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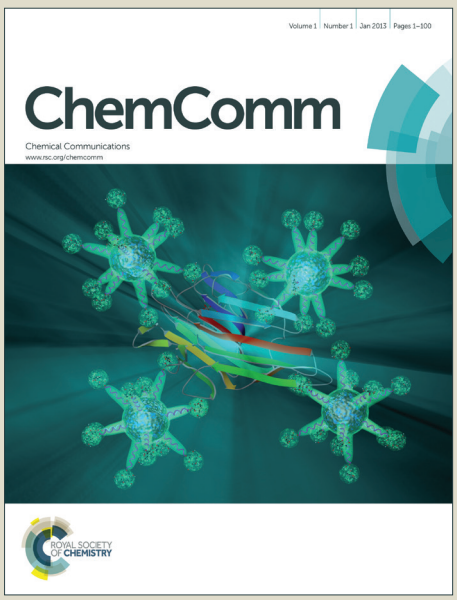

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Block copolymer self-assembly controlled by the "green" gas stimulus of carbon dioxide

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Qiang Yan and Yue Zhao*

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Stimuli-responsive macromolecules have spurred much interest in polymer science. Inputting an external stimulus to these polymers, they can modulate their chain structures and self-assembled architectures, for functional outputs. This appealing feature has made this class of polymer materials promising for many emerging applications. In order to apply these polymer systems in organisms and further make them adaptive to physiological environment, it is important to explore new stimulation modes. In this Feature Article, we review the recent development of using carbon dioxide (CO_2) as a stimulus for tuning or controlling block copolymer (BCP) self-assembly. We show that a series of CO_2-responsive functionalities can easily be incorporated into BCP structures, and that rationally designed BCPs can have their self-assembled structures undergo drastic changes in size, shape, morphology and function, controlled by the amount of CO_2 in aqueous solution. This gas stimulus has some distinct advantages over other conventional stimuli: it is truly "green" for the environment of the target polymer system without any chemical contaminations; the stimulating strength or magnitude can be precisely adjusted with the continuous gas flow; and, being a key metabolite in cells, it provides a convenient physiological signal to allow synthetic polymer systems to mimic certain properties of organelles and act as intelligent macromolecular machines and devices.

1. Introduction

Since the advent of polymer science as a significant discipline in chemistry, chemists have a strong desire to seek and design a class of "smart" macromolecules that can receive an external input-signal and automatically produce an output-reaction.[1-3] Stimuli-responsive polymers, defined as macromolecules that can sense a weak stimulating signal in their environment (e.g. pH, temperature, light, redox agents, enzymes, ions, mechanical force, electric and magnetic field)[4-10] and respond by displaying relatively large physical or chemical change for different functional expressions, have established themselves as such "smart" materials. In the past decade or so, stimuli-responsive polymers have attracted growing interest due to their tremendous potential in a broad spectrum of applications such as functional materials,[11-15] optoelectronics,[16-18] diagnostics,[19-21] bio-imaging,[22] sensors,[23-25] nanomedicine,[26-28] and nanotechnology.[29-30] In particular, one of the most exciting characters of such polymers is that some of their stimulus-response patterns are similar to the biosignal-reactive behaviors in biological systems, which might offer access to unravelling the mechanisms of biological activities and guide development of biomimetic materials. In recent years, many emerging and prospective applications of stimuli-responsive polymers require that they adapt to human physiological conditions for intracellular utilization. However, the traditional stimulation modes cannot meet certain requirements. For instance, majority of switchable stimuli, including pH, ion, redox, and enzyme, need repeated addition of chemical agents to the polymer solution, which may contaminate the system and weaken the sensitivity due to residue accumulation.[31] Beyond that, the field forces of other stimuli such as light, electrical, magnetic, and mechanic force, may cause damage to biological tissue and cellular genetic substance.[32] Therefore, to eliminate byproducts generation during the stimuli-responsive process and satisfy the demanding conditions for applications in human body, it is of primary importance to explore novel stimulation mode.

Carbon dioxide (CO_2) would be a proper stimulus to apply to the human physiological environment. It is a key metabolite in cells and possesses good biocompatibility and biomembrane permeability.[33] It can react selectively with a number of specific functionalities such as tertiary amine, amidine, and guanidine groups to convert them to hydrophilic species, and, due to the reversible nature of those reactions, its complete removal is readily achievable by passing an inert gas (argon or nitrogen) into or mild heating of the solution, which allows the CO_2-reactive functional groups to recover their initial forms. This robust switchability means that the CO_2 switch-on/-off cycle can be repeated many times without any contamination by accumulated chemical agents.[34] Hence, CO_2 is a truly mild and

"green" stimulus to the environment of the target polymer system. Moreover, as a stimulus, the continuous flow of the gas into a polymer solution means that the stimulating strength or magnitude can be precisely modulated by the amount of CO_2. As will be shown, this feature can be particularly useful for observing sequential evolution of polymer assemblies. Last, but not least, knowing that CO_2 is a "greenhouse" gas playing a crucial role in global warming and climate change,[35] any routes or strategies for valorizing the use of CO_2 will contribute to address the environmental concern.[36-37]

On the other hand, polymer self-assembly is an attractive and programmable strategy for fabricating diversified architectures from nano- to macroscopic scale.[38-39] In particular, block copolymers (BCPs) with amphiphilicity can self-assemble into different structures and morphologies in aqueous solution for functional materials.[40] Despite the enormous progress made in this field, there still remains a most challenging and fascinating problem as to how to improve the controllability and intelligence of polymeric self-assemblies. To address this issue, stimuli-responsiveness has been implemented into BCP self-assembled systems, and the various stimuli such as pH, temperature, redox, enzyme, and light, to name only a few, have been successfully developed to tune BCP self-assembly behaviors.[41-43] In general, a fundamental strategy to control the BCP self-assembly is to change the amphiphilicity, i.e., the balance of the hydrophobic-hydrophilic fraction, via the action of a given stimulus on the BCP. Basically, if the application of a stimulus can alter the amphiphilicity of a BCP, its self-assembly behavior in aqueous solution may be changed accordingly.[44] On the basis of this principle, considering that CO_2 can be used to change the BCP amphiphilicity in many ways due to its reactivity with some functional groups, it is anticipated that CO_2, thanks to all the interesting features as mentioned above, can become a valuable stimulus for controlling BCP self-assembly.

In this Feature Article, we present a review focused on the theme of recent emerging utilization of CO_2 in controlled BCP self-assembly and their potential applications in biomimicking and material science. These BCPs can be categorized into three types based on the difference in the used CO_2-reactive functionality (tertiary amine, amidine and guanidine). In particular, we discuss the latest developments by emphasizing the rational in the BCP structural design and how to realize the variety of CO_2-triggered changes in size, shape, morphology and function of their assemblies. Finally, we forecast the possible applications and potential perspectives of CO_2-responsive block copolymers.

2. CO_2-Responsive Functional Groups

2.1 Tertiary Amines

Bases can be defined as reagents capable of grabbing protons to generate carbanions. For organobases, the most commonly known and employed are amines (—NH_2), which can generally exhibit weak basicity for responding to the weak acids such as CO_2. One of the simplest basic functional group responding to CO_2 is tertiary amine (—NR_1R_2). As a traditional organobase, it can sensitively respond to pH stimulus, which is the reason for which polymers like poly(*N,N*-dimethylaminoethyl methacrylate) (PDMAEMA), poly(*N,N*-diethylaminoethyl methacrylate) (PDEAEMA) and poly(*N,N*-diisopropylaminoethyl methacrylate) (PDPAEMA) bearing tertiary amines possess typical pH-responsiveness.[45] Because of the pK_a values of these tertiary amine groups ranging from 6.5 to 8.0, not only they can react with strong acid such as HCl, they are also able to react with CO_2, the weak gaseous acid. Considering the CO_2 gas hydration equilibrium reaction, Eq.(1), and the following ionization reaction, Eq.(2), the whole equilibrium reaction is an amine protonation reaction as shown in Fig. 1, and the equilibrium constant (K_t) between tertiary amine and CO_2 gas is in the range of K_t = 1.3—45. In view of the magnitude order of K_t, this reaction is a typical reversible equilibrium. In general, one can simply bubble an inert gas such as argon (Ar) and nitrogen (N_2) to the aqueous media to fulfill an opposite deprotonation effect.

$$CO_2(g) + H_2O(aq) \Leftrightarrow H_2CO_3(aq).....K_h = 1.7\times10^{-3}.....(1)$$

$$H_2CO_3(aq) \Leftrightarrow H^+(aq) + HCO_3^-(aq).....K_{a1} = 2.5\times10^{-3}...(2)$$

$$-NR_1R_2(aq) + CO_2(g) + H_2O(aq) \Leftrightarrow -NHR_1R_2(aq) + HCO_3^-...K_t = 1.3 \sim 45...(3)$$

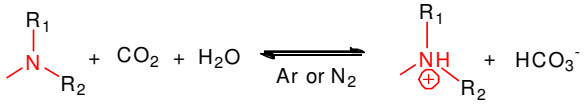


Fig. 1 The reversible protonation and deprotonation reaction of tertiary amine upon CO_2 and Ar stimulation

As a conventional functional group, tertiary amines can be readily synthesized and several tertiary amine-containing polymerizable monomers are commercially available. Moreover, one of the most important advantages of tertiary amine is their moderate CO_2-sensitivty and, generally, low hydrolysis side effect in aqueous media. Hence if we introduce tertiary amine groups to amphiphilic block copolymer chain structure, upon CO_2 stimulation, one or more specific blocks can be protonated, which results in the alternation of BCP amphiphilicity. The easily accessible continuous variation of the amphiphilicity and the robust reversibility of this change make CO_2 attractive for controllable and tunable BCP self-assembly.

2.2 Amidines

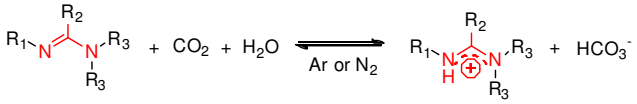


Fig. 2 The reversible protonation and deprotonation reaction of amidine species upon CO_2 and Ar stimulation

Amidines[46,47] are nitrogen analogues of carboxylic acids containing two nitrogen atoms in the 'amide' and 'imine' functional groups. Structurally, they correspond to the amine equivalent of carboxylic esters. As compared to tertiary amines, their pK_a values are within the range of 5—12 (average p$K_a \approx 9.0$) and the protonation reaction occurs on the imino nitrogen which leads to the formation of a symmetrical amidinium ion that can be stabilized by resonance, as shown in Fig. 2. Due to the stronger basicity of amidine groups, the equilibrium constant between CO_2 and amidine should be much larger ($K_t \approx 10^2$—10^5) than that of tertiary amines, which means that amidine-containing polymer is of higher CO_2-sensitivty and faster responsive speed. Although the amidine species possess a number of advantages and a few studies have succeeded, an inevitable problem is the natural hydrolysis effect that exists in

the absence of CO_2 stimulus, which is possible to influence the polymer self-assembly behaviors. Furthermore, as compared to tertiary amine with simple structures, the amidine structure is more complicated and may require multistep organic synthesis.

From an application viewpoint, amidine-containing molecule shows many interesting properties. Since Jessop *et al.* reported the aliphatic amidine-containing surfactants for CO_2-switchable solvent in 2005, amidine-containing molecules have been much studied and show lots of interesting features.[48-50] Furthermore, the amidine-based structural motifs are known to have a broad variety of biological activities. There is no doubt that the amidine functionality is among the most useful for designing CO_2-responsive BCPs and realizing the BCP self-assembly for biomimetic regulation.

2.3 Guanidines

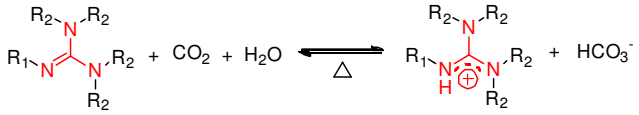


Fig. 3 The reversible protonation and deprotonation reaction of guanidine species upon CO_2 stimulation

Guanidines[51] are amine derivatives that carry three nitrogen functions (one 'imine' and two 'amides') on one carbon atom. This structure corresponds to the amine equivalent of orthoester (carbonimidic diamides). The general pK_a of such species is *ca.* 13.5, but this can be altered via appropriate substitutions of the compound.[52] Given the resonance stability of their conjugated acids, they are categorized as organic superbases, especially the alkyl-substituted guanidine derivatives. Normally, guanidines can be protonated by CO_2 to convert into guanidinium species (Fig. 3). However, in view of its high pK_a value, the reversible reaction through bubbling Ar or N_2 is too difficult to realize. Guanidine is common in most of biomolecules;[53] perhaps the most recognizable compound with this type of functional group is the naturally occurring α-amino acid L-arginine, which plays a crucial role in many biological activities such as cell division, the wound healing, removing ammonia from the body, and the release of hormones.[54] Thus constructing guanidine-containing block copolymer and exploring how to utilize CO_2 to drive their controlled self-assembly process holds promise for using synthetic polymer assemblies to biomimick cell bio-functions.

2.4 Imidazoles

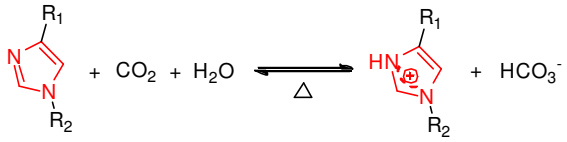


Fig. 4 The reversible protonation and deprotonation reaction of imidazole species upon CO_2 stimulation

Imidazoles[55] form a common family of planar 5-membered heterocycles sharing the 1,3-dinitro ring. This ring system is present in important biological building blocks, such as amino acid histidine, related hormone histamine, and many drugs. Alkyl substituted imidazole is of high basicity and its pK_a value is at the range of 10—14.5 according to the various substituent groups. When CO_2 is added in aqueous solution, the imidazole can be protonated and convert to an imidazolium salt (Fig. 4). Because of the ring π-structure, this imidazolium species is stable in solution. This feature can stabilize the BCP assemblies in the presence of CO_2 stimulation.

According to the different pK_a values of the above CO_2-responsive functionalities, a priori their sensitivity to the presence of CO_2 in aqueous solution may be different. However, all of them are capable of reacting with CO_2 and being protonated to a charged species, and, more importantly, their protonation degree can be continuously and precisely tuned by adjusting the amount of CO_2 in a given solution. Therefore, by introducing these functionalities in amphiphilic BCPs, the amphiphilicity can easily be controlled under CO_2 stimulation, which is the basis of using CO_2 as a convenient "green" yet powerful stimulus to govern and stimulate BCP self-assembly behaviors in various ways and for different applications (Fig. 5).

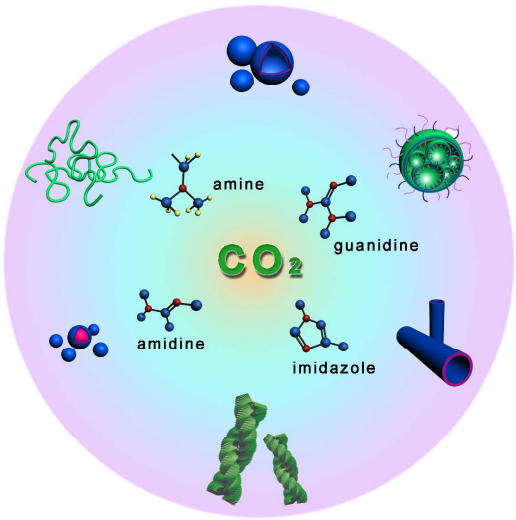


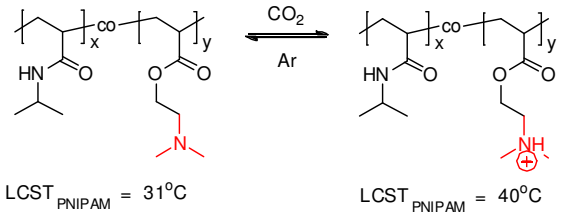
Fig. 5 CO_2-sensitive functional groups and their mediated BCP self-assembly.

3. CO_2-Tunable Block Copolymer Controlled Self-Assembly

3.1 Tertiary Amine-Containing Block Copolymers

In general, specific polymers with tertiary amine groups have been widely used in the pH-responsive BCP self-assembly process.[4] Great effort has been devoted to this topic. For example, PDMAEMA is a typical pH-responsive tertiary amine-containing polymer whose assemblies have been exploited for many applications including biomaterials, sensors, nanocarriers, and nanoreactors.[56] However, there were rare reports noticing that PDMAEMA in aqueous solution can also respond to the presence of CO_2 owing to its weak basicity. In 2012, Zhao's group reported that PDMAEMA exhibits a CO_2-switchable water solubility as indicated by a CO_2-tunable lower critical solution temperature (LCST) and, more importantly, demonstrated a general strategy based on using tertiary amine-containing monomers to turn, in principle, all LCST thermo-sensitive polymers switchable by CO_2.[45] The principle is shown in Figure 6. By simple polymerization, a statistical copolymer of poly(*N*-isopropylacrylamide)-*co*-PDMAEMA P(NIPAM-*co*-DMAEMA) was synthesized. PNIPAM was chosen because it is representative example of an important class of polymers

displaying a LCST in water. The P(NIPAM-*co*-DMAEMA) copolymer can be soluble in water below its LCST (31 °C) and becomes insoluble at temperature above the LCST. By passing CO_2 in the solution for 5 min, DMAEMA comonomer units in the copolymer chains are partially protonated and thus positively charged, which induces an increase in the polymer LCST to ~ 40 °C. Reversibly, bubbling Ar gas to the copolymer solution for 10 min for removal of CO_2 results in an opposite deprotonation effect of DMAEMA, which brings the LCST back to the initial value. The CO_2-induced LCST change means that the copolymer can be switched between soluble and insoluble state at a constant solution temperature near 40 °C by adding and removing CO_2, respectively. Likewise, CO_2-swichable water solubility was also easily obtained for poly[2-(2-methoxyethoxy)ethyl methacrylate] ($PMEO_2MA$), belonging to another important family of LCST polymers, by introducing a number of DMAEMA comonomers. In a similar way, other polymers with tertiary amine side groups such as PDEAEMA, PDPAEMA and poly(3-*N',N'*-dimethylaminopropyl acrylamide) (PDMPA), are also CO_2-responsive and their monomers can be used as CO_2-reactive units to be copolymerized to impart them with CO_2-sensitive water solubility.[57] The discovery is important, because by having one (or more) of these easily accessible CO_2-responsive polymers or random copolymers (using commercially available monomers) as one (or more) block(s) in amphiphilic BCPs, the hydrophilic-hydrophobic balance in aqueous solution can be continuously tuned or changed by the amount of CO_2. This great simplicity and generality makes the door wide open to CO_2-switchbale polymers in general and CO_2-controllable BCP self-assembly in particular.



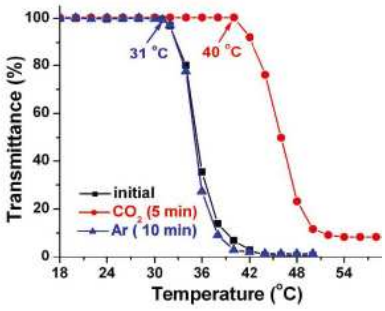


Fig. 6 CO_2-tunable LCST transition for a random copolymer P(NIPAM-*co*-DMAEMA) (top); and transmittance plotted against temperature for aqueous solutions of the copolymer before and after CO_2 and Ar stimulation (bottom). Rearanged from ref.45.

Stimuli-responsive polymer hydrogels, responding to light, pH, temperature, and redox, have been much studied in recent years due to their broad applications in controlled drug release, scaffolds for tissue engineering, and actuators in biomedical devices. ABA-type triblock copolymers with water-soluble B block and two hydrophobic A wings are able to form physically cross-linked hydrogels. Generally, this type of polymer hydrogels comprises a network of interconnected "flower" micelles that are self-assembled by the ABA triblock copolymer. If the A block is a thermosensitive polymer with a certain LCST, the gel state can be observed when the solution temperature is above its LCST and the gel-to-sol transition occurs below the LCST. Zhao's group has designed and synthesized a CO_2-responsive ABA triblock copolymer composed of the water-soluble poly(ethylene oxide) (PEO, acting as the B block) and hydrophobic P(DMAEMA-*co*-MEO_2MA) (acting as the A blocks), as shown in Fig. 7a.[58] Hydrogel was formed at 37°C, above the LCST of the P(DMAEMA-*co*-MEO_2MA) block (~30 °C); the gel-to-sol transition was observed upon addition of CO_2 due to the upward shift of the LCST to above 37 °C making all blocks soluble in water. In the same study, it was reported that altering the copolymer structure by replacing DMAEMA comonomer units with methacrylic acid (MAA) as CO_2-reactive groups, an opposite sol-to-gel transition could be observed, i.e., the triblock copolymer forms a gel upon addition of CO_2 as shown in Fig. 7b. In this case, at 35 °C, the triblock copolymer is soluble in water; upon addition of CO_2, the protonation of MAA converts charged carboxylic acid to the neutral form, which leads to a downward shift of the LCST of the P(MAA-*co*-MEO_2MA) block to 24 °C. As a consequence, the triblock copolymer becomes amphiphilic and the gel state is formed. In both cases, the transition between the gel and sol state is totally reversible and repeatable upon alternating CO_2 and Ar stimulus. This work demonstrates a general strategy to manipulate BCP's sol-to-gel self-assembly transition via tuning CO_2 stimulation. This work shows an example of utilizing CO_2 as a trigger to construct macroscopic polymeric self-assemblies with smart functions.

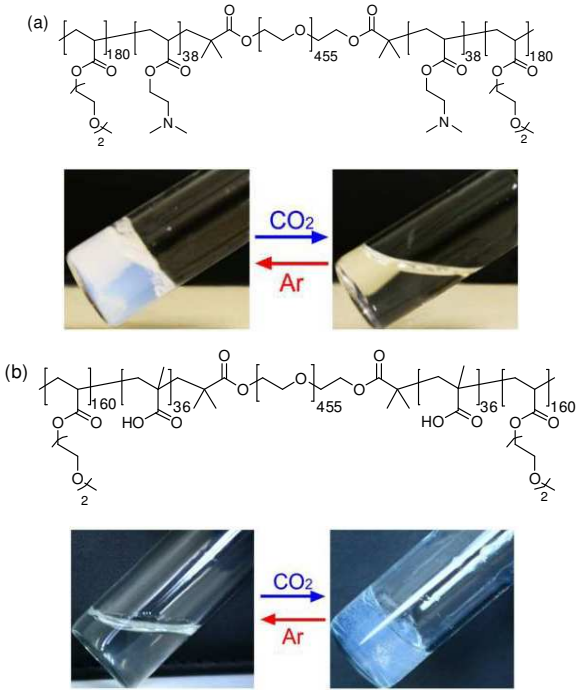


Fig. 7 (a) The ABA-type triblock copolymer P(DMAEMA-*co*-MEO_2MA)-*b*-PEO-*b*-P(MEO_2MA-*co*-DMAEMA) and its CO_2-induced gel-to-sol transition. (b) The triblock copolymer P(DMAEMA-*co*-MAA)-*b*-PEO-*b*-P(MEO_2MA-*co*-MAA) and its CO_2-induced sol-to-gel transition. Rearranged from ref.58.

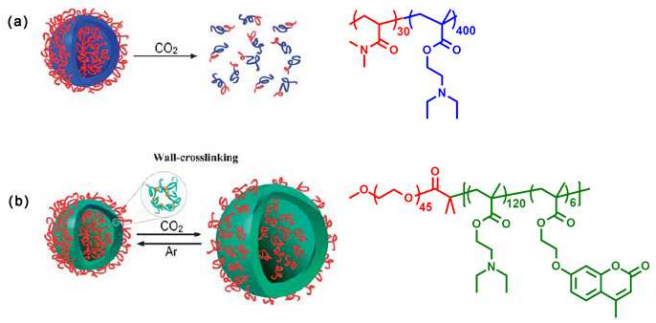


Fig. 8 (a) Diblock copolymer PDMA-*b*-PDEAEMA and the CO_2-induced dissociation of its vesicle self-assembled in aqueous solution. (b) Diblock copolymer PEO-*b*-P(DEAEMA-*co*-CMA) and the "breathing" motion (expansion/contraction) of its cross-linked vesicle upon addition and removal of CO_2. From ref.59.

The above studies have proven that the water solubility of tertiary amine-containing polymers can easily be controlled by CO_2. Applying this ability to BCPs should enable the control of their self-assembled nanostructures. To this end, Zhao and co-workers reported another example.[59] They synthesized a diblock copolymer comprising a water-soluble poly(*N,N'*-dimethylacrylamide) block and a PDEAEMA block (PDMA-*b*-PDEAEMA). In neutral aqueous solution, because PDEAEMA is hydrophobic, the BCP can self-assemble into typical vesicular nanostructure with a size around 410 nm. As illustrated by Fig. 8a, by increasing the amount of CO_2 gas injected into the BCP solution from 0 mol% to 18 mol% with respect to the content of tertiary amine groups in the solution, the PDEAEMA block is gradually and increasingly charged, which results in first the swelling of the vesicle membrane and then the total dissociation of the vesicle as the PDEAEMA block becomes soluble in water. Furthermore, if PDEAEMA chains in the vesicle membrane are chemically cross-linked, when they become soluble in water due to the reaction with CO_2, they cannot be dissolved and the vesicle wall can only swell like a hydrogel. In other words, as depicted in Fig. 8b, the cross-linking preserves the vesicle structure while allowing it to expand under the CO_2 stimulation; after removal of CO_2, PDEAEMA block becomes again insoluble and the vesicle should shrink back to the initial state. This "breathing" motion was confirmed by using a designed diblock copolymer PEO-*b*-P(DEAEMA-*co*-CMA), in which a small amount of CMA (coumarin methacrylate) units (~5 mol%) in the CO_2-sensitive block) affords photo-cross-linking of the vesicle wall. The results showed the reversible vesicular expansion and shrinking upon addition and removal of CO_2. The extent of vesicle expansion depends on the vesicle wall cross-linking degree that is tunable with the dimerization degree of coumarin groups. It was observed that by lowering the cross-linking density from a dimerization degree of 90% to 60% to 30%, the vesicle expansion under CO_2 stimulus became increasingly important. At 30% of coumarin dimerization, the average hydrodynamic volume of the vesicle can increase by about 2100% triggered by CO_2. This is probably one of the biggest volume expansions of BCP vesicles induced by a stimulus, which demonstrates that the CO_2 can trigger the morphological transition of BCP assemblies.

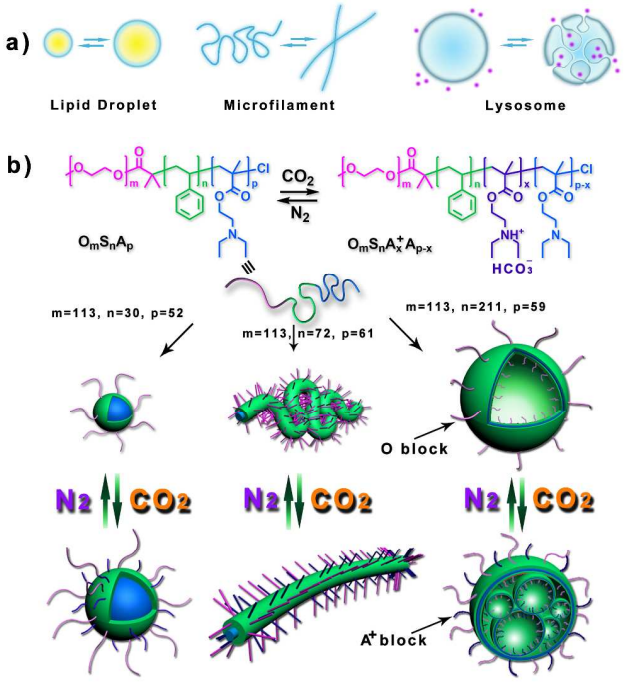


Fig. 9 (a) Schematic of the shape regulation of different organelles; and (b) CO_2-switchable triblock copolymers **OSA** and their CO_2-tunable controlled deformation for biomimicking the organellar shape. From ref.60.

As one of the most inherent characteristics and intriguing abilities of living organisms, the shape changes of organelles under physiological stimuli are keys to executing biological functions and maintaining cell vitality. For instance, several organelles show autonomous motions: intracellular lipid droplet organelle can self-regulate their globular size via some active biomolecules, so as to store or release internal nutrients; as cell moves or undergoes mitosis, microfilaments can alter shape from a curly status to a stretched fibrous form to assist cell motion; and lysosomes possess endocytosis whose membrane can be invaginated and pinched off for harmful solid particles uptake (Fig. 9a). Zhao's group recently demonstrated that CO_2 could act as a physiological trigger to biomimick these shape transformations of the organelles.[60] To this end, an ABC-type triblock copolymer, composed of outer hydrophilic PEO (termed as **O**), middle hydrophobic poly(styrene) (**S**), and CO_2-responsive PDEAEMA flank (**A**) was designed and synthesized. Having the same **O** block and a similar **A** block while varying the length of the **S** bridge, the **OSA** copolymers can self-assemble into three initial nanostructures: spherical micelles, worm-like micelles, and giant vesicles, in all of which the **A** blocks constitute the inner part of the cores (Fig. 9b). For the sample of $\mathbf{O_{113}S_{30}A_{52}}$ with the shortest **S** block, by adding CO_2 into the spherical micellar solution from 0 min to 30 min, these spheres can expand their size from 24 nm to 45 nm, which is in many ways reminiscent of the lipid droplet self-regulated "breathing" phenomenon (Fig. 9b, left). In the case of $\mathbf{O_{113}S_{72}A_{52}}$ containing a longer **S** block, the copolymer can self-assemble into curly and folded nanofibers in aqueous solution with an extremely high length/diameter ratio. When prolonging CO_2 stimulation time from 0 min to 30 min, the initial highly curly and folded nanofibers transform into straight and rigid nanowires (Fig. 9b, middle), which is similar to the elastic

telescopic motion of microfilaments. For the $\mathbf{O_{113}S_{72}A_{52}}$ with the longest **S** block, the copolymer can form giant lamellar vesicles with a size of ~600 nm. After CO_2 treatment, each giant vesicle is compartmentalized into dozens of smaller irregular vacuoles ranging from 40 to 180 nm and a continuous membrane separates these vacuoles (Fig. 9b, right). Such CO_2-triggered deformation of vesicles looks like, to some extent, the lysosomes' endocytosis behavior. The key in the triblock copolymer design, which allows the BCP assemblies to undergo various deformations, is to have the initially hydrophobic, CO_2-responsive PDEAEMA block located inside the inner part of the hydrophobic core and confined by the **S** layer; as the PDEAEMA chains become increasingly charged and hydrophilic upon CO_2 stimulation, they cannot dissolve freely but absorb more water. This study demonstrated that the synergy of corona-chain repulsion and core-chain restricted hydration is an effective principle for CO_2-regulated deformations of BCP assemblies and it is expected that the CO_2-controlled BCP models may offer new possibilities for biomimicking.

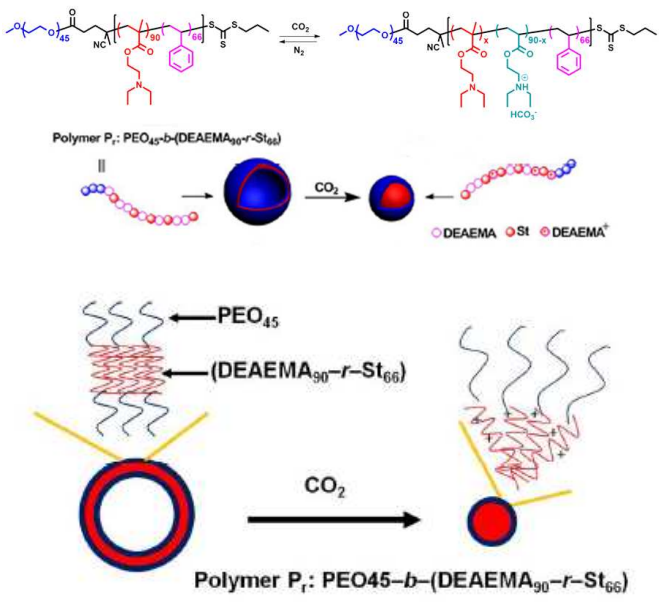


Fig. 10 CO_2-tunable vesicle-to-sphere morphological transition of block copolymer assemblies (top) and the transition mechanism (bottom). From ref.61.

In an alternative way, Feng et al. designed and synthesized a diblock copolymer, PEO-*b*-P(DEAEMA-*co*-S), in which the CO_2-responsive block is a random copolymer of DEAEMA and styrene.[61] The copolymer can initially self-assemble into typical vesicles in aqueous solution with a size of ~300 nm. When CO_2 gas was added to the system, the copolymer assemblies transformed from large vesicles to smaller micelles, due to CO_2-induced shift of the hydrophilic-hydrophobic balance (Fig. 10). As pointed out above, introducing tertiary amine groups in an LCST thermosensitive block that is linked to a hydrophilic block in a diblock copolymer makes it possible to switch the water solubility of the LCST block and thus convert reversibly the copolymer between amphiphilic and double-hydrophilic state. The work of Feng's group showed that in any amphiphilic BCPs, inserting tertiary amine groups in the hydrophobic block is a general way to use CO_2 to tune the balance of hydrophilic-hydrophobic fraction in order to alter the BCP self-assembly.

Most recently, Yuan's group has developed a new CO_2-thermal dual-responsive noncovalent triblock copolymer, composing PDMAEMA with a β-cyclodextrin (β-CD) end-capping, poly(ε-caprolactone) (PCL) with a methacrylate head group and an adamantane (Ada) distal, and PNIPAM with thiol end-group.[62] The three functionalized homopolymers are able to construct supramolecular triblock copolymer by host-guest interaction of β-CD and Ada and thiol-ene Michael addition. The copolymer can initially self-assemble into asymmetric three-layer vesicular nanostructure in aqueous solution, in which the hydrophilic PNIPAM blocks act as the outer corona, the hydrophobic PCL blocks as the "sandwiched" core, whereas PDMAEMA blocks as the inner layer. When CO_2 is added into the system, because of the protonation effect of PDMAEMA segments, the vesicles can undergo a swelling process. Reversibly, upon removal of CO_2 by N_2 gas, the vesicle volume can recover back to initial level. On the other hand, owing to the thermal-responsive PNIPAM block, the vesicles transform to spherical micelles when the solution temperature is above the LCST of PNIPAM. Drastic variation of the hydrophilic-hydrophobic balance induced by either CO_2 or temperature change was believed as the origin of the behaviors (Fig. 11). This dual-responsive supramolecular copolymer represents one step toward the development of CO_2-tunable supramolecular BCP self-assembly.

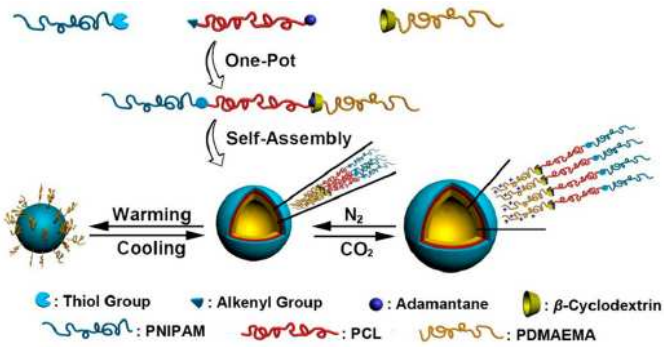


Fig. 11 Illustration for self-assembly of the supramolecular triblock copolymer PNIPAM-*b*-PCL-*b*-PDMAEMA as well as the assemblies evolution induced by either by CO_2 or temperature change. From ref.62.

Of course, owing to the great simplicity of using controlled radical polymerization techniques with easily accessible monomers, there are many ways to exploit the use of tertiary amine-bearing polymers in constructing BCPs. For example, Jiang et al.[63] prepared nanoparticles of a diblock copolymer PDMAEMA-*b*-PS via surfactant-free emulsion reversible addition-fragmentation chain transfer polymerization (RAFT). The dispersion/aggregation state in aqueous solution of the core-shell nanoparticles about 120 nm in diameter can be adjusted by alternatively bubbling of CO_2 and N_2. As expected, the dispersion state is observed when the PDMAEMA chains are charged and soluble in water in the presence of CO_2; while upon removal of CO_2, the aggregation of the nanoparticles occurs due to the diminishing water solubility of PDMAEMA.

3.2 Amidine-Containing Block Copolymers

In 2005, Jessop *et al.* successfully developed the amidine-containing CO_2-responsive surfactants to prepare the switchable solvents.[48] Since then, significant progress has been made on the utilization of amidine groups to design CO_2-sensitive materials. For example, Endo *et al.* reported the synthesis of a styrenic-based cyclic amidine side chain in polymer for preparing high CO_2-permeable films.[64] For reversible CO_2-fixation, Zhou *et al.* synthesized a new copolymer composing of styrene and *p*-chloromethylstyrene which was subsequently treated with 1-(2,6-diisopropylphyenyl)-1*H*-imidazole to give the amidine functionality.[65] Regarding the synthesis of amidine-containing polymers, Feng's group reported a very notable approach based on the use of click chemistry to link amidine groups to a polymer.[66] Considering the many possibilities of making polymers bear clickable functionalities, this post-functionalization method is important, because it avoids the direct synthesis of polymerizabale amidine-containing monomers, which may be difficult. Despite the growing interest in using amidine to render polymer materials response to CO_2, there was no reports in the literature exploring the use of CO_2 to tune the amidine-containing BCP self-assembly behavior until very recently.

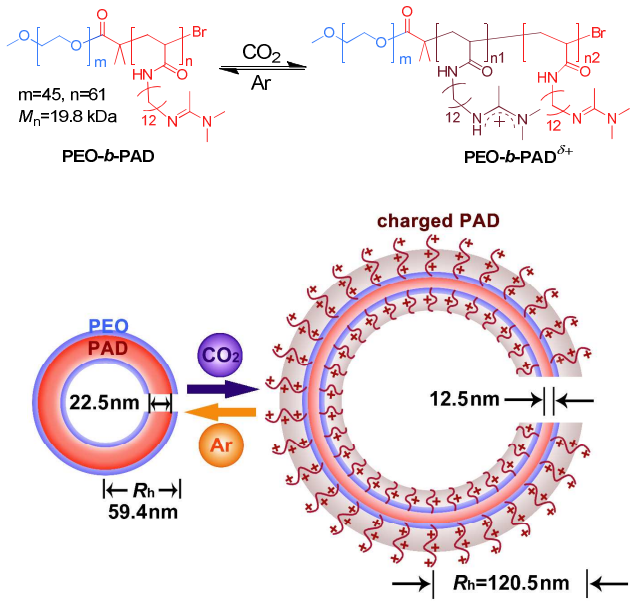


Fig. 12 CO_2-sensitive structural change of amidine-containing diblock copolymer PEO-*b*-PAD (top) and the illustration of the self-assembly into vesicles and their reversible gas-responsive "breathing" feature in aqueous solution (bottom). Rearanged from ref.67.

Yuan *et al.* successfully pioneered a new idea of utilizing a specific amidine-containing amphiphilic BCP to fabricate CO_2-responsive vesicles with biomimetic "breathing" feature.[67] To meet this target, a diblock copolymer, being comprised by hydrophilic PEO block and CO_2-responsive poly(*N*-amidino) dodecyl acrylamide (PAD), was designed and synthesized by atom transfer radical polymerization protocol (ATRP). The copolymer can initially self-assemble into typical vesicular nanostructure with the size of ~ 60 nm. While adding CO_2 into the vesicle solution for 20 min, interestingly, these vesicles expand their size to 120 nm and the volume increases up to ~ 800%. Reversibly, when Ar gas was added to remove CO_2, the vesicles could be contracted back to the initial size and shape. Repeatable expansion/contraction cycles can be realized by applying alternating CO_2/Ar gas stimulation. This process is in many ways reminiscent of the "breathing" behavior of the alveolar cells (Fig. 12). The mechanism of vesicle "breathing" motion is ascribed to the gradual protonation of PAD chains tuned by CO_2 concentration. This polymer self-assembly model driven by CO_2 stimulation provides an opportunity to use gas to precisely tune the size of polymer assemblies in a quantitative way. In addition, these vesicles can be served as nanocontainers for controlled drug release as an alternating CO_2/Ar stimulus is able to accelerate/retard the drug release rate.

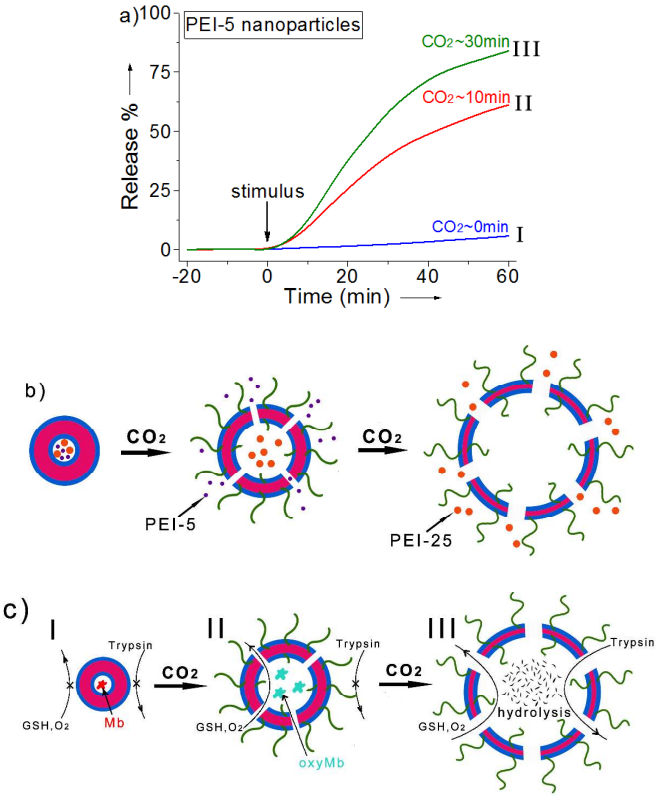


Fig. 13 Functions of PEO-*b*-PAD polymersomes: (a) tunable release curve for loading hyperbranched poly(ethylene imide) (PEI) nanoparticles by varying CO_2 stimulation levels, (b) size-selective separation of PEO nanoparticles of different size (PEI-5 and PEI-25) by adjusting CO_2 stimulation levels, and (c) biomimetic enzymatic nanoreactors (Mb: myoglobin, an iron-central endogenous protein; GSH: glutathione, an intracellular reduced agent; trypsin: a common hydrolyzed enzyme). Rearanged from ref.68.

Reversible vesicular expansive and contractive motion is an intriguing movement of polymeric assemblies. In this process, if the macromolecular aggregate number (N_{agg}) in per vesicle is unchangeable, the vesicle membrane should significantly increase and decrease its wall thickness to adapt to the vesicle volume expansion and contraction. Utilizing this feature Yuan's group further designed an intelligent polymeric bio-nanoreactor for size-selective drug release, nanoparticle separation and enzymatic reactions, biomimicking the selective molecular permeability and space compartmentalization of cell membranes.[68] As reported, the PEO-*b*-PAD polymersomes possess the CO_2-responsive "breathing" ability. Because in the

expansive process the vesicle membrane thickness is gradually decreased and meanwhile the membrane interfacial area is continuously increased, there should be a number of nanoholes (or nanoscaled defects) formed in the membrane and these nanoholes can also expand or contract their sizes modulated by CO_2 levels. As a result, one can readily tune the external CO_2 stimulation strength to control the size of these nanoholes for size-selective drug release (Fig. 13a), particle sieving (Fig. 13b), and various biochemical reaction compartmentalization (Fig. 13c). It is expected that these CO_2-tunable polymersomes will allow us to better mimic cytomembranes and understand cellular functions.

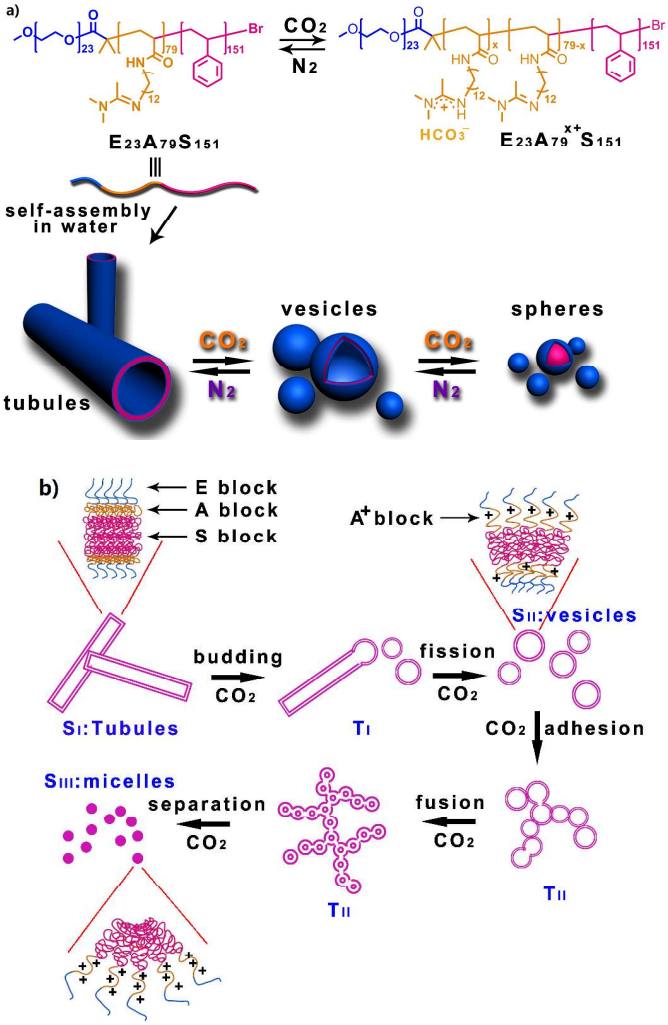


Fig. 14 (a) CO_2-controllable evolution of the assemblies of PEO-*b*-PAD-*b*-PS from tubules through vesicles to spheres, (b) CO_2-induced transformation mechanism of the triblock copolymer assemblies in aqueous solution. From ref.69.

Golgi apparatus is an important organelle that is responsible for protein post-modification, delivery and transportation. In this process, to execute different functions the Golgi apparatus can exhibit various self-organized morphologies from tubules though vesicles to cylinders and spheres. To simulate this transformable feature and build biomimetic polymer assemblies, Zhao *et al.* designed and developed an ABC-type triblock copolymer, PEO-*b*-PAD-*b*-PS,[69] which is composed of a hydrophilic PEO outer corona, CO_2-sensitive PAD intermediate layer and hydrophobic PS inner core (Fig. 14a). In aqueous media, the copolymers can initially self-assemble into rigid tubular geometry with the axial length more than several micrometers and the diameter ranging from 320 nm to 680 nm. After bubbling CO_2 through the polymer solution for 15 min, the tubular structure completely vanished and, instead, submicrometer vesicles with an average size of 410 nm were formed. Continuously purging with CO_2 for 25 min, the assembly morphology underwent a further transformation from vesicles through "spring-like" cylinders to spherical micelles, which is similar to the morphological evolution of Golgi apparatus in cells. The BCP assemblies transformation mechanism is originated from the triblock copolymer design: the middle PAD block can be increasingly protonated by CO_2 and thus increase the hydrophilic volume fraction of the BCP continuously (Fig. 14b). In the absence of CO_2, the lowest curvature of these tubules is attributed to the weak chain interactions and the compact chain arrangement; under CO_2 stimulus, as part of amidine pendants are converted to amidinium species, the increasing electrostatic repulsion among the corona chain forces the tubular objects to reduce its volume by adopting a higher curvature to minimize the interfacial free energy, leading to the vesicular shape. Further prolonging CO_2 stimulation will continue to enhance the electrostatic repulsion, which causes the vesicles to raise their curvature and transform into cylinders and spheres. Thereby, through modulating the CO_2 levels to tune the copolymer hydrophilic-hydrophobic ratio, it is proven that the interfacial curvature and geometry of the self-assembled BCP aggregates can be precisely controlled.

3.3 Guanidine- and Imidazole-Containing Block Copolymers

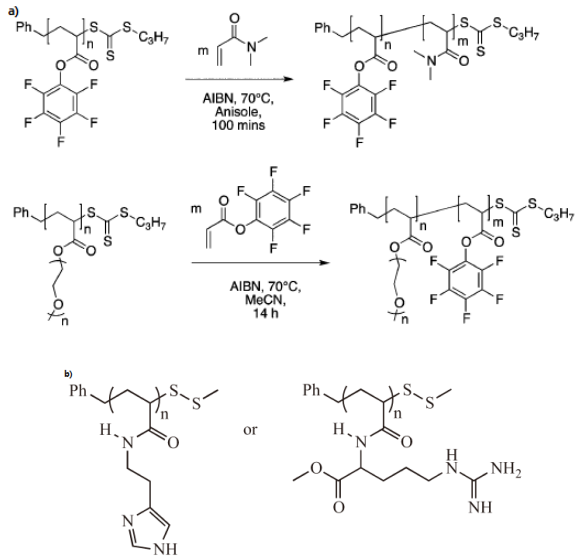


Fig. 15 (a) Synthesis of diblock copolymers PDMA-*b*-PFPA and PEGMA-*b*-PFPA. (b) Post-modification of PFPA by use of histamine and L-arginine to yield imidazole- and guanidine-containing diblock copolymers. From refs.57 and 70.

Because guanidine and imidazole functional groups possess higher pK_a values, guanidine- or imidazole-containing CO_2-responsive block copolymer should have rapid CO_2-response. Recently, Davis and Theato *et al.* reported the synthesis of amidine and imidazole-based BCPs.[57,70,71] Well-defined diblock

copolymers of PDMA or poly(ethylene glycol) methyl ether acrylate (PEGA) together with pentafluorophenyl acrylate (PFPA) were initially prepared by using RAFT polymerization as shown in Fig. 15a. This particular route takes advantage of the facile reaction of pentafluorophenyl esters with primary and secondary amines yielding the corresponding guanidine and imidazole-containing block copolymers. With the diblock copolymers in hand, the PFPA residues were post-modified into either guanidine-containing blocks by using L-arginine methyl ester or imidazole-containing blocks by using histamine (Fig. 15b). The yielded amphiphilic products can further self-assemble in water to form CO_2-sensitive BCP aggregates.

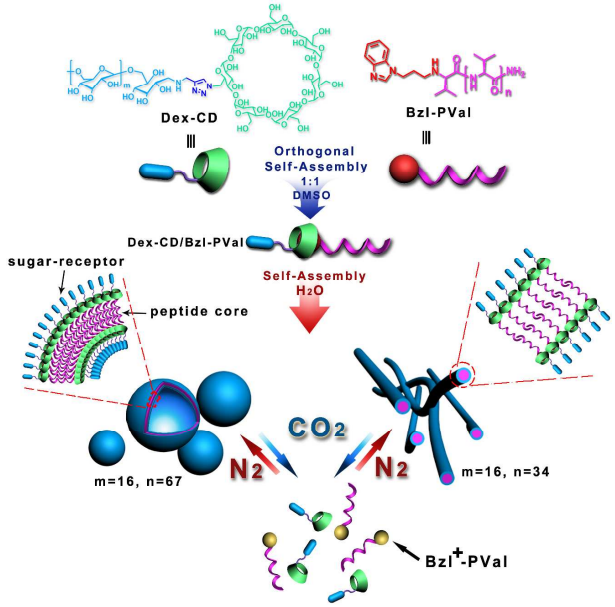


Fig. 16 Orthogonal connection of end-decorated polysaccharide (Dex-CD) and poly(L-valine) (BzI-PVal) to form supramolecular block glycopolypeptides and schematic illustration of their CO_2-switchable assembly and disassembly behavior mimicking the viral capsids. From ref.72.

Using imidazole, Zhao's group has developed a novel CO_2-cleavable supramolecular block glycopolypeptide.[72] As shown in Fig. 16, the pseudocopolymer was prepared via the orthogonal coupling of two distal-functionalized biopolymers, dextran bearing β-cyclodextrin terminal (Dex-CD) and poly(L-valine) with benzimidazole tail (BzI-PVal), through the end-to-end host-guest interactions. With the building blocks designed to imitate the viral composition and structure, the macromolecular adducts (Dex-CD/BzI-PVal) can self-assemble into either vesicular or fibrous aggregates according to their block lengths difference. Since the β-CD/BzI noncovalent connection can be cleaved by CO_2 stimulation, both vesicles and nanofibers in water can undergo a reversible process of disassembly upon "breathing in" CO_2 and re-assembly upon "breathing out" CO_2, which mimics, to some extent, the disintegration and construction of viral capsid nanostructures.

4. Conclusions and Perspectives

CO_2 has been emerging as a new and powerful stimulus to be applied for developing stimuli-responsive polymers in recent years. As compared with other traditional chemical or physical stimuli[37] (pH, temperature, radiation, redox, mechanical force, electric and magnetic field), CO_2 gas has several unique or prominent features and properties from which we can benefit: (i) CO_2 is inexpensive, abundant, and mild as a chemical agent; (ii) it is a "green" stimulus to the environment surrounding the target polymer system by effectively avoiding the formation of byproducts, the accumulation of chemical species and the contamination and damage to polymers; (iii) being a metabolite, CO_2 is an endogenous biological signal that can directly be applied in the body to stimulate reactions of polymer assemblies under physiological conditions; and (iv) unlike the majority of stimuli, the stimulation strength by CO_2 can easily be tuned in a continuous way by modulating the gas concentration or aeration time, which provides opportunity to observe the entire evolution process of polymer systems and makes it easy to adjust their reaction to fit in a specific application. While the topic of this review is CO_2-enabled controlled BCP self-assembly, it is clear that there are also numerous application possibilities with CO_2-responsive polymer materials that do not have BCP architectures. As a matter of fact, many examples can found in the recent literature, which include CO_2-controlled dispersion/aggregation state of carbon nanotubes[73,74], and gold nanoparticles used as in-situ recyclable catalysts,[75] CO_2-switchable polymer surfactants used in emulsion polymerization,[76,77] CO_2-sensitive polymer brushes for protein adsorption and desoprtion,[78] and the polymers for CO_2 capture and release.[79-82]

Although most BCP self-assembly controls described in this paper can be realized by using other stimuli, especially pH change,[37,78,83] in view of the many advantages of CO_2 as a "green" gas stimulus, more interest in CO_2-responsive polymers can be expected. In particular, great application potential remains to be unveiled for polymers with CO_2-switchable water solubility governed by the easy and robust gas-controlled shift of LCST. In principle, all applications of smart thermosensitive polymers in water based on either thermally or pH-induced LCST changes could be realized by using CO_2 at a constant solution temperature and without the need of adding acids or/and bases into the solution. To take advantage of the "green" nature of the CO_2 stimulation mode, in the future studies it will be particularly interesting to explore the use of CO_2-switchable polymers in those applications that currently require repeated on-off cycles through addition of chemical species (acids, bases, redox agents, ions or molecules). In order to gain more knowledge on CO_2-controllable polymers, another future direction in this area will be the investigation of more CO_2-recative functional groups of varying pK_a that can be introduced into polymers, and their effectiveness for CO_2-induced structural and property changes in terms of both speed and magnitude.

As for controlled BCP self-assembly, more effort are worth being dedicated to the application of CO_2 as a physiological trigger to stimulate self-assembled BCP nanostructures and make them simulate the biological activities of cells or organelles. So far in the literature, one has been able to allow BCP assemblies to biomimick a variety of structural and morphological transitions, shape changes and motions under CO_2 stimulation.[60,67-69,72] In the future, through rational and more sophisticated BCP design, it would be possible to realize biomimetic cellular biological functions, which contributes to addressing the ultimate challenge of creating synthetic cells based on artificial macromolecular building blocks. For this research topic, the easily accessible continuous tuning of the CO_2 stimulating strength is an asset.

To conclude, a more general statement or prediction can be made: all applications of amphiphilic BCP assemblies in aqueous solution based on stimuli-controlled shift of the hydrophilic-hydrophobic balance could be, in principle, realized using the CO_2 stimulation mode. Therefore, there are numerous research and development opportunities. One application example is to develop BCPs as rheology modifiers: how to achieve a CO_2-induced transition between spherical and worm-like micelles that can give rise to large-magnitude viscosity change of the solution, like what is known with CO_2-switchable small molecular surfactants.[83,84] A bright future is ahead of us in this emerging and exciting area of CO_2-controllable smart polymers.

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Corresponding author

Email: yue.zhao@usherbrooke.ca

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