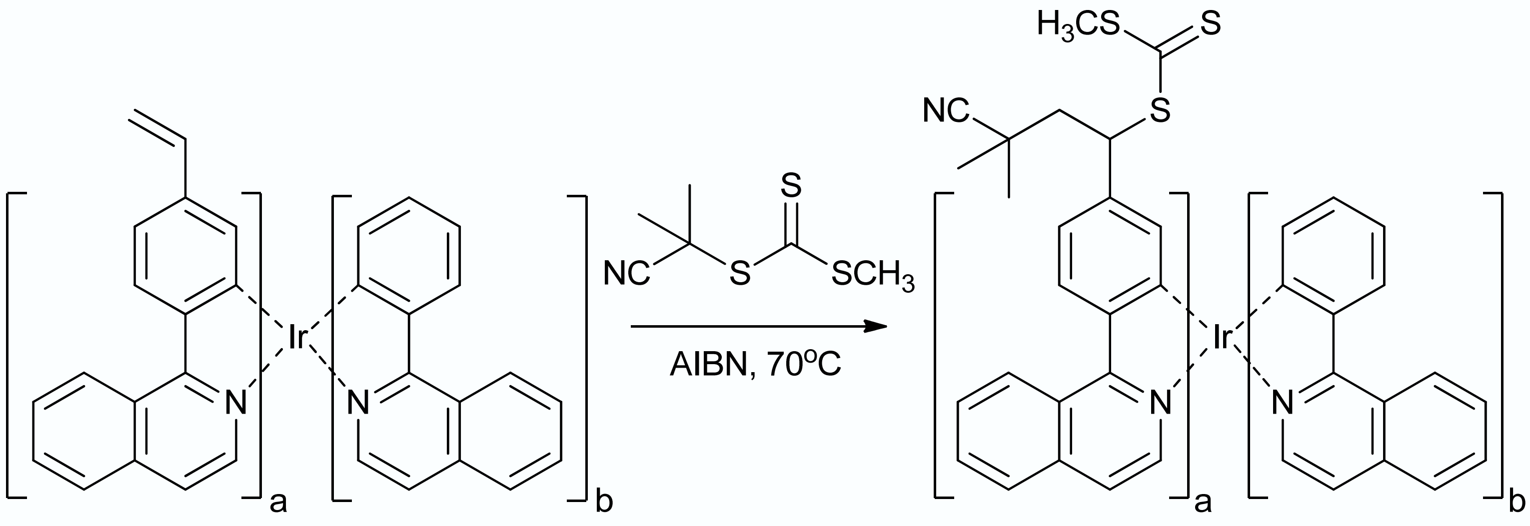


M_n (NMR) 5154

mole ratio					GPC	
Styrene	Macro-RAFT	AIBN	Time (h)	Conv. (%)	M_n	M_w/M_n
2000	4	1	20	57	86600	**1.12**

Chen, M.; Haeussler, M.; Moad, G.; Rizzardo, E., Block Polymers Containing Organic Semiconductor Segments by RAFT Polymerization. *Org. Biomolecular Chem.* **2011,** *9*, 6111-6119.

Polymer Light-Emitting Diodes (PLEDS)



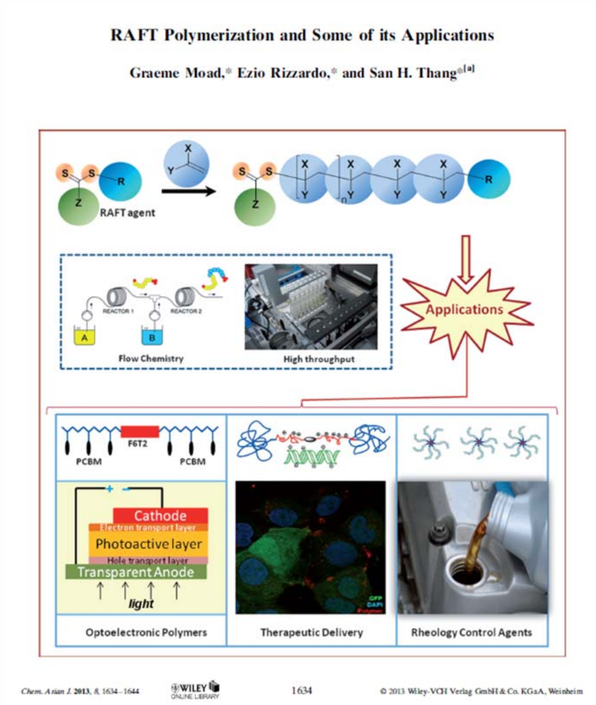
Macro-RAFT agent synthesis from iridium complex by single unit monomer insertion. Examples prepared with a=1,2,3; b=2,1,0. Used in mediating RAFT polymerization of “host monomer“.

R. Adhikari et al. *J Inst Image Inform Televis Eng* **2012**, *66*, 370-376

RAFT Polymerization 2011-2014

Continued focus on applications

- Biomedical
- Industrial
- Energy


RAFT Polymerization and Some of its Applications

Graeme Moad,* Ezio Rizzardo,* and San H. Thang*[a]

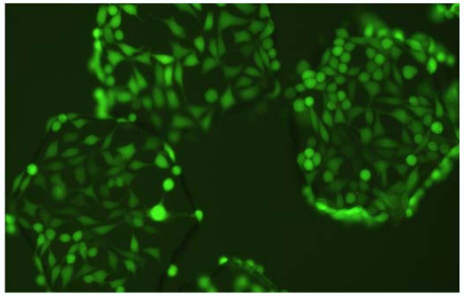
Chem. Asian J. 2013, 8, 1634–1644 1634

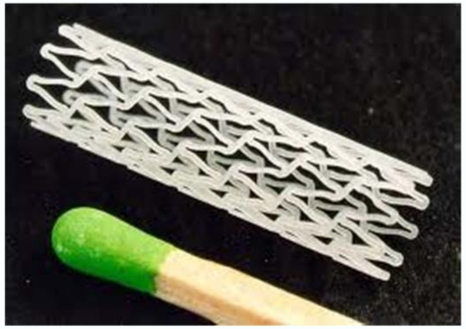
RAFT Biomaterials

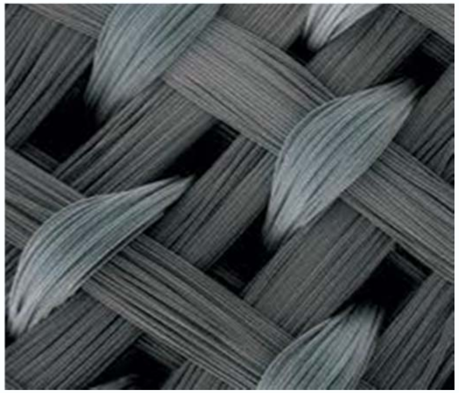
- Synthetic surface coatings on materials for large scale production of cells
  - Increased safety (no transmission of disease)
  - Reduced costs (synthetic materials)

- Coating of biomedical devices
  - Anti-infection coatings
  - Reduction of rejection by the body i.e. “foreign body response”
  - Integration of devices into tissue

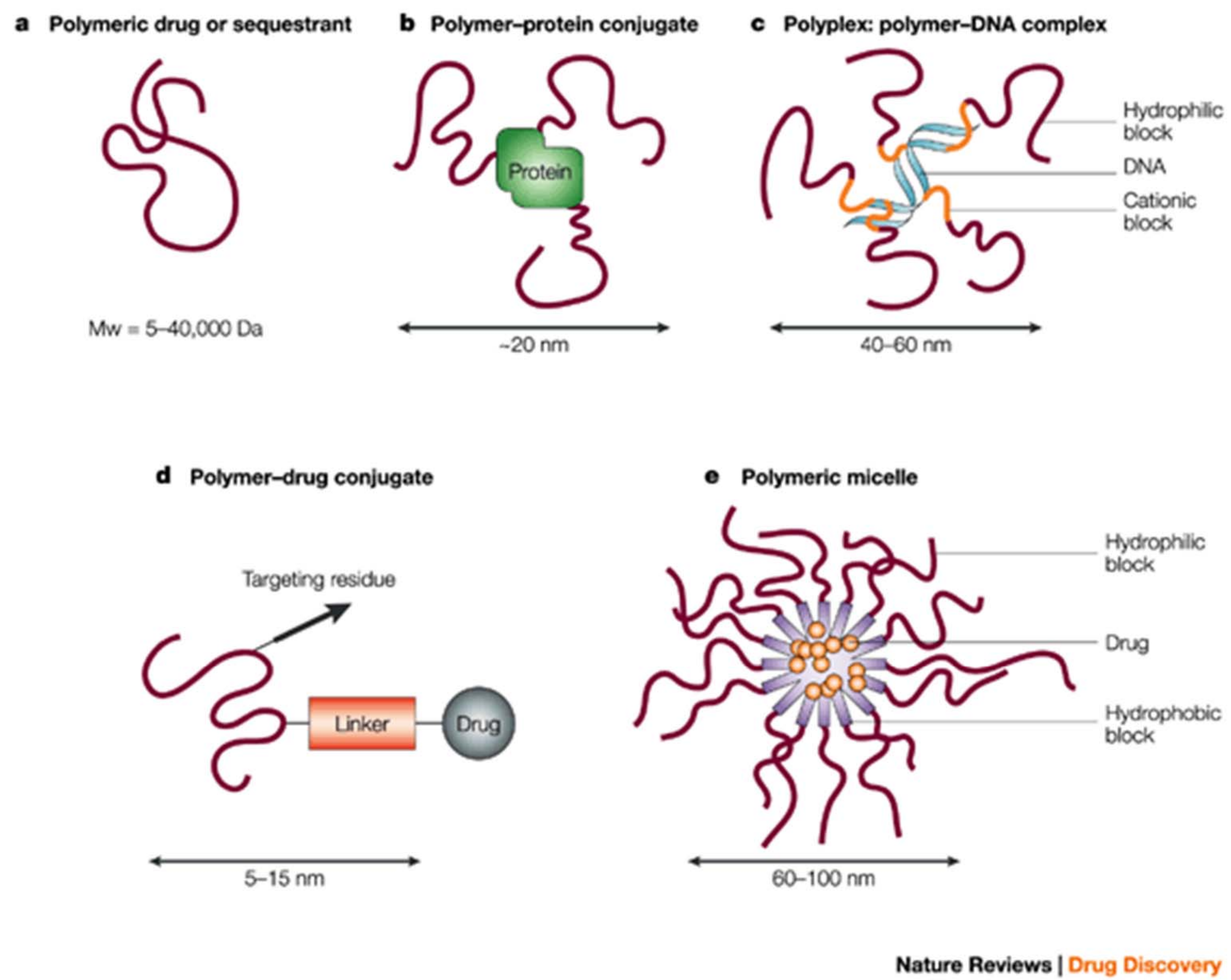
- Coatings on tissue engineering scaffolds
  - Synthetic coatings on scaffold materials e.g. textile meshes for hernia repair







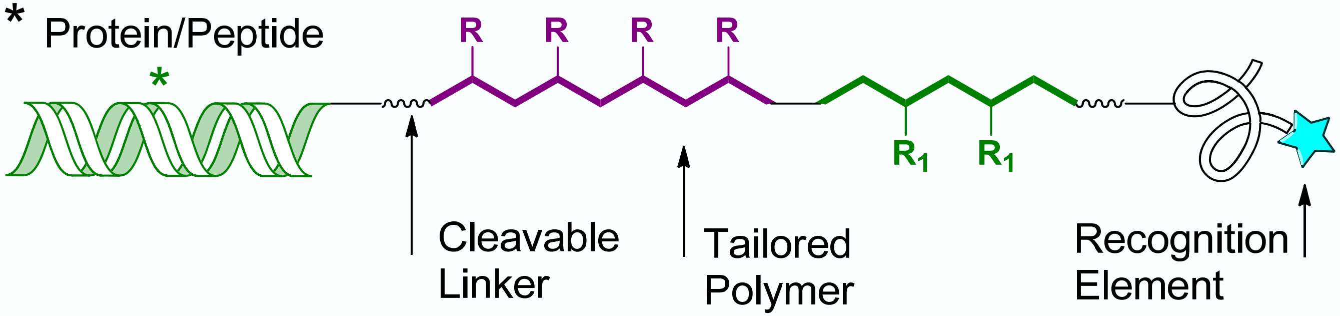
Polymer Therapeutics

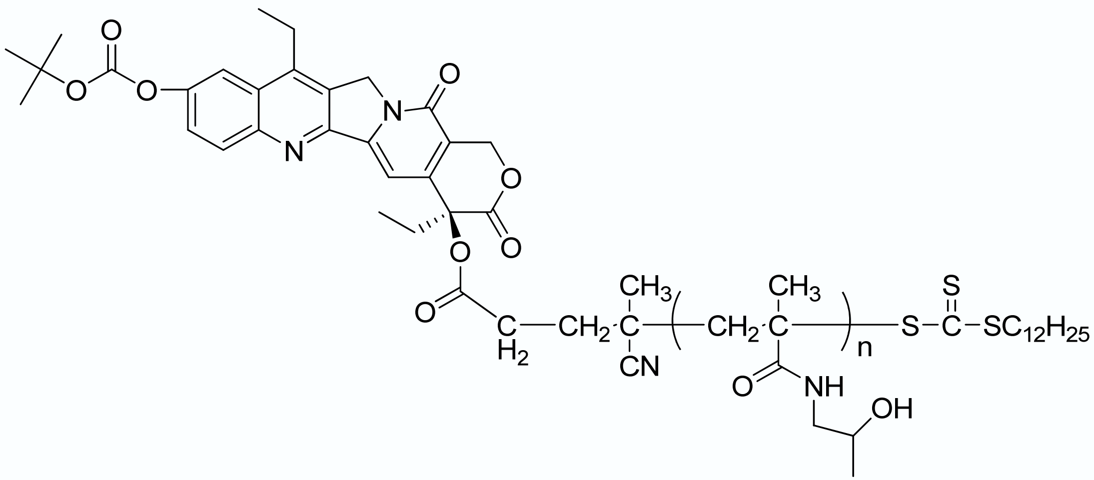


R. Duncan, 2003

RAFT Biopolymer Conjugates

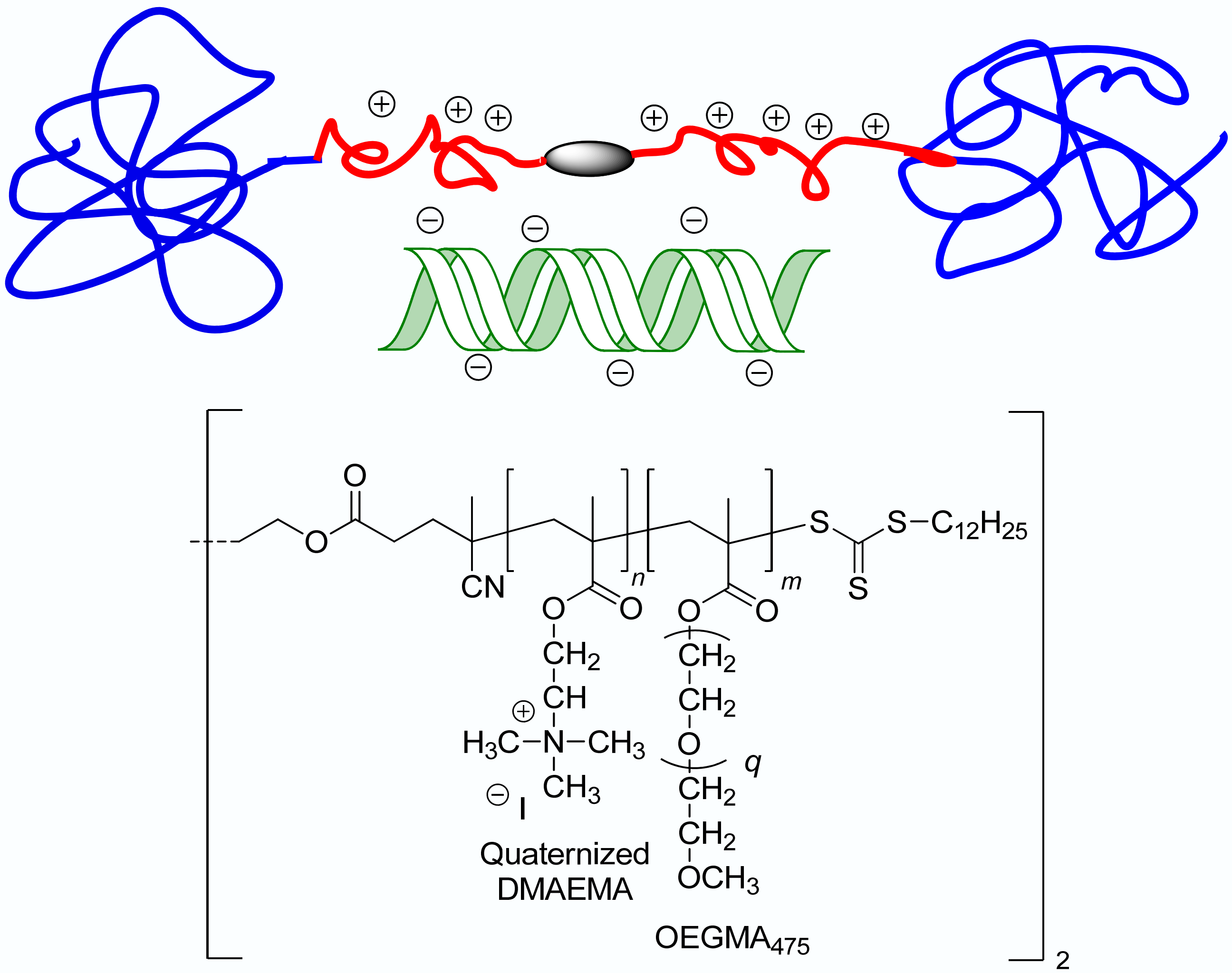
- * Small molecule
- * RNA
- * Protein/Peptide





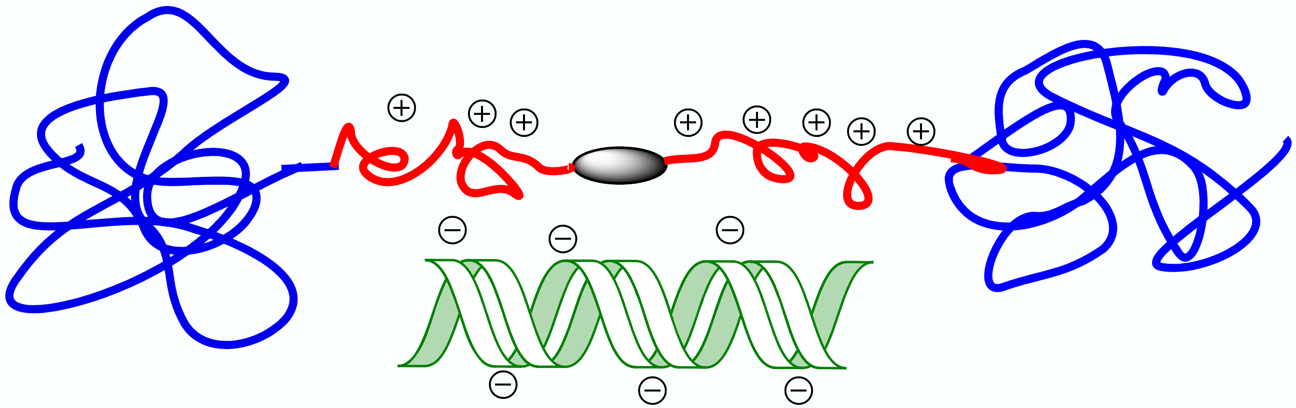
Williams et al. *ChemMedChem* **2012**, *7 (2)*, 281-291.

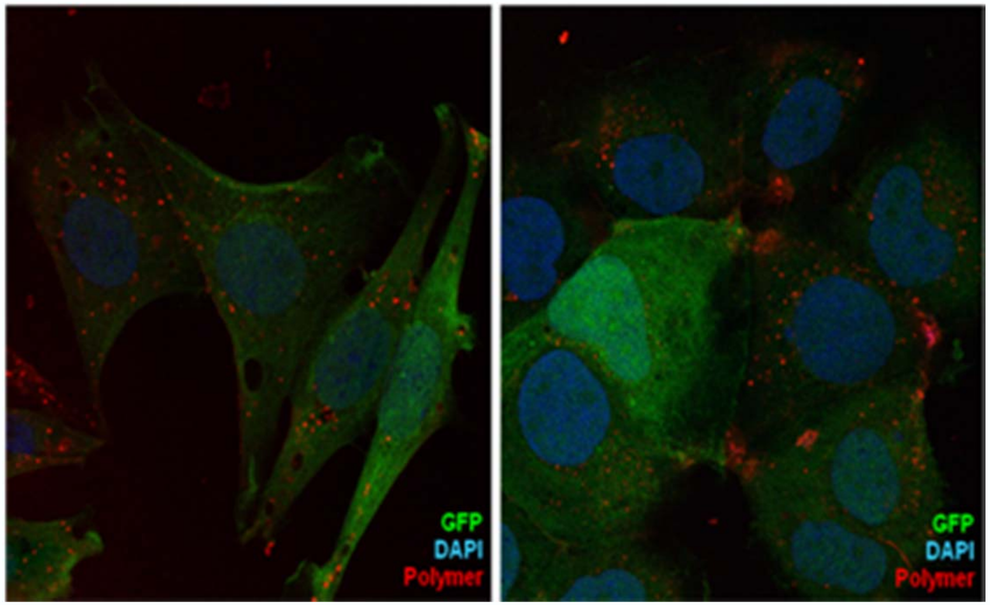
RAFT for siRNA Delivery

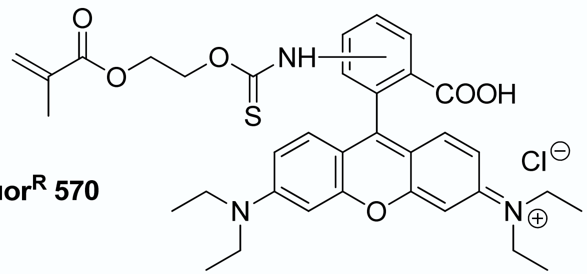


Hinton et al. *Biomaterials* **2012,** *33 (30),* 7631-7642.

RAFT for siRNA Delivery







PolyFluor[R] 570

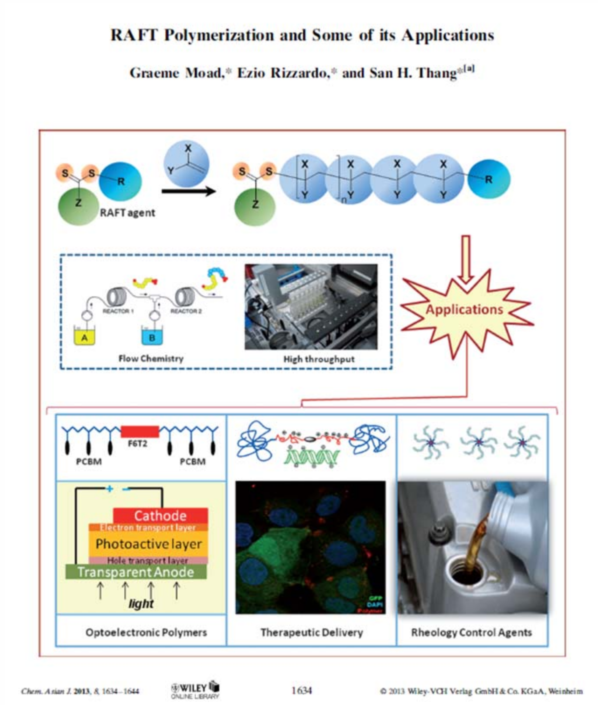
Confocal scanning microscopy images demonstrating cellular uptake of red fluorescent RAFT polymer-siRNA complex incorporating PolyFluor® 570

Hinton et al. *Biomaterials* **2012,** *33 (30),* 7631-7642.

RAFT Polymerization 2011-2014

Continued focus on applications

- Biomedical
- Industrial
- Energy

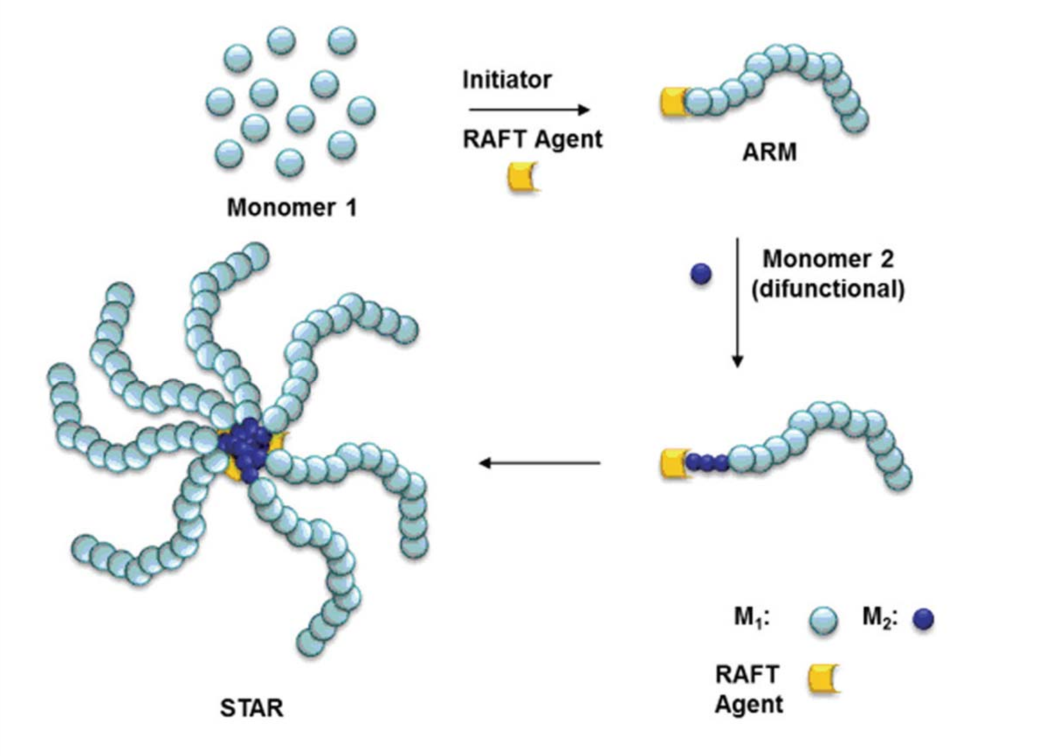

RAFT Polymerization and Some of its Applications

Graeme Moad,* Ezio Rizzardo,* and San H. Thang*[a]

Chem. Asian J. 2013, 8, 1634–1644 WILEY ONLINE LIBRARY 1634 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Lubrizol's Asteric™ PMA Viscosity Modifiers

Lubrizol

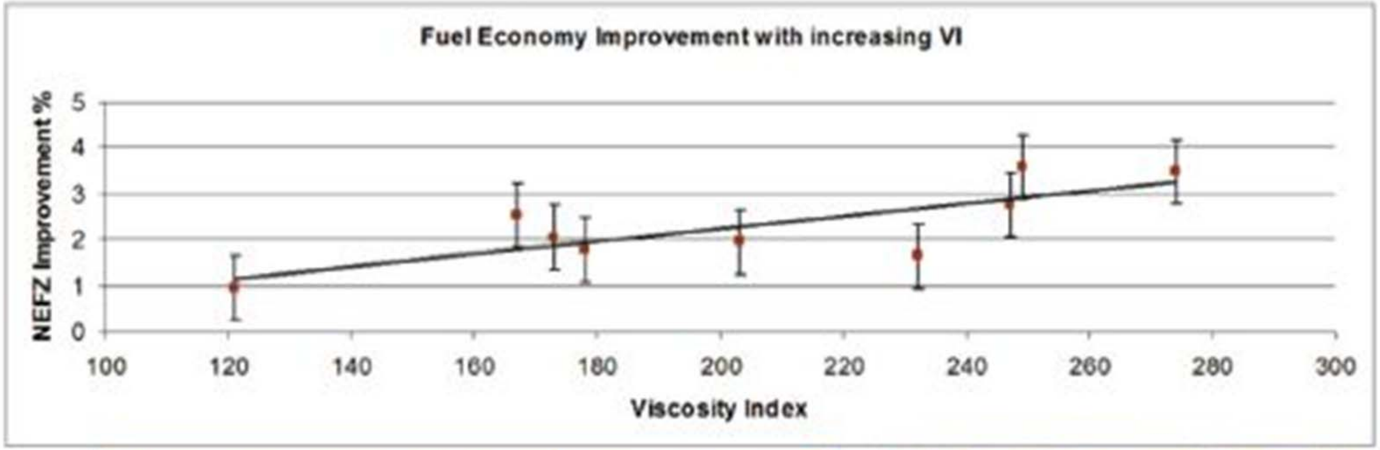


- Next generation of fuel and energy efficient lubricants
  - Lower viscosity at cold temperatures
    - Higher viscosity index

CSIRO

Fuel Economy Improvement

Lubrizol



European drive cycle testing showed a linkage between increased viscosity index and greater vehicle fuel economy

Figure 3. Higher VI linkage to improved fuel efficiency.

Low Fouling Desalination Membranes

Antimicrobial testing (*Staphylococcus epidermidis)*

Control

With polymer brush

Reversible Addition Fragmentation Chain Transfer

RAFT

RAFT Polymerization

Some Applications

Conclusions and Outlook

Take Home Messages

RAFT Polymerization can provide a multitude of polymers of varying size, shape and composition

Polymer chemists in collaboration with biologists, physicists, material scientists and others are developing a vast range of very exciting (many potential, some actual) products

Multidisciplinary teams are essential for success and so there is a need to collaborate

Acknowledgments

RAFT Team 2011-2015

Kristine Barlow
Erika Bicciocchi
Carl Braybrook
Ming Chen
John Chiefari
James Gardiner
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Xiaojuan Hao
Joris Haven
Matthew Hendrikx
Tim Hughes
Tracey Hinton
Christian Hornung
Shadi Houshyar
Oliver Hutt
Daniel Keddie
Guoxin Li
Stuart Littler
Ivan Martinez-Botella
Roger Mulder
Tash Polyzos
Almar Postma
Ezio Rizzardo
Julien Rosselgong
Simon Saubern
San Thang
John Tsanaktsidis
Kathleen Turner
XiaoHu Wei
Charlotte Williams

Thank you

CSIRO Manufacturing Flagship
Graeme Moad

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