# Controlled polymerization of multivinyl monomers: toward single chain cyclized/knotted polymers

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**Abstract:** Polymerization of multivinyl monomers (MVMs) can produce polymers with novel topological structure and different functionalities due to their inherent multiple reactive sites. However, the polymerization of MVMs would inevitably lead to a polymeric cross-linked network even at extremely low conversion rates (typically under 10%) according to the Flory-Stockmayer mean-field theory (F-S theory). Recently, the development of reversible deactivation radical polymerization (RDRP) paved the way towards kinetically-controlled polymerization of MVMs allowing the synthesis of novel macromolecular architectures. In particular, a novel knotted polymeric structure was obtained. This review summarizes the kinetically-controlled mechanism of RDRP as the recent, major development in the field of polymerization of MVMs. The synthesis methods, novel structures and applications of knotted/cyclized polymers are also included. Moreover, the prospects for the application of polymers with novel structures and the future development of CRP of MVMs are proposed. (Abstract Text, 800-1000 characters.)

## 1 Introduction

After around half century of development, worldwide production of synthetic polymers in 2014[1] was 311 million tonnes, half of which was prepared by radical polymerization of vinyl monomers. Vinyl monomers are certainly one type of the most heavily used starting materials for the modern synthetic polymer productions. However, to date, the vinyl polymers have been used mainly as commodity plastics, rubbers and fibres, because of the inherent drawback of the traditional linear vinyl polymerization: inadequate control over their molecular architecture. More valuable applications need high level of control and manipulation of the connection of polymer sub-chains within an individual macromolecule.[2,3] This research area is further excited by a recent report asking “How far can we push polymer architectures?”[4], as the development of novel strategies for the design and synthesize complex macromolecular architectures is always appealing goals enthusiastically pursued by the chemical community.

Controlled nonlinear polymerization of multifunctional vinyl monomers (MVMs) represents one of the most promising methods to prepare the architecturally complexed vinyl polymers, given that the architectures of final products can be manipulated by either the involvement of multiple reactive groups during the polymerization process or post-polymerization modifications. However, the main challenge associated with this process, according to the classical Flory−Stockmayer mean field theory (F−S theory)[5–7], is that the polymerization of multivinyl monomers would inevitably lead to gelation even at low monomer conversion owning to the presence of significant intermolecular cross-linking reactions, which have been verified experimentally numerous times[8,9]. It prevents the formation of controlled macromolecular structures and even high monomer conversion for the large scale commercial production.

There has been continued efforts to address this challenge. The contemporary strategies for the controlled polymerization of MVMs toward complex nonlinear architectures can be categorized as manipulation of monomer reactivity and steric structure[10–12], radical lifetime [13,14] and polymer sub-chains assemblage[15]. Another strategies with control of chain propagation direction has recently been achieved *via* the deactivation enhanced reversible deactivation radical polymerization (RDRP) method under the kinetically controlled strategy[16–23]. Remarkably, this technique allows for control of both the gelling point and the macromolecular architecture within the homopolymerization of commercially available MVMs without the need for a diluted reaction condition. This approach efficiently delayed the gelling point up to approximately *ca.* 80% monomer conversion in concentrated conditions, due to the significant intramolecular consumption of the same-chain pendent vinyl groups. Moreover, novel three-dimensional single chain self-cyclized polymeric architectures were formed due to the promotion of intramolecular cyclization and suppress of intermolecular crosslinking. These studies have opened the door for the design and expand the polymer architectures obtained from polymerization of vinyl monomers, and the use of the commercially available MVMs and the concentrated reaction condition make it promising regarding to the large scale production.

The present Minireview describes major developments in the field of polymerization of MVMs including the theoretical insights, synthesis approaches, structural characteristics and applications of single chain cyclized/knot polymers. In particular, the Minireview is organized into four main sections so as to systematically summarize the development of the MVMs polymerization and synthesis of the single chain cyclized polymers. It should be, however, clearly stated that the present Minireview is not meant to be fully comprehensive. Many specific aspects of copolymerization of the monovinyl monomers with MVMs and gelling point have been described in previous reviews[2,15,24] and are therefore not described in detail in the present text. Thus, the present Minireview was conceived to be a

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concise introduction to the controlled homopolymerization of MVMs toward single chain cyclized /knotted polymers.

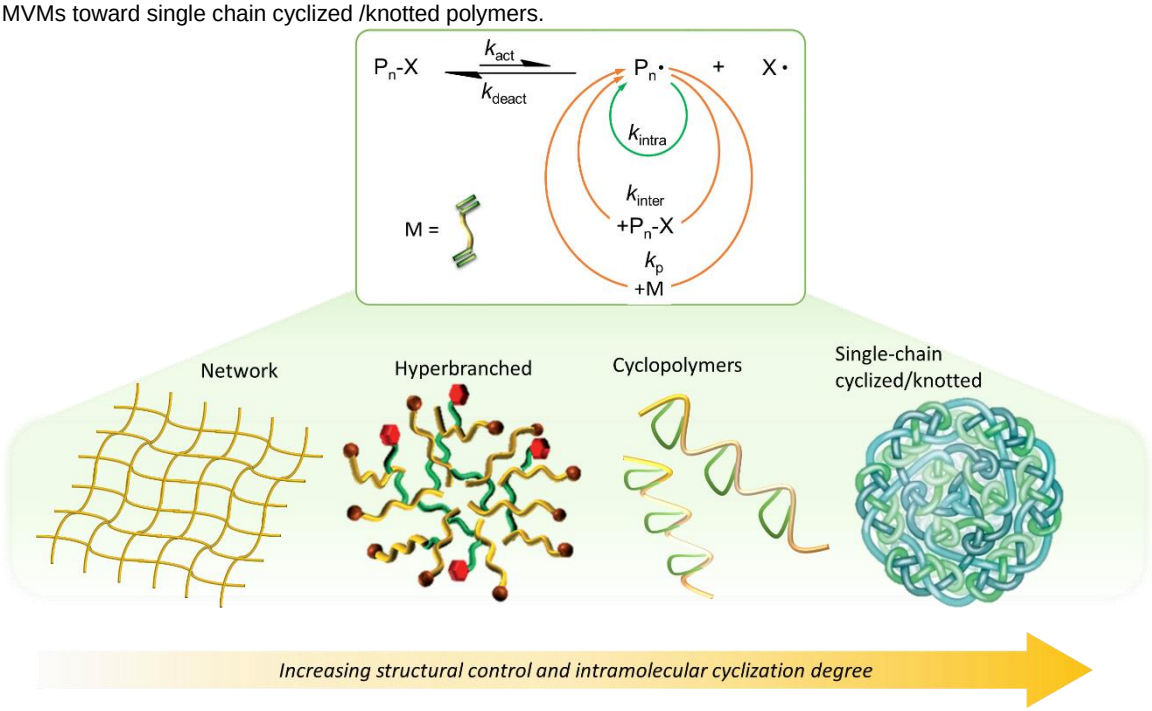


**Figure1** Illustration of reactions during polymerization of MVMs and the resulted polymer structures. Compared with monovinyl polymerization, the chain propagation in MVMs polymerization have another two pathways e.g. intermolecular crosslinking and intramolecular cyclization. Without proper control, MVMs polymerization leads to a network structure under a low monomer conversion. High level control to increasing the intramolecular cyclization degree leads to the formation of in-chain loop and ultimately a single chain cyclized/knotted polymer architecture can be synthesized.

## 2 General theoretical insights

Polymerization of multivinyl monomers features the generation of a number of pendent vinyl groups on the growing chains, which can continue to react with propagating radicals via either intramolecular or intermolecular pathways (Figure 1). MVMs thereby have traditionally been considered as crosslinkers to perform the free radical copolymerization with monovinyl monomers, coined as multivinyl/vinyl crosslinking polymerization or three-dimensional radical polymerization which is one of the three typical approaches for synthesis of polymeric network (gel). During such reactions, the primary chains are crosslinked gradually through bimolecular reactions between pendent vinyls with other chain-end radicals, with a change from soluble sols to insoluble gels. Theoretical study on the crosslinking reactions and the subsequent gelation is therefore of great significance to control and predict the structure and properties of resulting polymeric materials. In particular, the critical gelation conversion i.e. gel point is the most important fundamental and technological parameters for this polymerization reaction.

### 2.1 Flory-Stockmayer mean field theory

Theoretical prediction of the gel point was pioneered by Flory [7] and Stockmayer[5] 70 years ago. They defined the critical gel point as the weight-average number of crosslinker ($\nu_c$) (divinyl monomers both vinyl reacted) per primary chain equals unity (Eq. (1))

$$n_c = \alpha \rho (l_w - 1) = 1 \quad (1)$$

where $\alpha$ is overall reacted fraction of vinyl groups, $\rho$ is the overall fraction of vinyls residing on divinyl monomers in the original system. $\lambda_w$ is the weight average number vinyls per chain.

Flory-Stockmayer (F-S) theory is the first theoretical work about nonlinear polymerization with the predictions of basic relations between extent of reaction and resulting structure (size distribution of the finite polymers and gel point as a function of reaction extent). However, the mean-field theory nature and the necessity of the two fundamental assumptions: equal and independent reactivity of vinyl groups and no intramolecular cyclization reactions are often not fulfilled in realistic system.

### 2.2 Intramolecular cyclization effect

Intramolecular cyclization is one of the significant nonideal features, causing the main discrepancy between the F-S theory calculation and experimental results. During the intramolecular reaction, a pendent vinyl reacts with the radical on its own propagating chain, namely the radical which created the pendent vinyl via the MVMs addition, leaving behind a primary cycle in the propagating chain. Thus the intramolecular reaction is a type ring-closing reaction, which consumes pendent vinyls but do not

contribute the increase in the molecular weight of final products and thereby has dramatic influence on the polymer structure and gel point. General treatment of the intramolecular cyclization is of critical for fully understandings of the multivinyl polymerizations and of practical importance for polymer chemists. Statistical work with consideration of intramolecular cyclization was first reported in polycondensation system by Jacobson and Stockmayer[25], and later in multivinyl/vinyl chain polymerization system by Dusek and Ilavsky[26], with the consideration of the influence of conformational statistics on the cyclization probability based on cascade theory and spanning-tree approximation. However, limited time-dependent reaction information can be obtained from these statistical methods since the simulated polymerization process is characterized by state functions instead of time functions.

Intramolecular reactions extent is surprisingly high according to the percolation theory and kinetic modelling. By performing simulation in space, percolation theory takes into account spatial correlations allowing the intramolecular reaction happens[27–29]. Mannevile and de Seze[30] first reported the simulation method for the radical polymerization of multivinyl monomers using a cubic lattice with randomly moving of radicals through each site on the lattice which represents a multivinyl monomer. This method predicted that more cycles are formed at low conversions due to the high pendent vinyl reactivity represents by the closer spatial proximity of pendents to radicals in the lattice. Kinetic modelling based on all the elementary reactions, including intramolecular cyclization, further proved the cyclization degree at the beginning of the reaction estimated to be 30-60% in free radical homopolymerization system[31]. Remarkably, a non-mean-field kinetic modelling proposed by Bowman and coworkers with introduction of local radical concentration for intramolecular reactions, predicted the amount of cyclization is approximately 25% at zero conversion in homopolymerization system[32–34].

The significant involvement of the pendent vinyl groups especially the intramolecular reactions predicted by these theoretical study drives us to ask what novel macromolecular structure can be obtained if one can control both the intramolecular and intermolecular reactions in this traditional polymerization reaction.

## 3 Polymerization of multivinyl monomers (MVMs)

### 3.1 Copolymerization with monovinyl monomers

Experimental study of multivinyl radical polymerization can be traced back to 1935, Staudinger and coworkers[35] investigated the radical copolymerization of divinylbenzene (DVB) with styrene and first stated the product of this reaction is a three-dimensional molecule. Since then, the multivinyl/vinyl copolymerization approaches is one of most used approaches to synthesize the polymeric network[36–45]. However, Free radical copolymerization of divinyl/vinyl monomers leads to gelation typically at very low monomer conversion. Macosko et al.[8,9], for instance, copolymerized ethylene glycol dimethacrylate (EGDMA) with methyl methacrylate (MMA) via conventional radical polymerization, demonstrating the gel point is only 9.7% in the system with 0.57 mol % of EGDMA added, highly in agreement with F-S theory. Synthesis of other structured polymers was prohibitive due to the low gelation conversion and thus, continuous efforts have been made to control gelation conversion and get soluble products. Sherrington et al. [13,14,46] originally introduced a large amount of chain transfer agents into free radical polymerization of multivinyl/vinyl monomer system to inhibit the crosslinking and got a branched polymeric products. Alternatively, control and manipulation of intramolecular reactions in the multivinyl/vinyl copolymerization system is another effective way to suppress the gelation and get a soluble product, since intramolecular reactions in principle consume pendent vinyls without generating crosslinkages and increasing the molecular weight. Promotion of intramolecular cyclization is achieved either by using ultradiluted reaction condition[36,39] or performing the cyclopolymerization of designed multivinyl monomers which are in favour of the intramolecular reaction through an energy lowering effect and steric control[11,47]. Nevertheless, the fast and uncontrollable polymerization process and low gelation conversion limit the experimental accessibility to get a desire structured polymers from the conventional radical polymerization process.

The recent evolution of reversible deactivation radical polymerization (RDRP) opened a new chapter in polymer chemistry, in particular, for synthesis of architecturally complexed polymers. The nearly constant growing chain number and intermittent reversible activation of the dormant species featured in the RDRP enable control over the polymerization rate, chain-end functionality and chain architecture, which extend the control capabilities of multivinyl/vinyl copolymerization. RDRP of monovinyl monomers and small amounts of MVMs has been elaborated studied by nitroxide-controlled free radical polymerization (NMP)[48–57], atom transfer radical polymerization (ATRP)[58–76], and reversible addition−fragmentation chain transfer polymerization (RAFT)[10,72,77–86]. Armes and co-workers investigated the copolymerization of various monovinyl monomers, including 2-hydroxypropyl methacrylate, MMA with EGDMA, Bisphenol A dimethacrylate etc by ATRP[59] and RAFT[86]. They suggested that branched polymers can only be obtained at the condition where the divinyl monomer concentration is less than 1 per primary chain. Some results indicated that the intermolecular cross-linking degree at the gelling point was still in close alignment with the F-S theory. Matyjaszewski and coworkers[15,58,61,65,75,87] systematically studied the ATRP of multivinyl/vinyl monomers systems. By performing methyl acrylate (MA) and ethylene glycol diacrylate (EGDA)[87], they found the gelation occurred when the concentration of reacted pendant vinyl groups was larger than that of primary chains. Moreover, they found the resulted gel has a more homogeneous structure with minimum amount of cyclization substructures. Their subsequent simulation study however showed that the intramolecular cyclization occurred to a significant extent in this ATRP copolymerization system[88–91]. Other studies showed the existence of partial intramolecular cyclization lead to a discrepancy from F-S theory if the polymerization is conducted in a diluted condition[58,77,92].

### 3.2 Homopolymerization

Controlled homopolymerization of MVMs appears significantly more challenging, given that each MVM is a potential cross-linker, and hence much more "cross-linkers" existed in homopolymerization system compared to the copolymerization system. Zhu and coworkers[68,69,71,78] for instance, reported the homopolymerization of EGDMA via ATRP and RAFT, unsurprisingly, the gelation occurred at a monomer conversion less than 10%. Yet, with a careful control over the initial reaction condition, such as template addition and diluted reaction conditions[12,80], some soluble polymers was obtained with a high monomers conversion. Remarkably, Sawamoto et al.[12] reported cation template-assisted controlled radical polymerization of poly(ethylene glycol) dimethacrylates (PEG*n*DMA, *n*=4,5,6,8) to synthesize linear cyclopolymers with large in-chain PEG rings (Figure 2). The key to this strategy is to form the monomeric pseudo-cyclic conformation by the specific interaction of the PEG unit with the metal cation, as such the two intramolecular vinyl groups are brought adjacent and are thereby suitably positioned for alternating propagation of intramolecular cyclization and intermolecular addition. But still the diluted condition is needed to eliminate the intermolecular crosslinking.

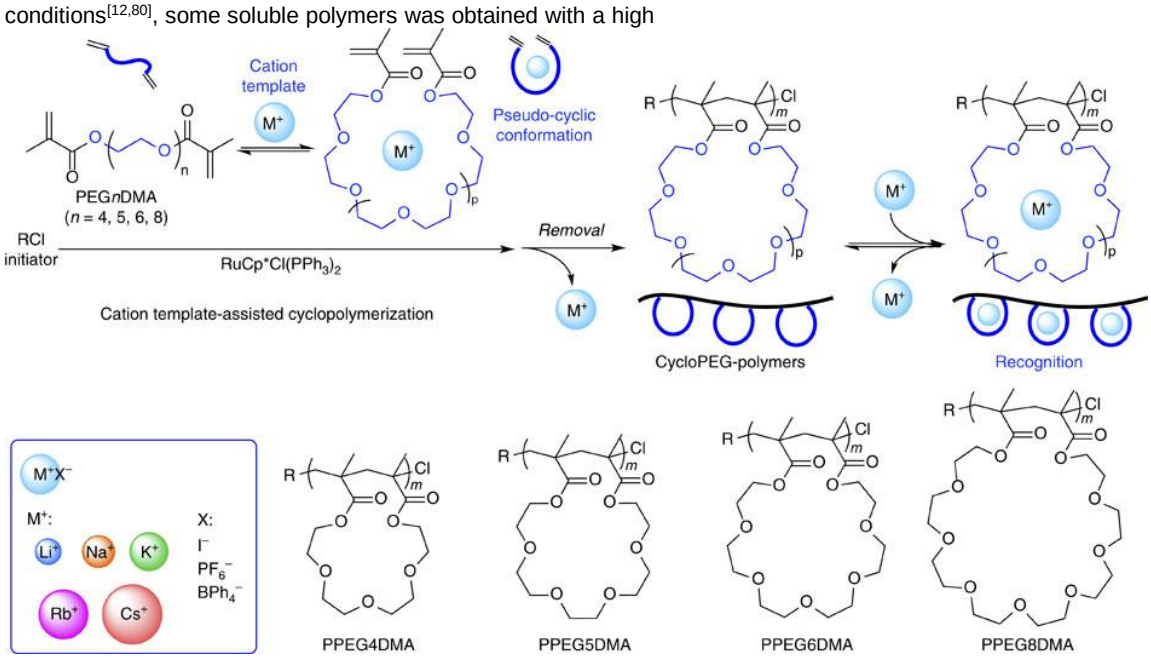


**Figure 2.** Cation template-assisted controlled living radical polymerization for linear cyclopolymers with large in-chain PEG rings. PEGnDMA efficiently interacts with metal cations to in situ form pseudo-cyclic conformation with the adjacent location of the two olefins, which induces the alternating propagation process of intramolecular cyclization and intermolecular addition to selectively give linear polymers comprising large in-chain cyclic PEG rings. Reprinted with permission from Ref.[12], copyright 2013 Nature Publishing Group.

**Table 1.** Reported methods for homopolymerization of normal multivinyl monomers via RDRP and the resulted structure of products

| Methods | Monomers | Feed ratio[a] | [M] | Yeild[b] | Product structures | Ref. |
|---|---|---|---|---|---|---|
| **ATRP** | PEG386DMA | 100:1 | Bulk | - | Network | [68] |
| **ATRP** | PEG330DMA | 50:1 | Bulk | - | Network | [69,71] |
| | PEG550DMA | | | | | |
| | PEG787DMA | | | | | |
| **ATRP** | EGDA | 1.5:1 | 0.39 M | 97 | Nanogel | [93] |
| **De-ATRP** | DVB | 57:1 | 3.51 M | 61.6 | Hyperbranched | [16] |
| | EGDMA | 50:1 | 1.22 M | 63 | | |
| ***In situ*** | EGDMA | 100:1 | 1.45 M | 54.2 | Single-chain cyclized/knot | [17] |
| **De-ATRP** | ACD | | | | | |
| ***In situ* De-ATRP** | BDA | 100:1 | 1.44 M | 15[c] | Single-chain cyclized/knotted | [20] |
| | BDA | 2:1 | | 69[c] | Hyperbranched | |
| | DEGDA | | | 70[c] | | |
| | EGDMA | | | 30[c] | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | DVB | | | 55[c] | | |
| | DSDA | | | 74[c] | | |
| ***In situ* De-ATRP** | EGDMA | 2:1 | 2 M | 72[c] | Dendritic | [94] |
| | DVB | | 2.5 M | 49[c] | | |
| ***In situ* De-ATRP** | PEG575DA | 2:1 | 60w/v% | 95.6 | Hyperbranched | [23,95] |
| | | 4:1 | | 94.1 | | |
| | | 8:1 | | 76.9 | | |
| | PEG700DA | 2:1 | | 90.5 | | |
| | | 4:1 | | 93.2 | | |
| | | 8:1 | | 70.9 | | |
| **$Cu^0$&$Cu^{II}$-mediated RDRP** | TEGDA | 100:1 | 1.5 M | 40.4 | Single-chain cyclized/knotted | [22] |
| | DSDA | | | 50 | | |
| **Cation template-assisted CRP** | PEG*n*DMA | 12.5:1 | 0.025 M | 87 | Linear 'in-chain' cyclic | [12] |
| | (*n*=4,5,**6**,8) | 25:1 | 0.05 M | 93 | | |
| | | 50:1 | 0.1 M | 90 | | |
| | | 100:1 | 0.1 M | 87 | | |
| **RAFT** | PEG550DMA | 50:4 | Bulk | - | Network | [78] |
| **RAFT** | EGDMA | 100:3 | Bulk | - | Network | [96] |
| **RAFT** | DVB | 220:0.87 | ~3 M[d] | 68 | Branched | [97] |
| **RAFT** | BDDA, | 200:5 | 0.1 M | 83 | Branched | [80] |
| | PEG258DA | | 0.2 M | 62 | | |
| | PEG575DA | | 0.2 M | 63 | | |
| | PEG700DA | | 0.1 M | 45 | | |
| **RAFT** | EGDMA | 100:1 | 1.67 M | 45 | Single-chain cyclized/knotted | [18] |
| **Iniferter** | EGDMA | 0.1wt% | Bulk | - | Network | [98] |
| | PEG200DMA | 0.1wt% | | | | |
| | PEG400DMA | 0.1wt% | | | | |
| | PEG600DMA | 0.25wt% | | | | |
| **Iniferter** | DEGDMA | 0.1wt% | Bulk | - | Network | [99] |
| | PEG200DMA | | | | | |

[a] Feed ratios determine the *DP*: $[M]_0/[I]_0$ for ATRP and $Cu^0$&$Cu^{II}$-mediated RDRP; $[M]_0/[CTA]_0$ for RAFT method and $[I]_0$ for iniferter; [b]monomer conversions before gelation; [c]vinyl group conversions. [d]recalculated from original sources: 22mmol DVB with 20% ethylstyrene in 5.96g toluene

Control over the polymerization process e.g. kinetics is another promising approach toward synthesize architecturally complexed polymers. Dynamic model for polymerization of MVMs such as kinetic gelation model shows that polymerization kinetics not only affect reaction rates but also the structures formed[100] indicating some kinetically preferred structures can be obtained in the multivinyl homopolymerization reactions with a proper control over polymerization kinetics. In 2007, Wang et al.[16] proposed a kinetically controlled strategy for homopolymerization of MVMs based on normal ATRP, where polymerization kinetics can be readily controlled by manipulating the feed ratio of activator ($Cu^I$) to deactivators ($Cu^{II}$). With addition of large amount of extra $Cu^{II}$ species, the deactivation reaction in the ATRP of multivinyl monomers systems was significantly enhanced and surprisingly the gelation conversion was greatly increased in a concentrated reaction condition. For example, the gel point in homopolymerization DVB system ([M] = 3.51 M) was delayed up to 61% monomer conversion with the addition of 0.133 equivalent $Cu^{II}$ (to initiator), far beyond F-S theory. Likewise, in homopolymerization of EGDMA with monomer concentration of 1.22 M, the gelation was occurred until 63% conversion in the presence of 0.063 equivalent $Cu^{II}$. To further enhance the deactivation rate, Zheng *et al*[17,20] reported an *in situ* deactivation enhanced atom transfer radical homopolymerization (in situ DE-ATRP) of MVMs, where the activator $Cu^I$ is in situ formed from the reduction of $Cu^{II}$ by small amount of added reducing agent (e.g., ascorbic acid, AA). In their subsequent study, EGDMA[17], acid cleavable divinyl monomer (ACD) [17], 1, 3-butanediol diacrylate (BDA)[20], DVB[20], DEGDA[20] TEGDA[22], PEGDA575[23] PEGDA700[23] and bis(2-acryloyl)oxyethyl disulphide (DSDA) [20] (Figure 3) have been successfully homopolymerized. Gelation conversion can be as high as 96% in homopolymerization of PEGDA575[23]. The kinetically controlled strategy is further applied to other RDRP systems, such RAFT[18] and $Cu^0$-mediated RDRP[22] in concentrated condition. By copolymerizing MVMs with monovinyl monomers under this kinetically controlled strategy, variety of multifunctional polymers are obtained, expanded their applications[19,21,23,95,101–106]. These results paved a new way toward the controlled polymerization of commercially available MVMs to reasonable monomer conversion without the necessity of diluted condition. Moreover, the high monomer conversion provides the possibility to obtain a controlled structured vinyl polymers.

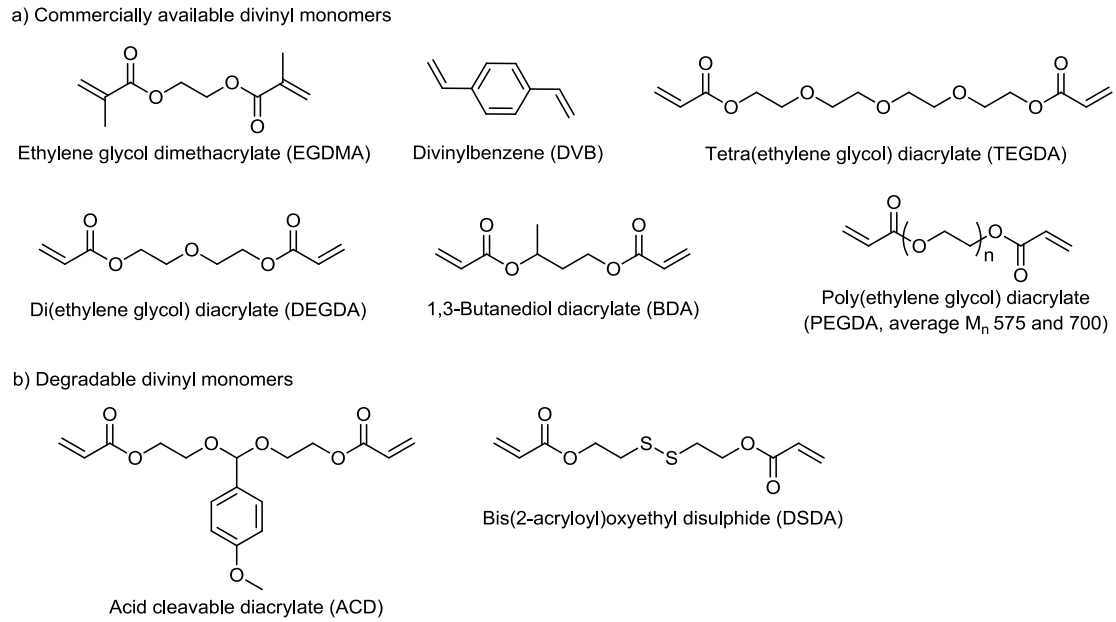


**Figure 3** Examples of divinyl monomers homopolymerized under kinetically controlled strategy. a) Commercially available divinyl monomers. b) Degradable divinyl monomers

The significant delay of the gel point during kinetically controlled polymerization of MVMs was attributed by the kinetical and spatial manipulation of chain growth related reactions including linear chain propagation, intramolecular cyclization and intermolecular crosslinking (Figure. 4). The reaction rates/possibilities of these three reactions are controlled by the growth boundary, chain dimension and chain concentration according the kinetic model[17,20,22]. Deactivation enhanced strategy has a distinct difference with FRP or normal ATRP is the addition of extra deactivator $Cu^{II}$, which thereby resulting in the decrease of kinetic chain length ($\nu$) - that is, number of double bonds added during one activation step $\nu=R_p/R_{deact}=k_p[M]/k_{deact}[Cu^{II}]$[107], related to the growth boundary. Under conventional FRP or normal ADRP conditions, much higher kinetic chain lengths results in a bigger the growth boundary, which allows a large number of vinyl groups to be added to an active centre each time. The resulting high $DP_n$ primary polymer chains would combine to form an insoluble gel instantaneously, regardless of chain dimension and concentration, due to the high rate of propagation and intermolecular cross-linking reactions according to the statistical probability, which is in good accordance with the F-S theory. However, in the deactivation enhanced approaches, a smaller growth boundary confines only those very few closest vinyl groups to be added into the active centre before it is deactivated and hence keeps the polymer chains growing in a limited space. In this way, unlike what happens in FRP, the formation of huge polymer chains and large scale combination even at the early stages are avoided. Therefore, a smaller growth boundary achieved by the deactivation enhanced strategy is the basic prerequisite for obtaining the control structured polymers. Under a smaller growth boundary, Zhao et al.[20] explored the possibilities to synthesize hyperbranched polymers from this multivinyl homopolymerization reactions system by promoting the intermolecular crosslinking and suppressing or eliminating the intramolecular cyclization. It was realized by manipulation the chain dimension and concentration. A high ratio of initiator to monomer (1:2) resulted the formation of shorter primary chain and thus suppresses the intramolecular reaction, but the high chain concentration obtained in the system increases the possibilities that one pendent vinyl fall into the growth boundary of another chain. Once monomers massively convert to short polymer chain, the intermolecular crosslinking increases and a hyperbranched polymeric structure is formed. On the other hand, the intramolecular cyclization during the multivinyl polymerization process can be dramatically promoted if one uses a low feed ratio of initiator to monomer (1:100)[17,18,22], which resulted a relatively longer primary chain but lower chain concentration. As such the growth boundary of one polymer is unlikely to overlap with that of other polymers. Those vinyl groups nearest the active centre (fall into the growth boundary) either belong to free monomers or are from the same polymer chain containing the active centre. Therefore, chain propagation and intramolecular cyclization reaction are promoted while intermolecular cross-linking is suppressed. The intramolecular cyclization of pendent vinyls in this context is kinetically preferred due to the higher concentration of the local same-chain pendent vinyls. The benefits of the high percentage of intramolecular consumption of pendent vinyl are twofold: first dramatically increases in the gelation conversion, second, allowing the formation of the novel single-chain cyclized/knotted polymers if the polymerization is quenched timely before the intermolecular crosslinking occurred.

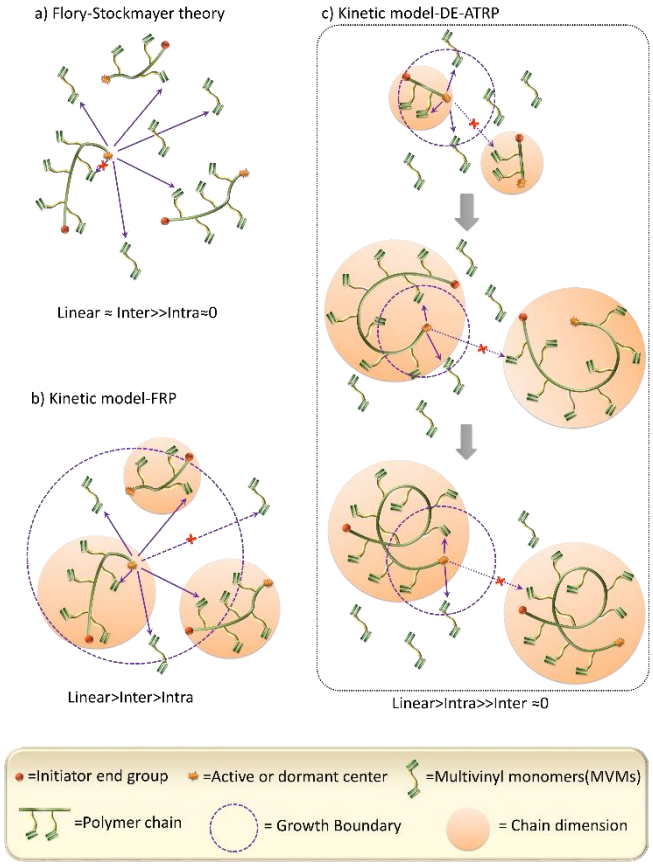


**Figure 4.** a) Model based on F-S theory, where intramolecular cross-linking is ignored; b) model of FRP; and c) model of in situ DE-ATRP based on the kinetics model. The kinetic model considered two parameters: the growth boundary which depends on the kinetics chain length of the polymerization (dotted circle) and polymer dimension depends on the polymer chain length and concentration (shaded part). The maximum growth of a polymer chain (defined as the instantaneous kinetics chain length), which depends on the possible number of vinyl groups reacted during its active lifetime during the propagation process. The probability of monomer addition to the chain decreases with distance from the active propagation centre up to the maximum growth boundary, moreover, past which the probability of monomers adding tends to zero.

## 4 Single-chain cyclized/knotted polymers

Among the existed various complex nonlinear polymers including branched, hyperbranched, star-like, brushed, and cyclic structures, those composed of cyclic units (macrocyclic[108–110], multicyclic[111–113], knotted cyclic[114–116], and folded cyclic[117–119]) are of significant interest due to their compact architectures and unique properties[120]. However, efficient and practical syntheses of the cyclic structure are among the most difficult tasks for polymer chemists, as the polymer chains must react with themselves prior to reacting with other chains[3,121]. Thus far, to achieve such intramolecular reactions rather than intermolecular reactions, it is necessary to work under extreme diluted conditions[25,121], or in one-dimensional channels[122], or, alternatively, to perform the cyclopolymerization of the designed monomers [11,47].

### 4.1 Formation process

The kinetically controlled polymerization of MVMs allows the efficient manipulation of intramolecular and intermolecular reactions in a concentrated conditions which should, in principle, open new avenues to efficiently design and synthesize polymers containing cyclic structures. In general, under a proper condition, the multivinyl polymerization process toward single chain cyclized polymers can be described as Figure 5. At the initial stage, similar the linear RDRP reactions, the rapid activation of initiator is followed by monomer addition to form the primary linear chains. The experimental evidence is the molecular weight increase linearly with monomer conversion and the polydispersity remains low with a unimodal molecular distribution (Figure 6). During this stage, as aforementioned, the low polymer volume concentration and the smaller growth boundary achieved by kinetical controlled strategy, prevent the growth boundary of one polymer to overlap with that of other polymers. Only the monomeric and same-chain pendent vinyls can be added to the propagating centre. Reaction of radical with monomeric vinyls results the linear chain propagation and the production of the pendent vinyls. While the addition of the latter type of vinyls to a chain-end radical causes the formation of a lasso-like covalent loop, with a radical locating on one end of the lasso which can further participate the chain growth either by monomer addition or intramolecular reactions. It is not clear and difficult to experimentally detect at what reaction extent (how many monomer added to the primary chain) the intramolecular cyclization reactions occurs. Yet, according to the calculation of pendent vinyl conversion by $^1$H NMR, 28.3% vinyls are consumed at the monomers concentration only 8.3% during this linear chain growth phase[22], which has been viewed as a typical symptom of intramolecular cyclization[31,33]. The alternating chain propagation/intramolecular cyclization process eventually result in the formation of multiple cyclic units within a single polymer chain. The significant involvement of the intramolecular reaction and resulted the multiple intramolecular looped bridges in situ knotted the polymer chain into a single chain cyclized/knotted polymers. Due to the existence of multiples vinyls the newly formed products eventually intermolecularly combined leading to an insoluble network as the polymerization proceed. Nevertheless, with a careful design, the single chain cyclized/knotted polymers are still accessible to a reasonable monomers conversion, given the high percentage of potential ‘crosslinkers’ - pendent vinyls – are intramolecularly consumed during the linear chain growth, if the polymerization is quenched timely before the intermolecular crosslinking occurred.

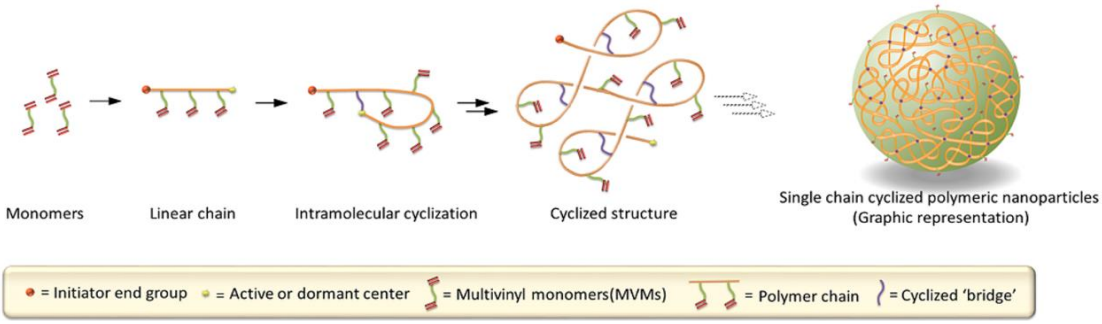


**Figure 5.** Illustration of the formation process of the single chain cyclized/knotted structure. Reprinted with permission from Ref.[22], copyright 2015 American Chemical Society.

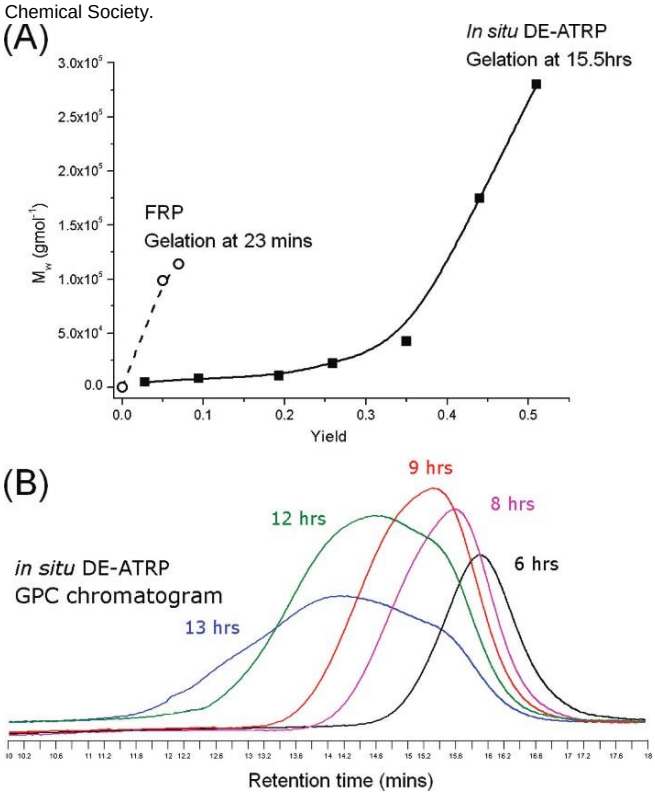


**Figure 6.** (A) Dependence of the weight-average molecular weight (Mw) of the polymers formed by FRP and in situ DE-ATRP on the polymer yield; (B) time dependence of the composition of the polymerization mixtures monitored by GPC equipped with a RI detector, showing the unimodal peaks at initial stages (<9 h) and multimodal peaks appearing later (>9 h) in the in situ DE-ATRP of EGDMA. Reprinted with permission from Ref.[17], copyright 2011 American Chemical Society.

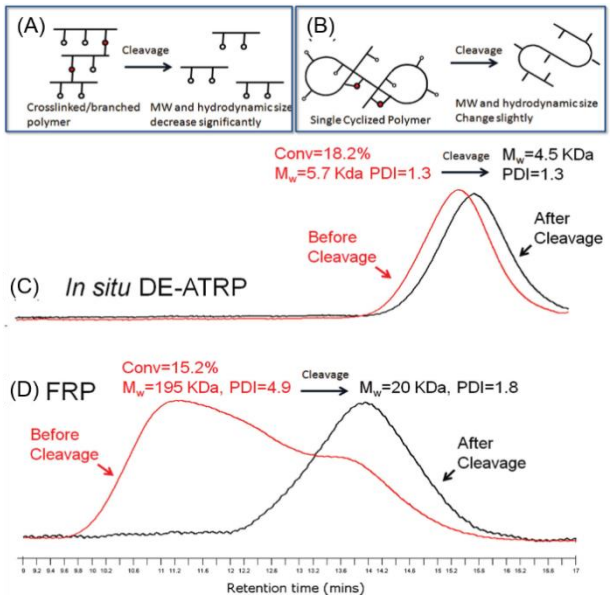


**Figure 7.** Cleavage reaction of acid cleavable divinyl (ACD) monomer, (A) MW and hydrodynamic size of polymer chains will decrease significantly in cross-linked/branched polymers, (B) but will only change slightly in single cyclized polymer, (C) the GPC trace before and after cleavage of ACD polymer at 18.2% yield with in situ DE-ATRP, proves the single cyclized structure because the MW and hydrodynamic size only slightly decreased after cleavage (from 5.7 kDa to 4.5 kDa), in contrast, (D) the polymer synthesized by FRP demonstrates a substantial reduction (from 195 kDa to 20 kDa). Reprinted with permission from Ref.[17], copyright 2011 American Chemical Society.

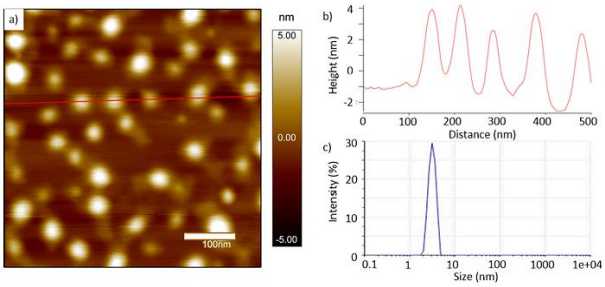


**Figure 8.** (a) AFM (0.5 × 0.5 μm) topography image of nanoparticles casted on a freshly cleaved highly oriented pyrolytic graphite (HOPG) surface recorded in amplitude modulation mode in air. (b) Height profile across the red line of the AFM image in (a). (c) DLS size distribution of the nanoparticles in (a). Reprinted with permission from Ref.[22], copyright 2015 American Chemical Society.

### 4.2 Structural features

The structure of single-chain cyclized/knotted polymers features the in situ self-knotted single polymer chains as detailed in previous section. Although the direct visualize the individual polymer chains are still challenging for polymer chemist, the structure features: multiple cyclic subunits and single chain are further confirmed by chemical degradation test. Several pendent/crosslinker degradable single chain cyclized/knotted polymers from homopolymerization of degradable multivinyl monomers such as ACD[17], DSDA[20,22] and ester-derived

monomers[22] were subjected to the chemical degradation to observe the degradation profiles and the constituent primary chains of the cleavable. For branched polymers where small molecular weighted primary chains linked by the degradable units, once degraded, the entire macromolecule separated into smaller fragments with a significant decrease in the molecular weight, as confirmed by Armes et al.[72,92] and Wang et al.[20] On the contrary, the pendent vinyls in single-chain cyclized/knotted polymers are reacted with their own carbon backbone (intramolecular cyclization reaction) to form the multiple "loops" subunits. After cleavage, a ACD-based single-chain cyclized/knotted polymer chain untied to a single linear chain via the breakage of every loop with slight decrease in molecular weight (from 5.7 kDa to 4.5 kDa), in sharp contrast with the dramatically decrease in molecular weight (from 195 KDa to 20 KDa) from FRP (Figure 7). It should be noted that the slight decrease in molecular weight of the single chain cyclized/knotted polymer is due to the removal of parts of the pendent chains after degradation, although the hydrodynamic volume of linear polymers is bigger. Similar cleavage result were also obtained in homopolymerization on DSDA and TEGDA. The morphology and size-distribution of the single-chain cyclized/knotted polymer characterized by atomic force microscope (AFM) and dynamic light scattering (DLS) showed good unimolecular dispersion. (shown in Fig. 8)

## 5. Applications

The novel single-chain cyclized/knotted structure provides some unique properties for the vinyl based polymers, which should in principle be desired for variety of application. Newland et al [19] first applied single chain cyclized/knotted polymers as gene delivery vectors. In their study, the readily available vinyl monomers: EGDMA, 2-(dimethylami- noethyl) methacrylate (DMAEMA) and polyethylene glycol methyl ether methylacrylate (PEGMEMA) was copolymerized by one-step DE-ATRP to synthesize the cationic functional single chain cyclized polymers (Figure 9). The gene transfection performance in terms of both luciferase transfection capability and preservation of cell viability tested over a range of cell types is superior to the dendrimer structured commercial agent SuperFect, which is attributed to the special interaction between cyclic polymers and plasmid DNA. Based on this promising results, they subsequently applied this newly synthesized polymers as transfection agent for the delivery of more challenging glial cell line derived neurotrophic factor (GDNF) encoding gene[101]. Compare with branched polyethyleneimine (PEI), while showing a similar transfection profile over multiple cell types, the cyclized knot polymer showed far lower toxicity. In addition, transfection of Neu7 astrocytes with the GDNF encoding gene was able to cause neurite outgrowth when cocultured with dorsal root ganglia (DRGs)(Figure 10). This single chain cyclized/knotted polymer was shown to have great potential for neuronal gene therapy applications.

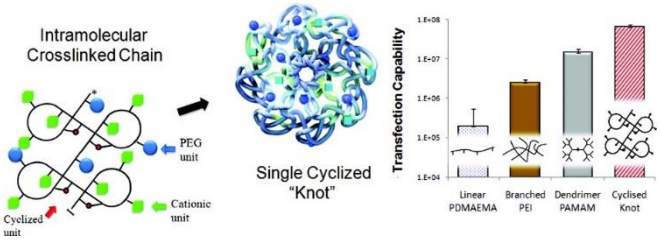


**Figure 9.** Comparison of gene transfection performance by linear, branched, dendritic and single-chain cyclized/knotted polymeric vectors. Reprinted with permission from Ref. [19], copyright 2012 American Chemical Society.

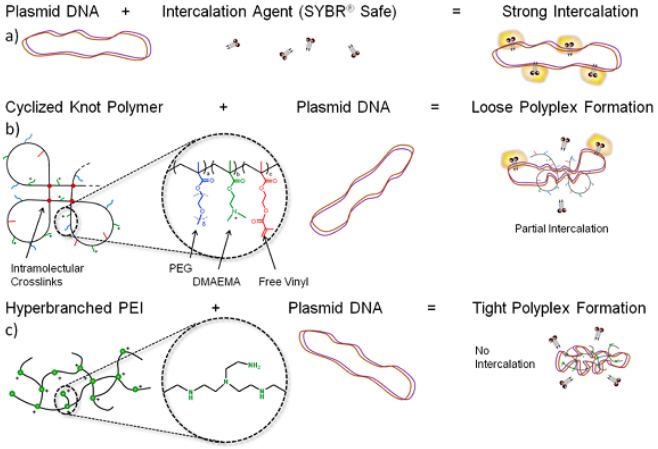


**Figure 10.** Representation of the action of fluorescent intercalating agent SYBR Safe on naked plasmid DNA (a), single chain cyclized/knotted polymers (b) and hyperbranched PEI(c). Unlike the strong intercalation on naked plasmid DNA and no intercalation on hyperbranched PEI, a certain degree of intercalation still takes place on this cyclized knot polymer with DNA, indicating loose polyplex formation. Reprinted with permission from Ref. [101] ,copyright 2013 American Chemical Society.

Interestingly, A biodegradable cationic single chain cyclized/knotted polymers was further developed by incorporating the biodegradable disulfide groups into crosslinking units (Figure 11)[105]. This knot structure can untie in cellular reducing conditions, showing a more favorable transfection profile for astrocytes than 25kDa-PEI (48- fold), SuperFect (39-fold) and Lipofectamine2000 (18-fold) whilst maintaining neural cell viability at over 80% after four days of culture. The high transfection/lack of toxicity of this knot structured polymer in vitro, combined with its ability to mediate luciferase transgene expression in the adult rat brain, demonstrates its use as a platform transfection technology which should be investigated further for neurodegenerative disease therapies. Cutlar et al[106] further applied the biodegradable knotted polymer (DSP) with the residual vinyls are end capped by amine in skin cells, keratinocytes. Compared with commercial gene vector, the DSP exhibited high transfection efficacy with both Gaussia luciferase marker DNA and the full length COL7A1 transcript encoding the therapeutic type VII collagen protein (C7). The effective restoration of C7 in C7 null- RDEB skin cells indicates that DSP is promising for non-viral gene therapy of recessive dystrophic epidermolysis bullosa (RDEB).

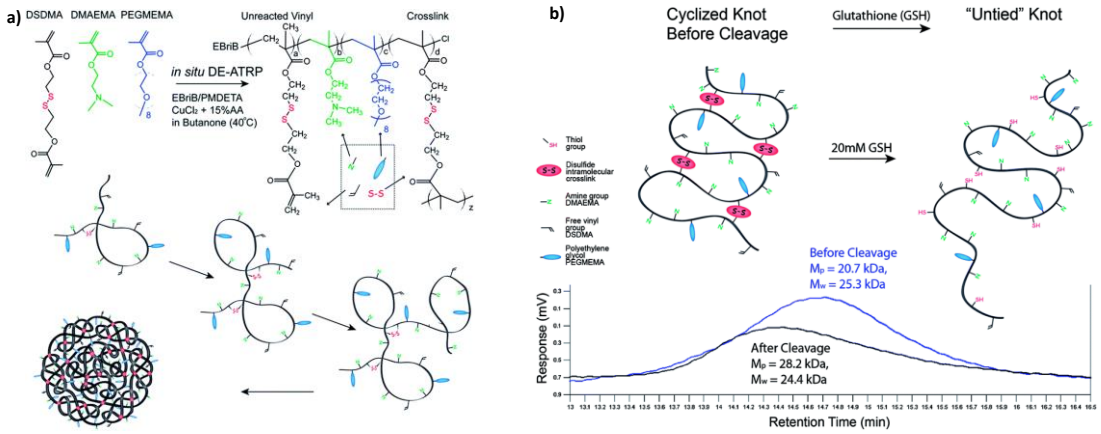


**Figure 11.** Synthesis approach (a) and degradation profiles of the biodegradable single chain cyclized/knotted polymer (b). Reprinted with permission from Ref. [105] ,copyright 2014 Royal Society of Chemistry.

Besides these single knot polymers, Aied et al.[104] applied a multiknot structured polymer for the correction of collagen type VII-null skin cells of RDEB. The multiknot vectors were synthesized via in situ DE-ATRP copolymerization of DMAEMA with DSDA, and post- functionalized by 1,3-diaminopropane (Figure 12). They found the unique disulfide-reducible multiknot polymeric gene vectors exhibits significantly enhanced transfection potency and low cytotoxicity in vitro, evaluated by collagen VII expression in 3D skin equivalents made from cells of recessive dystrophic epidermolysis bullosa patients. Their findings suggested that the marked improvements stem from the dense multiknot architecture and degradable property, which facilitate both the binding and releasing process of the plasmid DNA.

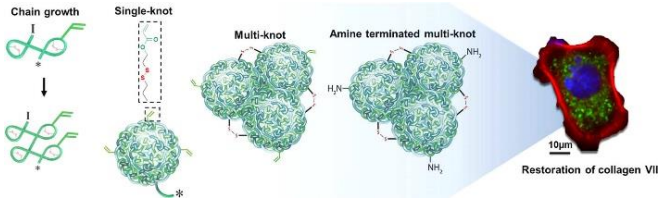


**Figure 12** Synthesis of multiknot polymer as a gene transfection vector. Reprinted with permission from Ref.[104], copyright 2014 American Chemical Society.

## 6. Summary and Outlook

Under kinetical controlled strategy, single chain cyclized/knotted polymers previous unachievable theoretically and experimentally have been now successfully synthesized from controlled homopolymerization of MVMs. Great progress has been made in term of synthesis approaches, structure control and the biomedical applications. However, the study of this novel structured polymer is still in its infancy. For future work, particular attention should be drawn on the following aspects.

First, theoretical framework for kinetically controlled polymerization of MVMs and synthesis of single chain cyclized/knotted polymers should be studied. Based on the kinetics equations of a series of RDRP elementary reactions, the non-mean-field kinetic model should be built taking the kinetically controlled strategy and intramolecular cyclization favoured condition into consideration. Several computer simulation techniques such as Monte Carlo based on the dynamic lattice liquid algorithm can be utilized to reveals the intramolecular cyclization extent and structure evolution.

Second, to build the structure-property relationship, more precise characterization techniques to quantitatively determine the structural features (such as pendent vinyl conversion, molecular conformation) or imperfections including the amount of the crosslinked polymer chains, and precisely visualize the individual macromolecular structure. To correlate the single chain cyclized/knotted structure with the final properties, the single chain properties including the polymer solution and melts and bulk materials assembled from this single chain cyclized/knotted polymers should be studied in detail.

Third, application of this single chain cyclized/knotted polymers in variety field should be explored. Considering the single-chain nature and multiple intra-chain crosslinking bridges, it can used as conductive polymers or high-strength/high-elastic polymer in engineering materials. The inherent nano-sized internal cavity structure make it be possible to be used carriers for the delivery of catalysis, contrast agent and drug. Furthermore, the structural similarities between the single chain cyclized/knotted polymers with some natural proteins make it be helpful for the understanding of the protein structure formation pathways and the special properties.

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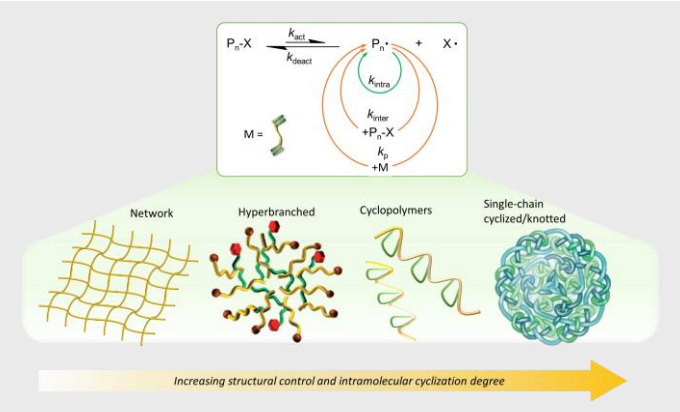


Chain propagation in MVMs polymerization have three pathways e.g. monomer addition, intermolecular and intramoleuclar crosslinking. High level control to increasing the intramolecular cyclization degree leads to the formation of in-chain loop and ultimately a single chain cyclized/knotted polymer architecture can be synthesized

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**Title Controlled polymerization of multivinyl monomers: toward single chain cyclized/knotted polymers**