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Feature article

Recent advances in alternating copolymers: The synthesis, modification, and applications of precision polymers

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ABSTRACT

Alternating copolymers represent a special class of copolymers, in which the two comonomers copolymerize in a regular alternating sequence along the chain. Their interesting physical and chemical properties, as well as the underlying mechanism, have attracted significant attention in both academia and industry. The electron-donor benzylidene monomers – styrene and stilbene, readily form alternating copolymers with the electron-acceptor monomers – maleic anhydride and *N*-substituted maleimides. The rich chemistry of the substitution groups on these monomers offers enormous combinations for the synthesis of alternating copolymers for different applications. In this paper, we aim to provide a general overview of recent publications on the specific field of these benzylidene-containing alternating copolymers, and the emphasis is placed on the synthetic progress, structure-property relationships, and the applications of these copolymers.

Contents

1. Introduction

Copolymers are polymers synthesized from two or more species of monomers [1]. The study of copolymers could be traced back to the 1930s since synthetic rubber was invented and developed [2]. Ever since then, the research on copolymers has received considerable attention because an infinite variety of different copolymer composition could be synthesized and specific desired properties could be tailored by varying the species and composition of the comonomers. Based on different arrangements of the comonomers, the copolymers can be typically categorized as random or statistical copolymers, block or segmented copolymers, graft copolymers, alternating copolymers, periodic copolymers [3], while some new types of copolymers, such as gradient copolymers [4] and aperiodic copolymers [5] emerged in recent years (Fig. 1) [6–8].

In an alternating copolymer, the two comonomers arrange in a regular alternating sequence [1], and the alternating copolymerization is characterized by the product of the two monomer reactivity ratios as $r_1r_2 = 0$, in which r_1 and r_2 represent the ratio of the rate constant of homopropagation to the rate constant of cross-propagation of each reactive propagating species [9]. In other

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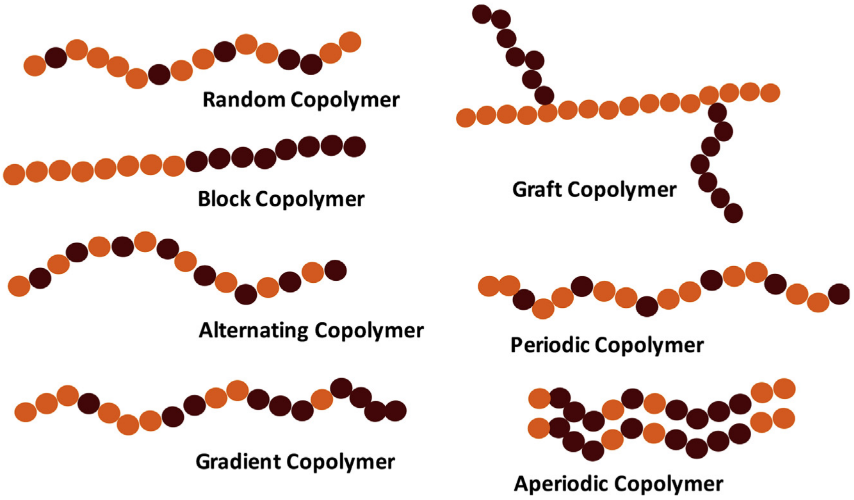


Fig. 1. Types of copolymers.

words, each of the propagating species prefers to add the other monomer rather than react with its own type of monomer. Perfect alternation happens when r_1 and r_2 are both equal to zero, where no dyads or homo-addition will be found in the copolymer, while such dyads can be found when both r_1 and r_2 are very small or one r is small and the other r is zero, where the copolymer shows alternating behavior but does not strictly alternate. The comonomer systems that can form alternating copolymers include electron donor-acceptor pairs, complexes formed with Lewis acids, Ziegler-Natta or metallocene catalyzed ethylene and cis-olefins, zwitterion intermediates, and etc. Although two difunctional monomers also polymerize alternatively in step growth, the polymers from step growth are not usually considered as alternating copolymers [10], and the two units are often seen as one repeat unit. Among all these systems, of special interests are in the radical polymerizable electron donor-acceptor pairs. The electron donor monomers, such as styrene, stilbene, vinyl ethers, dienes and *N*-vinylcarbazole, and electron acceptor monomers, such as maleic anhydride, *N*-substituted maleimides, dialkyl fumarates and fumaronitriles, provide numerous combinations and possibilities in achieving alternating copolymers of different properties and applications.

Several models have been proposed to explain the alternating behavior from a mechanistic point of view (Fig. 2). The earliest Mayo-Lewis model suggested that the rate constant of the propagation of the polymer chain relates to the terminal radical and the incoming monomer (thus it's also referred as the terminal model) [11]. The terminal model could be used to describe the copolymer composition as a function of monomer feed composition, but fails to explain the relationship of rate constant versus monomer feed composition [12]. However, this relationship could be explained well using the penultimate unit model, which suggests that the rate of propagation of the polymer chain does not only rely on the terminal radical, but also on the penultimate monomer unit [12–15]. One plausible interpretation from the theoretical calculations was that the transition state of the propagation can be represented by three hindered rotors, and one of the rotors is greatly affected by the penultimate unit [16]. Another well-known model, the complex participation model suggests that the charge-transfer complex, which is formed *via* the interaction between the electron donor monomer and the electron acceptor monomer pairs, participates in the copolymerization [17,18]. The existence of the charge-transfer complexes have been confirmed by spectroscopic evidence [18–21], but it is still questionable whether the complexes are actually added to the propagating radicals, or the complexes dissociate upon the polymerization and only one monomer is added to the propagating chain each time [22–24]. Generally speaking, there still remains a debate over the exact mechanism of the alternating behavior, and efforts are continuously made to study the mechanistic steps behind alternating copolymerization.

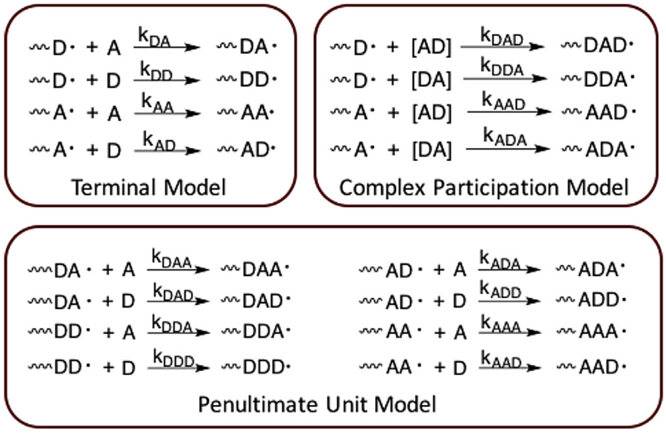


Fig. 2. Demonstration of three models of the mechanism of alternating copolymerization, D and A represent donor and acceptor monomers, respectively.

Examination of the literature shows that there is a lack of review articles on alternating copolymers since 2000. Cowie's book on alternating copolymers was published in 1985 [10], and a few reviews focusing on the mechanisms of alternating copolymerization [15,25,26] or specific applications of some alternating copolymers [27] were reported. However, much progress has been made on the synthetic techniques, mechanistic studies, property evaluation and applications. In this review, we specifically focus on the alternating copolymers that were formed by benzylidene monomers styrene or stilbene with maleic anhydride or *N*-substituted maleimides. The detailed synthetic pathways, the miscellaneous modifications, fundamental structure property measurements, and various applications of the alternating copolymers of styrene or stilbene with maleic anhydride or maleimides monomers will be discussed in this paper.

2. Recent development of benzylidene-containing alternating copolymers

2.1. Traditional and controlled radical copolymerization for alternating copolymers

The alternating copolymerization of maleic anhydride with styrene was among the earliest academic studied copolymer systems, and one of the earliest studies by Alfrey and Lavin in the early 1940s [28] showed that this copolymer could be prepared using common free radical initiators at 70–80 °C [29]. Ever since then, the styrene-maleic anhydride (SMAh) copolymer has been one of the most extensively investigated alternating copolymers. The incorporation of maleic anhydride unit increases the heat resistance of polystyrene proportional to the maleic anhydride content [30]. The thermoplastic SMAh has high glass transition temperature, high deflection temperature under load, high heat and chemical resistance, low melt flow rate, good impact, rigidity and dimensional stability [31]. It was first commercialized by Sinclair Petrochemicals in the 1960s, and in 1972, the injection molding SMAh resin was first used for automotive dashboards by Nova (Arco) Chemicals using the trade name Dylark®, which is no longer produced. Currently, the commercial SMAh products are by Cray Valley (Beaufort, TX, USA) as SMA®, Polyscope (Geleen, NL) as Xiran® and Solenis (Wilmington, DE, USA) as Scripset® [32]. SMAh copolymer finds wide ranging applications as a molding resin in the automotive, packaging and construction industries, as well as a compatibilizer in plastic blends and alloys to improve their mechanical and thermal performance and other properties [33,34]. SMAh was studied as an additive to acrylonitrile butadiene styrene (ABS) copolymer and poly(methyl methacrylate) (PMMA). SMAh could broaden the processing window and increase the surface polarity of the base resin, which is desired for molding and surface painting purposes, respectively. SMAh also increases the miscibility of ABS and PMMA with other additives and polymers and reduces phase separation [33,34]. In addition, SMAh and PMMA are fully miscible, and the clear SMAh has minimal influence on the refractive index and transparency of PMMA polymer, which helps to maintain the attractive optical features of PMMA while improving its other properties. However, SMAh polymers are not resistant to UV degradation, therefore they require a UV-resistant protective coating when used for outdoor applications [31]. Moreover, SMAh polymer, along with its hydrolyzed from, styrene-maleic acid (SMA) alternating copolymer were also applied in diverse applications such as surface sizing, pigment dispersion, ink modification, powder coating, leather retanning, floor care products and etc.

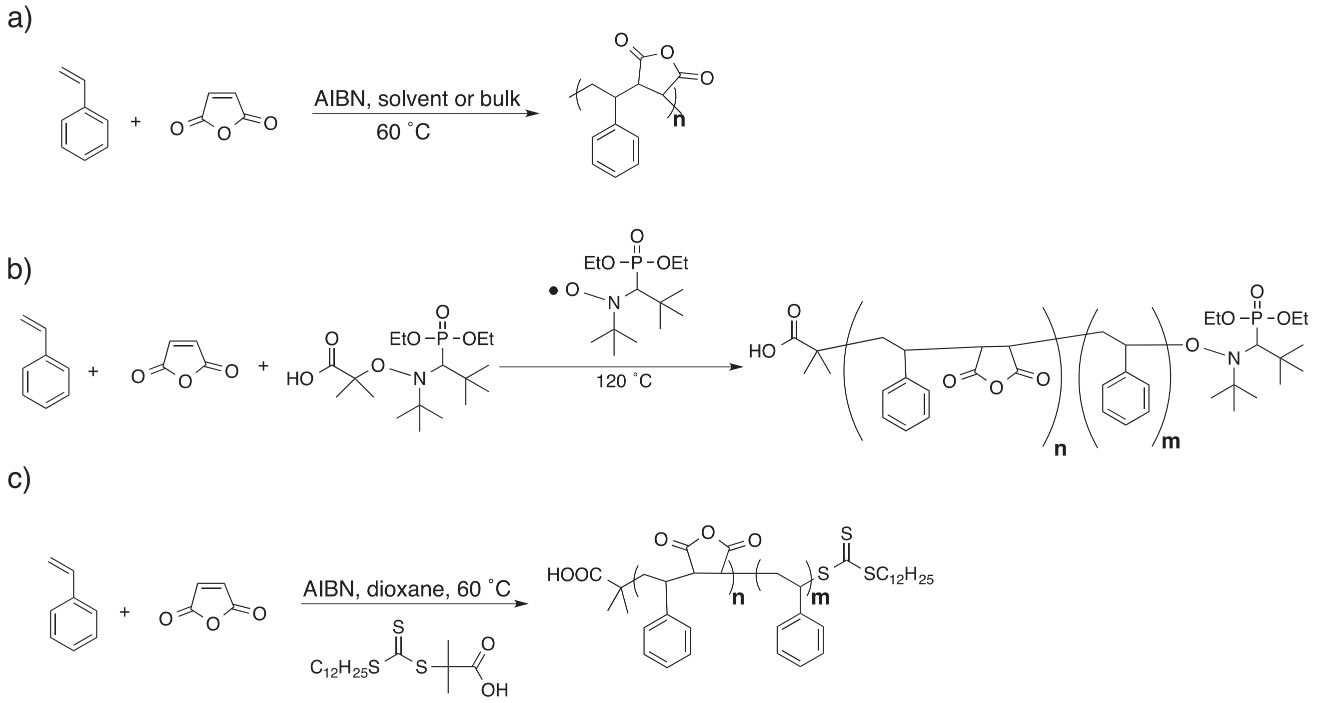
The early studies mostly focused on the kinetics and mechanism of the alternating copolymerizations [13,19,35–41]. The SMAh copolymers are mostly synthesized using free radical polymerization (Scheme 1a). The most commonly used initiators are benzoyl peroxide (BPO) and azo-bis-(isobutyronitrile) (AIBN), while spontaneous initiation [40,42], UV initiation [43], and some other initiators [44] were also reported. The copolymerization could be conducted in bulk and common organic solvents such as THF, DMF, acetone, methyl ethyl ketone, benzene, carbon tetrachloride, benzene and saturated hydrocarbons. Supercritical CO_2 was also reported as a suitable synthesis media, especially for high molecular weight SMAh ($Mw > 10^6$) [45]. Due to the non-homopolymerizable nature of maleic anhydride, no more than 50 mol% of it could be incorporated into the copolymer [28], and ^{13}C NMR [46] and pyrolysis-gas chromatography [31] showed a strong tendency of 1:1 equimolar alternation at 1:1 infeed of styrene and maleic anhydride unless using a starved feeding technique, in which the in feed maleic anhydride is added in a very low level [31]. However, when the infeed maleic anhydride content is lower than 50 mol%, conventional free radical copolymerization may result in copolymers with compositional drifts [47], evidenced by ^{13}C NMR that segments with more maleic anhydride and segments with less maleic anhydride are statistically distributed along the chain [48]. Controlled radical polymerization techniques provide better control over the alternating monomer sequence at imbalanced infeed ratio. (The details and mechanism of controlled radical polymerizations were elaborated in books and review articles [49–51].) Both nitroxide mediated polymerization (NMP) (Scheme 1b) and reversible addition-fragmentation chain transfer (RAFT) (Scheme 1c) are applicable to the synthesis of the SMAh copolymer, while atom transfer radical polymerization (ATRP) seems incompatible for SMAh synthesis, which may due to the interaction of maleic anhydride with the copper complex that is required for ATRP. However, ATRP could be used to copolymerize styrene and N-substituted maleimides [52–55].

In controlled radical polymerization (CRP), the copolymerization of styrene and maleic anhydride showed a very strong alternating tendency even at imbalanced monomer ratio. That is to say, if the polymerization starts with a very low level of maleic anhydride, the copolymerization will still start as an alternating copolymerization until all maleic anhydride is consumed, and then the homopolymerization of styrene starts [58]. Eventually, it can yield a block copolymer with an SMAh block and a styrene block in one step (Scheme 1b and 1c) [56,59–61]. In contrast, the same situation would result in a heterogeneous mixture of copolymer and homopolymer in conventional radical polymerization [15]. This strong alternating feature has been utilized in sequence control polymerization (see 2.4). The choice of RAFT agent in alternating copolymerization is crucial, because it affects the reaction rate and the terminus group of the chain. An initialization period was found at the initial stage of the RAFT polymerization of styrene and maleic anhydride, during which the RAFT agent combines with either styrene or maleic anhydride to form the monomer adduct [62,63]. The preference on monomer selectivity during this step depends on the electronic structure of the RAFT agent, i.e. the electron rich RAFT agent will preferably add to maleic anhydride. Electron spin resonance (ESR) spectroscopy showed that the intermediate propagating radical is predominate with maleic anhydride at the chain ends. This is probably due to the fast addition of the maleic anhydride chain end to the C=S of the RAFT agent [64]. The composition of monomer feed also plays an important role, when the proportion of maleic anhydride was large, the copolymerization rate was faster while the control over the molecular weight and molecular weight distribution was poor [65]. In addition to enhancing the alternating behavior of the copolymerization, CRP also provides pathways to synthesize hybrid composites [66], nanostructures [57,67,68], and different architectures, such as polymer brushes [69,70], di-blocks [71], stars and Miktoarm stars [72], and hyperbranch structures [73].

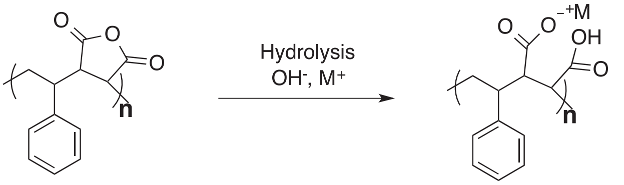
2.2. Modification and functionalization of alternating copolymers

Maleic anhydride, or succinic anhydride when enchained, can be easily functionalized when the carbonyl carbons are attacked by nucleophiles [29]. Although the stability of the reactive anhydride groups can be troublesome when the SMAh copolymers are exposed to moisture or other chemical environments, they provide a reactive site for modification of the SMAh copolymers, and several important functionalized polymers were prepared using this chemistry [27].

One example is the styrene-maleic acid (SMA) alternating copolymer, which is hydrolyzed from the styrene-maleic anhydride copolymer under basic conditions (Scheme 2). The hydrophilic



Scheme 1. a) Conventional free radical alternating copolymerization of styrene and maleic anhydride [27]; and the one step synthesis of poly((styrene-*alt*-maleic anhydride)-*b*-styrene) using b) nitroxide mediated polymerization (NMP) [56], or c) reversible addition-fragmentation chain transfer (RAFT) polymerization [57].



Scheme 2. The preparation of SMA copolymer from SMAh through basic hydrolysis [27].

carboxylic acid (and/or salt) and the hydrophobic styrene impart to SMA amphiphilic property, and the amphiphilicity is dependent on the pH of the local environment. The dissociation behavior of SMA copolymers was studied by Colby and coworkers [74,75]. The two carboxyl groups have different pK$_a$s of 6 and 10, which means SMA bears two charges on both carboxyl groups at high pH, one charge at neutral pH, and is not charged at low pH [76]. The conformation and aqueous solubility of SMA are also affected by the local pH: at high or neutral pH, the electrostatic repulsions of the carboxylates prevail and overcome the hydrophobic effect, therefore the polymer adopts a random coil conformation and shows good solubility in aqueous solution; at low pH (lower than pH 6), the carboxylates are protonated and the hydrophobicity of the styrene dominates, which results in a compact globular conformation with poor aqueous solubility [77]. As one of the most significant interfacially active polymers, SMA has been used as a polymeric emulsifier or dispersing agent for various applications, such as for dispersing dyes for ink formulations [78], but the most common applications of SMA are in life science [27,79]. SMA forms stable polymeric micelles in aqueous solutions with a low critical micelle concentration [80]. SMA micelles were found to be an excellent tumor-targeting drug delivery system for hydrophobic drug molecules, such as doxorubicin [81], pirarubicin [82], and zinc protoporphyrin IX (ZnPP) (Fig. 3) [83]. Because of the unique characteristics of the

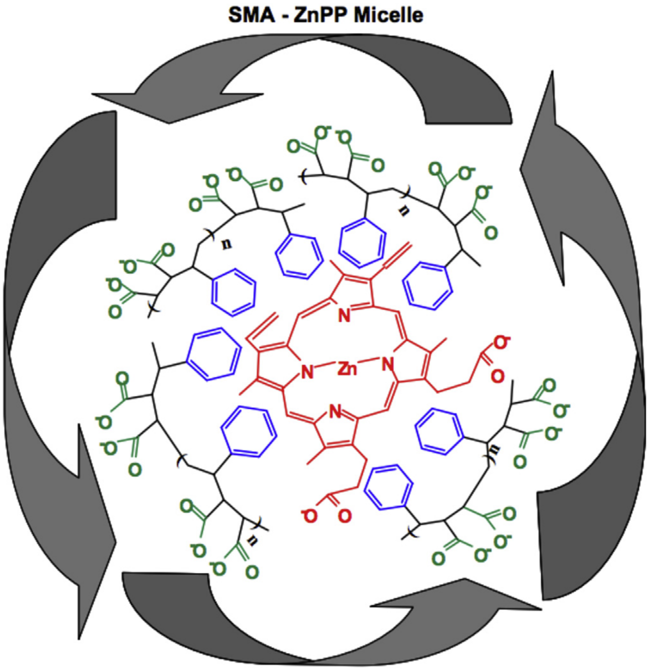


Fig. 3. The micelle formation of SMA and ZnPP for drug delivery. Each ZnPP (red) is surrounded by four SMA chains, the benzene rings (blue) interact with ZnPP through hydrophobic interaction, and the carboxylic acids (green) provide aqueous solubility. Reprinted from [83] with permission. Copyright 2007 Elsevier.

tumor vasculature, drug molecules of certain sizes tend to accumulate in tumor tissue, which is called the enhanced permeability and retention (EPR) effect [84]. The size of a single SMA micelle ranges from 100 to 200 nm, depends on the structure of the encapsulated drug and the loading. The large molecular size of SMA micelle-drug complexes showed great therapeutic properties due to the EPR effect [85]. In addition, SMA could noncovalently bind to albumin, which is one of the most biocompatible macromolecules, thus the bound albumin could serve as the second drug carrier and further enhance the EPR effect [86].

Another important application of SMA is on the research of membrane proteins [27], which usually requires the separation and stabilization of these hydrophobic proteins from cells. In traditional methods, the membrane proteins are solubilized using small molecule detergent micelles, but often the lipid bilayers are disturbed because of the different physical-chemical properties of the detergents. SMA is now considered as one of the most promising alternatives for membrane solubilization, because it shows a distinctive behavior than other amphiphilic materials: when adding to lipid membranes, it can form discoidal particles spontaneously (Fig. 4) [87,88]. Moreover, these nanodiscs could preserve the bilayer integrity of the lipid as well as the protein functions [89,90]. Therefore, SMA showed a fascinating potential of direct extraction and stabilization of membrane proteins from cells in one step [91]. The resulting membrane nanodiscs are termed SMALP (SMA-lipid particles). It is noteworthy that the reported SMA polymers in membrane research were not strictly alternating, and had a ratio of styrene to maleic acid of 2:1 or 3:1, therefore styrene dyads or small blocks may be presented.

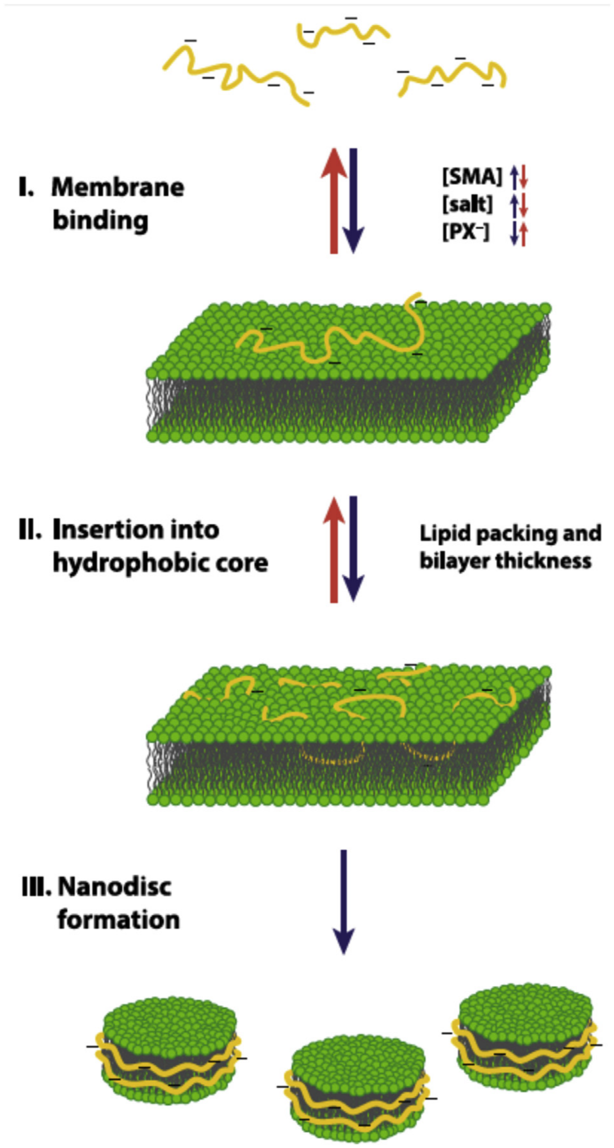


Fig. 4. The solubilization of lipid membranes by SMA copolymers. SMA first binds with the surface of the membrane with the modulation of the concentration of SMA, salt and negatively charged lipids (PX^-)(I); then SMA inserts into the hydrophobic core of the membrane through the hydrophobic effect (II); finally the membrane is solubilized in the form of nanodiscs (III). Reprinted from [88] and [27] with permission. Copyright 2015 Elsevier and 2015 Springer.

SMA copolymer has also been utilized in nanotechnology. SMA could disperse single-walled carbon nanotubes as a surfactant, and in the meanwhile work as templates for binding metal ions and metal nanoparticles [92]. At 50% protonation, SMA could self-assembly into nanotubes [93] due to the stiffening effect of the multiple intrapolymer hydrogen bonding among the acid groups [94]. SMA can also disperse TiO_2 nanocolloidal and patterned on substrates by micro-fluid-contact printing, and well-defined nanostructured TiO_2 layer was achieved by removing the SMA polymers by calcination [95].

The maleic anhydride groups in SMAh polymers can be easily modified by reacting with amines or hydroxyl groups and forming corresponding amic acid or acid ester, and the amic acid can be further converted to maleimide group with loss of water. Various functional molecules can be introduced to SMAh polymers utilizing this method, which is particularly useful in attaching drug molecules bearing amine groups. SMAh could improve the pharmacological properties of the drugs by increasing their circulatory half-life and increasing their lipid solubility [96]. Moreover, SMAh showed neither teratogenic nor acute or chronic toxic effects [97]. When binding tumor-targeting drugs, they also work to enhance the EPR effect. An important example is using SMAh to deliver the anti-tumor protein neocarzinostatin (NCS) [98,99]. In the polymer-drug conjugate, 70% of maleic anhydride groups were reacted with butanol, and the rest were used to bind with NCS (Fig. 5). The resulting SMANCS conjugate has been clinically used for liver cancer treatment, and commercialized in Japan [100]. Other drugs and biomolecules, such as pirarubicin [101], fenoprofen [97], gemfibrozil [97], and laminin peptide YIGSR [102], and etc [103] were also conjugated with SMAh by the reaction of amine group with maleic anhydride for delivery. A pH-responsive fluorescent specie, rhodamine-deoxylactam, was attached to SMAh, the fluorescence could be activated by lysosomal pH [104]. The copolymer is likely to accumulate in tumor cells due to the EPR effect, and it could work as a nanoprobe for detecting tumors. When binding with antimicrobial compounds, the modified copolymer showed high bactericidal effect [105,106], which enabled the preparation of antibacterial fibers by electronspinning [105,107]. In addition to bioactive groups, some functional groups could bring interesting properties and applications to SMAh polymer. For example, the insertion of the N-sulfonic acid group made SMAh polymer an efficient solid catalyst for a variety of organic reactions [108]; and the modification with diamines [109], 3-aminobenzoic acid [110], and aminothiophene derivatives [111] turned SMAh into polymeric sorbents for toxic heavy metal ions like Fe(II), Zn(II), Pb(II), Cu(II), and Cd (II).

Other than binding with functional molecules, the anhydride groups could also be used for purposeful modification of certain surface properties, such as hydrophilicity and complex forming ability. The ring-opening of the maleic anhydride would result in anionic carboxylate groups, which show the pH-dependent amphiphilicity, and the amphiphilicity and their surface activity could be further tuned by binding the anhydride group with different amines or alcohols. For examples, the partially imidized alkyl amines-modified SMAh polymers formed stable latex in water [112], and the dopamine-modified SMAh polymer self-assembled into stable micelles [113]. The short-chain alkyl amines-modified SMAh polymers showed pH-dependent membrane destabilizing

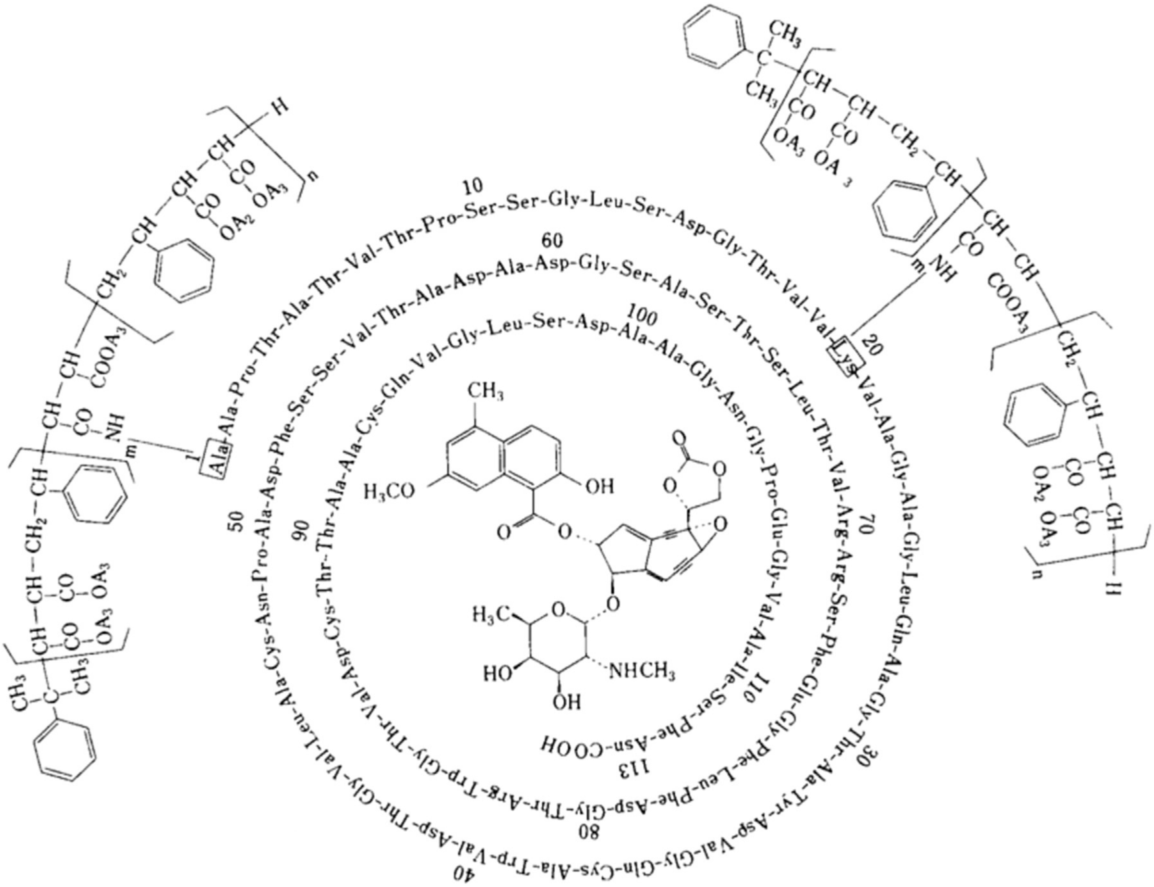


Fig. 5. The chemical structure of SMANCS. Reprinted from [99] with permission. Copyright 2013 WILEY-VCH.

activity, since they are hydrophilic and membrane-inactive at physiological pH, while they become hydrophobic and membrane-disruptive at endosomal pH [96]. The cysteamine-grafted SMAh shows similar behavior as SMA polymer to form nanodiscs with membrane protein, in addition, the pendant SH groups provide sites for functionalization using thiol-reactive chemistry [114]. Cationic quaternary nitrogen units were also inserted to SMAh polymers using the same chemistry [115]. They formed core-shell nanoparticles and showed potential for gene delivery. When binding with aminopyrene, the modified SMAh worked as a “polysoap” surfactant that mimics the structure of DNA to disperse single-walled carbon nanotubes (SWNTs), in which the aromatic base interacts with the SWNT wall, while the charged backbone is at the exterior side of the micelles. Compared to DNA, SMAh is easily modified, more available, and the more flexible structure further improves the SWNT dispersion property [116].

Some modified SMAh polymers exhibited distinguishable thermal and mechanical properties compared to the unmodified SMAh, and attempts to use these modified SMAh polymers as additives to change the properties of other materials were made. A series of plant oil derivatives were attached to the SMAh polymer, and the epoxidized soybean oil modified SMAh showed a dramatic increase of storage modulus around 190 °C [117]. A novel organic/inorganic polymer hybrid was obtained by the imidization of the SMAh polymer using an amine-containing polyhedral oligomeric silsesquioxane (POSS) [118]. Phase separation was observed in the resulting material, and the films showed excellent transparency and increased hydrophobicity. The methoxyl poly(ethylene glycol) (MPEG) grafted SMAh polymer was added to polyethersulfone (PES) membranes at the phase inversion process [119]. This amphiphilic additive increased the hydrophilicity and protein adsorption resistance of the PES membranes. Aminolyized SMAh polymer as an additive in the wood adhesive urea-formaldehyde (UF) resins during the synthesis could decrease the formaldehyde emission and improve the bonding strength [120]. A smart, electro-active material was achieved by adding the sulfonated aromatic diamine-crosslinked, imidized polymer to poly(vinylidene fluoride) (PVDF) as a potential material for artificial muscles [121]. The obtained ionic membrane exhibited improvement in both electrical and mechanical performance compared to the Nafion-based actuator. SMAh was also used as a compatibilizer in making flame retardant polystyrene material by reacting with the amine groups of the flame retardant poly(diaminodiphenyl methane spirocyclic pentaerythritol bisphosphonate) (PDSPB) [121]. The addition of SMAh improved the limiting oxygen index and deduced the peak heat release rate.

The modification of SMAh could also be utilized to achieve polymers of special architectures. Dimethyl-N, N-propylamide imidized SMAh was found to self-assemble into nanotubes, which were said to arise from the π-stacking of the styrenes and the van der Waals interactions between the maleimide units [122]. Theoretical studies showed that only racemo-diisotactic configuration of imidized SMAh polymer could form complexes by π-stacking, when the phenyl groups and maleimides are symetrically distributed [123]. Layer-by-layer stacking of SMAh and polyethylenimine (PEI) were reported to fabricate into nanotube structure using an alumina template [124]. Dendronized copolymers were synthesized by attaching poly(amidoamine) dendrons to SMAh. The butylamide terminated poly(amidoamine) dendrons brought thermo-responsive property to the copolymer, the copolymers showed lower critical solution temperatures (LCSTs) of 33.1 °C–49.0 °C, depends on both the generation of the dendrons and the local pH (Fig. 6) [125]. When the dendrons were terminated with the UV-responsive molecule *o*-nitrobenzyl alcohol, the structure of the copolymer aggregates dramatically loosened under UV irradiation, which made this dendronized copolymer a candidate for drug encapsulation and release [126].

Graft copolymers could be prepared by reacting SMAh with amine- or alcohol-terminated polymer chains, the resulting graft polymers bear negative charges on the carboxylate group next to the side chain, and the side chains are designed to impart to the SMAh copolymers a variety of useful properties. One of the commonly used side chain polymer is poly(ethylene glycol) (PEG) [127,128]. The resulting amphiphilic graft copolymer exhibited LCST in the range of 33.7 °C–74.7 °C, and the LCST is highly dependent on both pH and molecular weight of the side chain PEG [129]. Hydrogel microspheres were prepared by crosslinking this PEG-grafted SMAh polymer with polyamines, the microsphere swelled in response to increased salt concentration due to the shielding effect of the electrostatic association [130]. When the PEG side chain was attached to SMAh by using lithium alcoholates, the film fabricated from this graft copolymer showed conductivity in the range of 10^{-7} to 10^{-5} $S \cdot cm^{-}1$ due to the anion mobility with segmental motions, and the conductivity further increased to $5 \times 10^{-4}\ S\ cm^{-1}$ after adding BF_3, which suggests this polymer to be considered for potential lithium battery applications [131]. Polyethylenimine was grafted on to SMAh for gene delivery. The copolymer established effective DNA condensation and protect DNA from degradation by DNase [132]. Another strategy to synthesize graft copolymers is to polymerize macromonomers with maleimide or vinylbenzyl endgroups, and which resulted in a densely grafted copolymer (graft on each monomer) with alternating main chains [133]. A series of LCST copolymers were synthesized from the polymerization of 4-vinylbenzyl methoxytetra(oxyethylene) ether and N-substituted maleimides, and the transition temperature could be tuned by the side chain length [134]. Recently, this method was employed to synthesize graft copolymers with sequence regulated side chains (Fig. 7). The side chains were first synthesized via atom transfer radical addition to yield halide-ended sequence-controlled oligomers, followed by reacting the halide end with a furan-protected maleimide [135,136]. After deprotection of the furan group, the resulting maleimide-ended macromonomer readily form an alternating copolymer with styrene. Some properties of the copolymers, such as solubility and T_g could be tuned by both the sequence of the side chain and the ratio of the two monomers in the main chain.

Functional groups can also be incorporated by using functionalized styrene or N-substituted maleimide. A wide variety of functional groups could be attached onto styrene or maleimide monomers using easy chemistry, and the functional groups could impart a variety of physical and chemical properties. For example, a water soluble alternating copolymer was synthesized by the free radical polymerization of sulfonated styrene and sodium-*N*-(4-sulfophenyl)-maleimide monomers [137]. Polymers with active pendant double bonds are difficult to be prepared by direct radical polymerization of monomers with two different double bonds, which would result in crosslinked or cyclized structures in most cases. However, an active pendant double bond could be achieved

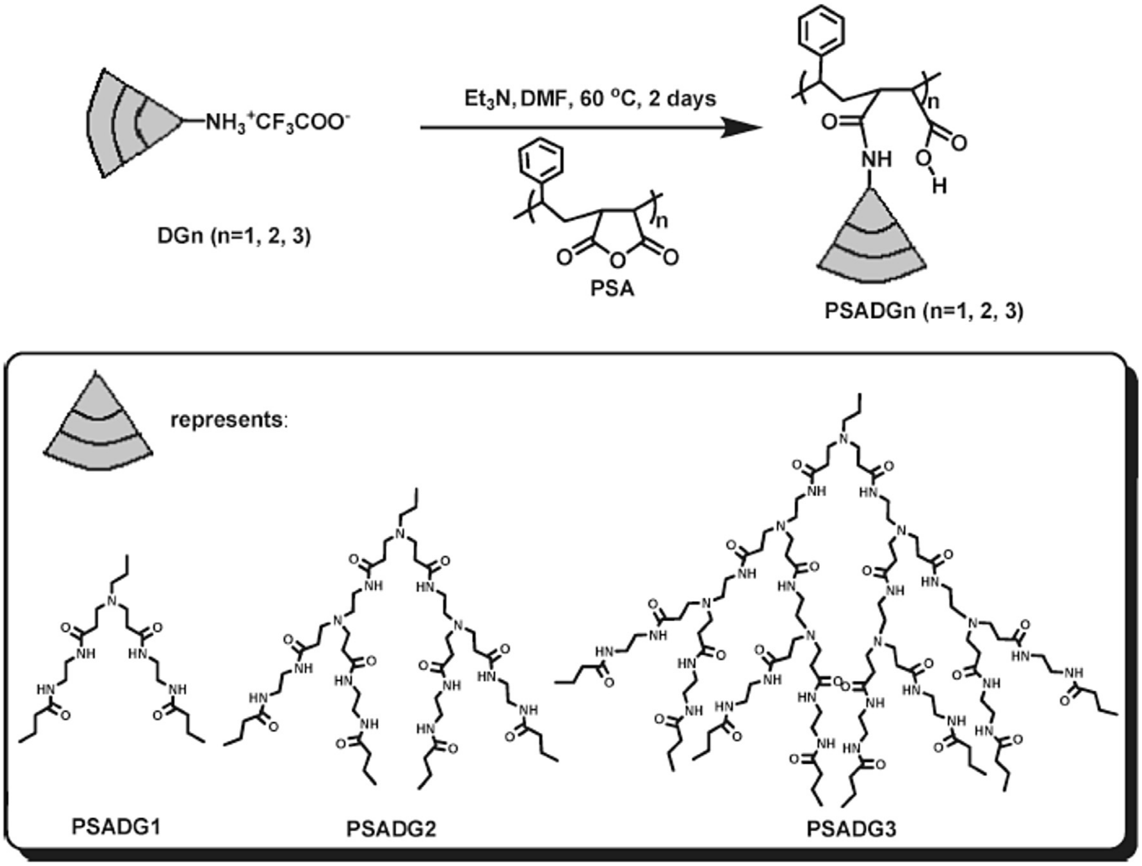


Fig. 6. Synthesis and structures of thermo-responsive dendrimers. Reprinted with permission from [125]. Copyright 2009 American Chemical Society.

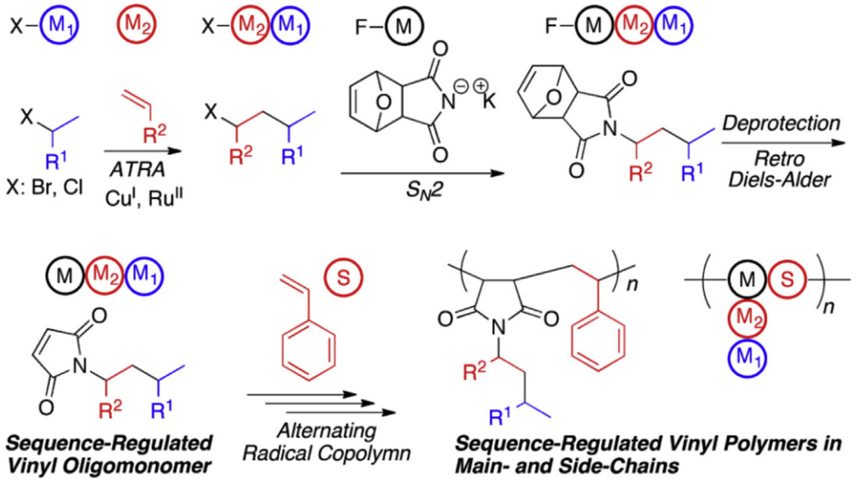


Fig. 7. Graft copolymer with sequence-regulated side chains by atom transfer radical addition and alternating radical copolymerization. Reprinted from [136] with permission. Copyright 2015 American Chemical Society.

by the direct radical polymerization of N-allylmaleimide with substituted styrene due to the strong alternating behavior and predominant fast cross-propagation of styreneic and maleimide double bonds [138]. The pendant double bonds are available for future modification. The RAFT cyclocopolymerization of maleic anhydride and difunctional styrenic monomers that contain tri- or tetra(ethylene glycol) moieties led to a series of copolymers with crown ether cavities [139]. The crown ether cavities exhibited selectivity for dialkylammonium ions and the copolymers may have potential in size-selective complexations.

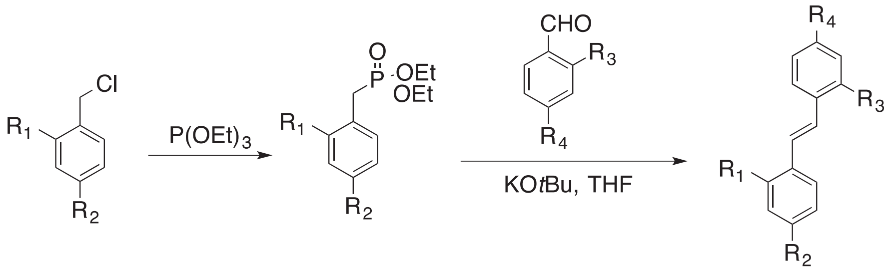
2.3. Semi-rigid stilbene-containing alternating copolymers

The chain-growth homopolymerization of *trans*-stilbene ((*E*)-1,2-diphenylethylene) is very difficult to achieve because of its steric constraints [9]. However, electron-rich *trans*-stilbene monomer readily radically copolymerize with electron-poor monomers like maleic anhydride or N-substituted maleimides in an alternating fashion due to both the electronic effects and reduced steric stress [140]. The first preparation of the stilbene and maleic anhydride alternating copolymer was reported in 1930 by Wagner-Jauregg [141], and it was also said to be the earliest report of a copolymerization in literature [142]. The copolymer was insoluble in common solvents and the insolubility was assumed to be from crosslinking [140,141]. Vogl, however, discovered that these copolymers were not crosslinked by finding that the stilbene-maleic anhydride copolymer was soluble in basic solution, when anhydride rings were opened and converted into salts [143].

Another possible reason of the poor solubility of unsubstituted stilbene and maleic anhydride is the strong aggregation of the copolymers, therefore the solubility of the substituted copolymers greatly increased due to the disruption of copolymer aggregation [144]. Moreover, functional substituents work as a powerful tool in the construction of highly functional polymeric materials. Our group has been working on the design and synthesis of functionalized stilbene and maleic anhydride/N-substituted maleimide comonomers and the corresponding alternating copolymers [140,144–157]. These novel copolymers possess sterically congested backbones and precisely placed functional groups arising from the strictly alternating copolymerization. We have incorporated these alternating sequences into block copolymers and crosslinked copolymers and studied their interesting properties and potential applications.

Most of the substituted stilbenes in our studies were synthesized by the Wittig–Horner reaction (Scheme 3) [158]. The substituents include methyl [144,149], dialkyl amino [145,148,154,155], and *tert*-butyl carboxylate [146,147,149,150,152,153]. Both the type and the position of the substituents on the stilbene monomer affect the rate of the copolymerization and the properties of the copolymers. Stilbene with electron-donating groups, like methyl and dialkyl amino groups undergo faster copolymerization while the stilbene bearing electron-withdrawing carboxylate needs a higher temperature to efficiently copolymerize [147]. The N-substituted maleimides were usually synthesized from a two-step route, in which maleic anhydride was mixed with a primary amine to produce a maleamic acid, which was then dehydrated to form a maleimide. The substituents have minimal effect on the electron-deficient nature of maleimides, but different from maleic anhydride, maleimides can radically homopolymerize [159]. Therefore, although alternating copolymerization predominates when stilbene or styrene monomers are present, there will be maleimide-maleimide dyads in the copolymers [140].

Our initial studies of substituted stilbene-maleic anhydride alternating copolymers indicated significant chain stiffening in solution, as evidenced by a constant hydrodynamic radius (10 nm) in the temperature range of 10 °C and 40 °C, and no observable glass transition below 250 °C [155]. Furthermore, the ^{1}H NMR of these polymers showed broad backbone and aromatic peaks [144], which is related to strong homonuclear dipolar coupling and slow proton relaxation rates [160]. Double-quantum heteronuclear local field solid state NMR showed that the maleic anhydride was enchained in all *cis* configuration when N,N,N′,N’-tetraethyl-4, 4’-diaminostilbene was the comonomer [148]. Moreover, the cast film of the stilbene and N-(2-methylphenyl)maleimide copolymer exhibited large negative birefringence induced from the conformational constraints [157]. All this evidence revealed the hindered rotation and the limited movement of these alternating copolymers due to their sterically crowded backbones. A detailed study on the chain stiffness of a series of *tert*-butyl group-containing stilbene and styrene alternating copolymers was conducted using SEC and SAXS, and the persistence lengths (l_p) of these copolymers fell into the range of 2 and 6 nm [147]. Compared to the flexible polystyrene ($l_p = 0.9$ nm) [161] and the rigid polyphenylene ($l_p = 13$ nm) [162], these alternating copolymers are classified as semi-rigid polymers (Fig. 8). The same series of copolymers also showed nanoporosity, which is due to the internal free volume resulted from the



R_1, R_3 = H, Me; R_2, R_4= H, Me, $N(alkyl)_2$

Scheme 3. Synthesis of substituted trans stilbenes using Wittig-Horner reaction. Reproduced from [144] with permission. Copyright 2010 Elsevier.

inefficient chain packing, and the BET surface area of these polymers increased as the increasing of the l_p [151]. When the semi-rigid stilbene-maleimide alternating sequence was incorporated into divinyl benzene hypercrosslinked polymers, the precursors showed increased T_g, which reduces some pore collapsing during the post-crosslinking step [149].

Among the various functional groups we incorporated into the alternating copolymers, the dialkylamino [145,148,154,155,157] and the *tert*-butyl group carboxylate [146,147,150–153] groups are of special interests, since they can be converted into ammonium and carboxylic acid, respectively. In addition, the enchained maleic anhydride groups can be hydrolyzed and form two carboxylic acid groups. Using the chemistry described above, we synthesized a series of semi-rigid polyelectrolytes and polyampholytes [145,152–154,156]. The polyampholyte diblock copolymers formed polyion complexes, and exhibited an unusual “like-charge” attraction in response to pH and salt changes (Fig. 9) [145,156]. This antipolyelectrolyte effect is manifested by the semi-rigid polymer backbone induced dipole-dipole interactions of the condensed counter ions. The polyanions were prepared from the *tert*-butyl group protected precursors, and the organic soluble precursors facilitated accurate molecular weight determination by SEC [153]. The resulting polyanions showed excellent anti-HIV activity. It is hypothesized that the increased rigidity of the polyanions enhanced the electrostatic interaction with the V3 loop of the HIV-1 glycoprotein 120 or glycoprotein 41 [146]. This deprotection strategy was also utilized in a novel two-step synthesis of nanoporous polymers. The semi-rigid polymer backbone along with the high crosslinking density resulted in a highly functionalized network with high BET surface areas (up to 810 m^2/g) and good potential in CO_2 capture applications (Fig. 10) [150].

The alternating copolymerization behavior of stilbene and maleic anhydride or maleimide was also used to synthesize specially structured polymers. For example, a processable polymer resin was resulted from the self-polymerization of a stilbene-maleimide A-B monomer [163], and the single-chain polymer nanoparticles were synthesized from the alternating copolymerization of maleic anhydride or N-ethyl maleimide with stilbene functionalized polystyrene chains [164].

2.4. Sequence-controlled alternating copolymers

Biomacromolecules, such as DNA and protein, store enormous genetic or functional information by arranging the sequence of nucleic acids or amino acids in their primary structures. However, synthetic polymerization techniques usually lack control over the monomer sequential arrangement. Although the library of synthetic polymers contains hundreds of thousands of different monomers, the potential of information storage in synthetic polymers is still limited [165]. Much effort has been invested to tap this potential in synthetic copolymers, however, the resulting step-by-step solid-state synthesis or other semibiological approaches are restricted by the speed and scale of synthesis [166].

Over the last decade, the unique kinetic feature of donor-acceptor alternating copolymerization has inspired polymer chemists to design a new strategy in the sequence-controlled polymerization. In 2007, Lutz and coworkers first introduced a sequence-control strategy which is based on the ATRP

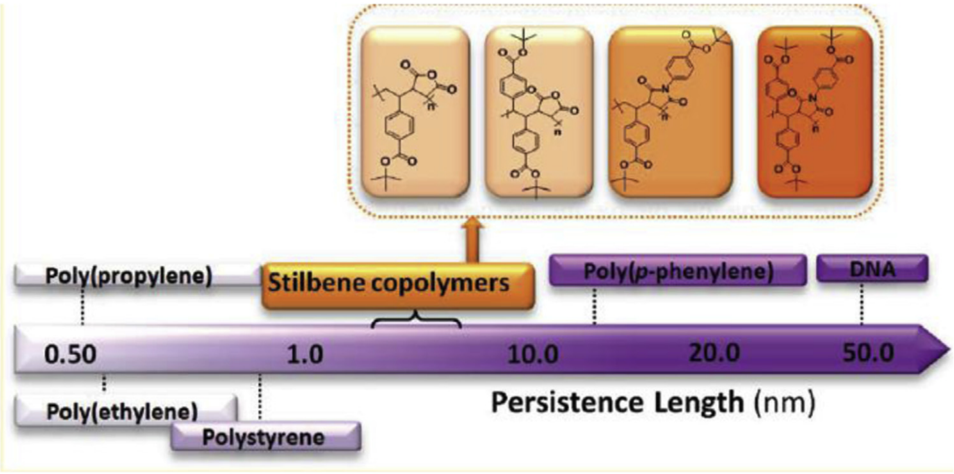


Fig. 8. The comparison of the persistence length of a series of semi-rigid alternating copolymers with other polymers. Reprinted from [147] with permission. Copyright 2012 American Chemical Society.

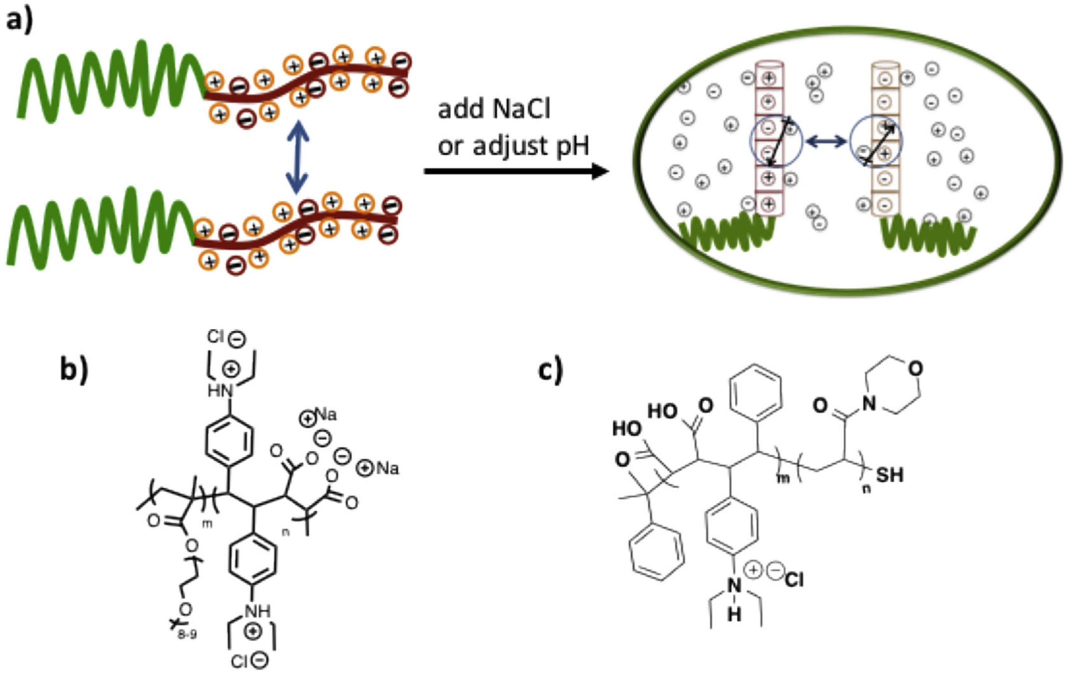


Fig. 9. a) The graphic demonstration of “like-charge” attraction, and the structures of two block copolymers b) OEGMA-*b*-(TEDASti-alt-MA) and c) (DEASti-alt-MA)-b-ACMO that shows “like-charge” attraction. Reproduced with permission from [156], [145], and [154], respectively. Copyright 2016 WILEY-VCH, 2007 American Chemical Society, and 2014 WILEY-VCH.

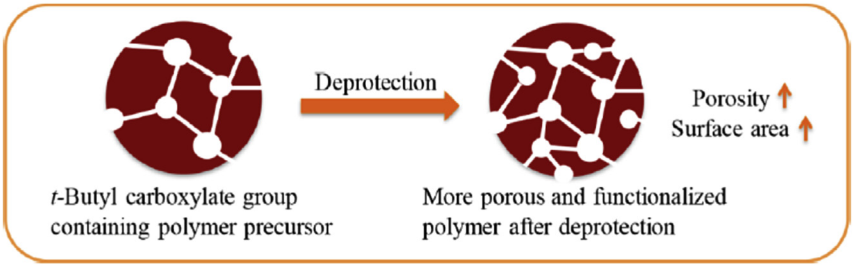


Fig. 10. Nanoporous polymers from cross-linked polymer precursors via *tert*-butyl group deprotection. Reprinted from [150] with permission. Copyright 2015 American Chemical Society.

copolymerization of donor and acceptor monomer pairs (Fig. 11) [167]. The basic principle of this method was to utilize the time-controlled addition of a small amount (usually 1 mol equiv. as compared to initiator) of the acceptor monomers (i.e. N-substituted maleimides) during the controlled polymerization of a large excess donor monomer (i.e. styrene) [167]. The strong alternating copolymerization tendency of the newly added acceptor with the donor monomers leads to an immediate consumption of the acceptor monomer. Ideally, one acceptor monomer is inserted into each polymer chain at the same chain-location after each addition. However, although the alternating copolymerization is kinetically favored, the distribution of the acceptor in each chain is not strictly uniform and remains statistical in a rather narrow range [166]. Still, this method revealed new opportunities for precisely encoding information into polymer chains.

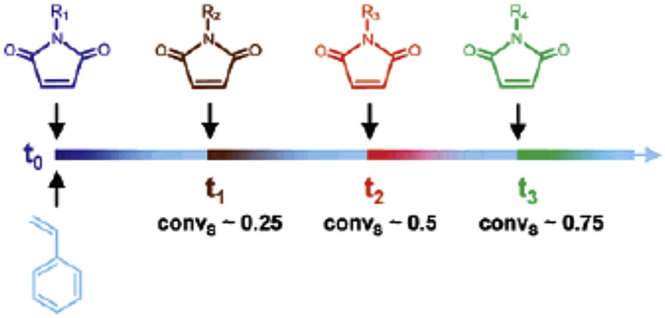


Fig. 11. Concept of the Sequence-Controlled Copolymerization of Styrene and Various N-Substituted Maleimides. Reprinted with permission from [180]. Copyright 2011 WILEY-VCH.

N-substituted maleimides are mostly used as the acceptor monomer in this approach. One major reason is that the functionalization at the N-site is relatively easy and does not significantly affect the electron-deficient nature of the maleimide double bond [9]. Therefore, the enormous stockroom of N-substituted maleimides provides abundant combinations for encoding information into the polymer chains. The substituents include alkyl, aryl, acyl, benzyl, propargyl, PEG, and etc [166,168,169]. Some substituents may hinder the polymerization by interfering with the radical or interacting with the metal catalyst, therefore substituents such as phenol [168], terminal alkynes [168,170,171], carboxylic acids [168], and primary amines [170] need to be protected before

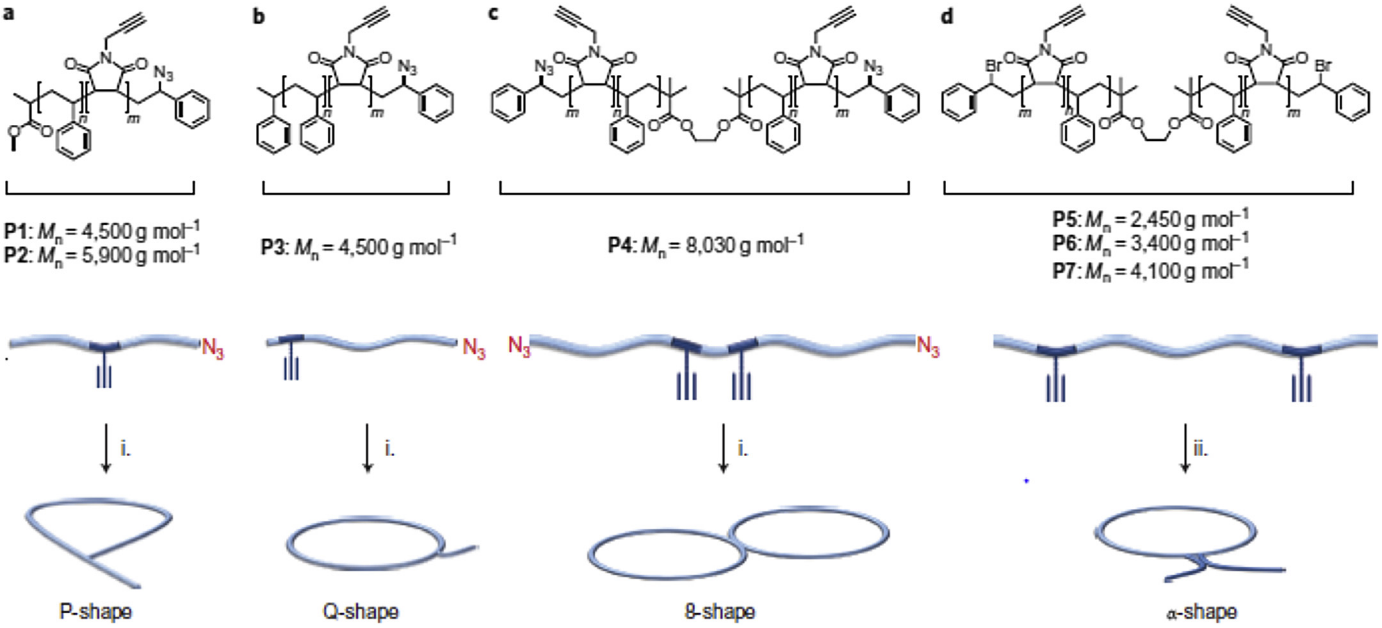


Fig. 12. Different topology (α-, P-, Q-, and 8- shapes) achieved using sequence-controlled polymers, i represents coppor-catalyzed azide-alkyne 1,3-dipolar cycloaddition, and ii represents Glaser coupling. Reprinted with permission from [170]. Copyright 2011 Nature Publishing Group.

being used in this sequence-controlled procedure. There are also some substituents that cannot be used in this procedure due to solubility or other problems, such functionalities can be achieved by post-polymerization modification [166,168]. For example, protected alkyne-containing maleimides could be easily modified by Cu-catalyzed azide-alkyne "click" reaction, Glaser coupling, thioyne reaction, Sonogashira coupling [166,170–173], or self-reacted by Eglinton coupling [174], and pentafluorophenyl ester-containing maleimide could attach the amine groups or add on a variety of functional groups using the thiol-*para* fluoro "click" reaction [174].

The donor monomer provides the main backbone of the polymer, therefore it defines the most of the properties like the chain rigidity, solubility, and crystallinity [166,175–177]. Styrene is often used as the donor monomer mainly because the controlled radical homopolymerization and copolymerization of styrene has been extensively studied and it is convenient to monitor the kinetics in the sequence-controlled process [167,168]. Some substituted styrene monomers can also be employed as the donor monomer, however, only electron-donating substituents are suitable for this process because they are favorable to the alternating copolymerization and can ensure the precise insertion of the acceptor monomers into the chains [166]. Therefore, *para*-alkyl-substituted styrene [167,175], 4-acetoxystyrene [178], 4-*tert*-butoxystyrene [178], and vinyl benzyl amine [179] showed better performances in the precise insertion of maleimides compared to the esters of vinyl benzoic acid or vinyl benzyl chloride [166].

Controlled radical polymerization (CRP) is crucial for this sequence-controlled procedure because it ensures all chains grow simultaneously [167]. ATRP is the most commonly used technique in their process [166,167,180], while NMP was also reported [175,177]. The precision in time-controlled addition also affects the precision insertion of the maleimides units, therefore robotic, automated protocols were shown to improve the experimental conditions [181]. Under such conditions, up to 8 nonoverlapping maleimide zones could be inserted within 100 styrene units, which corresponds to n^8 microstructure arrangements within a chain length of 100 when n kinds of different maleimides are used. Other than encoding information on the primary structure of the polymer chains, the precisely enchained maleimides units could also be utilized for creating secondary structures, and further affect the properties of the materials. For example, the small amounts of maleimides have significant influence on the side-chain crystallinity of poly(octadecylstyrene) [175], and the insertion of maleimides which contain reactive functional groups after deprotection could result in intramolecular bridges [170,182] (Fig. 12) and achieve different topology such as α-, P-, Q-, and 8-shapes [182], periodic multi-block polymers [183] and compartmentalized single-chain objects [174].

3. Conclusion

Alternating copolymerization has origins dating back, almost 90 years, to the early days of synthetic polymer chemistry [141], and it has grown to be a vibrant and productive area of current polymer chemistry for producing new creative functional polymer structures with precise placement of functional groups along the polymer backbone. This feature article focuses on one important class of alternating copolymers—electron rich benzylidene monomers such as styrene and stilbene derivatives and their alternating copolymers with electron poor maleic anhydride and N-substituted maleimides. The unique nature of the fast cross-propagation step that leads to alternation enables the copolymerization of monomers that do not homopolymerize, such as stilbene and maleic anhydride, to form strictly alternating copolymers. The fast cross-propagation also results in predominately alternating dyad placements of styrenic monomers with N-substituted maleimides at 1:1 comonomer feeds.

The alternating copolymer structures provide a plethora of functional polymer backbones with semi-rigidity, which can be controlled by comonomer selection, that suggest unique optical, mechanical, solution, and biological properties. The fast cross-propagation is now enabling the synthesis of unprecedented sequence regulated structures providing new insights into the power of synthetic polymer chemistry to synthesize precision copolymers. In the future, it is no doubt that benzylidene based monomers will be creatively employed to make new and interesting alternating copolymers that assist polymer scientists in understanding fundamental polymer structure property relationships as well as providing new materials with desired properties for applications in emerging technology areas.

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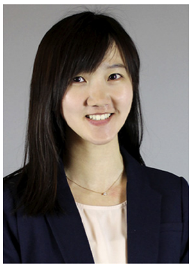

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