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Cite this: *Chem. Commun.*, 2012, **48**, 3085–3087

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COMMUNICATION

Single cyclized molecule structures from RAFT homopolymerization of multi-vinyl monomers†

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Received 12th December 2011, Accepted 2nd February 2012
DOI: 10.1039/c2cc17780c

We explore a kinetically controlled strategy to suppress the gelation in the homopolymerization of multi-vinyl monomers (MVMs) *via* RAFT polymerization. We report the generation of 3D single cyclized polymer structures from the RAFT process, which significantly contradicts the classic F–S theory. This approach enables synthesis of a new generation of nanosize macromolecular architectures.

Classical theory has long stated that the polymerizations of multi-vinyl monomers (MVM) inevitably lead to insoluble crosslinked materials, as defined by P. Flory and W. Stockmayer (classical F–S theory) 70 years ago, and has since been numerously observed experimentally.[1,2] Put simply, the gelation process of MVMs during addition polymerisations such as free radical polymerization (FRP) in the F–S theory occurs through the growth and combination of linear polymer chains, which results in crosslinked structures. In recent decades, the introduction of living polymerizations[3] and controlled/living radical polymerizations (CRP), including atom transfer radical polymerization (ATRP),[4] reversible addition fragmentation chain transfer (RAFT)[5] and nitroxide-mediated radical polymerization (NMP),[6] has led to a significant advancement in both synthetic polymer chemistry and physics. These CRPs, now considered to have formed the foundation of modern polymer nanotechnology, allow such tight control over molecular weight and molecular weight distribution that new well-defined polymer architectures and topologies can be produced.[7,8] Surprisingly, soon after CRPs were introduced for the (co)polymerisation of MVMs, some compromising data under certain reaction conditions showed critical gel points of MVMs far higher than the F–S theory predicted.[9,10]

Until recently, the majority of polymerisations involving MVMs were carried out by using a co-polymerization system containing only a low percentage of MVMs. The nitroxide-controlled free radical copolymerization of styrene with a small amount (<3 mol%) of crosslinker was studied by Ide and Fukuda, which shows that the pendant-vinyl reactivity could significantly influence the intra or intermolecular trend.[11,12] The typical examples are the experiments conducted by Armes's group[10] and Matyjaszewski's group,[13,14] which resulted in small cyclization reactions on a classically branched polymer; the homopolymerization of MVMs therefore still seemed a formidable task. However, we have developed a deactivation enhanced strategy for ATRP that efficiently delayed the point of gelation in the homopolymerization of ethylene glycol dimethacrylate (EGDMA) to over 60% monomer conversion in a concentrated polymerization system.[15] With this method, termed *in situ* deactivation enhanced ATRP (*in situ* DE-ATRP), we produced a new 3D 'Single Cyclized' molecule architecture that consisted of a single polymer chain cyclized within itself. To explain both the kinetic control over macromolecular structure and the occurrence of intramolecular reactions, we then introduced a new kinetic model to supplement the F–S theory. This seeding work has driven us to continue thinking and exploring this new kinetic model, as we believe that it can, in principle, be applied to other controlled/living polymerization mechanisms *e.g.*, RAFT, NMP, cationic, group transfer, or ligated anionic polymerization.[15,16] If the model is to stand as being universally applicable, then it must be applied to these mechanisms outside of ATRP.

In comparison to other CRP techniques, RAFT has unique advantages for applications including a wide range of potential monomers and the absence of metal and ligand compounds.[17–19] Herein, following predictions based on the kinetic control model, we demonstrate that the homopolymerization of EGDMA can be successfully accomplished *via* RAFT methods without gelation up to *ca.* 60% conversion. The generation of a single cyclized polymer chain structure from the RAFT process was indeed achieved as hypothesized by the new model (Scheme 1). We therefore highlight that internal cyclizations can no longer be ignored, and are in fact prevalent here, due to the naturally deactivation enhanced nature of RAFT polymerization. The RAFT homopolymerizations of MVMs enable the production of a new generation of polymeric materials.

At first, the comparisons between FRP and RAFT polymerization of EGDMA were conducted in toluene using two different commercially available RAFT agents: 2-cyanoprop-2-yl benzodithioate (CPBD) and 2-cyano-propyl dodecyl trithiocarbonate (CPDTC) termed RAFT1 and RAFT2 respectively. The reaction conditions are detailed in Table 1 and the results of the kinetic studies are shown in Fig. S1 in ESI.† As expected, FRP of EGDMA shows fast gelation at low yield (<10%) with high

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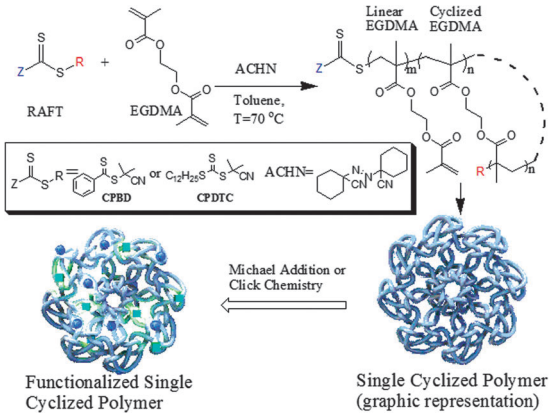
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc17780c



Scheme 1 Homopolymerization of EGDMA *via* RAFT, and subsequent formation of a 3D single cyclized chain (graphic representation).

Table 1 Polymerization conditions and molecular weight characteristics of the polyEGDMA from FRP and RAFT. Further details are given in Experimental section and Table S1 in ESI

Reaction[a]	Time/h	M_w/kDa	PDI	Conv (%)	Yield (%)	Branch ratio
FRP	0.4	140	4.4	10	6	4%
RAFT1	2	6.7	1.3	7.5	3	14%
(CPDB)	3	11.4	1.5	29	21	18.5%
	4	26.7	2.3	48.2	37	20%
	5	69.5	4.2	45	45	21%

[a] FRP [ACHN] : [EGDMA] = 0.4 : 100; RAFT1 [ACHN] : [CPDB] : [EGDMA] = 0.4 : 1 : 100, all reactions conducted at 70 °C in toluene, [EGDMA] = 1.67 M.

molecular weight (M_w) and high polydispersity (PDI) as defined by the F–S theory. However, in comparison, the two RAFT polymerizations reveal a reaction process much different from that of FRP (see ESI† Fig. S1 and S2 for RAFT1 and Fig. S3 and S4 for RAFT2) and significantly delay the onset of gelation under concentrated reaction conditions ([EGDMA] = 1.67 M or 36.6% wt), which again conflicts with the present understanding of crosslinking reactions for the polymerization of MVMs. Firstly, the time *versus* conversion plots of RAFT1 of EGDMA obtained from GPC data show an induction period which is due to the formation of intermediate radicals that is typical of RAFT polymerization.[20] After the induction period, the conversion increased with time until a much delayed onset of gelation occurred after 5.5 hours at over *ca.* 60% monomer conversion (Fig. S1A, ESI†), which is far higher than would be predicted by the F–S theory. This process occurs in two distinct phases, whereby during the first stage the polymer chains display an initial linear-like growth, *i.e.* the increase in molecular weight is linear with monomer conversion and the PDI remains low (Fig. S1B, ESI†) with unimodal molecular distribution (Fig. S1C, ESI†). This first stage differs dramatically from the molecular weight characteristics typically encountered in classical hyperbranched polymerization systems where chain combination leads to a rapid non-linear increase in M_w and PDI.[21] It appears that the combination of chains only occurs at the later stages of RAFT polymerization with a large rise in both M_w and PDI, marking the second stage of a two phase process. This phenomenon exactly matches our predication with the RAFT polymerisation of MVMs based on the new kinetic model, which demonstrates the formation of a single cyclized chain structure.

Solid evidence for the single cyclized chain structure is also found through monitoring the early reaction samples of RAFT1, pre-chain combination, *via* ^{1}H NMR (Fig. S2 in ESI†). Whilst there is a high proportion of branched EGDMA units (14–21%, see Table 1 and Eq. S1 in ESI†) even at a very early reaction stage, these are predominantly intramolecular crosslinks within a single chain. This is further deciphered through the comparison of the resonance of the protons in EGDMA units and the CPBD end group (Fig. S2 in ESI†), giving a degree of polymerization (DP_n) of 34 with a $M_{w\ by\ NMR}$ = 6.9 kDa (see Eq. S2, ESI†). Once more, this provides solid proof that each polymer chain structure is a single cyclized chain rather than a combination of multiple chains. Moreover, we have been able to exploit the large number of residual double bonds in the single cyclized chains to further functionalize the single cyclized molecules. The pendant vinyl groups can be easily modified by thiol reactants *via* Michael addition to yield functional single cyclized macromolecules which is confirmed by ^{1}H NMR (see Fig. S9 in ESI†).

To further prove these findings, a cleavable polymer *via* RAFT from an acid cleavable divinyl (ACD) monomer was designed, within which is an acetal linkage that can cleave quickly in acidic conditions (Fig. 1A).[22] We choose CPDTC as the RAFT reagent since, as previous studies show, it is ideal for acrylate-type monomers. According to the F–S theory, if the polymer is a branched structure formed from the combination of multiple chains, then it can be expected that the polymer would degrade and separate into much lower molecular weight chains as the intermolecular crosslinked points are broken. This predication was indeed demonstrated recently by Armes *et al.* with their hyperbranched polymers from the copolymerisation of MVMs *via* the 'Strathclyde synthesis' approach. However, the polymer formed at the early stages of RAFT2 of cleavable MVM (22.6% conv.), despite having a high branch ratio of 19% (see ESI† Fig. S5, Fig. S6 and Eq. S7), shows little reduction in the hydrodynamic volume and the molecular weight as determined by GPC-RI (Fig. 1B). In contrast, although it has a low branch

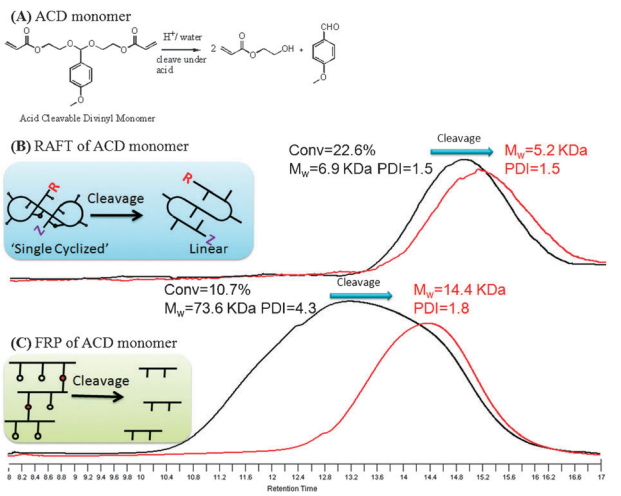


Fig. 1 (A) Cleavage reaction of acid cleavable divinyl (ACD) monomer. (B) The GPC trace before and after cleavage of ACD polymer at 22.6% conversion with RAFT proves the 'Single Cyclized' structure, since the M_w and hydrodynamic size only slightly decreased after cleavage from 6.9 kDa to 5.2 kDa, in contrast, (C) the polymer synthesized *via* FRP demonstrates a substantial reduction from 73.6 kDa to 14.4 kDa.

ratio of 6.7% (10.7% conv., M_w = 73.6 kDa, PDI = 4.3), the polymer obtained from FRP of cleavable MVM has a very different degradation profile. The high molecular weight polymer chains were degraded into small chains and the molecular weight shows a very large reduction after degradation (Fig. 1C). The degradation studies show, contrary to common understanding, that a predominantly intramolecular linked knot structure is formed by RAFT rather than a branched structure.

The newly developed kinetic model can now be used to gain a further understanding of why RAFT polymerization occurs in a two phase process and how it differs from FRP by suppressing intermolecular crosslinking. More specifically, the model predicts which reaction process (propagation, intramolecular or intermolecular crosslinking) will occur by taking into account: the growth boundary, the chain length and the chain concentration. Fig. S7 in ESI† outlines the models for both RAFT polymerization and FRP. For polymerizations with a large kinetics chain length, such as FRP (Eq. S5, ESI†), the growth boundary (dotted circle) is very large allowing all three reaction processes to occur. The propagation and intermolecular crosslinking reactions are simply higher due to statistical probability[2] regardless of chain length and concentration, thus instantly combining chains and forming an insoluble gel. The true effect of the kinetic model becomes apparent when considering RAFT polymerization. In this case the growth boundary is constricted (smaller dotted circle) because the growth of the propagating chain depends on the deactivation. The deactivation in this case is caused naturally by the propagating chain reacting with either free RAFT agents (at early stage) or with RAFT end-capped polymer chains (at later stage) when the RAFT agent is becoming exhausted (Eq. S6, ESI†). At early stages, the propagating chain only has the probability to either propagate linearly or perform intramolecular cyclization before transfer to the RAFT agent. The constant of chain transfer (k_{tr}) that is 10^2 to 10^3 times higher than the vinyl propagation (k_p) helps to eliminate the intermolecular crosslinking since the propagation centre cannot reach another primary chain. Combining the effects of the small growth boundary and the short chain length (shaded area) constraining chain overlap (at the initial reaction stages), the intermolecular crosslinking reactions are indeed suppressed during the early phase of RAFT polymerization.

It must be noted that the model does not indicate a promotion of intramolecular crosslinking. The reason that chain combination becomes a more dominant feature during the second phase of RAFT is due to an amalgamation of the following factors: the exhaustion of free RAFT agent, the large polymer chain length and the high polymer chain concentration at the late stage of reaction. Now the propagating chain has the probability to either transfer to the RAFT group or to react with the free vinyl groups within the other chain. Moreover, the increased polymer chain number and larger chain length increase the chance of other chains coming into the proximity of the propagating chain.[23] This results in many vinyl groups from these neighbouring chains being well within the growth boundary which allows the intermolecular crosslinking reactions to finally become a likely event. Under our experimental conditions, the RAFT process can halt the intermolecular crosslinking up to approximately 30% conversion, leading to the formation of predominantly single cyclized polymer structures. It is worth noting that the RAFT polymerization of divinyl benzene (contains *ca.* 20% molar ratio monovinyl monomer) studied by Perrier and co-workers resulted in a product that was recognized as a highly branched structure.[24] We reason that this is mainly due to the rigid styrenic monomer sterically hindering a cyclization looping back to the chain, as well as the high ratio of RAFT agent to monomer.

In conclusion, this study demonstrates that the kinetic model can be applied to RAFT polymerization of MVMs, which accurately predicts that due to the deactivating nature of the RAFT agent, single cyclized molecules, consisting predominantly of intramolecular cyclization, are formed. Through RAFT polymerizations, we fulfil and explain the production of the 3D single cyclized structure from the homopolymerization of MVMs. The understanding of the naturally deactivation enhanced RAFT process opens a new route to allow a broad range of nanosize 3D polymeric materials to be designed and synthesized in a facile manner. More importantly, the results show once again the highly applicable nature of the kinetics model to the controlled living polymerizations.

Heath Research Board (HRB) of Ireland and Science Foundation Ireland (SFI)–SFI Principal Investigator programme, DEBRA Ireland, SFI-Strategic Research Program (07/SRC/B1163) and National University of Ireland, Galway, are gratefully acknowledged for funding.

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