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Aliphatic polycarbonates from cyclic carbonate monomers and their application as biomaterials

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Abstract: Aliphatic polycarbonates have gained increased attention as biomaterials largely owing to their biocompatibility and tunable degradation. Moreover, the ability to introduce functional handles in the polymer backbone through careful design of cyclic carbonate monomers or copolymerization with other biodegradable polymers, has significantly contributed to the interest in exploiting this class of materials for biomedical applications. Such investigations have enabled their utility to be expanded to a wide variety of applications in the biomedical field, from drug delivery to tissue regeneration and the design of vascular grafts. Herein, we review the synthesis, degradation and studies into biomedical applications of aliphatic polycarbonates obtained by ring-opening polymerization of cyclic carbonate monomers (ring sizes between 6 and 8). While all synthetic methods will be covered, particular emphasis will be given to materials that have been exploited for therapeutic applications *in vitro* and *in vivo*.

Contents

1. Introduction

An important target for biomaterials research is the preparation of materials that display biocompatibility, controlled degradation, and high performance for their chosen application. Creating the perfect balance between these characteristics, and still generating biomaterials tailored to the target tissue, remains a critical challenge in the field of biomaterials chemistry. The wide variety of chemistries currently available for the synthesis of materials in which the physical and mechanical properties can be tuned, makes synthetic

polymers more attractive than natural ones, also as a consequence of their easier manipulation and high batch-to-batch reproducibility. Among them, aliphatic polycarbonates (APCs) have been identified as a promising class of materials, as they can be obtained from a range of resources, including natural and renewable sources, as well as being biodegradable.[1-3] As such, APCs have received extensive attention as biocompatible materials for drug delivery, polymer-based therapeutics, and imaging contrast agents (Figure 1).[4] The true potential of this polymer platform lies in its versatility with respect to chemical structure and handles that can be placed within the polymer structure with precision.
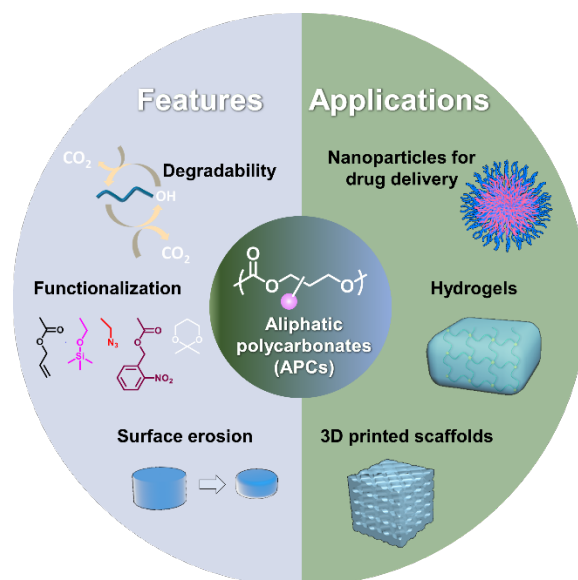
Figure 1. Summary of the unique features and biomedical applications of aliphatic polycarbonates.

Three synthetic routes have been explored for the synthesis of APCs: polycondensation of aliphatic polyol and diallyl carbonates, copolymerization of carbon dioxide (CO_2) with an epoxide, or ring-opening polymerization (ROP) of cyclic carbonate (CC) monomers.[5] Polycondensation involves a two-step process: i) an initial condensation to get an oligomer, and ii) the transesterification or carbonate metathesis polymerization to achieve high molar mass polymers.[6, 7] Copolymerization of carbon dioxide with an epoxide represents a greener alternative for the polycarbonate synthesis, yielding polymers with tunable properties from an inexpensive, nontoxic, renewable feedstock.[8-10] However, this polymerization technique has typically not been used for the synthesis of polycarbonates for biomedical applications, most likely on account of the need for high pressure reactors and limited reports of functional polymers from this route. Using advanced, yet simple, living ROP of CCs by cationic, anionic, coordination-insertion, organocatalytic, and enzymatic methods,[11-14] biomedically relevant polycarbonates can be accessed with high levels of control over polymer molar mass, dispersity and end-group fidelity. Perhaps one of the most attractive aspects of this platform is reflected by the way in which the preparation of functional polycarbonates has opened the possibility to the synthesis of biocompatible materials with tunable degradation rates and mechanical performance. Together with copolymerization or blending with other biodegradable polymers, such as poly(lactide), poly(glycolide), poly(caprolactone), the introduction of functional handles has been used as an alternative method to finely tune the properties of polycarbonates, precisely tailoring the polymer structure to enable specific interactions with cells or tissues.[15-17]

Herein, we highlight the potential for APCs in biomedical applications by reviewing the biomedical applications reported for these materials alongside studies that have reported their synthesis, focusing on ROP of 6-8 CCs and their degradation behavior. Notably, the synthetic methods section will aim to highlight the potential of the platform, many of which have not been used in biomedically-focused studies. This shows the huge potential of APCs to be adapted for a wide range of applications. When discussing the biomedical applications, emphasis is given to materials for which biological effect has been investigated at least *in vitro*, with particular attention given to reports where *in vivo* biocompatibility and efficacy have been explored.

2. Synthetic methods for the preparation of cyclic carbonate monomers and corresponding polymers

2.1 Synthesis of 6-8 membered ring cyclic carbonates from phosgene and its derivatives

APCs have received considerable attention as biocompatible materials for drug delivery, polymer-based therapeutics, and imaging.[18] Access to cyclic monomers that present a wide variety of functional groups and can be synthesized in a simple and cost-effective manner has been exploited over the past few decades to expand the versatility of CCs and correspondent polycarbonate materials.[19] Unlike 5-membered ring carbonates, 6-8 membered CCs are more susceptible to polymerization, as a consequence of their higher ring strain.[20] Traditionally, CCs are synthesized using phosgene from a diverse range of precursors, from glycerol to amino acids and sugars.[3, 21-26] Despite being high yielding, the use of phosgene is highly toxic and laborious, as reactions are performed at -78 °C with exhaustive workups, rendering this chemistry difficult to scale up. As such, the use of phosgene alternatives, such as various chloroformates, nitro-substituted diphenylcarbonates, and carbonyl diimidazole, have been suggested to overcome some of these synthetic issues.[27-31] However, phosgene derivatives come with their own challenges, as they often lead to unwanted side reactions and subsequent difficult purification procedures, as a consequence of their lower reactivity. In this section, we report a comprehensive list of the different synthetic methods that have been described for the synthesis of 6-8 membered ring CCs using phosgene and its derivatives (Table 1).

2.1.1 Synthesis of 6 membered ring cyclic carbonates from glycerol and derivatives

Glycerol is an abundant, inexpensive compound sourced from biomass feedstock, which makes it an ideal starting material for CC synthesis. It can be reduced to a diol through a palladium/carbon (Pd/C) catalyzed reduction with hydrogen gas to make the precursor for 6 membered ring CCs.[32, 33] 1,3-Propanediol can be converted into the simplest 6 CCs, trimethylene carbonate (TMC), as demonstrated by Endo and coworkers who used ethyl chloroformate alongside a catalytic amount of triethylamine (TEA) in tetrahydrofuran (THF) to afford a 62% yield of TMC.[34]

A range of functionalized CCs have been synthesized from glycerol and derivatives with the aim to afford functionalized APCs *via* ROP. Burk and coworkers used triphosgene with pyridine as a catalytic base to synthesize a range of substituted 6CCs from substituted 1,3-pentanediols in dichloromethane. Low temperatures of -70 °C were employed in order to eliminate competing chlorination side reactions.[35] Zhuo and coworkers synthesized 5-benzyloxyl trimethylene carbonate (BTMC) through a multi-step procedure starting with a glycerol that was protected and then cyclized through a reaction with ethyl chloroformate and TEA in THF.[36] Moreover, Parzuchowski and coworkers synthesized the 6CC monomer 5-(3-[(2-hydroxyethyl)thio]propoxy)-1,3-dioxan-2-one (HETTMC) from a protected glycerol. The three-step reaction included the addition of the allyl functional group to the secondary alcohol in the glycerol, deprotection of the resultant compound, cyclization of the glycerol with ethyl chloroformate and TEA in THF and finally conversion of the allyl group to a 2-mercaptoethanol group.[37]

2.1.2 Synthesis of 6 membered ring cyclic carbonates from pentaerythritol, trimethylolethane and their derivatives

Synthesis of functional monomers derived from pentaerythritol is typically realized by partial functionalization/protection of two of the hydroxyl functionalities leaving a 1,3-diol that can be cyclized using a phosgene derivative. This route provides an excellent opportunity to introduce two hydroxyl groups per monomer unit into the polycarbonate backbone. Pentaerythritol was used by Vandenberg and Tian to synthesize the 6CC, 2,2-dimethyl-5,5-bis(hydroxymethyl)-1,3-dioxane from pentaerythritol and then cyclized by ethyl chloroformate and TEA in THF to afford the 6CC.[38] The Zhong group synthesized two similar 6CCs, mono-2,4,6-trimethoxybenzylidene-pentaerythritol carbonate (TMBPEC) and mono-4-

methoxybenzylidene-pentaerythritol carbonate (MBPEC). These were derived from the reaction of pentaerythritol and 2,4,6-methoxybenzaldehyde or *p*-methoxybenzaldehyde respectively followed by cyclization of the resultant diols by ethyl chloroformate and TEA in THF.[39] Using a similar chemistry, Dove and coworkers reported the synthesis of a norbornene-functionalized spirocyclic carbonate, 9-norbornene-2,4,8,10-tetraoxaspiro[5,5]undecan-3-one (NTC) from pentaerythritol and 5-norbornene-2-carboxaldehyde, followed by ring-closure using ethyl chloroformate and TEA.[40]

A similar synthetic strategy can be applied to trimethylolethane and its derivatives. This can be used as a starting material to prepare 6CCs, by protecting two hydroxyl groups and allowing the third one to react. Indeed, initially Akashi and coworkers[41] and subsequently Amsden and coworkers[42] reported the synthesis of a 6CC bearing a methoxyethoxy side group from trimethylolethane. In the monomer synthesis, two hydroxyl groups were protected through the formation of an acetal ring using benzaldehyde, while the third one was reacted with a triethylene glycol monomethyl ether. The protected hydroxyl groups were then deprotected in an acidic environment and reacted with 1,1-carbonyldiimidazole (CDI) to obtain the 6CC. In a similar fashion, dimethyl carbonate and diethyl carbonate have also been used to protect trimethylolethane derivatives by forming acetal or ether functionalities, affording 6CCs with pendant functional groups.[43-45]

2.1.3 Synthesis of 6 membered ring cyclic carbonates from amino acid derivatives

Amino acids are natural products indispensable for life processes, hence highly attractive, biocompatible starting materials for the synthesis of CCs. Originally, the synthesis of CC monomers derived from L-serine and L-threonine, reported by Sanda *et al.* and by Gross and coworkers, was realized by protection of these amino acids *via* conversion of the amino groups to carbamic acid benzyl esters or carbamic acid *tert*-butyl esters (Boc) followed by reduction and carbonate formation with triphosgene.[46, 47] In an alternative report, a serine-derived CC was prepared from the alcohol analogue of serine, serinol, as reported by the Zhuo and Zhong groups for the synthesis of 2-(dimethylamino)trimethylene (DMATC). Serinol was methylated to form an intermediate that underwent cyclization when reacted with triphosgene and TEA. The purpose of the methylation step was to allow the monomer to undergo controlled ROP, as the unprotected amine functionality can potentially interfere with the ROP catalyst. The result was a 6CC that contained a protected secondary amine functionality.[48] Moreover, Jing and coworkers described another route for the synthesis of the 6CC (2-oxo[1,3]dioxan-5-yl)carbamic acid benzyl ester (CAB) from serinol. Serinol was reacted with benzyl chloroformate to produce a protected intermediate that underwent a cyclization with ethyl chloroformate and TEA in THF at room temperature to afford the 6CC.[49] Finally, a route to a 6CC bearing an amine functionality was shown by Endo and coworkers. Serine was protected using benzyloxycarbonyl and TEA or using NaHCO₃ and zinc chloride, and then reacted with triphosgene to produce an amine-functionalized 6CC.[46]

2.1.4 Synthesis of 6 membered ring cyclic carbonates from 2-(dihydroxymethyl)-propanoic acid

A number of synthetic pathways for the preparation of functionalized CCs starting from 2,2-bis(hydroxymethyl)-propionic acid (bis-MPA) have been reported (Scheme 1). The functionalization of the carboxylic acid group under acidic or basic conditions, followed by the carbonate ring-closure, was presented as a straightforward method to obtain functional 6CC (path A). Although alternative pathways enable coupling of more sensitive functional groups, steps such as protection/deprotection are required prior to polymerization (paths B and C).

Scheme 1. Reported synthetic routes to functionalized cyclic carbonate monomers. Reprinted with permission from reference [50]. Copyright (2010) American Chemical Society.
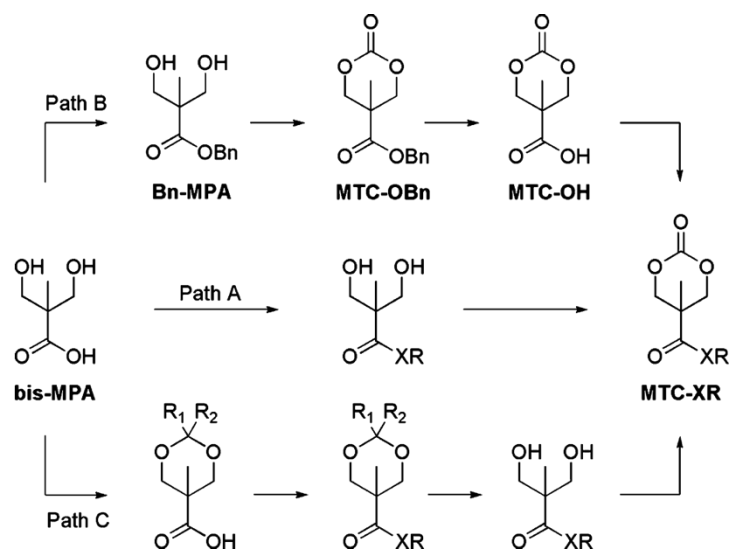
Bisht and coworkers synthesized the 6CC, 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one (MBC) from a bis-MPA, benzyl 2,2-bis(hydroxmethyl)propionate, ethyl chloroformate and TEA in THF in a one-pot reaction.[51] Further work undertaken by the group included the synthesis of 5-methyl-5-carboxyl-1,3-dioxan2-one (MCC) from MBC by reducing MBC with hydrogen gas (0.414 MPa) and a Pd/C catalyst in anhydrous ethyl acetate, affording MCC with a 98% yield.[52] Pratt *et al.* substituted the hydroxyl group in MCC with a range of different functionalities through two different synthetic routes, either *via* direct coupling with *N,N'*-dicyclohexylcarbodiimide (DCC) or through the formation of an acyl chloride intermediate.[31] Hedrick and coworkers synthesized CCs bearing a broad range of functionalities in high yields, using a common and versatile pentafluorophenyl ester intermediate. Reaction of bis-MPA with commercially available bis(pentafluorophenyl)carbonate (PFC) resulted in the one-pot transformation of the carboxylic acid into a pentafluorophenyl ester group and ring-closure of the 1,3-diol to generate a CC. The pentafluorophenyl ester intermediate and the PFC have the advantage of being easy to store and handle on the benchtop, as opposed to phosgene.[50]

The Jing group synthesized the 6CC, 5-methyl-5-(2-nitro-benzoxycarbonyl)-1,3-dioxan-2-one (MNC), from a reaction between 2-(dihydroxymethyl)-propanoic acid, potassium hydroxide, and 2-nitrobenzyl bromide in DMF followed by cyclization of the resultant diol with ethyl chloroformate and TEA in THF.[53] The Zhuo group synthesized the 6CCs 5-methyl-5-methoxycarbonyl-1,3-dioxan-2-one (MMTC) and 5-methyl-5-ethoxy carbonyl-1,3-dioxan-2-one (EMTC) *via* the cyclization of their analogues 2-(dihydroxymethyl)-propanoic acids using ethyl chloroformate and TEA in THF.[29] Finally, the Malkoch group synthesized a range of 2,2-bis(methylol) propionic acid carbonates (bis-MPA-carbonates) and trimethylolpropane carbonates (TMP-carbonates) from 2,2-bis(methylol) propionic acid and trimethylpropane feedstocks respectively. 1.1'-carbonyldiimidazole (CDI) was used as the cyclization reagent owing to its low cost and safety.[54]

2.1.5 Synthesis of 6 membered ring cyclic carbonates from other sources

Chen and Gross synthesized the 6CC, 1,2-*o*-isopropylidene-D-xylofuranose-3,5-cyclic carbonate (IPXTC), from the natural sugar 1,2-*o*-isopropylidene-[D]-xylofuranose and ethyl chloroformate and TEA in THF in a one-pot reaction, affording IPXTC in 41% yield.[55] Wooley and coworkers prepared bicyclic carbonate monomer of a D-glucal derivative, which originated from the natural product D-glucose, in an efficient three-step procedure, involving a Ferrier rearrangement, a deprotection step, and a ring-closure reaction,
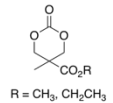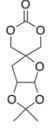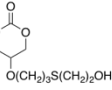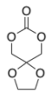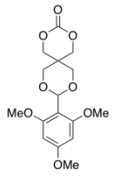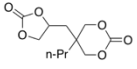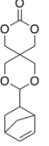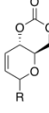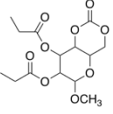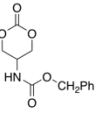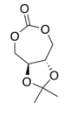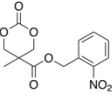
with an overall 38% yield.[56] The same group also used methyl-4,6-*o*-benzylidene-α-D-glucopyranoside as a starting materials to achieve substituted 6CCs. By convenient functionalization of the hydroxyl groups in 2 and 3 position and subsequent removal of the benzylidene followed by ring-closure, a series of 4,6 CCs, such as the methyl-2,3-O-n-ethyloxycarbonyl-4,6-O-carbonyl-α-D-glucopyranoside (GC(EEC)) could be obtained.[57-59] Wang, Cheng and Zhuo synthesized the 6CC 2,2-ethylenedioxypropane-1,3-diol carbonate (EOPDC) with a 47% yield from an ethylene ketal dihydroxyacetone. Diethyl malonate was oxidized to diethyl ketomalonate with ceric ammonium nitrate as a catalyst. Diethyl ketomalonate was then cyclized with ethyl chloroformate and TEA in THF.[60] Endo and coworkers synthesized the bis-(cyclic carbonate), 5-(2-oxo-1,3-dioxolan-4-yl)methyl-5-propyl1,3-dioxan-2-one (65CCP), which contains both a 5- and 6-membered carbonate ring through a multi-step reaction from allylmalonic acid diethyl ester.[61] Chen, McCarthy and Gross synthesized the 6CC, 2,2-(2-pentene-1,5-diyl)trimethylene carbonate (*c*HTC), by a one-pot reaction of cyclohexene-4,4-dimethanol with ethyl chloroformate and TEA in THF conducted at 0 °C.[62] The Cramail group synthesized the bis-(cyclic carbonate), Und-6CC, from methyl undecenoate. The methyl undecenoate was used to produce an Und-malonate, this was reduced to a 1,3-diol and then cyclized using ethyl chloroformate and TEA in THF to afford Und-6CC.[63]

2.1.6 Synthesis of 7 and 8 membered ring cyclic carbonates

Endo and coworkers synthesized the simplest 7CC, 1,3-dioxepan-2-one, from 1,4-diols and triphosgene using pyridine as a catalytic base, with an overall yield of 30%.[64] Further work by the same group demonstrated a synthesis of methyl- and phenyl-substituted 7CCs from substituted 1,4-butanediols that were in turn synthesized from the reduction of analogous acids. In the synthesis of the 7CCs from their respective 1,4-diol analogues, triphosgene in anhydrous chloroform was used as a carbonyl source and antipyrine as the base, affording 11-30% yields.[65] The Carpentier and Guillaume group synthesized the methyl-substituted 7CCs, 4-methyl- and 5-methyl-1,3-dioxepan-2-one, from their respective 1,4-diols. Triphosgene, anhydrous chloroform and pyridine were used for the cyclization and yields of up to 70% were reported. Lower temperatures employed in the reaction led to a higher yield of the 7CC by minimizing side-formation of oligocarbonates.[66] An allyl-substituted 7CC, 5-allyl-1,3-dioxepan-2-one, was also reported by Endo and coworkers, using 2-allylbutane-1,4-diol as a precursor obtained from the reduction of allyl succinic anhydride with LiAlH₄. Triphosgene and antipyrine in THF were then used for the cyclization, affording the desired product in 79% yield.[67] Bisht and coworkers synthesized a 7CC, (5S,6S)-dimethyl-5,6-isopropylidene-1,3-dioxepin-2-one (ITC), from L-tartaric acid in three steps. First the secondary alcohol groups were protected, then the ketone groups were converted to alcohol groups and finally the resultant diol was cyclized with triphosgene and pyridine in THF.[68]

While research has mostly focused on the synthesis of *N*-substituted 8CC intended for the preparation of polyurethanes,[69] there are a few reports on the synthesis of 8CC intended for the preparation of APCs. A methyl-substituted 8CC, 6-methyl-1,3,6-dioxazocan-2-one, was synthesized by Pascual *et al.* through a reaction between *N*-methyl diethanolamine, ethyl chloroformate, and TEA in dichloromethane, achieving a yield of 84%.[70] Moreover, Venkataraman *et al.* synthesized a range of *N*-substituted 8CCs from their respective *N*-substituted diethanolamines through cyclization reactions promoted by either ethyl chloroformate or triphosgene in the presence of a base, with yields varying from 21 to 53%.[22] The same group also reported step-efficient routes to access *N*-substituted 8CCs directly incorporating tertiary amines, without any requirement for post-polymerization modification steps, for a wide range of biomedical applications.[71]

Table 1. 6-8 membered ring cyclic carbonates synthesized using phosgene and its derivatives.
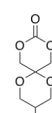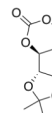
Name	Structure	%Yield [ref.]	Name	Structure	%Yield [ref.]
TMC		62 [34]	MMTC, EMTC	CO_2R, R = CH_3, CH_2CH_3	44, 59 [29]
BTMC	OCH_2Ph	58 [36]	IPXTC		41 [55]
HETTMC	$O(CH_2)_3S(CH_2)_2OH$	52 [37]	EOPDC		47 [60]
TMBPEC	MeO, OMe, OMe	45 [39]	65CCP	n-Pr	74 [61]
			cHTC		81 [62]
NTC		59 [40]	D-glucal-based bicyclic carbonate	R	40 [56]
DMATC	N	39 [48]	GC(EEC)	OCH_3	51 [57]
CAB	HN–C(=O)–O–CH_2Ph	68 [49]	1,3-dioxepane-2-one		30 [64]
MBC	CO_2Bn	89 [51]	5-allyl-1,3-dioxepan-2-one		79 [67]
MCC	HOOC	98 [52]	ITC		57 [68]
MNC	NO_2	60 [53]	6-methyl-1,3,6-dioxazocan-2-one		84 [70]

2.2 Synthesis of 6-8 membered ring carbonates from diols or sugars using carbon dioxide as a C1 source

As previously outlined, the production of CCs has typically relied on the utilization of phosgene and its derivatives. As a consequence of the impracticalities and safety concerns of using highly toxic phosgene on a laboratory scale, alternative sources of starting materials have recently begun being investigated for the synthesis of CCs. Carbon dioxide represents an ideal starting material for the cyclization of a diol into a CC, owing to its lack of toxicity, abundance, and renewability.[72] The direct coupling of carbon dioxide with

different starting materials is now also a well-established reaction that has been exploited to yield CCs (Table 2).[73]

Table 2. Synthesis of various cyclic carbonates from 1,3-diols and CO_2. Adapted with permission from reference [74]. Copyright (2015) The Royal Society of Chemistry.

Substrate	%Yield	Product
	68	
	68	
	70	
	53	
	55	
	53	
	49	
	46	
	41	
	11	

Tomishige and coworkers used CeO_2 as a catalyst and 2-cyanopyridine as a dehydrating agent to synthesize a range of 6CCs from 1,3-diols and CO_2 gas (5 MPa) with yields of 62-99% for the resultant products. Carbon dioxide was inserted into the Ce-O bond, then an intramolecular nucleophilic attack of the other alcohol group on the carbonyl in the intermediate leads to the CC and the elimination of a water molecule. Hydration of 2-cyanopyridine with water affords the corresponding amine as a by-product.[75] Bobbink *et al.* performed a carbene-catalyzed fixation of carbon dioxide (1 atm) with a phenyl-substituted 1,3-propanediol

using a carbene catalyst, excess ^nBuBr, and Cs_2CO_3 in DMF solvent to give the corresponding CC with a 53% yield. The base and alkyl halide were essential for this reaction as no carbonate product was formed in their absence.[76]

Buchard and coworkers reported a milder route to achieve CCs from a 1,3-diol, using 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) as a catalytic promoter and carbon dioxide (1 atm). Ester and ether functional groups were well tolerated under these conditions. The disadvantage of this reaction is that DBU is a strong, moisture sensitive base and hence this synthesis has to be performed in air-free conditions and requires two sequential steps.[73] To address these concerns, further work by the group reported the production of CCs from milder bases and only stoichiometric amounts of tosyl chloride in a one-step, one-pot reaction. This led not only to the synthesis of 6CCs but also the first 7CCs and 8CCs synthesized directly from CO_2. The simplest 7CC was afforded from the analogous 1,4-diol at a 45% conversion from the same procedure, while 38% of the 1,4-diol was converted to oligomers. A methyl-substituted 8CC was afforded with a 73% conversion of 1,5-diol.[77]

Sun and coworkers used urea and 1,3-propanediols to synthesize 1,3-propylene carbonate. The reactions were performed in the presence of a variety of metal oxide catalysts and carbon dioxide. In all cases, the selectivity of 5CCs, up to 99%, was greater than the selectivity of 6CCs, 83%.[78]

2.3 Synthesis of 6-8 membered ring carbonates from other sources using carbon dioxide as a C1 source

2.3.1 Homoallylic alcohol-derived cyclic carbonates

Alcohols are ubiquitous compounds in nature and offer modular building blocks for synthetic chemistry. As such, different classes of alcohols have been used to afford linear and CCs by coupling with carbon dioxide, highlighting the potential of this chemistry to recover a waste carbon feedstock. Cardillo *et al.* reported a one-pot, three-component reaction between homo-allylic alcohols, carbon dioxide and molecular iodine. The synthesis was regio- and stereo-selective and was catalyzed by ^nBuLi used as a base in dry THF, followed by the addition of iodine. The proposed mechanism involved a carbon dioxide addition to the alkoxide group to produce an intermediate followed by electrophilic iodo-cyclization.[79] Minakata *et al.* developed a metal-free, base-free synthesis of 6CCs from a homoallylic acid and carbon dioxide (1 atm). Carbon dioxide first reacted with the homoallylic acid to form an intermediate that further reacted with the iodonium source, ^tBuOI, so that an iodocyclization could take place to afford the 6CC.[80] The Johnston group enantioselectively synthesized a range of 6CCs via a dual Brønsted acid/base organocatalyzed reaction between a range of homoallylic alcohols, carbon dioxide (1 atm), and N-iodosuccinimide. Fluoro, chloro, bromo and alkoxy functional groups on the homoallylic acid were well tolerated during the reaction.[81]

2.3.2 Oxetane-derived cyclic carbonates

The organocatalytic coupling of oxetanes and carbon dioxide offers a sustainable route to poly(trimethylene carbonate)s and/or functional six-membered CC monomers. Pioneering work by Baba *et al.* reported the synthesis of TMC from oxetane by ring expansion with carbon dioxide (4.9 MPa) and Ph_4SbI as an iodonium source for cyclization. Notably, this reaction was performed under solvent-free conditions at 100 °C, affording TMC in 96% yield.[82] The same group further explored the synthesis of TMC *via* cycloaddition of carbon dioxide and oxetane catalyzed by Bu_3SnI and hexamethylphosphoric triamide (HMPA), which delivered TMC at 100% yield.[83] Further work explored the synthesis of 6CCs from mono- and di-substituted oxetanes using Ph_4SbI. As expected, yields for mono-substituted 6CCs were greater than those for di-substituted 6CCs.[84] Darensbourg *et al.* achieved a 95% yield of TMC using $VO(acac)_2/n\text{-}Bu_4NBr$ as the catalyst system in toluene at 60 °C and a carbon dioxide pressure of 3.5 MPa.[85] Kleij *et al.* synthesized

substituted 6CCs from a range of 2-,3- and 3-,3-disubstituted oxetanes and carbon monoxide (1-4 MPa). The mechanism followed a ring expansion of the oxetane with carbon dioxide (0.2 MPa) mediated by the catalyst [Fe(TPhOA)]$_2$ (0.5 mol%) and iodonium source Bu$_4$NI (5 mol%) in methyl ethyl ketone at 85 °C yielding 98% TMC, with the yields of the disubstituted CCs being 28% and 38%, respectively.[86] Further investigation by the group found that replacing [Fe(TPhOA)]$_2$ with an aluminum triphenolate catalyst resulted in a lower yield.[87] Buckley *et al.* described the first attempt of TMC synthesis by electrochemistry. An electrochemical cell with a copper cathode and a magnesium anode was used and 1 equivalent of Bu$_4$NI as a supporting electrolyte in acetonitrile. Reaction conditions of 50 °C and 0.1 MPa carbon dioxide pressure afforded a 70% yield of TMC.[88] More recently, Coulembier, Dove and coworkers reported a metal-free procedure to synthesize TMC using carbon dioxide and commercially available organocatalysts in a temperature-selective process. An extremely high level of TMC selectivity with good conversion was achieved from the catalytic coupling of oxetane and carbon dioxide under mild conditions using iodine in combination with tetrabutylammonium acetate at low temperatures.[89]

2.4 Synthesis of cyclic carbonates from other sources

Inoue and coworkers synthesized highly substituted 6CCs from the reaction of 3,4-alkadienols and carbon dioxide. Phenyl iodide was used as a halide source and a palladium complex catalyst mediated the reaction through a π-allylic palladium intermediate species.[90] Zhang and coworkers synthesized a range of 6CCs from commercially available 3-(pseudo)halo-1-propanols and carbon dioxide through a Cs$_2$CO$_3$-catalyzed intermolecular ring-closing strategy, under mild reaction conditions. Other bases such as K$_2$CO$_3$ and ^{t}BuOK were also found to promote reaction but in lower yields. This strategy was also tested for 7 and 8 membered CCs but these reactions were not successful.[91] This is not unexpected taking into account that 7- and 8-membered rings are kinetically not favored. In addition, the carbonyl bond distorts the ring which most likely decreases the thermodynamic stability.

Finally, functional 6CCs have been synthesized from the upcycling of a commodity polymer, bisphenol-A polycarbonate (BPA-PC), using a variety of diols and an ionic organocatalyst based on triazabicyclodecene (TBD) and methane sulfonic acid (MSA). The glycolysis of BPA-PC yielded 6CCs with a wide range of substituents that could be used to generate high added value polycarbonate-based materials (Figure 2).[92]
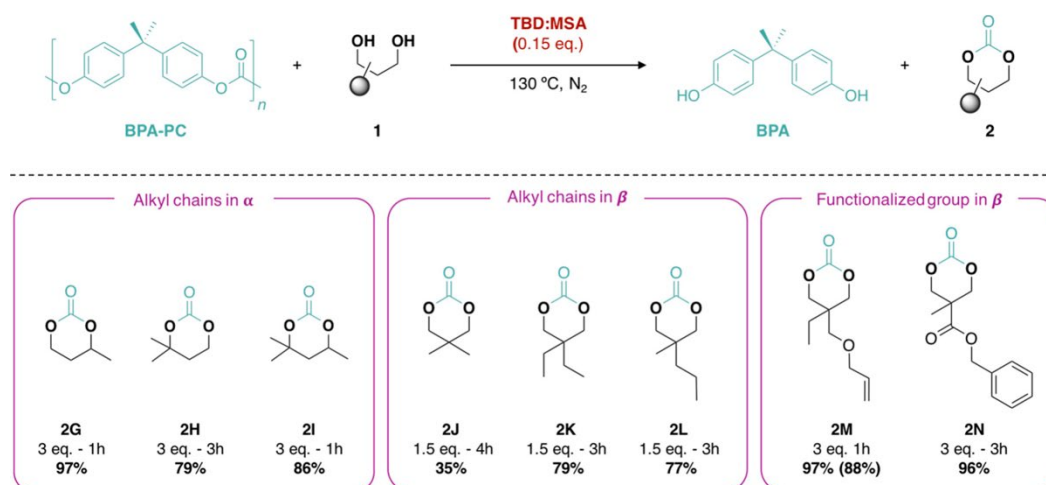
Figure 2. BPA-PC depolymerization with different diols yields substituted 6-membered cyclic carbonates. Reprinted with permission from reference [92]. Copyright (2020) American Chemical Society.

2.5 Ring-opening polymerization of cyclic carbonates

APCs are of interest in biomedical applications as a consequence of their controlled polymer structure and tunable hydrolytic degradation.[93] ROP of 6-8CCs allows for an effective and reproducible way to afford polycarbonates with high molar mass and low dispersities, which is crucial to obtain materials with properties tailored to the desired application.[5] ROP provides the best route for the introduction of functional groups into the polycarbonate backbone and for controlling the afforded polycarbonate's molar mass and dispersity through changing the monomer/initiator ratio, as typical of a living polymerization where the rate of initiation is greater than the rate of propagation. ROP requires a catalyst (Figure 3) or initiator and acts through four different mechanisms: cationic, anionic, coordination, and enzymatic. Originally, metal-based catalysts were developed for the synthesis of APCs. However, the presence of residual metals in the afforded polymers, which can lead to cytotoxicity, encouraged the development of more biocompatible catalysts, including metal-free and enzymatic catalysts. Metallo-organic catalysts are among the most used for the preparation of APCs, owing to their high activity. While metal-free catalysts are also widely employed, they need high loadings (often too high for industrial applications) to achieve efficiencies comparable to their metallo-organic analogues.
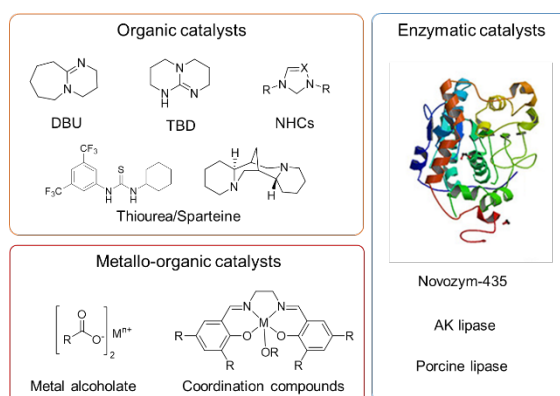
Figure 3. Representative catalysts for the ROP of cyclic carbonates. Adapted from reference [94]. Copyright (2019) American Chemical Society.

2.5.1 Cationic ROP

The dipolar moment of the CC group allows the monomer to act as a Lewis base in a reaction with an electrophilic initiator. As such, the cationic ring-opening polymerization of CCs can be achieved using Brønsted or Lewis acids. The cationic ROP of TMC, the simplest 6 CCs, was first reported by Kricheldorf *et al.* The mechanism was shown to proceed by the methyl triflate initiator alkylating the carbonyl moiety of the monomer, thus generating a trioxocarbenium cation. The counter ion then ring-opened the monomer, establishing an equilibrium with the triflate. Either the trioxocarbenium ion can attack another monomer leading to alkyl-oxygen (alkyl-O) cleavage and alkylation of the carbonyl moiety of the nucleophile or the covalent triflate can react with the monomer to produce the same propagating species. The polymerization was hindered by a decarboxylation side reaction which led to the presence of 3-10% mole concentration of ether groups in the afforded polycarbonate.[95] Ether linkages in the afforded polymer are highly undesirable, owing to their faster degradation when compared to carbonate bonds. Decarboxylation and hence ether linkages were also present in the cationic bulk ROP of TMC by Albertson *et al.*, where the use of $BF_3 \cdot OEt_2$ was reported to afford PTMC (M_n = 129,000 g mol^{-1}, $Đ_M$ = 1.88). It was also established that solvent choice affected the polymerization, as the limited solubility of PTMC can lead to phase separation of the reaction mixture and hence the formation of oligomers instead of the desired high molar mass polycarbonates.[96] Endo *et al.* avoided decarboxylation during the cationic ROP of TMC by using alkyl halides, but only afforded low molar mass polycarbonates (M_n up to 3700 g mol^{-1}).[5] Using molecular orbital calculations it was shown that decarboxylation occurs when the monomer attacks the

propagating end in preference to the attack of the polymer at the propagating end. This is because the monomer is more nucleophilic than the polymer. Thus, decarboxylation competes with propagation. This is why an alkyl halide propagating species with a lower reactivity, such as methyl iodide and benzyl bromide, affords polycarbonates without ether linkages.[9] Kricheldorf *et al.* produced high molar mass polycarbonates (M_w = 250,000 g mol^{-1}, ≥90% yield) without decarboxylation from cationic ROP of TMC with butyltin chloride initiators.[97]

Hyun *et al.* reported the cationic ROP of 6CCs such as TMC, using (semi-)telechelicpoly(ethylene glycol)/HCl·Et$_2$O initiator systems.[98] Subsequently, Endo *et al.* reported the same method using different alcohol/ HCl·Et$_2$O systems.[99, 100] This synthesis proceeds by the activated monomer (AM) mechanism that suppresses unfavorable reactions such as backbiting (intermolecular transesterification). HCl·Et$_2$O predominantly interacts with the carbonyl oxygen of the TMC monomer rather than the corresponding polymer carbonyl. Thus, the hydroxyl end-group of the initiator can attack the carbonyl of the protonated TMC rather than that of the PTMC polymer. This is in comparison with the active chain-end (ACE) mechanism, where the CC is protonated in the absence of hydroxyl groups and reacts with non-protonated monomers to give a trialkylcarbenium ion located at the end of the growing chain. Competition between AM and ACE may exist in ROP of CCs.[101] Delcroix *et al.* investigated ROP of TMC in toluene at 30 °C using n-pentanol and methyl sulfonic acid (MSA) as initiator and catalyst respectively, to gain insight on the two mechanisms. MSA was shown to be effective for the synthesis of PTMCs with controlled molar masses (M_n < 9,000 g mol^{-1}) and narrow dispersity ($Đ_M$ < 1.12). It was determined that the TMC monomer when activated by MSA undergoes nucleophilic attack by the alcohol at an early stage of the polymerization, thus confirming AM mechanism occurred. The activated monomer began ring-opening by O-alkyl cleavage as a result of the nucleophilic attack of non-activated TMC. Competing ACE mechanism meant that spontaneous decarboxylation occurred, leading to the propagating species becoming a bifunctional initiator that can enable polymer growth *via* two different mechanisms: AM from the hydroxyl chain-end and ACE from the oxonium chain-end. The undesirable ACE mechanism could be reduced by decreasing the instantaneous TMC concentration, thus achieving well-controlled ROP with MSA catalyst.

Weakly acidic fumaric acid[102] and diphenyl phosphate[103] are also widely used in the cationic ROP of CCs. Diphenyl phosphate catalyst with 3-phenyl-1-propanol yielded polycarbonates from a wide range of CCs: TMC, 5,5-dimethyl-1,3-dioxan-2-one, 5,5-dibromomethyl1,3-dioxan-2-one, 5-benzyloxy-1,3-dioxan-2-one, 5-methyl-5-allyloxycarbonyl-1,3-dioxan-2-one, and 5-methyl-5-propargyloxycarbonyl-1,3-dioxan-2-one with no backbiting, decarboxylation or transesterification. Moreover, low dispersity ($Đ_M$ ≤ 1.2) was achieved in all polymerizations. Among other acid catalysts for cationic ROP, Brønsted acids, such as phosphoramidic acid, were employed to catalyze the living ROP of TMC.[104] Furthermore, Barker and Dove reported the use of triarylsulfonium hexafluorophosphate salts as photoactivated acidic catalysts for ROP. When excited with UV light, these catalysts generate free protons which initiate the ROP of TMC.[105]

In order to better understand how acidity affected catalytic activity, Hedrick and coworkers used molecular modelling to calculate reaction mechanism energetics.[106] Their studies demonstrated that the catalysis is actually dependent on both acid strength and the ability of the conjugate base to act as a hydrogen-bond acceptor, suggesting a bifunctional activation. Phosphoric acid and imidodiphosphoric acids were thus employed as bifunctional catalysts for the ROP of TMC.[107, 108] A bifunctional acid-base catalyst system of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) and TFA with benzyl alcohol (BnOH) as a coinitiator was also employed to afford PTMC with low dispersity (M_n = 14,390 g mol^{-1}, $Đ_M$ = 1.10) through a living mechanism.[109] Single-group bifunctional hydrogen-bonding catalysts based on thiazolium were used for the ROP of TMC affording polycarbonates with low molar mass and narrow dispersities (M_w = 3,300 g mol^{-1}, $Đ_M$ = 1.28).[110] Finally, bifunctional catalysts of squaramide and amine were also used for the ROP of TMC with BnOH as initiator.[111]

2.5.2 Anionic ROP

Carbonate monomers are also susceptible to anionic ring-opening polymerization on account of the electrophilic nature of the carbonyl group. Here, the initiation and propagation steps are induced by the nucleophilic addition of anionic initiator and anionic chain-end, respectively. The first ROP of a 6 CCs, TMC, was reported using K_2CO_3 as an anionic initiator in the 1930s.[112, 113] TMC undergoes spontaneous bulk anionic ROP above 100 °C producing high molar mass PTMC (M_w = 210,000 g mol^{-1}) in high yields (90%). Once the TMC is cleaved, a zwitterion intermediate of the trioxocarbenium ion and an alkoxide ion is formed, which is stabilized through delocalization. However, a dimethyl substituted TMC, 2,2-dimethyltrimethylene carbonate (DTC), does not spontaneously polymerize as the monomer's cyclic structure is stabilized by two geminal methyl groups and thus equilibrium is shifted to the CCs.[114] The advantage of spontaneous polymerization is the absence of a potentially toxic catalyst that provides good biocompatibility for the afforded polycarbonate. Macroinitiators such as polymeric lithium, sodium, and potassium alcoholates have been employed to afford the highest polycarbonate yields, with the lithium-oxygen bond having a more covalent character and thus the lithium alcoholate having lower nucleophilicity.[115-117] Takojima *et al.* used alkali metals in conjunction with alcohol initiator 3-phenyl-1-propanol (PPA) in solvent-free conditions for the ROP of TMC. These included sodium acetate (CH_3COONa) and sodium benzoate (PhCOONa) which are used as food additives so already meet industrial standards for safety and implementation. Sodium acetate only required a catalyst loading of 0.001 mol% to efficiently afford polycarbonates at 70 °C (M_n = 9,780 g mol^{-1}, $Đ_M$ = 1.23), much lower than standard organocatalytic catalyst loadings of 0.1-5 mol%, thus addressing the problem of very high catalytic loadings for industry. Higher molar mass polycarbonates were afforded from higher catalyst loadings (M_n up to 34,200 g mol^{-1}). As the catalysts are mildly basic, no ether linkages were observed from decarboxylation in the polymer backbone.[118]

Many alkoxide and alkyllithium initiators have been employed for anionic ROP of polycarbonates including n-BuLi[119], lithium alkoxides[120], sec-butyllithium[121, 122], sodium methoxide[122] and potassium dihydronaphthylide[122] but their instabilities and high reactivities limit their industrial application. Thus, attention turned to alternative anionic initiators. Brønsted base initiators 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), quinuclidine, 1,4-diazabicyclo[2.2.2]octane (DABCO) and 4-(dimethylamino)pyridine (DMAP) were found to successfully afford polycarbonates from the ROP of 5,5-(bicyclo[2.2.1]hept-2-en-5,5-ylidene)-1,3-dioxan-2-one (NBC). DBU was shown to be the most active catalyst and afforded poly(NBC) with a M_n = 6,500 g mol^{-1} after 1 h at 120 °C. Triethylamine was found not to afford polycarbonates as a consequence of the steric hindrance around the central nitrogen atom. Similarly, aromatic amines such as aniline, *N,N*-dimethylaniline, and pyridine, owing to their low nucleophilicities, did not promote ROP of CCs.[123] Hedrick and coworkers reported the ROP of TMC using DBU, 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD), 7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene (MTBD) and (-)-sparteine as amine-based catalysts coupled with a primary alcohol initiator. With the exception of (-)-sparteine, these catalyst systems afforded PTMC with high molar mass (≤ 50,000 g mol^{-1}) and high end-group fidelity without decarboxylation occurring. DBU mediated the synthesis of PTMC with low dispersity ($Đ_M$ < 1.1). TBD was found to be a superior catalyst to DBU in catalytic activity.[13, 124] The bulk ROP of TMC with TBD catalyst and a large excess of a chain transfer agent alcohol (5 ≤ [ROH]$_0$/[TBD]$_0$ ≤ 200) at 110 °C afforded the corresponding polycarbonate in high molar mass (M_n = 44,850 g mol^{-1}, $Đ_M$ = 1.52). Conducting the polymerization at 150 °C led to low molar mass polymers as a consequence of a loss of control during the polymerization.[125]

Phosphazene bases are another example of a highly active catalyst for the ROP of CCs. The bulk ROP of TMC with 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) with an alcohol initiator afforded high molar mass PTMC at 100 °C (M_n = 45,800 g mol^{-1}, $Đ_M$ = 1.49). BEMP gives lower molar mass and lower dispersity polymers at lower temperatures (60 °C), but the control over polymerization is lost at higher temperatures leading to greater dispersities.[125, 126] *N*-heterocyclic carbenes (NHCs) have been applied to the ROP of CCs as Lewis base initiators. Nederberg *et al.* investigated two NHCs, 1,3-diisopropyl-4,5-dimethyl-imidazol-2-ylidene and 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene, which were found to be active for the ROP of TMC. Both achieved similar molar mass polycarbonates but the high basicity of the alkylated NHC contributed to a rapid ROP process (0.1 min for

a DP of 50), which was accompanied by the loss of polymerization control and broad dispersity ($Đ_M > 2$). In contrast, the less basic aryl-substituted NHC achieved PTMC with a low dispersity ($Đ_M \sim 1.06$).[13] Three substituted imidazole-2-ylidene carbenes in THF achieved the high catalytic activity for the ROP of DTC to afford poly(DTC) ($M_n = 28,000$ g mol⁻¹, $Đ_M \sim 1.3$). A first order rate was observed by kinetic studies in both the monomer and NHC suggesting that a monomer-activated process occurs.[127]

As shown above, organocatalysts for anionic ROP are typically strongly basic. As exceptions, 2-(dimethylamino)ethanol (DMAE) and 2-(dimethylamino)ethyl benzoate (DMAEB) were both shown to control the ROP of TMC, affording polycarbonates with low dispersity ($Đ_M \geq 1.21$). The afforded polymer chains were α,ω-heterotelechelic meaning that they contained the same distinct functional end-groups as the DMAE initiator molecule.[128] Other milder routes included the use of supramolecular catalysts for ROP. Dove *et al.* first applied a thiourea-based bifunctional catalyst, the Takemoto catalyst developed to exploit hydrogen bonding in catalytic processes, to the ROP of lactide.[129] The same catalyst was further explored in the ROP of TMC affording 88% conversion after 6 days ($M_n \sim 4,500$ g mol⁻¹). A more efficient bifunctional thiourea/(-)-sparteine catalyst was shown to afford polycarbonates of $M_n = 5,000$ g mol⁻¹ after 12 h. The catalyst displays good selectivity for CCs and produces low dispersity PTMC ($Đ_M \leq 1.09$) thanks to the absence of transesterification reactions.[13] Todd *et al.* discovered that (-)-sparteine could be substituted for bispidine base in the ROP of TMC to produce comparable activity and low levels of side reactions.[130] Another class of hydrogen-bond donor catalysts are alcohol-containing catalysts such as bisphenols and chiral diols reported by Coulembier *et al.* for the ROP of TMC.[14, 131]

2.5.3 Coordination-insertion ROP

Metallo-organic coordination catalysts have two different mechanisms for the ROP of 6CC. One proceeds *via* an insertion mechanism and involves a Lewis acid metal halide, oxide or carbonate in cooperation with water or alcohol. Another mechanism, the coordination-insertion, involves metal alkoxides containing free p-, d- or f-orbitals of a favorable energy, which first form a complex with the CCs and then undergo a rearrangement leading to the cleavage of a metal-oxygen bond of the propagating species and an acyl-oxygen bond (*O*-acyl) of the cyclic monomer.[21]

Metal-carboxylates used for the ROP of 6CCs have included zinc stearate,[132] tin-based catalysts such as the di-n-butylstannic diiodide-triphenylphosphine system,[133] or porphinatoaluminum compounds like (TPP)AlOR[134]. These catalysts mediate the successful production of polycarbonates without decarboxylation. In each case O-acyl cleavage of the cyclic ring produced a metal alcoholate propagating species.

The tin-based catalyst BuSnCl₃ was shown to be an incredibly active initiator affording polycarbonates of high molar mass and high yields. The bulk ROP of DTC at 120 °C gave poly(DTC) with a M_n up to 150,000 g mol⁻¹ and high crystallinity ($T_m = 127$ °C).[132] Stannous octoate (SnOct₂) is a highly efficient initiator of cyclic ester ROP (lactides)[135] and was applied to the ROP of DTC to afford polycarbonates with molar mass determined by monomer/initiator ratios.[132] This initiator is the most commonly used in industry for ROP of CCs owing to its approval by the US FDA as a food additive.[136] Tin, zinc and aluminum-based organometallic catalysts are commonly used in the ROP of cyclic esters. Kuhling *et al.* investigated the ROP of DTC with a range of organometallic catalysts, tri-sec-butoxyaluminum (Al(Osec-Bu)₃), diethyl zinc (ZnEt₂), and dibutyldimethoxytin (Bu₂Sn(OMe)₂) in toluene. Unlike with aluminum and zinc catalysts, which polymerizations are characterized by a rate of propagation much higher than the rate of transesterification,[137] with the tin catalyst the rate of backbiting is equivalent to the rate of propagation.

Organometallic weak Lewis acids are effective for the ROP of cyclic esters. Protic species such as alcohols act as co-catalytic initiators, forming active metal-alkoxide species *in situ*. This enables the ROP to be living and the molar mass to be controlled by means of the monomer-initiator ratio.[136] Aluminum catalysts, methylaluminoxane (MAO) and isobutylaluminoxane (IBAO) were employed in the bulk ROP of TMC at 60-140 °C to afford polycarbonates with high molar mass ($M_n \leq 81,700$ g mol⁻¹) but broad dispersities ($Đ_M$

= 1.9-6.2).[138] NHC bis-phenolate aluminum complexes were used as catalysts in the ROP of TMC affording high molar mass, low polydensity PTMC (M_n = 31,900 g mol^{-1}, $Đ_M$ = 1.15) from a 99% monomer conversion at 90 °C in toluene.[139] The N,O,N-supported tetracoordinate amidoaluminum (η_3(N,O,N)-(C$_5$H$_9$)N-C$_6$H$_4$)$_2$OAlNMe$_2$ was shown to be effective for ROP of TMC at room temperature in the presence of a BnOH co-initiator to successfully afford high molar mass PTMC (M_n = 20,400 g mol^{-1}, $Đ_M$ = 1.12).[140] More recently, a highly active and well defined aluminum amide complex supported by a phenylene-diamine ligand was used for the ROP of TMC to efficiently afford polycarbonates after 2 min at 70 °C (M_n = 14,000 g mol^{-1}, $Đ_M$ = 1.59-2.10).[141] Moreover, bis(phosphinimino)methanide bisborohydride complexes of lanthanum, yttrium and lutetium have been investigated in the ring-opening polymerization of TMC. All three initiators afforded linear PTMCs in toluene at 23 °C.[142]

More biocompatible metals such as Zn, Mg and Ca have been investigated for metallo-organic catalysis. Darensbourg *et al.* used metal Schiff bases of zinc, magnesium and calcium alongside anion initiators to effectively catalyze the ROP of TMC at 86 °C. The order of activity for the catalysts as a function of their central metal ion was found to be Ca(II) >> Mg(II) > Zn(II). It was determined that *O*-acyl cleavage occurred when the cyclic monomer was ring-opened. Molar mass could be predetermined by the monomer/initiator ratio and dispersities were low indicating a highly controlled ROP.[143-145] Helou *et al.* used the Coates catalyst, a zinc complex supporting a ß-diiminate ligand, alongside a BnOH co-initiator to polymerize TMC between 60 and 110 °C with a living character to afford high molar mass, low dispersity polycarbonates (M_n ≤ 185,200 g mol^{-1}, $Đ_M$ ≥ 1.10). The activity of the catalyst was good enough that it could be used in very low loading, reducing its toxicity.[146, 147]

H$_3$PW$_{12}$O$_{40}$/CeO$_2$ is an effective heterogeneous catalyst for the ring-opening polymerization of 6-membered ring carbonates and afforded well-controlled polycarbonates with no ether bonds, a high M_n (up to 30,000 g mol^{-1}) with a $Đ_M$ of 1.4-1.8. However, this system required methyl iodide as an initiator and was not reusable.[148] A heterogeneous calcined CeO$_2$ catalyst was used at high temperature (1273 K) for the ROP of TMC to exploit the efficiency of an metallo-organic catalyst whilst avoiding contamination of the polycarbonate, by keeping the catalyst in a separate phase. In this case, the catalyst system was reusable and did not require co-catalysts, achieving in 24 h a polycarbonate with M_n = 11,000 g mol^{-1}, $Đ_M$ = 1.74.[149]

2.5.4 Enzymatic ROP

Enzymatic ROP represents an effective alternative to conventional chemically catalyzed polymerizations. It offers significant advantages, including mild reaction conditions, low toxicity, and high selectivity, resulting in improved quality and performance of the end products. The versatility of lipases to polymerize a wide range of monomers, such as large ring systems that are otherwise difficult to polymerize by conventional metal-based catalysis, represents a clear advantage. Indeed, different types of bacteria are able to synthesize aliphatic polyesters, and isolation of the enzymes responsible for the ROP of cyclic monomers has allowed their use as metal-free ROP catalysts. The advantages of enzymatic catalysis compared to all the previously mentioned techniques can be found in their relatively mild reaction conditions and biocompatibility. As a consequence of these desirable properties, these catalysts do not need to be removed from the afforded polymers, can be recycled, can be applied to bulk ROP without the need for an organic solvent, and are insensitive to impurities in the reaction mixture.[150, 151] However, unlike organocatalytic and metal catalysts, enzymes are usually less efficient and allow less control over polymer molar mass and dispersity. Kobayashi *et al.* described for the first time a lipase-initiated polymerization of TMC in bulk using a library of different lipases, and the commercial lipase Novozym-435 (from *Candida Antarctica* B) showed to be efficient to catalyze the ROP of TMC.[152]

Cyclic lactones and CCs are often copolymerized to improve the mechanical and degradation properties of polyesters. In a lipase-based ROP process, the ability to polymerize a CC monomer is dependent on the capability of the enzyme to welcome the substrate in its active cavity. Unlike chemical catalysis, controlling the polycarbonate composition by random copolymerization of functional cyclic monomers still remains a challenge. Al-Azemi *et al.* showed that MBC was preferably incorporated when copolymerized with TMC

in bulk at 80 °C and in the presence of AK lipase, with the polymer composition matching the molar feed ratio.[153] Copolymerization of CC monomers with lactones was also carried out successfully with lactide[154] or ε-caprolactone,[155] broadening the scope of the resulting polymer properties including degradation kinetics, thermal properties and mechanical performance.

Bisht *et al.* screened several lipases for bulk ROP of TMC at 70 °C for 120 h.[156] Novozym-435 from *Candida antarctica* B achieved 97% monomer conversion and PTMC with M_n = 15,000 g mol^{-1} and $Đ_M$ = 2.2. Lipases AK and PS-30 derived from *Pseudomonas* and porcine pancreas lipase (PPL) also afforded monomer conversions above 80% but gave lower molar mass polycarbonates with broader dispersities. A Novozym-435-catalysed polymerization resulted in terminal -CH$_2$OH functionalities at both chain-ends and showed chain-type propagation kinetics. ROP at 55 °C was found to be the optimum temperature for highest molar mass giving M_n = 24,400 g mol^{-1}. Increasing water content resulted in faster polymerization rates but lower molar mass polycarbonates. In a subsequent study, Matsumura *et al.* obtained contrasting results to Bisht and coworkers.[157] Novozym-435 could not catalyze the TMC polymerization when used at 100 °C, as a consequence of the enzyme inactivity at temperatures higher than 60 °C. PPL gave the highest monomer conversion and molar mass of polycarbonate of the lipases screened, with a M_w of up to 170,000 g mol^{-1} after 24 h at 100 °C. Immobilizing PPL on celite was shown to increase the yield of PTMC. Indeed, compared to native lipases, it was found that a supported lipase catalyst displayed higher thermal stability and activity and could be recycled many times.[158-163]

For APCs used in biomedical applications, the use of biocompatible initiators is essential. Hematin is an insoluble pigment formed from the breakdown of hemoglobin and has been used for the ROP of TMC and DTC at 100 °C in bulk. Only ROP of TMC gave high molar mass (up to 75,000 g mol^{-1}) and yields, with no ROP occurring in solution.[114]

2.5.5 ROP of functional monomers

While a wide range of successful approaches to produce PTMC with controlled molar mass and narrow dispersities have been reported, as described in the previous sections, the high hydrophobicity and slow degradation rate of this polymer limit its application in the biomedical field. Therefore, the introduction of side-chain functionalities such as carboxylic acid[51, 52, 153, 164], hydroxyl[68, 165-167] or amine[46, 48, 168, 169] groups has been investigated to generate polycarbonates with tunable degradation and additional pendant groups for attachment of drugs, imaging agents, and hydrophilic arms. However, adding reactive substituents to a CC can alter the reaction mechanism and thus potentially influence the polymerization kinetics and the microstructure of the resultant product. Indeed, Endo and coworkers showed that cationic polymerization of an olefin-substituted 1,3-dioxan-2-one led to a distorted and complex polymer structure as a consequence of the high reactivity of the unsaturated group, which leads to side reactions in the polymerization conditions.[34] This is in contrast with unsubstituted 1,3-dioxan-2-one, which polymerization afforded the expected polycarbonate.[34] In an attempt to suppress the high reactivity of the pendant group, the same authors reported the selective ROP of 5-methylene-1,3-dioxan-2-one bearing an exomethylene functionality with neighboring deactivating groups. In this case, a linear polycarbonate was afforded when the polymerization was initiated in bulk with BF$_3$·OEt$_2$ at 60 °C, as the vinyl reactivity was suppressed by the neighboring electron-withdrawing carbonate group.[170] It is important to note that, unlike in cationic polymerizations, the allyl group does not interfere with the anionic polymerization mechanism.[121]

The introduction of pendant unsaturated groups in polycarbonates has received further attention in the past few years as a consequence of their capability to undergo orthogonal reactions, such as Michael addition, Huisgen 1,3-dipolar cycloaddition, and UV-crosslinking.[3] The ROP of allyl ester-functional cyclic carbonate 5-methyl-5-allyloxycarbonyl-1,3-dioxan-2-one (MAC), has been described in the preparation of a range of (co)polymers.[3, 171-178] However, in all cases polymerizations showed relatively poor control and resulted in branched polymers. More recently, Dove and coworkers demonstrated that the ROP of MAC using efficient organocatalysts led to a high level of control over the resulting polymer such that the

application of the sparteine/TU catalyst system resulted in the isolation of PMAC with M_n up to 13,000 g mol^{-1} and low dispersities ($Đ_M$ = 1.12).[179]

Al-Azemi *et al.* were the first to report the preparation of carboxylic acid-containing polycarbonates by enzymatic ROP of the MBC followed by debenzylation *via* catalytic hydrogenation.[153] Among the enzymes screened, AK lipase from *Pseudomonas fluorescens* displayed the highest activity and afforded high molar mass PMBC (59,000 g mol^{-1}). While this approach enabled direct polymerization to functional polymers, cationic ROP was used to polymerize CCs bearing ester groups. 2-Acetoxymethyl-2-methyltrimethylene carbonate (AMTC), 2-acetoxymethyl-2-ethyltrimethylene carbonate (AETC), and MMTC were polymerized in toluene using sec-BuLi to afford polymers with yields between 78% and 88%.[27] Nemoto *et al.* reported the cationic ROP of ester-substituted cyclic carbonates 5-methyl-5-benzoyloxymethyl-1,3-dioxan-2-one and 4-benzoyloxymethyl-1,3-dioxan-2-one with TfOMe, TfOH, and BF$_3$OEt$_2$ as initiators. The activity order of the initiators was identified as TfOMe ~ TfOH > BF$_3$OEt$_2$, as deduced from the monomer conversion. Additionally, by using methyl iodide as an initiator, the highest molar mass was achieved (M_n = 11,000 g mol^{-1}), with a decrease in decarboxylation.[180] Kinetic studies on the polymerization of these ester-substituted 6CCs revealed that the ester side-chain enhances the propagation rate when compared to the polymerization of DTC.

6CCs with different protected hydroxyl groups (trimethylsilyl, benzyloxycarbonyl and phenylcarbamoyl) were polymerized by anionic ROP with lithium alkoxide at -30 °C. The resultant polymers could be subjected to hydrolysis or hydrogenation whereby protective groups were removed, affording the desired polycarbonate with pendant hydroxyl groups.[120] Zhuo and coworkers compared the use of metal-alkoxide catalysts Sn(Oct)$_2$, aluminum isopropoxide (Al(O^{i}Pr)$_3$) and aluminum isobutoxide (Al(O^{i}Bu)$_3$) for the ROP of a functionalized TMC, BTMC. BTMC is a useful monomer for APC synthesis as deprotection of the benzyl group post-polymerization affords a more hydrophilic polymer that can degrade faster than PTMC. Polymerization with Al(O^{i}Bu)$_3$ yielded the highest molar mass polymers with a M_n of 22,400 g mol^{-1}, when compared to polymers obtained using Sn(Oct)$_2$ (M_n = 13,400 g mol^{-1}) or Al(O^{i}Pr)$_3$ (M_n = 11,100 g mol^{-1}) as catalysts.[36]

3. Polycarbonate degradation

The degradation profile of biomaterials is crucial for a better understanding of their route and excretion after implantation in the body. Several factors such as stability, toxicity of the degradation products and loss of mechanical properties should be taken into consideration before employing a polymer for biomedical applications. Generally, a hydrolysable polymer can undergo chemical, mechanical, oxidative, photo- and thermal- degradation. However, chemical degradation and, more specifically, hydrolytic and enzymatic degradation are arguably the most used for *in vitro* material degradability assays (Figure 4A).[181]

The synthesis of CCs that undergo ring-opening polymerization (ROP) has allowed the synthesis of numerous degradable and biocompatible polymers in the last few years.[182] The first reports on polycarbonate degradation mostly focused on PTMC and its ability to degrade *in vivo*.[183, 184] In contrast to the degradation of polyesters in which toxic, acid products are observed upon degradation leading to an inflammatory response as a consequence of the acidification of the surrounding tissue, no carboxylic acid products are observed during the degradation of polycarbonates. This makes this class of polymers extremely attractive in the biomedical field. As such, the advances in polycarbonates' synthesis and modification, together with their mechanical properties, have increased the number of potential applications and interest in this class of polymers for biomedical applications.

3.1 Hydrolytic degradation

It has been demonstrated that several factors can influence the hydrolysis of polymers, including chemical bond type, polymer composition, steric and electronic effects, pH, diffusion rate of reactants and products

and the thermodynamics of polymer-water interactions.[181, 185] In order to eliminate this last factor, some degradation tests use polymers in solution. In this regard, the hydrolysis rate is restrained by the relation between the water concentration and chemical bonds, and not diffusion. Nevertheless, most studies utilize polymers in bulk, such as films and cylinders, in which case the water is diffused into a polymer material, hydrolyzing its chain.[185]

The hydrolytic degradation of polymers in bulk can follow two main modes: bulk erosion and surface erosion (Figure 4B). One of the driving factors of this mechanism is the water diffusion into the material followed by the cleavage of hydrolysable bonds. When polymers degrade *via* surface erosion, the materials gradually decrease their mass from the surface to the inner core while keeping their shape.[181] More specifically, the water diffusion in the sample is not homogeneous and its rate is usually lower than the rate of degradation. In this case, the water molecules will first be in contact with the sample's surface and, once low molar mass products are formed, surface erosion takes place. In contrast, bulk erosion involves mass loss and degradation of the whole polymer, not just the surface. In this circumstance, water reaches a homogeneous concentration in the sample, avoiding the early erosion of the surface. In bulk degradation, molar mass decreases with time, while in surface degradation it remains unchanged.[186] Even though water diffusion and hydrolysis of the sample play an important role in its degradation, the sample thickness, morphology and molar mass are also of great relevance.[185, 187]
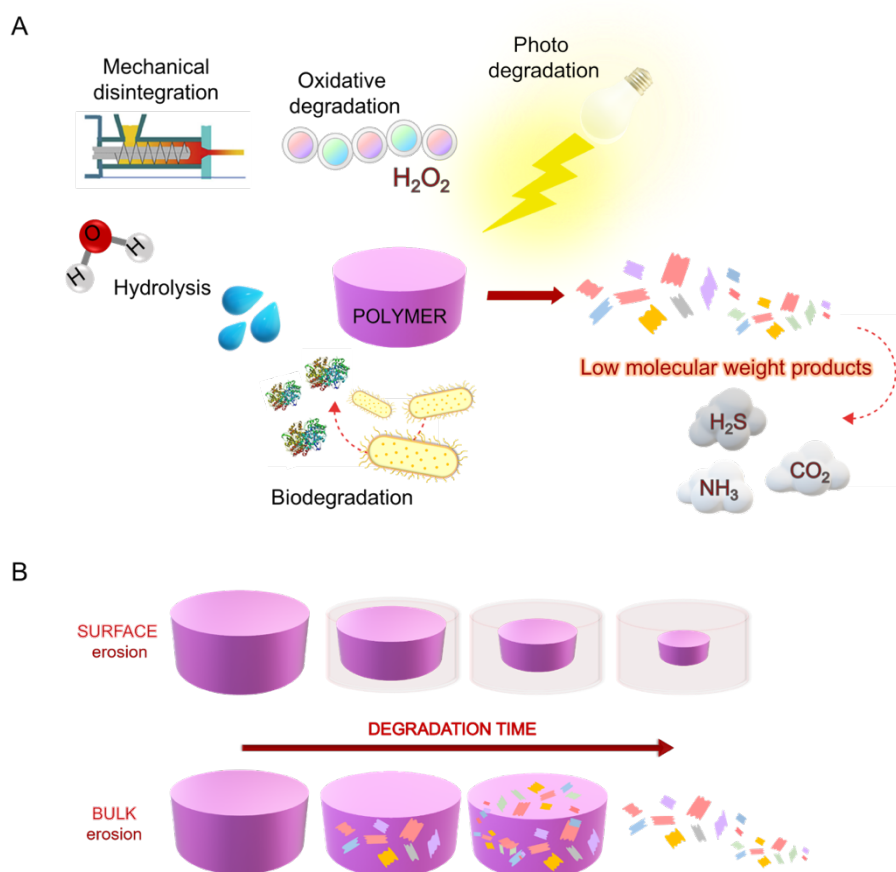
Figure 4. Degradation mechanisms of degradable polymers. A) is adapted with permission from reference [187]. Copyright (2020) Elsevier. B) is adapted from reference [93] with permission from the Royal Society of Chemistry.

Whilst polyesters degrade mainly *via* bulk degradation, the degradation of polycarbonates is controlled *via* surface erosion, and releases nontoxic products that include alcohols and CO_2 (Figure 5A). The degradation products play an important role during the process by changing the surrounding pH and hence affecting

the degradation rate. In bulk systems, the release of acidic products can accelerate the material degradation. However, in the case of surface erosion, degradation products do not accumulate as they are readily released from the surface.[93, 185] Hence, the changes in the physical and chemical properties of the polymer - such as mechanical behavior, drug release and shape - linearly change with time, which makes erosion-degradable polymers very attractive for many biomedical applications.[185]

PTMC has been extensively explored in recent years and offers an avenue to biodegradable materials owing to its excellent biocompatibility, biodegradability, and flexibility. As a result of its hydrolysable bonds, PTMC has a slow hydrolysis rate *in vitro* with no significant degradation over a period of 7 months to 2 years for homopolymers with a range of different molar masses.[183, 184] However, the lack of side functional groups limits the application of this polymer in more robust biomedical applications. To meet this expectation, copolymerization,[188-191] blends,[192] crosslinking,[193-196] side-chain[3, 40, 197-199] and end functionalization[200] have been devised to tune PTMC properties. Pêgo *et al.* studied the *in vitro* degradation of P(TMC-*co*-DLLA) and P(TMC-*co*-CL) copolymers obtained from ROP using SnOct$_2$ as a catalyst. The authors observed complete degradation of amorphous P(TMC-*co*-DLLA) containing 20 and 50 mol% of TMC after 11 months, while semi-crystalline P(TMC-*co*-CL) copolymers degraded much slower. Moreover, the degradation was mainly controlled by the hydrolysis of the ester segment *via* bulk erosion.[190] Han *et al.* prepared P(TMC-LLA) copolymers with different ratios of TMC and a composite of P(TMC-*co*-LLA) with poly(L-lactide-*co*-glycolide) PLGA fibers. While the composite presented 25% mass loss after 11 months, the copolymers were reduced by only 5-9% of their weight in the same period.[201] These data demonstrate that the degradation profile of PTMC copolymers strongly depends on the chemical structure of the components, as well as backbone packing and crystallinity. Numerous other studies displayed an increase in the hydrolysis rate of PTMC copolymers when the ester content was raised in the composition, followed by a reduction of molar mass and tensile strength with time.[202-204]

Polycarbonates bearing hydroxyl and carboxyl groups can undergo rapid hydrolysis and the polymers can be further modified by using the pendant functionality. In this instance, a wide range of protected CCs have been ring-opened and subsequently hydrogenated to obtain functional polymers.[164, 205-207] Hydroxy functional poly(5,5-bis(hydroxymethyl)1-3-dioxan-2-one (HPC) obtained from a ketal-protected CC showed complete degradation after 16h in phosphate-buffered saline (PBS) solution[165] while ketal-protected polymers presented only 7% weight loss after 2 months.[208] Benzyl-protected poly(5-benzyloxy-trimethylene carbonate) PBTMC showed no degradation over a period between 5 and 20 days.[209, 210] However, unprotected poly(5-hydroxyl-trimethylene carbonate) PHTMC polymers bearing hydroxyl pendant groups showed rapid hydrolysis after a few days of incubation in PBS (100% weight loss) and while the cause was not studied, most likely displayed a bulk erosion-type behavior on account of their ability to draw water into the bulk structure.[211, 212] Micelles and polymersomes composed of polyethylene glycol (PEG) and poly(2,4,6-trimethoxy benzylidene pentaerythritol carbonate) (PTMBPEC) or PEG, PTMBPEC and acryloyl carbonate (AC) showed an increase in their size after incubation in different pHs. In harsh acidic conditions (pH 4.0 at 37 °C), the acetal groups from PTMBPEC degraded completely in less than 2 days to form pH-sensitive nanostructures with pendant hydroxyl functionalities.[213, 214] Dove and coworkers also observed fast acetal group cleavage under acidic conditions for polymers obtained from the ROP of a norbornene-cyclic carbonate and post-modified through different chemistries. After modification, the materials could self-assemble into micelles leading to a pH-responsive delivery vehicle for triggered release.[40]

Functional degradable polycarbonates were also obtained from the ROP of 6- or 8 CCs containing amine,[193, 215] amide,[216] and fluorine groups.[217] In addition, polymers containing pendant guanidine groups were obtained after modification of polycarbonates bearing alkyne functionalities *via* a Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) click reaction.[218] Using a different approach, polymers were obtained from the ROP of Boc-protected guanidine monomers followed by removal of the Boc groups to achieve water-soluble guanidinium polycarbonates.[219] Although all the polymers underwent fast hydrolysis as a consequence of their pendant functionality, they also presented important characteristics that make them

suitable for biomaterial applications, such as non- or low toxicity,[48, 193, 216, 218, 219] antimicrobial activity,[193, 218, 219] and the ability to self-assembly in nanostructures.[216, 217]

3.2 Enzymatic degradation

Enzymes are not capable of diffusing into solid materials to the same extent as water molecules. Therefore, the main mechanism of enzymatic degradation involves enzyme adhesion on the polymer surface followed by formation of the activated enzyme-polymer complex that consequently leads to chain cleavage. A wide range of enzymes has been used to degrade polycarbonates, and several studies demonstrated that they are more efficient to mimic polycarbonates *in vivo* degradation when compared to hydrolysis itself.[220] Although lipases and esterases are capable of degrading polycarbonates *in vitro*, it is not yet known which enzyme is responsible for their erosion *in vivo*.

The enzymatic degradation of copolymers containing carbonates with different functionalities,[221, 222] poly(ester-carbonate)s copolymers,[154, 166, 223-228] poly(ester-carbonate)s terpolymers,[229] poly(peptide-carbonate)s copolymers[230] and many other combinations have been reported in the literature. Importantly, these materials degraded faster in enzymatic solutions when compared to hydrolysis in PBS, and the degradation rates were strongly related to their composition and molar mass. It has been stated that high-molar mass PTMC degrades faster than low molar mass PTMC *via* enzyme-mediated degradation. Yang *et al.* observed that the mass loss of PTMC films with number average molar mass (M_n) of 329,000 g mol^{-1} and 72,000 g mol^{-1} was respectively 50.69 and 11.64% after 12 weeks of incubation in *Thermomyces lanuginosus* solution. The authors suggested that the degradation was mainly controlled *via* surface erosion, once no molar mass and pH (in the degradation medium) reduction was observed after incubation.[231] Additionally, SEM images of the copolymers after incubation in PBS and PBS containing enzyme confirmed the surface erosion hypothesis. After a week, the appearance of numerous holes could be observed on the polymer surface when incubated in lipase solution, whereas a smooth surface was observed for polymers incubated in PBS after 50 weeks (Figure 5B).
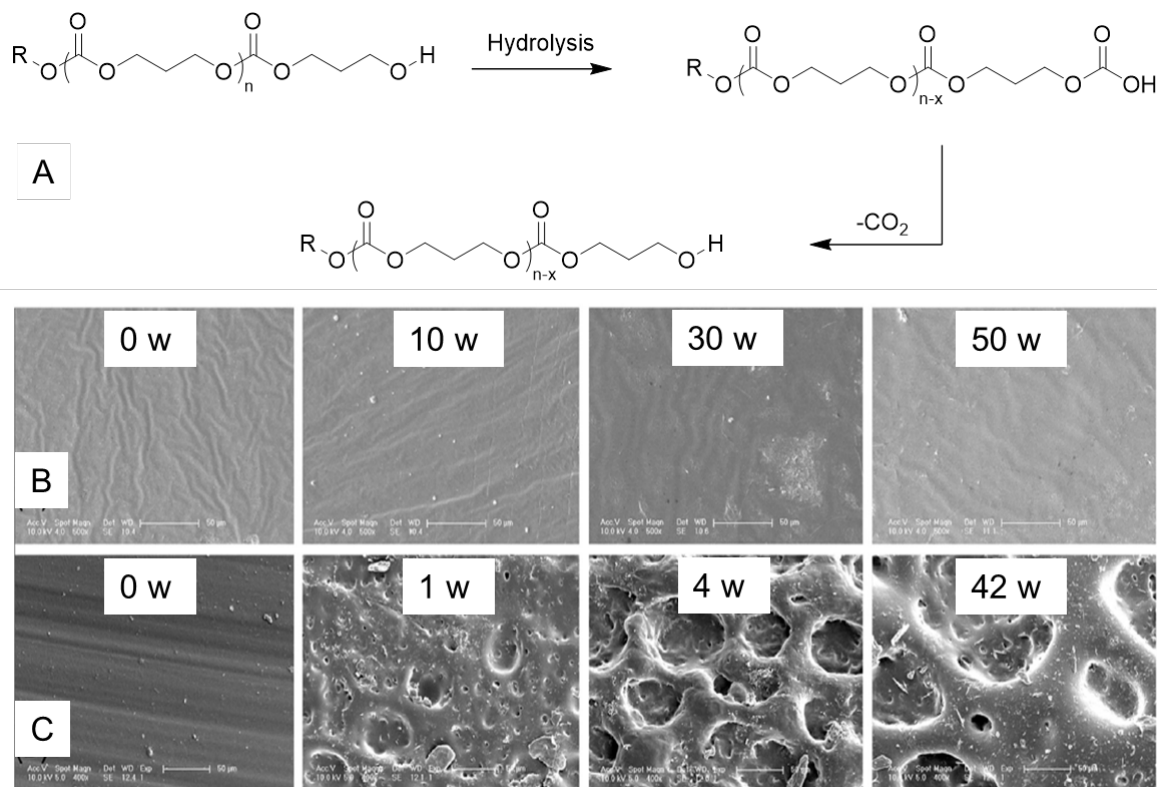
Figure 5. Hydrolysis of PTMC (A), scanning electron microscopy (SEM) on the surface of PTMC implants before and after degradation without (B) and with lipase (C). B) and C) are adapted from reference [231] "The

The same effects related to low and high molar mass polycarbonates were observed for copolymers composed of TMC and 2,2'-dimethyltrimethylene carbonate (DTC). P(TMC-*co*-DTC) copolymer containing 75 mol% of TMC and M_n of 213,000 g mol^{-1} reduced by nearly 30% of its mass after 24 weeks of incubation in *Thermomyces lanuginosus* solution. Over the same incubation time, the mass loss of P(TMC-*co*-DTC) with the same composition but lower M_n (118 kg mol^{-1}) was 16%.[221] The enhanced degradation of polymers with higher molar mass can be ascribed to the greater affinity of the enzyme active site with more hydrophobic components. Tsutsumi *et al.* reported the influence of different TMC molar ratios on the degradation profile of poly(lactide-*co*-trimethylene carbonate) P(LLA-*co*-TMC) copolymers. When TMC content was raised from 8 mol% (M_n = 171,000 g mol^{-1}) to 72 mol% (M_n = 48,000 g mol^{-1}), the remaining polymer mass after incubation in proteinase K was around 0 and 82% after 120 and 240 h, respectively. The authors did not observe a reduction in the molar mass within this time and, in tandem with morphology images, a surface erosion mechanism was proposed.[225] In a subsequent report, Yang *et al.* demonstrated the ability of the Novozym-435 lipase (NVZ 435) to degrade poly(butylene succinate-*co*-cyclic carbonate)s P(BS-*co*-CC)s copolymers using carbonates with different functionalities, such as pendant double bonds, methyl and benzyl groups. Whereas no degradation was observed for poly(butylene succinate) (PBS) when incubated in NVZ 435, the remaining weight of copolymers composed of PBS and benzyl protected polycarbonate (PBMTC) was respectively 95, 70 and 46% for polymers containing 6.5, 13 and 21.9 mol% of BTMC. In agreement with previous studies, the molar mass remained unchanged after the incubation time and the pore cavities formed on the film surface increased their size with degradation time.[232] Designed materials, such as PBMTC, can undergo deprotection to afford polycarbonates with hydroxyl pendant functionalities, which are more susceptible to degradation and also enable the covalent attachment of different biological species for biomedical applications.

The hydrophilic and hydrophobic balance of polymers can also be controlled by changing the polarity of the polymer terminal units using functional initiators during the polymerization. Watanabe *et al.* designed PTMC membranes with terminal cholesterol or poly(ethylene glycol) monomethyl ether (mPEG) groups to evaluate their surface wettability and weight loss when incubated in porcine pancreas solution. PTMC-based coatings containing cholesterol-PTMC and mPEG$_8$-PTMC with number average molar mass M_n of 35,500 and 39,300 g mol^{-1} showed almost complete enzymatic degradation after 2h of incubation, while no significant degradation was observed in the absence of enzyme.[233] Together with copolymerization and end chain functionalization strategies, crosslinking also pave a route for the design of polycarbonates with tailored degradation properties. Crosslinked materials can circulate for longer in the organism as a result of their dense network, which can make them attractive for certain applications, such as long-term vehicles for drug delivery or long-term implants. Crosslinked PTMC-based materials were obtained *in situ* during the bulk ROP of TMC with bis(trimethylene carbonate) (BTB) or bis(ε-caprolactone) (BCP). For non- and crosslinked polymer (0.5 mol% of crosslinker) with an initial molar mass of 256,000 g mol^{-1}, a mass loss of 46% and 30% was observed after 12 weeks of incubation in *Thermomyces lanuginosus* solution.[234]

More recently, reports on polycarbonates and their enzymatic degradation have been directed towards more robust applications in the biomedical field. Xiong and coworkers showed the potential of amphiphilic polycarbonates with pendant carborane units as carriers for boron neutron capture therapy for cancer. After polymer synthesis *via* ROP using a PEG macroinitiator, the polymers were self-assembled in water to form nanoparticles with diameters varying from 50 to 150 nm. In the sequence, the polycarbonate nanoparticles were incubated in *Thermomyces lanuginosus* solution and, after 7 days, total degradation of the polycarbonate segment was observed by size exclusion chromatography.[235]

3.3 Oxidative degradation

Macrophages can differentiate on the surface of implanted biomaterials after a few weeks in the organism, releasing hydrolytic enzymes and reactive oxygen species (ROs) that agglomerate to form foreign body giant cells (FBGCs). FBGC formation is different depending on material type and chemistry and they can secrete a great number of enzymes and reactive species. The *in vivo* degradation of polycarbonates can be controlled by many different mechanisms, such as acid-base, enzyme-mediated hydrolysis and oxidation from reactive oxygen species.[236, 237] Indeed, some works have reported the similarity between the PTMC degradation rate *in vivo* and *in vitro* when incubated in solutions containing ROs. In aqueous media, superoxide ions act as oxygen nucleophile agents to attack the biomaterial surface while stable superoxide solutions can be used to simulate *in vivo* conditions for studies *in vitro*.

Chu and coworkers have demonstrated the susceptibility of a commercial absorbable suture composed of glycolide (67.5 wt%) and TMC (32.5 wt%) towards superoxide ion-induced degradation. However, the authors attributed the initial mass loss to the nucleophilic attack of the glycolide segments, which are more reactive.[238] Chapanian *et al.* reported the preparation of PTMC and PTMC-*co*-CL networks obtained from the photopolymerization of modified oligomers *via* ROP. Although the materials could degrade in cholesterol esterase and *Thermomyces lanuginosus* solution, degradation in a superoxide anion solution showed a comparable degradation profile to that performed *in vivo* in rats. The authors then indicated that oxidation was the main dominant mechanism in the degradation process.[239] Bat *et al.* showed that enzyme-mediated degradation and also superoxide radical anions played an important role in the degradation rate of γ-irradiated PTMC films. When the concentration of superoxide radicals was increased (1.0 M), a PTMC mass loss of 51.8% was observed after 8 weeks.[237]

More recent reports have explored the design of responsive polycarbonate nanocarriers for drug delivery applications, and more specifically for guided cancer therapy. Mostly, cancer and inflammatory cells have a great number of ROs in their surroundings, which make the design of ROs-responsive nanocarriers extremely attractive in biomedical science. Qiu *et al.* designed oxidation-responsive polycarbonates with a pendant phenylboronic pinacol ester group from the ROP of a functional six-membered CC. Nanoparticles were then obtained *via* oil in water emulsion and they showed fast surface degradation when incubated in H_2O_2.[240] The same group reported the synthesis of a responsive polymer containing phenylboronic ester, but synthesized from the ROP of an eight-membered CCs with a secondary amine. The nanoparticles were demonstrated to undergo rapid degradation when incubated in H_2O_2 while they remained stable in neutral pH.[241] Other studies have also reported the oxidative degradation of responsive nanocarriers obtained from the ROP of CCs containing different ROs-sensitive groups,[242, 243] offering an avenue towards the targeted delivery of drugs for cancer treatment.

3.4 *In vivo* degradation

Notably, there are several reports confirming that, as might be expected, the degradation rate of polycarbonates *in vivo* is considerably faster than their hydrolysis *in vitro*.[244] Macrophage cells significantly contribute to PTMC-based materials erosion after their implantation in rats, by releasing hydrolytic enzymes and ROs.[239] The first work concerning PTMC degradation *in vivo* was reported in 1991 by Pitt and coworkers. Even though no significant weight loss was observed in PBS (after 210 days) or PBS containing-lipase (after 17 days), PTMC films of 19,800 g mol^{-1} (M_n) reduced their mass gradually after 6 months *in vivo*. Interestingly, the authors observed molar mass reduction on the polymer surface whereas the inner core was kept constant, suggesting a controlled erosion mechanism.[184] Conversely, Albertson *et al.* observed no weight loss in PTMC homopolymer with M_n of 75,100 g mol^{-1} after 180 days post-implantation in rats.[183]

In an attempt to understand PTMC degradation *in vivo* and synthesize polymers with improved stability and predictable degradation rates, subsequent reports showed more detailed investigation of PTMC homopolymers' degradation *in vivo* and their copolymerization with different materials. As previously mentioned, the molar mass has a dramatic effect over PTMC degradation *via* the enzymatic route, and the same behavior was also observed *in vivo*. Feijen and coworkers demonstrated that PTMC homopolymers with M_n of 457,000 g mol^{-1} and 89,000 g mol^{-1} showed 60% and 20% mass loss after 8 weeks' implantation

in rabbits.[244] The same effect was observed by Yang *et al.* and mass losses of around 3% (PTMC M_n = 72,000 g mol^{-1}) and 90% (PTMC M_n = 329,000 g mol^{-1}) were found after 12 weeks of PTMC implantation in rats.[231]

P(LLA-*co*-1,3-TMC) copolymers were readily prepared *via* ROP from the respective CCs and showed 35% and 5% weight loss after 90 days *in vivo* for copolymers containing 15 and 60 mol% of LLA, respectively. The mechanism of degradation was strongly related to the LLA content and below 40 mol% of LLA the polymers degraded *via* surface erosion rather than bulk.[245] Later studies also showed the same dependency on the degradation mechanism by varying the ester/TMC initial content.[246-248] In a typical study, copolymers with higher contents of caprolactone in P(TMC-*co*-CL) degraded *via* bulk erosion, while copolymers containing higher TMC contents degraded *via* surface erosion when injected in the back of rats.[249] Moreover, Pêgo *et al.* have shown that semi-crystalline P(TMC-*co*-CL) degraded slower than amorphous PTMC and P(TMC-*co*-DLLA) copolymer after implantation in rats (Figure 6).[247] In respect of the copolymers' interaction with tissues, materials composed of 50/50 molar ratio of TMC and D,L-LA or TMC and L-LA showed reduced cell inflammation in rats when compared to pure PLLA, especially after 90 days of implantation.[250] Presumably, the release of greater concentrations of acidic products from polyesters contributes to the inflammation of the tissue surrounding the implant.
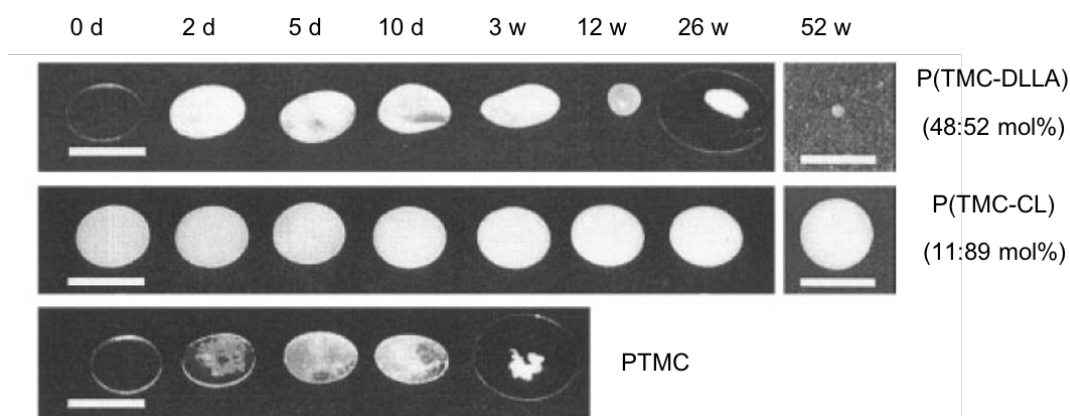
Figure 6. Polymer samples after retrieval from *in vivo* degradation in rats. Adapted with permission from reference [247]. Copyright (2003) Wiley Periodicals.

PTMC-based materials have shown excellent histocompatibility as a consequence of their neutral degradation. Lee *et al.* synthesized triblock copolymers containing vitamin D- or vitamin E-functionalized polycarbonate and PEG segments (VitD$_m$-PEG-VitD$_m$ and VitE$_m$-PEG-VitE$_m$) to form functional hydrogels for cancer therapy. When the materials were injected subcutaneously in mice, no acute or chronic inflammation was observed, and the hydrogels degraded completely after 6 weeks post-injection.[251, 252] Huang and coworkers designed a PTMC coating on magnesium alloy to reduce its corrosion in stent applications. As expected, PTMC-coated Mg materials showed better biodegradation, hemocompatibility and protective performance than PCL-coated Mg when implanted in rats. In the first case, the degradation was observed from the surface to the inner core rather than non-uniform bulk degradation. Additionally, 55% of the thickness of PTMC coating was kept after 16 weeks.[253]

The use of polycarbonate-based polymers without inconvenient side effects offers a platform towards polymer application in the biomedical field. Notably, the number of works regarding the use of polycarbonates as biomaterials has increased over the last decades and *in vivo* degradation studies have been fundamental to support their use in substitution to non-degradable and non-compatible polymers. The tunable degradation properties of polycarbonates combined with their controlled erosion mechanism enhances their potential in applications such as subcutaneous implants and injectable networks.

4. Polycarbonate nanoparticles for drug delivery and imaging

The key challenges in the design of diagnostic and therapeutic agents - whether natural drugs based on proteins and nucleic acids, or synthetic, polymer-based conjugates, or other systems - are the loss of therapeutic activity through rapid clearance or degradation and the inefficient delivery to the desired sites. Polymeric nanoparticles are widely investigated, to enhance the selectivity of therapeutics and imaging probes to target sites, as well as to increase the circulation lifetime and water solubility of poorly soluble drugs (Figure 7). These nanoplatforms, including micelles and polymersomes of different sizes, are generally prepared from the self-assembly of amphiphilic block/graft copolymers *via* a solvent-switch or a direct dissolution approach. Among the numerous biodegradable polymeric materials used in drug delivery applications, APCs are among the most interesting materials, on account of their outstanding biocompatibility, nontoxic degradation products, and ease of functionalization.[254-257] Indeed, a range of modification strategies have been exploited in polycarbonate-based nanomaterials in an effort to enhance drug-loading capacity, nanostructural stability (without aggregation and dissociation *in vivo*), as well as selective drug release to targeted tissues, whether the delivery agents are physically encapsulated or chemically conjugated - all of which are discussed below.
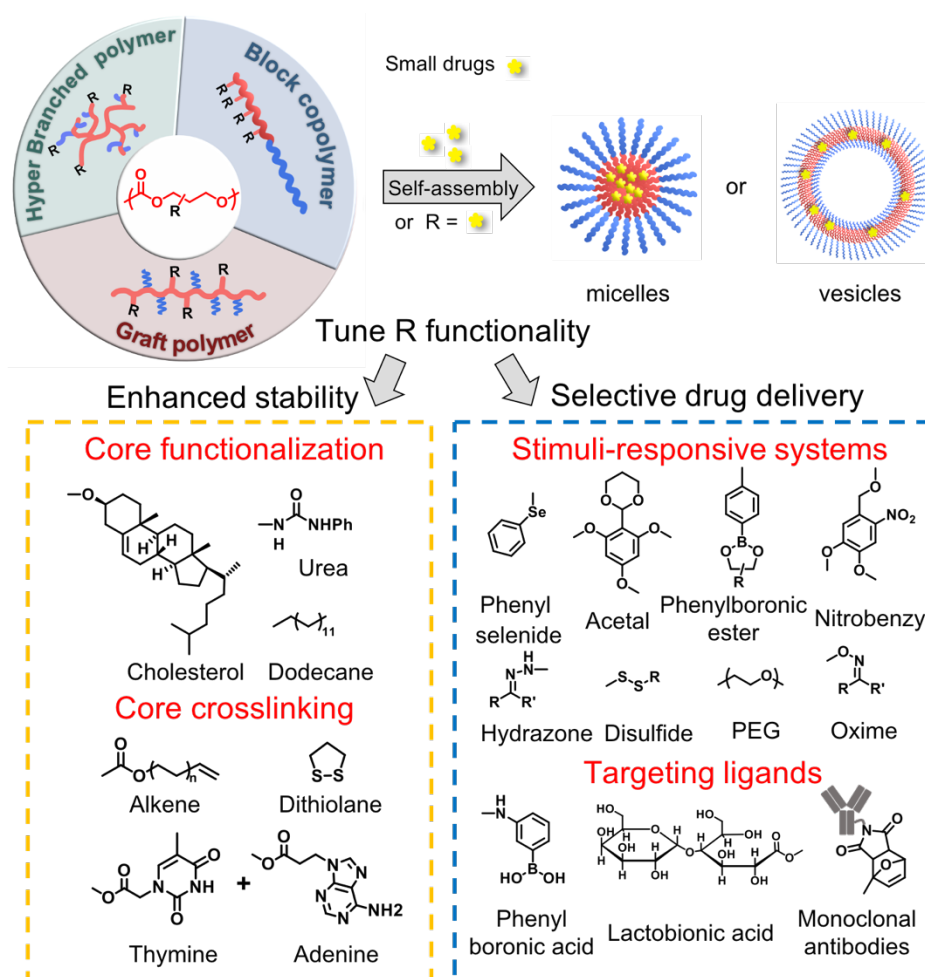
Figure 7. Polycarbonate-based amphiphilic polymers can assemble into micelles or vesicles, while small drugs are either physically blended or chemically conjugated on those nanoparticles. A variety of functionalities can be accessed on polycarbonate segments to enhance nanoparticle stability and provide sustained drug release, as well as realize selective drug delivery.

4.1 Delivery of physically encapsulated small drugs

Most polycarbonate-based micelles have been designed to encapsulate hydrophobic cargoes through physical interactions within micellar core segments. This results in the encapsulated drugs being relatively

unstable compared to drug-polymer conjugates, where the therapeutic is covalently linked to the polymer backbone. Moreover, the instability of the nanocarriers, which are prone to dissociation upon dilution *in vivo*, and non-selective drug delivery are also of concern in such systems, greatly compromising their therapeutic efficacy. To retain nanoparticle stability *in vivo* and realize sustained drug release, strategies such as polymer topology optimization, grafting functionalities on hydrophobic segments, as well as crosslinking of the micellar core have been exploited. On the other hand, to improve the delivery efficacy to the target sites and minimize adverse side effects, stimuli-responsive linkers or targeting ligands can be introduced into the polycarbonate delivery system.

4.1.1 Polycarbonate topology

The rational design of polymer architectures plays a crucial role in controlling drug loading and release performance, influencing nanostructure stability and drug encapsulation efficacy. For example, micelles derived from a combination of block and graft copolymers such as PEG-*b*-(polycarbonates-*g*-polycarbonates) demonstrated more sustained drug release and improved *in vitro* stability (with lower critical micelle concentration) compared to their diblock counterparts as a consequence of the grafted structure enhancing the interaction between hydrophobic chains and encapsulated drugs.[258] Analogously, shell branched topologies, such as poly(ε-caprolactone)-*b*-(PC-*g*-poly(2-hydroxyethyl methacrylate) (PCL-*b*-(PC-*g*-PHEAM)) and PCL-*b*-(PC-*g*-PEG), and the star-like architecture derived from the PTMC/PEG copolymer were also reported to confer the obtained nanoparticles greater kinetic stability and higher drug loading capacity, substantially outperforming their linear analogues.[259-261] These examples show that branched/grafted topologies from aliphatic polycarbonate-based polymers not only facilitate micelle formation and controlled drug release, but also enhance drug encapsulation efficacy, thus improving the therapeutic effects. Importantly, this is achieved simply by altering the polymer architectures while maintaining the same polymer composition.

4.1.2 Functionalization of the polycarbonate core

Despite the advantages previously discussed, adapting the polymer topology is not a suitable strategy for all delivery scenarios. Indeed, in certain cases additional chemical modification on hydrophobic domains is required to alter the micellar core properties and achieve high drug-loading capacity and prolonged circulation time. For example, it was reported that the incorporation of a polycarbonate segment in a PEG-*b*-polylactide delivery system (resulting in PEG-*b*-poly(carbonate-*co*-lactide)) considerably increased the drug-loading capacity, up to four times compared to its diblock counterpart, and imparted sustained drug release properties to the resultant micelles, as a consequence of the enhanced hydrophobic interaction between the polycarbonate chain and bicalutamide.[262] Furthermore, the advantages of this delivery system, including high drug loading and sustained drug release, were not only limited to bicalutamide, but also applicable to other categories of drugs including microtubule destabilizing agents, antiandrogens and cyclopamine for the treatment of different types of cancer.[206, 263, 264]

Adding a pendant functionality to the polycarbonate backbone is a widely employed approach to modify micellar core properties, owing to the easy incorporation of a wide variety of functionalities by either polymerization of a functional carbonate monomer or post-polymerization modification.[1, 2, 265, 266] For example, Li *et al.* prepared lipopolymers from PEG-*block*-poly(2-methyl-2-benzoxycarbonyl-propylene carbonate) (PEG-*b*-PBC). The pendant benzyl group was substituted with dodecanol to allow for the attachment and delivery of the anticancer drug embelin. Specifically, owing to the structural similarity between embelin and dodecanol grafted on the polycarbonate, which in turn led to improved hydrophobic interaction, the lipopolymers demonstrated enhanced drug-loading capacity and sustained drug release behavior compared to un-functionalized PEG-*b*-PBC, resulting in significant inhibition of C4-2 prostate cancer cell proliferation.[267] In another example, PEG-*b*-polycarbonate block copolymers designed for the delivery of paclitaxel (PTX) were functionalized with cholesterol through esterification of pendant carboxyl groups on the carbonate monomer before copolymerization with PEG.[268] These PTX-loaded micelles were

found to have sub-50 nm size and exceptional kinetic stability. The strong physical interaction between cholesterol and PTX substantially improved the loading efficacy from 8 wt%, which represents the standard PTX loading efficacy in common polymeric delivery systems, to 15 wt%.[269]

The urea group, as one of the most investigated pendant functionalities included on a polycarbonate motif, has gained particular attention owing to its ability to enhance micellar stability and the loading capacity of carboxylated drugs through hydrogen bonding.[169, 270, 271] Indeed, micelles formed from PEG-*b*-poly(urea-carbonate), where the urea moiety was conjugated onto the polycarbonate through an ester bond, demonstrated lower critical micelle concentration (CMC) in an aqueous environment, enhanced kinetic stability *in vitro*, as well as improved drug loading capacity (from 6.9 wt% to 10.3 wt%) compared to micelles obtained from PEG-*b*-PTMC.[270] To expand the application of such delivery vehicles to amine-containing cargoes, a carboxyl group was also introduced in the cores of the micelles, by removing the protective benzyl group from PBC, to stabilize encapsulated molecules through ionic interactions.[272] Specifically, doxorubicin-loaded mixed micelles derived from PEG-*b*-poly(urea-carbonate) and PEG-*b*-poly(acid-carbonate) had a desirable size for drug delivery (66 nm), and high doxorubicin levels (28.9 % by weight), while the *in vitro* release studies showed that the doxorubicin release was sustained, without an obvious initial burst release. More importantly, *in vivo* studies demonstrated that the drug-loaded mixed micelles inhibited tumor growth more effectively than free doxorubicin without causing significant side effects, such as weight loss or cardiotoxicity. Further studies included optimization of the urea/acid group ratio in the mixed micelles for further enhancement of drug-loading capacity and micelle stability *in vivo*, as well as co-delivery of doxorubicin and thioridazine for targeting both cancer cells and cancer stem cells, to enhance the anti-tumor therapeutic efficacy.[273-275]

Modifying the micellar core chemistry of polycarbonate-based nanoparticles has been demonstrated to be a powerful strategy to tune the physical properties of the micelles' hydrophobic core, fulfilling different drug delivery requirements. However, this strategy also faces some disadvantages: 1. The multi-step synthesis and purification route are laborious and time-consuming, which is a limiting step for further scalability and potential clinical translation. 2. The advantageous drug delivery effect that arises from such chemical modification is normally limited to specific types of drug, limiting the applicability of these systems to a wider range of cargoes.

4.1.3 Crosslinking of the polycarbonate core

Crosslinking of the micelles' core is an approach that has been used to minimize leakage of encapsulated drugs and prolong the blood circulation *in vivo*. This strategy is considered easy to apply and can be used for a wide variety of drugs.[276] In early examples, polycarbonates bearing alkene-terminated functional groups could be leveraged to produce core-crosslinked micelles *via* a radical crosslinking process, and therefore endowed the resultant crosslinked micelles with advantageous properties including sustained drug release, increased thermal stability, and greater resistance to hydrolytic degradation in comparison to their non-crosslinked counterparts.[102, 214, 277, 278]

More recently, reversible crosslinking based on disulfide bonds has received considerable attention for intracellular drug delivery, owing to the capability to be cleaved under reducing conditions within the target cell, thus enabling a controlled release and targeted delivery approach.[279] A more comprehensive introduction of stimuli-responsive delivery systems will be the object of later discussion, while in this section we will focus on the role of the disulfide bond as a crosslinker. Jing and coworkers designed a protected-thiol functional polycarbonate, which was crosslinked, upon deprotection, *via* oxidation of the free thiol groups.[280] In another example, a CC monomer with an alkyne pendant group was modified with a lipoic motif before PEGylation, and the formed micelles were crosslinked with the addition of dithiothreitol.[281] To further simplify the preparation of such micellar systems containing disulfide bonds, Zhong and coworkers designed a dithiolane trimethylene carbonate (DTC) monomer that could be directly polymerized and crosslinked in one-pot. The corresponding drug-loaded micelles showed favorable features of high stability, minimal drug leakage, long circulation time, and triggered drug release inside the

tumor cells *in vitro*.[282] In their following study, the monomer TMC was included in the polymer design, to achieve a PEG-*b*-P(TMC-*co*-DTC) block copolymer with tunable crosslinking density. Notably, the corresponding doxorubicin-loaded micelles showed superior anticancer properties in lung cancer xenograft nude mice, resulting in effective tumor suppression, significantly improved survival, and markedly reduced adverse effects.[282] Subsequently, a wide range of delivery systems based on such polycarbonate nanoplatforms were fabricated, demonstrating excellent chemotherapy efficacy towards various cancers: glioma,[283-285] hepatic cancer,[286-289] melanoma,[290] multiple myeloma,[291, 292] ovarian cancer,[293] triple negative breast tumor,[294] non-small cell lung cancer,[295-297] as well as colorectal cancer.[298]

The supramolecular interaction between nucleobases was also shown to be a non-covalent core crosslinking strategy that improves the micellar stability and drug-release efficacy for anticancer therapeutics.[299, 300] Specifically, adenine (A) and thymine (T) derivatives bearing carboxyl groups were conjugated on the polycarbonate backbone of block copolymers PEG-*b*-poly(lactide-*co*-carbonate) through esterification. Owing to the complementary hydrogen bonds between A and T in the micellar core, the formed nanoparticles demonstrated a low CMC value, slow drug release profile, and enhanced stability in aqueous solution. More importantly, the pH sensitivity of the hydrogen bonds enabled controlled drug release for anti-tumor therapy *in vitro*.

4.1.4 Active and passive targeting

Most of the polymeric nanocarriers (including polycarbonate-based nanoparticles) for application in nanomedicine are designed to load therapeutic agents for cancer therapy.[301] While the polymeric matrix allows for increased drug-loading capacity and prolonged circulation time *in vivo*, non-specific distribution of the delivery carrier and its cargo in the body leads to systemic toxicity associated with potentially serious side effects. Therefore, the development of drug delivery systems able to target the tumor site is becoming a real challenge that still needs to be addressed. Nanoparticles can reach solid tumors passively through the leaky vasculature surrounding the tumors. This characteristic is called the Enhanced Permeability and Retention (EPR) effect, where ligands grafted at the surface of nanocarriers allow active targeting by binding to specific receptors overexpressed by cancer cells.[302, 303] Nevertheless, to further improve the selective delivery of drugs to the tumor environment, active targeting is needed, with targeting ligands attached either to the hydrophobic polycarbonate core or the hydrophilic part of the nanoparticle. For instance, 3-aminophenylboronic acid, which is able to recognize sugar molecules overexpressed on the membrane of hepatic cancer cells, was conjugated to carboxyl-functionalized polycarbonates *via* an amide coupling. The corresponding nanostructures, loaded with the anticancer drug doxorubicin, were able to identify HepG2 cells and promote drug uptake.[304] Moreover, ligands such as carbohydrates and monoclonal antibodies can also be incorporated into polycarbonate chains either by post-polymerization modification or by direct polymerization of the functionalized monomer, which endowed the corresponding nanocarriers with the ability to precisely deliver anti-tumoral therapeutics.[257, 305-308] Together with the direct conjugation of targeting agents and ligands to the polycarbonate backbone, hydrophilic segments (*e.g.* PEG) can also be used for functionalization. These polycarbonate-based micellar systems can specifically deliver anti-cancer drugs to different receptors overexpressed in cancer cells, and, therefore, result in high anti-tumor activity as well as negligible adverse effect using a combined passive/active targeting.[274, 284, 290, 295, 309-311]

4.1.5 Stimuli-responsive polycarbonates

A well explored and efficient strategy to selectively deliver therapeutics to the desired site of action is the use of "activated" nanocarriers. These nanocarriers stay intact when circulating in the blood and, upon being triggered by the unique tumoral extracellular environment, allow release of the carried drug or interaction with a specific target, which in turn increase their therapeutic efficacy while reducing adverse reactions. To this end, polycarbonate-derived nanocarriers have been designed to respond to various stimuli for achieving spatio-temporal control of drug release.[40, 312-317] For example, an acid-labile acetal linkage was incorporated into CC monomers such as TMBPEC, imparting pH-sensitivity to the micellar systems. The

hydrolysis of the acetal bond in the polycarbonate segment under mild acidic condition, which characterizes the microenvironment of solid tumors, resulted in significant swelling of the nanocarriers and rapid drug release.[39, 213] The following *in vivo* study revealed that the doxorubicin-loaded PEG-*b*-PTMBPEC nanoparticles could dramatically reduce the systemic toxicity of the anticancer drug and exert excellent tumor-killing activity.[318] To further target the delivery system to the site of action, Chen *et al.* reported the synthesis of redox and pH dual-responsive nanoparticles from a PEG-SS-PTMBPEC copolymer. The drug-loaded micelles responded not only to mildly acidic endosomal compartments but also to the highly reducing conditions in the cytoplasm, resulting in superior anti-tumor activity.[260] Dove and coworkers reported the synthesis of linear poly(NTC) with predictable molar mass and narrow molar mass distributions. The norbornene handle was used to conjugate hydrophilic arms (PEG) and imaging agents through photoinduced radical thiol-ene addition, 1,3-dipolar cycloaddition, and inverse electron demand Diels-Alder. Moreover, the cyclic acetal group allowed release of the attached functionality after exposure at pH 5.0 for 12 h.[40] Arno *et al.* reported a cyclic polycarbonate that can undergo a topological change and disassembly process in response to an external stimulus, such as reducing environment or low pH.[312] Inspired by the observation that self-assemblies of cyclic graft copolymers were significantly more stable than equivalent linear graft copolymer assemblies, the authors exploited this topology effect to trigger particle disassembly through incorporation of a cleavable disulfide linkage or an acetal bond in the cyclic polymer backbone. Upon cleavage, the cyclic graft copolymer assembly switched to an unstable linear graft copolymer assembly, which disassembles, releasing its cargo. When the anticancer drug camptothecin was encapsulated in the cyclic polymeric nanostructure, a time-dependent drug release *in vitro* associated with a decrease in cancer cell viability was observed.[312]

Polycarbonate copolymers with PEG at the side-chain have been reported to show temperature sensitivity.[41, 319] For instance, with hydrophobic hydrocarbon and hydrophilic PEG functionalized on methyltrimethylcarbonate (MTC) monomers respectively, a thermo-responsive nanocarrier was produced after copolymerization. The lower critical solution temperature (LCST) of the system could be tuned in the range of 36-60 °C by varying the molar mass of PEG chains and the composition of the copolymers. When the temperature is set above the LCST, the hydrophilic shell of the micelles would collapse, leading to deformation of the micelles' structure and thus accelerating drug release. Indeed, paclitaxel-loaded nanoparticles affected the proliferation of HepG2 human liver carcinoma cells more efficiently at body temperature, above the LCST of the system (36 °C), compared to free paclitaxel and paclitaxel-loaded micelles at temperatures below the LCST.[60]

Among all the available stimuli, light has attracted wide attention since it can be spatially and temporally controlled, as well as triggered from outside the body.[320] A facile approach to construct a light-responsive micellar system is to incorporate a photocleavable linker onto a polycarbonate side-chain. 4,5-Dimethoxy-2-nitrobenzyl has been conjugated to a carbonate monomer *via* a urethane linker, obtaining a light-responsive polycarbonate. Under light, the urethane linkage was cleaved, exposing a primary amine functionality which could further degrade the polycarbonate backbone and disassemble the micelles. Upon encapsulation of a photosensitizer, the light-sensitive micelles represented an intelligent drug delivery system for safe and efficient photodynamic therapy.[321] Furthermore, light was also used as an indirect stimulus for the ROs-responsive delivery of chlorin e6 (Ce6) and doxorubicin from chalcogen-containing (selenide and telluride) carbonate monomers. Upon light irradiation, Ce6-sensitised production of $^1O_2$ triggered the degradation of nanoparticles by oxidation of chalcogen, which altered their hydrophobicity resulting in an accelerated payload release. Consequently, the Ce6 and doxorubicin co-loaded nanoparticles exhibited a synergistic cell-killing effect against human breast cancer cells.[243]

4.2 Delivery of conjugated cargoes

In contrast to the encapsulation of cargo into nanostructures, the conjugation of therapeutic or imaging agents directly to the polymer backbone allows better control of the drug loading and selective triggered release. Indeed, pendant functional groups on polycarbonates have been widely used to conjugate a range

of anti-cancer drugs.[322-325] For example, Mondal *et al.* coupled gemcitabine to polycarbonate chains *via* an amide linkage and prepared self-assembled micelles decorated with a targeting agent. *In vivo* studies demonstrated that such drug-polymer conjugates significantly prolonged gemcitabine circulation time, providing sustained drug release and effectively inhibiting tumor growth.[311, 326] Additionally, polymer-metal complexes generated from the conjugation of oxaliplatin to a carboxyl group on the polycarbonate backbone was also exploited to enhance the drug stability in nanoparticles and resulted in improved anti-tumor efficacy.[327]

Stimuli-responsive cleavage of conjugated cargoes can minimize the release of toxic drugs to undesired sites and further reduce side effects. pH-sensitive bonds such as hydrazone, acetal, oxime, and boronate ester are commonly used to prepare polycarbonate-based prodrugs. Such prodrug micelles are sensitive to hydrolysis at acidic pH, and therefore selectively accelerate the drug release in cancer cells rather than normal cells.[109, 328-332] Yang and coworkers designed bortezomib (BTZ)-polycarbonate conjugate micelles using the pH-responsive boronate ester linkage and tested their anti-tumor efficacy in a human breast cancer BT-474 xenograft mouse model. In comparison to free BTZ, it was found that the smart delivery system not only mitigated hepatotoxicity of BTZ but also inhibited the tumor growth to a greater extent.[333] Moreover, micelles with a similar composition also demonstrated efficacy conjugating drugs for the treatment of Parkinson's disease, such as apomorphine.[334] Together with pH-labile linkers, disulfide bonds that respond to reductive environments can also be readily introduced to polycarbonate side-chains to selectively deliver anticancer drugs to cancer cells.[310, 335-339]

While polycarbonate-based delivery systems can increase the concentration of chemotherapeutics in tumor tissues, cellular resistance mechanisms may still limit the overall effectiveness of the drug. To circumvent drug-resistance issues, other cationic groups and nitric oxide were conjugated to polycarbonate backbones, overcoming multidrug resistance (MDR) *via* different mechanisms.[340] For instance, tertiary amines attached to polycarbonates could be quaternized to fabricate cationic polycarbonate chemotherapeutics, which can selectively bind and lyse cancer cell membranes. Nanoparticles that contain the polycarbonate-cationic motif demonstrated not only *in vitro* and *in vivo* efficacy with negligible toxicity but also the ability to prevent cell migration and inhibit proliferation of drug-resistant cell lines and cancer stem cells, including human breast cancer, liver cancer, lung cancer, and epidermoid carcinoma.[341] In another example, nitric oxide (NO), used to improve chemosensitivity by reversing multidrug resistance, could be stabilized as nitrate functionality in polycarbonate-based micelles encapsulating doxorubicin, where the nitrate moiety was anchored on the CC monomer before polymerization. Notably, accelerated NO release was triggered by intracellular reduction conditions leading to rapid doxorubicin release from nanoparticles, which resulted in highly selective and combinational cancer treatment of MDR breast tumors *in vivo* with minimal systemic toxicity.[342] Micelles derived from polycarbonate were also used to encapsulate carborane for boron neutron capture therapy, where the carborane motif was grafted on a CC monomer *via* azide-alkyne cycloaddition before copolymerization with PEG and self-assembly. These nanoparticles could accumulate at the tumor site, and exhibited high therapeutic efficacy and low systemic toxicity *in vivo* upon thermal neutron irradiation, showing great promise as boron carriers for cancer therapy.[343, 344]

4.3 Protein delivery

Protein-based drugs are a unique and versatile class of biotherapeutics that have not only high biological activity but also superb specificity. While many proteins have demonstrated striking anticancer activities and have emerged as advanced alternatives to cytotoxic chemotherapeutic agents for cancer therapy, their clinical translation is severely hindered by their fast degradation *in vivo*, poor cell penetration, and inefficient intracellular transportation.[345] In recent years, polymersomes with large aqueous compartments as well as robust hydrophobic membranes have emerged as ideal nanocarriers for encapsulation and controlled delivery of proteins.[279, 346] Indeed, carboxyl or amine functionalities have been attached *via* thiol-ene chemistry to a polycarbonate backbone to obtain nano-sized polymersomes from PEG-PTMC(COOH) or PEG-PTMC(NH₂) and featuring an ionizable membrane that substantially enhanced cytochrome C encapsulation efficiency over four times compared to the non-charged counterpart.[347] Based on this design

principle, a similar and more advanced polycarbonate vesicle with a combination of a pH-acetal linker, a targeting ligand, as well as carboxyl functionality, was subsequently developed for efficient delivery of apoptotic proteins to prostate cancer cells (Figure 8A).[348] Remarkably, granzyme B-loaded polymersomes caused effective apoptosis of LNCaP cells with a low half-maximal inhibitory concentration (IC$_{50}$) of 1.6 nM, while preliminary *in vivo* experiments demonstrated its long circulation time with a half-life of 3.3 h in nude mice. Protein delivery systems with a similar configuration could further extend their therapeutic effect to human lung cancer and human multiple myeloma *in vivo* by replacing suitable targeting agents and protein cargoes.[349, 350] Moreover, polycarbonate-based polymersomes have also emerged as a highly promising delivery system for the treatment of glioblastoma, which is one of the most intractable and high-mortality malignancy cancers as a consequence of the low accessibility of this type of tumor resulting from the blood-brain barrier (BBB). Specifically, featuring angiopep-2 as a targeting ligand, the 76 nm polymersome formed from PEG-*b*-P(TMC-*co*-DTC)-*b*-PEI could successfully cross BBB and was selectively delivered to glioblastoma cells before releasing the protein toxin chaperone saporin (SAP) as the therapeutic agent. The systemic administration of SAP-loaded nanoparticles to U-87 MG orthotopic glioblastoma tumors developed in mice led to effective tumor inhibition and significantly improved survival rate, with minimal side effects.[351, 352] Despite the success of these systems for anti-tumor therapy, reports on protein drug delivery using polycarbonate matrices are still very limited.

4.4 Gene delivery

Gene therapy is a promising approach for the treatment of genetic and intractable diseases, and its success relies on the capability of gene vectors to deliver the therapeutic agent to the desired site. Compared to viral vectors, non-viral gene carriers have many advantages, such as higher clinical safety, simplicity of preparation, and easy large-scale production. In this regard, cationic polymers have been studied as non-viral gene carriers, owing to their ability to encapsulate and retain the negatively charged gene motifs such as plasmid DNA (pDNA), microRNA (miRNA) and small interfering RNA (siRNA), forming gene-polymer complexes (called "polyplexes"). These nanostructures have the ability to protect the gene cargo from enzymatic and hydrolytic degradation as well as effectively facilitate cellular uptake through endocytosis. In the case of polycarbonate-based polyplexes, cationic functionalities such as polyethylenimine (PEI), guanidinium, and bis-tertiary amines are commonly grafted onto the polycarbonate backbone, facilitating gene binding and endosomal escape of the formed nanocarriers.[175, 353-360] For instance, Ong *et al.* developed a polycarbonate gene vector through ROP of haloalkyl functionalized CCs, followed by functionalization with bis-tertiary amines and quaternization. The cationic polycarbonate effectively condensed DNA, generating nanoparticles (*ca.* 100 nm in diameter) with positive zeta potentials (27 mV). Importantly, the polycarbonate delivery agent introduced high gene expression efficiency in four cell lines that were comparable, or even superior, to the PEI standard without causing overt cytotoxicity.[361] In their later studies, the gene transfection efficiency could be further improved by tuning side-chain alkyl spacer length between polycarbonate backbone and the bis-tertiary amines, and through the design of triblock architectures such as polycarbonate-*b*-PEG-*b*-polycarbonate, where the polycarbonate is cationic.[362, 363]

Gene therapy for cancer treatment was recently reported by Zhong and coworkers where the polycarbonate-based vector (*ca.* 100 nm in diameter), obtained from co-assembly of two block copolymers PEG-*b*-P(TMC-*co*-DTC)-*b*-PEI and cNCQ-*b*-PEG-*b*-P(TMC-*co*-DTC), could mediate high-efficiency targeted delivery of polo-like kinase1 specific siRNA (siPLK1) to orthotopic human lung cancer in nude mice. With a PEI moiety conjugated on the polycarbonate chain-end through an amide bond and a ligand coupled on the PEG end, the reversibly crosslinked polymersomes efficiently encapsulated siRNA and selectively released the payloads to the cytoplasm of A549 lung cancer cells, inducing highly potent and sequence-specific gene silencing *in vitro*. More importantly, the *in vivo* studies demonstrated that the siRNA loaded vehicles could induce increased blood circulation, superb tumor accumulation, and effective suppression of tumor growth (Figure 8B).[364] Simply by varying the targeting agent, the same delivery carrier could also be employed to boost RNA interference therapy for the treatment of orthotopic glioblastoma *in vivo*.[365] Aside from anti-cancer applications, Yin and coworkers further leveraged such nanocarriers to encapsulate anti-inflammatory siRNA and hydrophilic drugs toward the treatment of inflammatory bowel diseases.[366] These polycarbonate-based virus-mimicking chimeric polymersomes provided a robust and potent platform for targeted siRNA therapy.
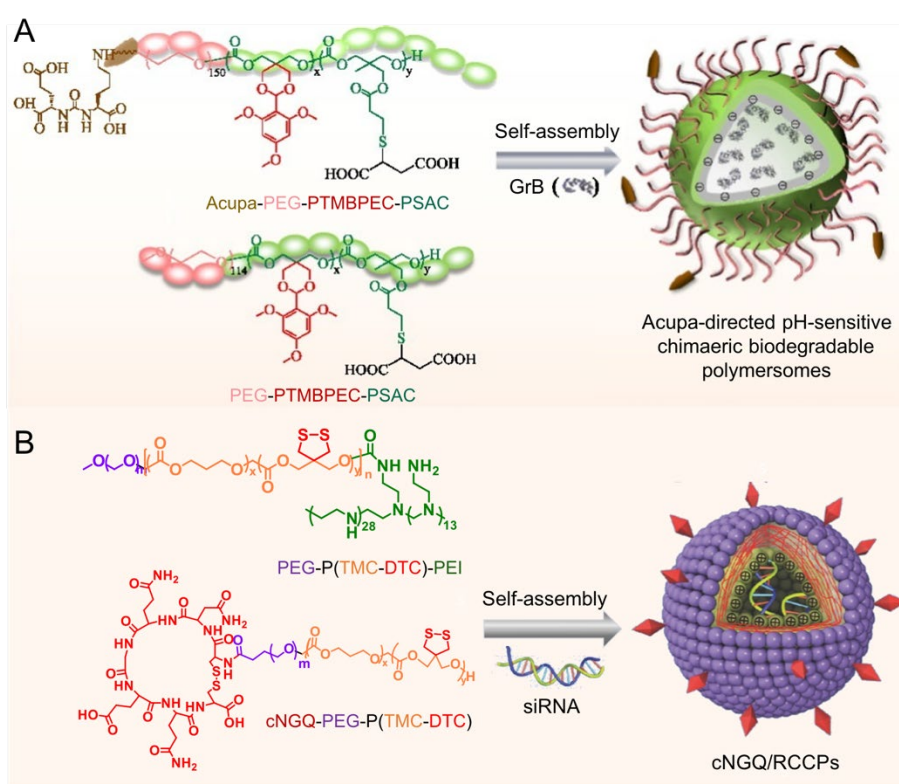
Figure 8. A) Schematic illustration of the prostate specific membrane antigen targeting, pH-sensitive biodegradable chimeric polymersomes for active loading and triggered intracellular release of GrB (apoptotic protein) into prostate cancer cells. Adapted from reference [348] "Efficacious delivery of protein drugs to prostate cancer cells by PSMA-targeted pH-responsive chimaeric polymersomes" *J. Control. Release* 2015, 220 (Pt B), 704, Copyright (2015), with permission from Elsevier. B) Efficient and targeted siRNA delivery to orthotopic lung tumors in nude mice by cNGQ peptide-directed reversibly crosslinked chimeric polymersomes (cNGQ/RCCPs). cNGQ/RCCPs are co-self-assembled from biodegradable PEG-P(TMC-DTC)-PEI asymmetric triblock copolymers and cNGQ-PEG-P(TMC-DTC) diblock copolymers. cNGQ/RCCPs can efficiently load siRNA into their lumen and protect siRNA from degradation. Adapted with permission from reference[364]. Copyright (2017) John Wiley & Sons.

4.5 *In vivo* imaging

Nanostructures formed by polycarbonate-based block copolymers have been employed to conjugate or encapsulate fluorophores or tracers for medical imaging, owing to their ability to direct imaging agents to a target site. In an early example, PEG-*b*-(PLA-*co*-polycarbonate) was used as a platform to attach small-molecule fluorophores (rhodamine) grafted on the polycarbonate backbone *via* an ester linkage. Self-assembled nanoparticles of 60-100 nm in diameter were injected in mice and the relative fluorescence was monitored by analyzing organ accumulation *ex vivo* (Figure 9A).[367]

Non-invasive medical imaging, including X-ray computed tomography (CT), magnetic resonance imaging (MRI), near-infrared, fluorescence imaging, positron emission tomography (PET), and single photon emission computed tomography (SPECT) can be used to monitor the accumulation and progression of the polymeric carrier *in vivo*. Among these, near-infrared and fluorescence imaging are the most widely used *in vivo* imaging techniques as a consequence of their relatively low cost and ease of preparation, where the imaging agent could be physically encapsulated in the nanoparticles during the self-assembly process (Figure 9B).[268] Despite the higher cost, PET and MRI have also been widely used to image polycarbonate systems where the polymer backbone has been functionalized with specific tracers.[4] For example, persistent organic radicals (*e.g.* PROXYL) were conjugated to a polycarbonate system (PEG-*b*-polycarbonate) *via* an amide linkage, imparting the formed nanoparticles (*ca.* 100 nm in diameter) with paramagnetic properties. Through T1 relaxation NMR studies, as well as MRI studies on mice, these biodegradable nanomaterials exhibited excellent imaging performance, simultaneously enabling real-time visualization of bioaccumulation and retention of polymeric nanoparticles *in vivo*.[368]

More recently, Zou *et al.* prepared nanopolymersomes (*ca.* 100 nm in diameter) from PEG-*b*-poly(iodine trimethylene carbonate) diblock copolymers and subsequently labelled these with radioactive iodine (^{125}I) for application in CT diagnosis (Figure 9C).[369] The *in vivo* imaging and pharmacokinetics studies showed that these radiopaque nanopolymersomes possessed a prolonged circulation time and could be used for blood pool as well as reticuloendothelial system imaging over a few hours, while maintaining low systematic toxicity. Furthermore, by using tumor homing peptides as targeting agents, these nanoparticles were investigated for early diagnosis of various malignancies, demonstrating superior imaging properties to commercial iodinated small molecules for CT imaging. The same authors also reported the use of this nanoplatform for combinational diagnostic and therapeutic purposes, with the additional incorporation of ^{131}I for radioisotope therapy (Figure 9D).[370, 371] The iodine-rich polymersomes enabled versatile SPECT/CT dual-modal imaging and potent anticancer effect in breast cancer *in vivo*, making them excellent theranostics.
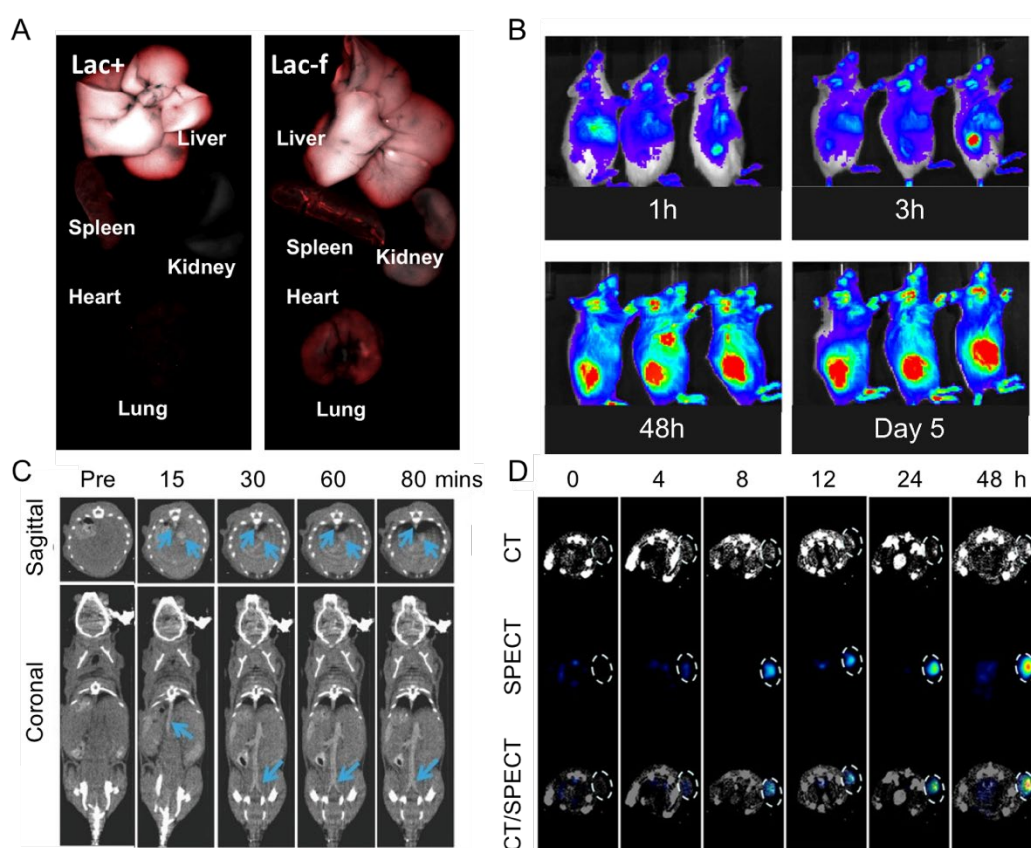
Figure 9. A) Imaging data of *ex vivo* organs 12 h after the injection of rhodamine-functionalized micelles. Lactose decorated particles are found to exclusively accumulate in the liver. Lac+: lactose containing micelles, Lac-f: lactose-free micelles. Reprinted with permission from reference [367] "Lactose mediated liver-targeting effect observed by ex vivo imaging technology" *Biomaterials* 2010, 31 (9), 2646, Copyright (2010), with permission from Elsevier. B) Near infrared fluorescence images of 4T1 tumor-bearing mice following intravenous administration of DiR-loaded nanoparticles. Reprinted from reference [268] "The use of cholesterol-containing biodegradable block copolymers to exploit hydrophobic interactions for the delivery of anticancer drugs" *Biomaterials* 2012, 33 (6), 1921, Copyright (2012), with permission from Elsevier. C) Sagittal and coronal sections of several major organs after i.v. injection of iodine-rich nanopolymersomes at different time intervals. Reprinted with permission from reference [369]. Copyright (2017) John Wiley & Sons. D) Coronal section of microSPECT/CT dual-modal imaging of 4T1 tumor-bearing mice at 0, 4, 8, 12, 24, and 48 h post-injection of ^{125}I functionalized polymersome. Reprinted with permission from reference [370]. Copyright (2019) American Chemical Society.

5. Antimicrobial polycarbonates

Macromolecular antimicrobial agents such as antimicrobial peptides (AMPs) and synthetic cationic polymers are a highly promising class of therapeutics with immense potential for the treatment of multidrug resistant microbes.[372] These antimicrobial agents selectively target the microbial membrane *via* electrostatic attractions between their cationic groups and the anionic membrane's surface (Figure 10A).[373, 374] Although AMPs have demonstrated efficacious antimicrobial properties, their applicability is still beset with several limitations for clinical usage, such as high cytotoxicity (*e.g.* hemolysis), poor proteolytic stability and pharmacokinetics (*i.e.* short half-life *in vivo*), and high production cost.[375] In contrast, a number of synthetic macromolecular antimicrobials (including PEI, polyacrylate, polyacrylamide, polynorbornene, and many others) have emerged with characteristics that mimic AMPs while addressing their drawbacks.[376]

Nevertheless, most antimicrobial polymers reported in the literature are non-biodegradable, which limits their *in vivo* application.

Recently, Hedrick and coworkers reported the first biodegradable antimicrobial polymer using a polycarbonate matrix fabricated through the "segregated monomer" approach, where an hydrophobic monomer is copolymerized with a cationic monomer to afford either statistical or block copolymers (Figure 10B).[198] Specifically, ROP was used to synthesize triblock copolymers of TMC and MTC bearing a chloride functional group, which were then further functionalized with quaternary ammonium and self-assembled into nanoparticles. These nanostructures were able to inhibit the growth of a wide range of Gram-positive bacteria and fungi while showing insignificant hemolytic activity. Importantly, a strong microbicidal activity was shown against clinically threatening methicillin-resistant *Staphylococcus aureus* (MRSA) at a concentration that did not induce toxicity to liver and kidney in a mouse model. To further improve the antimicrobial activities and broaden the antimicrobial spectrum of these polymers, many studies have focused on investigating the role of the polymer chemical structure on antimicrobial activity and selectivity, including hydrophobic/hydrophilic balance, cationic chemical functionality, and molar mass.[377-380]

The hydrophilic/hydrophobic ratio and the polymer sequence play a pivotal role in achieving selective antimicrobial activity.[376] For example, while the above-mentioned triblock polycarbonates were ineffective towards Gram-negative strains,[198] randomly copolymerized carbonates with a similar structure were able to inhibit the growth of Gram-negative bacteria, such as *Escherichia coli*, possibly as a consequence of the random copolymer readily interacting with the lipid domain of the bacterial membrane.[150] Together with the conventional "segregated monomer" approach, the "same-centered" is an alternative and widely used strategy to alter the amphiphilicity of antimicrobial polycarbonates (Figure 10B). In this approach, a hydrophobic moiety (usually an alkyl chain) is directly conjugated to a cationic center, allowing the facile optimization of the polymers' amphiphilicity by varying different structural parameters. In an early example, the hydrophobic/hydrophilic balance could be controlled simply by varying the spacer (propyl, hexyl, or octyl) between the charged quaternary ammonium moiety and the polycarbonate backbone (MTC derivative).[380] It was also reported that these "same-centered" polymers do not need to exist in the nanoparticle form to be active, and more importantly the polymer amphiphilicity is critical in determining hemolytic activity. This could be employed to achieve high selectivity of antimicrobials toward bacteria over mammalian cells. Analogously, other parameters such as cationic appendages (*i.e.* pendant structures attached on quaternary ammonium) and counter-anions (*e.g.* trifluoroacetate and citrate) have also been proved to be valid in tuning the amphiphilic balance of these antimicrobial polycarbonates, thus inducing substantial antimicrobial potency while maintaining low hemolysis (Figure 10C).[381-383]
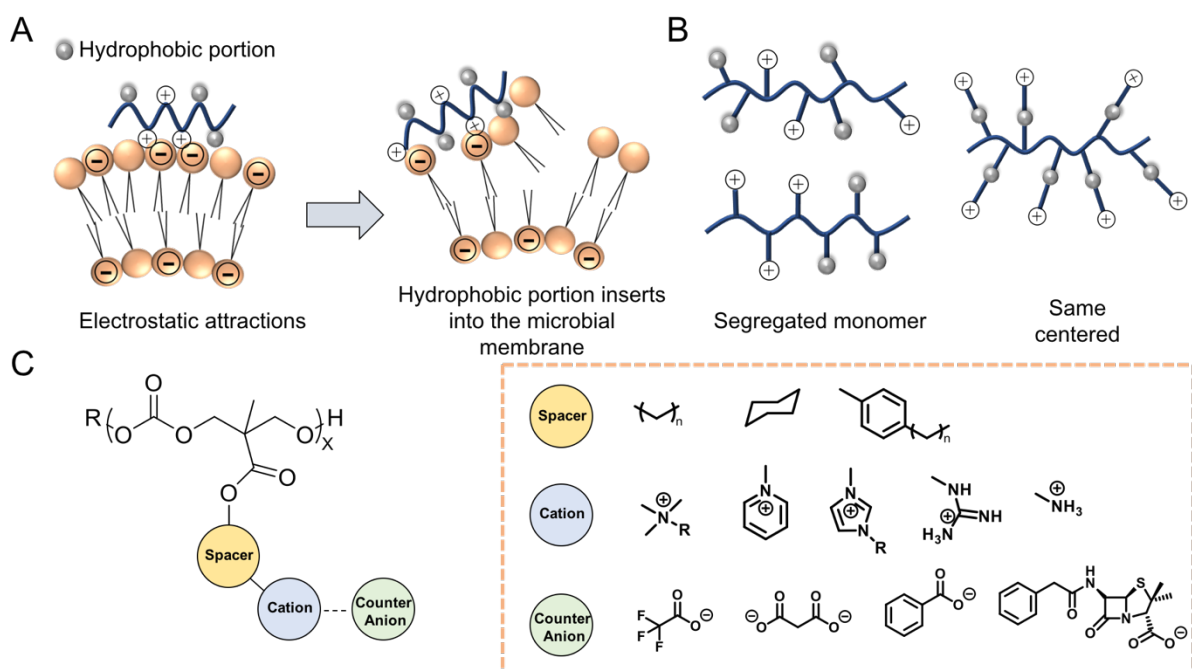
Figure 10. A) Simplified demonstration of the interactions between antimicrobial and bacterial membranes. B) Schematic depiction of strategies for balancing hydrophobicity and hydrophilicity of antimicrobial polycarbonates, including the "segregated monomer" and "same centered" approaches. C) For antimicrobial polycarbonates prepared using the "same centered" approach, the amphiphilicity could be modulated by using different spacers, cations, counter anions.

The chemical structure of the cationic groups in the polymer side-chain plays a key role not only in the electrostatic binding of polymers to bacterial membranes, but also the molecular mechanism of membrane insertion and disruption.[373] Apart from quaternary ammonium, other functionalities *e.g.* quaternary phosphonium,[384] primary amines,[385, 386] imidazoles,[387] pyridines,[381] and guanidinium[218, 388] have also been used to prepare antimicrobial polycarbonates. Guanidine-functionalized polymers can form multidentate binding with the anionic phosphate head groups on the bacteria cell membrane, thus resulting in stronger interactions with cell membranes and superior potency against bacteria compared with amine or quaternary ammonium-functionalized counterparts.[389, 390] Polycarbonates featuring guanidine side-chains could be fabricated through the ROP of Boc-protected guanidine-functionalized carbonate monomers (MTC derivatives) followed by post-polymerization deprotection.[219] With the optimization of the molar mass (DP varied from 5 to 40) and amphiphilic properties (the hydrophobic spacer ranged from straight chain alkyl and cyclohexyl to phenyl), the "same-centered" guanidinium-functionalized polycarbonate demonstrated broad spectrum *in vivo* antimicrobial activity against MDR *Acinetobacter baumannii*, *Escherichia coli*, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*, while remaining nontoxic to mammalian cells.[219, 391] The guanidine functionality was also conjugated to alkyne-containing polycarbonates *via* azide-alkyne cycloaddition in the post-polymerization modification process, and the effect of charge density and polymer molar mass on the antimicrobial activity was investigated.[218] While there is a minimum charge density requirement for the attachment of the polymer to the bacterial membrane, an increment in cationic charge density above the threshold did not significantly increase the antimicrobial polymer's potency but induced a stronger hemagglutination as a side effect. In terms of molar mass effect, low molar mass polymers (8 kDa) showed an overall greater potency than the higher molar mass counterparts (15-30 kDa), possibly as a consequence of the quicker translocation of smaller polymers across the bacteria membranes, hence leading to a greater growth inhibition.[392] It is worth mentioning that guanidinylated polycarbonates significantly outperformed polymethacrylate analogues with regards to antimicrobial activity, possibly owing to some synergistic effect between polycarbonate and guanidinium.[390] Though some general trends have been observed as to how molar mass, amphiphilicity, and charge density

affect the antimicrobial and hemolytic activity of polycarbonates, the final effects still highly depend on the specific polymer system and the strain of bacteria considered.

Positively-charged polycarbonates have also been formulated as hydrogels and coatings with antimicrobial activity.[393-395] While cationic groups are normally attached to polycarbonate side-chains, they can also be incorporated into a polymer backbone. Sardon and coworkers synthesized quaternary ammonium-containing eight-membered CCs and prepared antimicrobial hydrogels *via* crosslinking of mono- and di-functional monomers. These hydrogels exhibited a broad-spectrum antimicrobial activity and showed great potential for applications in the areas of wound care and medical implants for the prevention of acute infections.[193, 396] Moreover, antimicrobial polycarbonates can be used as coating for medical devices to efficiently prevent surface fouling and infections. For instance, a coating of cationic PEG-*b*-polycarbonate on silicone rubber (a widely used catheter material) inhibited the formation of a biofilm of *Staphylococcus aureus* and *Escherichia coli* over 7 days, demonstrating its potential for the prevention of catheter-associated bloodstream infections.[397, 398] To date, antimicrobial polycarbonate is the only synthetic polymer that meets all the critical requirements for *in vivo* clinical applications including biocompatibility, biodegradation, and antimicrobial activity. However, the development of antimicrobial polycarbonates is still at an early stage, with more research needed to understand the complex, long-term interactions of these polymers with microorganisms and tissues.

6. Polycarbonate hydrogels

6.1 Methods for polycarbonate-based hydrogel preparation

6.1.1 Covalent polycarbonate-based hydrogels

Hydrogels are crosslinked polymeric 3D networks that contain a large amount of water, up to 99% of their weight. This unique feature and the ability to readily tune their mechanical properties make this class of materials ideal for cell encapsulation and tissue regeneration. APCs have been widely employed for the preparation of hydrogel networks, owing to their versatility and ease of synthesis (Figure 11).[399] In early reports, ring-opening polymerization of CCs could be directly employed to create a crosslinked network, where the carbonate motif featuring bifunctionality, such as bis-carbonate PEG macromonomer or bifunctional CC monomer, acted as the crosslinker (Figure 11A).[193, 195, 396, 400-404] However, polymerizations had to be performed in an organic solvent before transfer in water by dialysis to obtain biologically relevant hydrogels.

In contrast to direct ring-opening polymerization, highly efficient click-type chemistries such as thiol-ene and azide-alkyne cycloaddition are more widely used in the preparation of polycarbonate-based hydrogels as they can be conducted in aqueous media, at physiological pH, and at room temperature (Figure 11 B and D).[395, 405] As an example of thiol-ene chemistry *via* Michael-type addition, by simply mixing the aqueous solution of triblock copolymers poly(acryloyl carbonate)-*b*-PEG-*b*-poly(acryloyl carbonate) and thiolated glycol chitosan under physiological-like conditions, a robust hydrogel could be rapidly formed at remarkably low total polymer concentrations of 1.5-4.5 wt%.[406] The copper-catalyzed azide-alkyne cycloaddition has also received particular attention for the preparation of polycarbonate-based hydrogels owing to its high reaction yields as well as a high level of functional group tolerance. Indeed, alkyne-functionalized PTMC crosslinked with PEG-bisazides has been used as a hydrogel matrix, producing an amphiphilic hydrogel with less than 4% of the end-groups remaining unreactive. However, the amount of copper used to catalyze the azide-alkyne cycloaddition raised severe concerns regarding the use of such prepared hydrogels as biomaterials, considering copper's ability to interact with the DNA of living cells and subsequent cell damage.[407] In an attempt to avoid the use of copper-based catalysts, copper-free strain-promoted azide-alkyne cycloaddition reactions have been used for preparing polycarbonate-based networks, where crosslinking typically occurs between PEG bis-terminated aza-dibenzocyclooctynes and azide functionalized PTMC (Figure 11B).[408-411] Notably, this approach does not require any catalysts or external stimuli and avoids the formation of potentially toxic by-products, making it ideal for cell encapsulation in the field of tissue engineering.
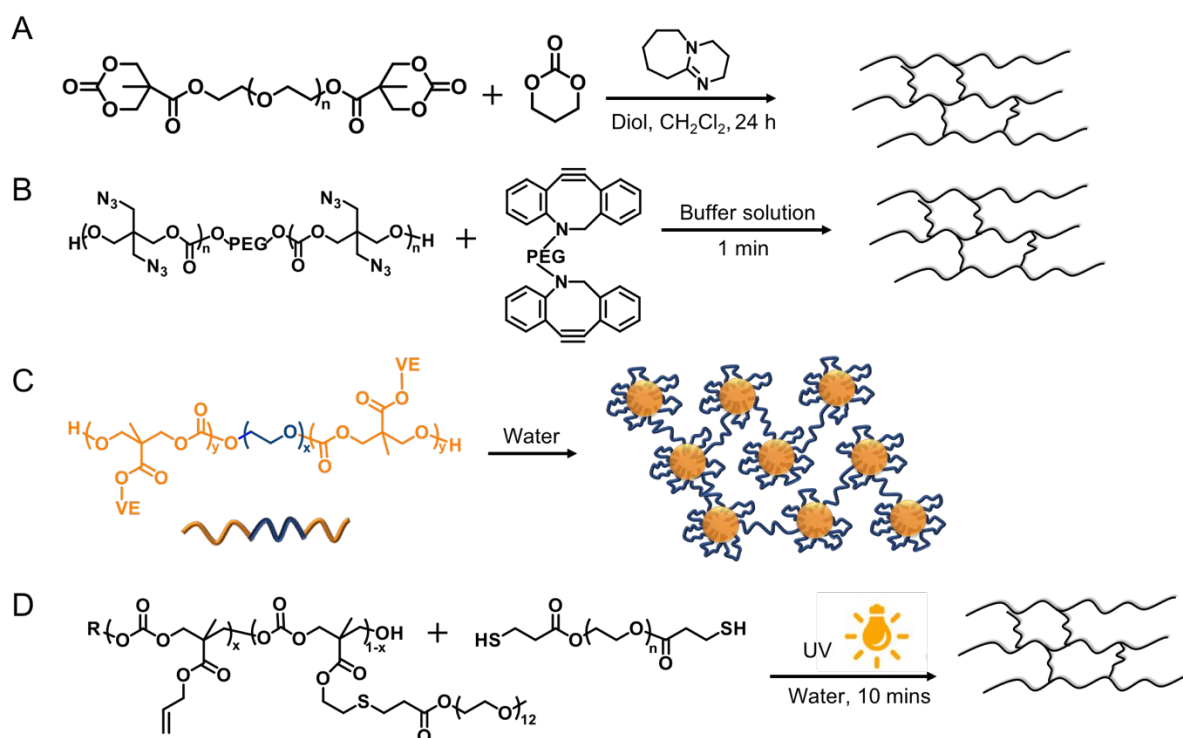
Figure 11. Different strategies used to prepare crosslinked polycarbonate-based hydrogels. A) Crosslinking of cyclic carbonate TMC and bis-carbonate PEG macromonomer through ROP. Adapted from reference [401] with permission from The Royal Chemical Society. B) PEG bis-terminated aza-dibenzocyclooctynes and azide functionalized PTMC were employed to prepare hydrogels through strain-promoted azide-alkyne cycloaddition reactions. Reprinted with permission from reference [410]. Copyright (2016) American Chemical Society. C) Hydrogel formation from physical crosslinking of polycarbonate(VE)-*b*-PEG-*b*-polycarbonate(VE) micelles. VE refers to vitamin E. Adapted with permission from reference [251]. Copyright (2013) John Wiley & Sons. D) Preparation of in situ-forming poly(5-methyl-5-allyloxycarbonyl-1,3-dioxan-2-one)-poly(ethylene glycol) hydrogels with tunable swelling, mechanical strength and degradability. Adapted from reference[195] with permission from The Royal Chemical Society.

6.1.2 Non-covalent polycarbonate-based hydrogels

Apart from covalent crosslinking, polycarbonate-derived hydrogels can also be obtained through non-covalent binding, including ionic and hydrophobic interactions and hydrogen bonding. For example, triblock copolymers of polycarbonate-*b*-PEG-*b*-polycarbonate functionalized with guanidine and carboxylic acid groups were able to form hydrogel networks *via* ionic and hydrogen bonding, which in turn endowed the system with pH-responsive properties.[412] Similarly, Kristina *et al.* reported the synthesis of a self-healing hydrogel fabricated through ionic interactions between Fe^{3+} ions and dopamine, conjugated on allyl-functional polycarbonate through thiol-ene chemistry.[413] It is important to note that simple hydrophobic interactions among polycarbonate segments could contribute to the formation of a network.[319, 414-419] For example, aqueous solutions of the diblock copolymer PEG-*b*-PTMC with relatively short PEG and PTMC segments were used to generate thermo-responsive hydrogels. The mixture underwent a sol-gel transition with a temperature increase, where the transition temperature could be controlled from 20 to 75 °C by varying polymer concentration, molar mass, and composition. Subcutaneous injection of aqueous polymer solutions (30 wt%, 0.5 mL) into rats led to *in situ* gelation, and the hydrogel system was determined to be stable in buffer solution and *in vivo* (15 wt% mass loss) for over three months.[420] Nevertheless, these hydrogel formulations normally require high polymer content (at least 16 wt%) and/or hydrophobic content (17-37%) for gelation to occur, which could lead to adverse side effects in *vivo*. In order to lower the polymer concentration needed for gelation, Lee *et al.* introduced vitamin E to

the polycarbonate backbone *via* an ester linkage, which substantially altered the hydrophobic interactions and gelation mechanism of polycarbonate-*b*-PEG-*b*-polycarbonate triblock copolymers. A hydrogel with storage modulus ranging from 1400 to 12000 Pa was directly formed by dissolving polymer motif, VitEm-*b*-PEG-*b*-VitEm, in water at a relatively low concentration (4-8 wt%). Without the presence of vitamin E, a polymer content of 30 wt% was required for gelation.[404]

6.1.3 Polycarbonate-based hydrogels prepared *via* photopolymerization

Although non-covalent hydrogels exhibit remarkably decreased toxicity and consequently increased biocompatibility, owing to the absence of covalent crosslinkers and initiators, they generally suffer from inadequate mechanical properties. Photopolymerization has emerged as an alternative strategy for *in situ* hydrogel formation that generates a strong network.[421-425] (Meth)acrylated precursors, typically end-group acrylated PTMC–*b*-PEG–*b*-PTMC triblock copolymers, have been widely used for preparing polycarbonate-based hydrogels *via* photopolymerization. With optimization over the block lengths on both hydrophobic and hydrophilic segments, the network formed demonstrated good mechanical properties including toughness (215 KJ/m³), high Young's modulus (15 kPa) and fracture strain (98%). Importantly, these hydrogels showed negligible cytotoxicity, supporting proliferation and spreading of human-bone-marrow-derived mesenchymal stem cells and primary bovine articular chondrocytes.[102, 426, 427] To further increase the mechanical properties of such hydrogels, different strategies have been exploited, which include the addition of nanocomposites (such as halloysite nanotubes and laponite nanoclay) and the design of double networks.[425, 428, 429] Together with traditional chain growth radical polymerization, thiol-ene chemistry has also been exploited to prepare polycarbonate hydrogels through photopolymerization (*e.g.* using precursor poly(5-methyl-5-allyloxycarbonyl-1,3-dioxan-2-one)-*b*-PEG), having the advantage of high oxygen tolerance and low side-product formation.[195]

6.2 Polycarbonate-based hydrogels for drug delivery

The high water content (typically 70-99%) lends hydrogels excellent capability to encapsulate hydrophilic drugs, which are otherwise difficult to deliver as a consequence of rapid denaturation and aggregation upon exposure to organic solvents.[430] As a result of this important feature, polycarbonate-derived hydrogels are perfectly suited for the delivery of biological drugs, in addition to being highly biocompatible and biodegradable. For example, an injectable hydrogel derived from triblock copolymers poly(VitEm-carbonate)-*b*-PEG-*b*-poly(VitEm-carbonate) was reported to encapsulate herceptin, a monoclonal antibody that binds to the HER2 receptor and finds application in targeted cancer therapy.[431] *In vitro* studies demonstrated that herceptin-loaded hydrogels achieved specific binding towards HER2-overexpressing cancer cells and the resultant cytotoxic action was comparable to that of herceptin alone. Moreover, no acute or chronic inflammatory response was observed after subcutaneous injection of the herceptin-loaded poly(VitEm-carbonate)-*b*-PEG-*b*-poly(VitEm-carbonate) hydrogels up to 6 weeks post-administration, despite degradation occurring in this time frame. The *in vivo* studies also showed that the hydrogel matrix not only enhanced the retention of the antibody within the tumor but also provided extraordinary sustained release of herceptin. Indeed, the anti-tumor efficacy of herceptin-loaded hydrogels after subcutaneous injection was comparable to that of weekly intravenous injection (i.v.) administration of free herceptin over four weeks. Furthermore, by simply modifying the carbonate backbone to include carbamate, more sustained antibody release and thus superior anticancer efficacy could be achieved as a consequence of the introduction of hydrogen-bonds.[391] Analogously, such a hydrogel platform could be readily adapted by replacing vitamin E with vitamin D for the delivery of Avastin, showing enhanced therapeutic efficacy against metastatic colorectal cancer.[252]

Together with biologics, hydrophobic drugs such as doxorubicin and bortezomib (BTZ), can also be loaded into polycarbonate-based hydrogels after being encapsulatated into polymeric nanoparticles.[432-434] In the case of BTZ delivery, the drug was firstly conjugated to a phenylboronic acid-functionalized polycarbonate through a pH-sensitive linkage before assembling into 42 nm nanoparticles. Triblock copolymers of

polycarbonate-*b*-PEG-*b*-polycarbonate functionalized with a guanidinium group were then used to form hydrogel networks by ionic coacervation with phenylboronic acid-functionalized analogues, which encapsulated the drug-loaded micelles. The *in vitro* release of BTZ from the composite gel was pH-dependent, with sustained gradual release in an acidic endo-lysosomal environment and minimal drug leaching at physiological pH. When tested in a multiple myeloma xenograft mouse model, anti-tumoral efficacy was significantly enhanced in the case of the BTZ-loaded hydrogel composite when compared with BTZ-loaded micelles, highlighting the need for the hydrogel matrix for sustained drug release.[434] While drug delivery using polycarbonate-based hydrogels has mainly focused in inhibiting tumor growth, limited research has been carried out for the treatment of other diseases, and hence more relevant studies in other disease areas are necessary.[417]

6.3 Polycarbonate-based hydrogels as tissue engineering scaffolds

Hydrogels have been investigated as potential candidates for the regeneration of natural extracellular matrices and have recently emerged as a promising 3D platform to investigate cell proliferation and migration.[435] In the case of polycarbonate-derived hydrogels for tissue engineering applications, triblock copolymers of PTMC-*b*-PEG-*b*-PTMC diacrylate are commonly used as precursors to prepare scaffolds through thermal or light-initiated polymerization or Michael addition reaction. In an early example, primary articular chondrocytes were encapsulated in such PTMC-*b*-PEG-*b*-PTMC diacrylate hydrogels *via* photopolymerization. Compared to the pure PEG hydrogel, the extra polycarbonate motif in the hydrogel network not only enhanced the overall mechanical properties but also promoted the aggregation of encapsulated chondrocytes and stimulated cartilage matrix production, highlighting their potential as scaffolds for cartilage repair.[427] In subsequent reports, the mechanical properties, micro-cavitary structure, as well as surface functionalization of these hydrogels could be readily manipulated to meet the necessary requirements as scaffolds for cartilage regeneration.[425, 436, 437] The application of this hydrogel platform was further extended to include *in vivo* cardiac and *in vitro* nerve regeneration.[416, 438] In particular, in the treatment of peripheral ischemia, PTMC-*b*-PEG-*b*-PTMC diacrylate precursors were crosslinked with methacrylated glycol chitosan by thermally initiated polymerization at 37 °C, making it an injectable, *in situ*-gelling hydrogel for loading stem cells and promoting angiogenesis in the tissue. In a model of hindlimb ischemia, intramuscular retention of the stem cells over 28 days was significantly improved when delivered using the injectable scaffold compared to direct intramuscular injection of cells, with improvements in cell proliferation and capillary density in the surrounding muscle tissue.[439] Despite these successes, polycarbonate-based hydrogels for tissue engineering applications are still very limited, and in-depth investigations towards the development of new biocompatible chemistries are required to further advance the field.

7. Polycarbonates as medical devices and cell culture scaffolds

7.1. 3D printed polycarbonate scaffolds

Although complex and versatile hydrogel scaffolds have been designed to generate an ideal three-dimensional environment for cell growth, able to allow transport of nutrients to cells and efflux of metabolic waste, the mechanical properties of such networks are often insufficient to meet the needs of hard tissue regeneration. Alternative scaffold fabrication approaches such as solvent casting/particulate leaching,[440] electrospinning,[441-445] sintering,[446] and 3D printing[447, 448] have been employed to prepare tough tissue engineering scaffolds using polycarbonate matrices. Among them, the 3D printing methodology has gained significant attention for the creation of a well-defined porous matrix and patient-specific biomimetic structures. Stereolithography (SLA) is the most widely used 3D printing technique for the manufacturing of polycarbonate-based 3D-printed scaffolds.[220, 449, 450] In SLA, a liquid, photocrosslinkable resin is solidified upon irradiation with a laser beam. A software is used to break the desired 3D design into sequential layers of masks consisting of individual 2D pixel patterns, which define the position of the liquid resin voxels that need to be crosslinked. Upon computer-controlled sequential photocrosslinking of the layers through the

masks, a 3D structure is finally generated, where each layer is cured on top of the other.[451] Using this technique, three-armed PTMC macromers functionalized with methacrylate end-groups were employed as the printable precursor, and with the addition of a non-reactive diluent and a photoinitiator, 3D porous structures were fabricated upon photocrosslinking. The mechanical properties of such obtained scaffolds, such as tensile strength, elongation at break and toughness could be readily tuned by varying molar mass of the PTMC macromer, the addition of another macromer with different molar mass, as well as the introduction of inorganic nanomaterials.[452-457] Moreover, this process allows other parameters, such as pore structure and surface curvature to be tuned, endowing such networks with a wide range of properties intended for various tissue engineering applications.[458, 459] Indeed, this scaffold system prepared *via* SLA using three-armed PTMC macromers has been employed for meniscus regeneration,[460] microvascular grafts,[461] orbital floor implants,[462, 463] as well as bone replacement.[464] SLA has also been used to prepare polycarbonate-based scaffolds for tissue engineering *via* thiol-ene chemistry, using aliphatic polycarbonate precursors bearing pendant alkene functionalities and four-armed thiols as crosslinkers.[199]

In contrast to homopolymers, the use of copolymer resins has been proposed as a way to increase the range of mechanical properties accessible within one scaffold and tune degradation behaviors of the final material. For instance, Kuhnt *et al.* designed PCL-*co*-PTMC urethane acrylate resins to prepare scaffolds through digital light processing, which is a variant of SLA where UV light comes from projectors instead of lasers.[465] While PTMC is an aliphatic polycarbonate with a low glass transition temperature and amorphous in nature, the semi-crystallinity of PCL allows an increase in the mechanical strength of the PCL-*co*-PTMC 3D scaffold.[226] On the other hand, polycarbonates generally demonstrate longer degradation times than polyesters, and thus, through rational changes in comonomer ratios, scaffolds with different degradation times and tunable mechanical properties can be easily fabricated.[249]

7.2 Polycarbonates as tissue engineering scaffolds

7.2.1 Scaffolds for bone regeneration

The application of SLA for the construction of biodegradable composite scaffolds combined with bioactive compounds is a promising strategy in bone regenerative medicine. Indeed, biodegradable scaffolds fabricated *via* SLA have been produced using (meth)acrylate functional polyester precursors, including PCL, PLA, and poly(propylene fumarate)-based resins, and enriched with calcium phosphate ceramic particles to induce osteoconductivity.[466, 467] Nevertheless, as previously noted, the degradation of polyesters driven by hydrolysis leads to the release of acid by-products, which can cause inflammatory reactions and subsequent bone resorption. Recently, polycarbonates have been proposed as alternative degradable polymers for the formulation of 3D printing resins for bone tissue engineering, owing to their safer degradation mechanism, which does not involve the formation of acidic degradation products and allows structural mechanical integrity to be retained (Figure 12).[448, 454, 462, 464] It was found that the incorporation of hydroxyapatite (HA) nanoparticles in the PTMC macromer resulted in increased hydrophilicity and improved the mechanical properties of the fabricated scaffold (SLA manufacturing), compared with PTMC only. More importantly, the introduction of ceramic particles in polycarbonate scaffolds helped to improve human bone marrow stem cell osteogenic differentiation *in vitro* and reduced the time needed for bone healing *in vivo*. In the case of orbital floor repair, the customized scaffold (prepared from 40 wt% of HA in PTMC resin through SLA) led to rapid neovascularization and bone morphogenesis, both ectopically and in the orbital floor region, without the need for additional biological stimuli, while standard titanium meshes resulted in fibrous tissue encapsulation (Figure 12B).[463] Besides the use of SLA for the fabrication of 3D printed scaffolds, composite sheets made from PDLLA and biphasic calcium phosphate incorporating PTMC matrices and scaffolds produced by electrospinning (PDLLA-*co*-PTMC) have also been used to support bone repair.[443, 468, 469]
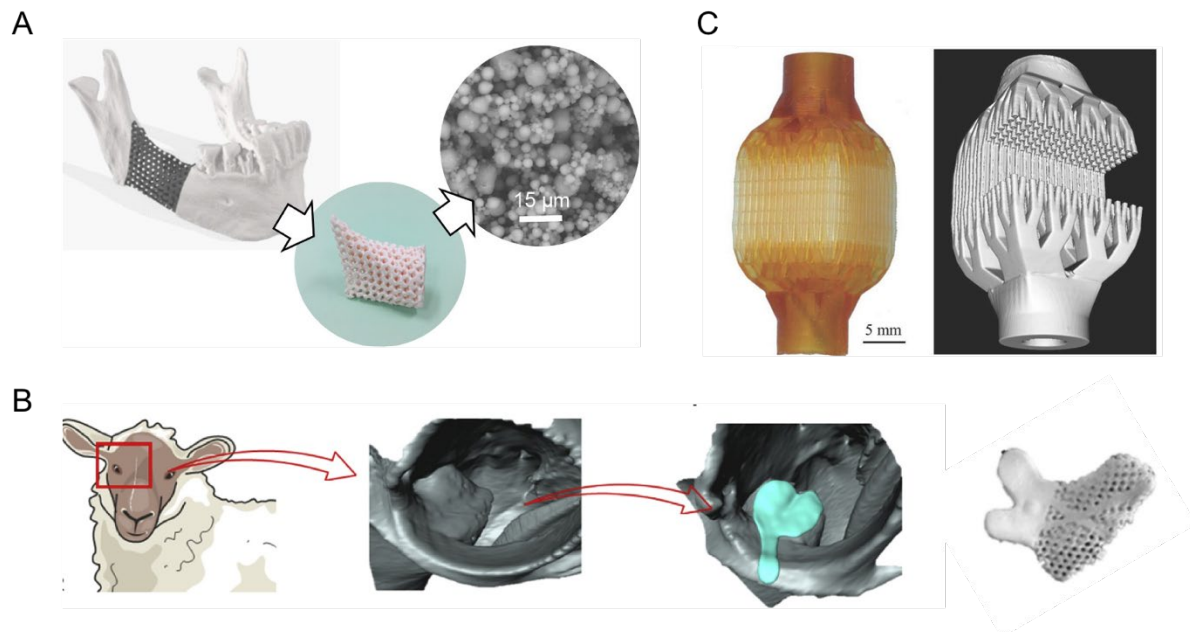
Figure 12. Polycarbonate-based 3D printing scaffolds for tissue engineering. A) Engineering route to manufacture a porous individualized implant based on imaging data including a large mandibular defect PTMC prototype containing 51 wt % β-tricalcium phosphate printed with SLA. SEM of printed scaffold demonstrates a clear microscaled topographical roughness. Reprinted with permission from reference [464]. Copyright (2020) American Chemical Society. B) CT-scan of the orbital area of a sheep and the preparation of Osteo-PTMC implants through SLA. Reprinted with permission from reference [463] "Orbital floor repair using patient specific osteoinductive implant made by stereolithography" *Biomaterials*, 2020, 233: 119721, Copyright (2020), with permission from Elsevier. C) Photograph and reconstructed μCT image of the microvascular network built by SLA using a PTMC-based resin. Reprinted with permission from reference [461]. Copyright (2014) John Wiley & Sons.

7.2.2 Scaffolds for cartilage repair

Articular cartilage tissue possesses shape-consistency and repetitive load bearing capacity together with three-dimensional shape.[470] Therefore, flexible and elastic three-dimensional porous scaffold materials are considered the gold standard for cartilage tissue regeneration.[471] As previously mentioned, the mechanical properties and pore characteristics of SLA-fabricated scaffolds derived from a three-armed PTMC macromer can be readily tuned, allowing the creation of structures with the desired modulus, elongation, and strength.[472] Indeed, upon seeding bovine chondrocytes in the designed PTMC scaffolds (with a pore diameter of 350 μm and a porosity of 54%), cells adhered and spread on the PTMC surface. After culturing for 6 weeks, cells with a round morphology were detected, indicative of the differentiated chondrocyte phenotype. Moreover, sulfated glycosaminoglycans and fibrillar collagen were deposited by the chondrocytes, suggesting that the cells recognize the scaffolds as an ideal environment for proliferation and tissue growth.

PTMC porous scaffolds have also been investigated for intervertebral disc repair, especially tailored to the regeneration of the annulus fibrosus (AF), primarily composed of fibrocartilage.[447, 473-475] Specifically, a PTMC scaffold (SLA manufacturing) seeded with human bone marrow-derived mesenchymal stem cells (hMSCs) and covered with a poly(ester-urethane) (PU) membrane was assessed for AF repair in a bovine organ culture annulotomy model under dynamic load. Implanted hMSCs showed an up-regulated gene expression indicating the ability to differentiate *in situ*. Moreover, the PTMC network not only restored annulotomized discs, but also prevented the herniation of the inner intervertebral tissue into the AF defect, hence representing an ideal platform for the repair of AF rupture after herniotomy and partial discectomy.

Interestingly, copolymerization with *D,L*-lactide (PDLLA-*co*-PTMC) imparted shape memory properties to the polycarbonate-based network.[428, 443] When the shape memory device (switching temperatures of 0 °C and 40 °C) was inserted through a small slit in a canine intervertebral disc for AF repair, it could self-sufficiently deploy within the disc cavity, allowing implantation to be minimally invasive.[476]

7.2.3 Vascular grafts

Cardiovascular disease is one of the leading causes of death worldwide, with common disorders associated with stenosis or occlusion of blood vessels. Biocompatible, degradable porous scaffolds with mechanical properties tailored to the vascular tissue have great potential to stimulate cell proliferation and facilitate re-growth of natural tissue.[477, 478] PTMC scaffolds have been widely used for vascular tissue engineering, as a consequence of their biocompatibility, predictable degradation products, and tunable mechanical strength.[479-481] Moreover, the PTMC matrix has been reported to facilitate the adhesion of human smooth muscle cells (SMCs) and endothelial cells (ECs) and support the differentiation of mesenchymal or adipose-derived stem cells towards SMCs.[482] Notably, upon proliferation of SMCs for 14 days, the maximum tensile strength of the constructs, determined in the radial direction, increased from 0.16 (unseeded scaffold) to 0.48 MPa (dynamic culturing), which is close to that of natural blood vessels.

To further tune the mechanical properties and degradation times of the vascular scaffolds, copolymerization or blending strategies of polycarbonates with other polymeric matrices have been employed.[441, 444] Dargaville *et al.* prepared copolymers of TMC and LLA, where the hydroxyl end-groups were further functionalized with acrylates for light-triggered crosslinking. Such prepared networks demonstrated constant tensile strength between 5 and 11.7 MPa and no plastic deformation after 10000 continuous mechanical cycles, while Young's moduli under wet conditions (*i.e.* after incubation in phosphate-buffered saline overnight) ranged from 1.5 to 1.8 MPa, which represents a significant improvement over other similar materials.[16] When implanted into the rat peritoneal cavity, the material elicited formation of tissue capsules composed of myofibroblasts, resembling immature vascular smooth muscle cells.[16] Although polycarbonate-derived scaffolds have emerged as promising materials for application as vascular grafts, achieving blood compatibility, and particularly antithrombotic properties, still remains an unmet requirement for which further in-depth *in vivo* evaluation is needed.[483, 484]

8. Outlook

This review has focused on the synthesis and application of APCs in biomedical and pharmaceutical fields. The ease of synthesis of this class of materials, together with their versatility - including a plethora of functionalities - allows the realization of materials with tunable thermal, degradation, and mechanical properties. Furthermore, these properties can be modified through copolymerization with other degradable polymers, targeting molar mass profiles, and by varying polymer morphology. The wide availability of functional CC monomers also allows the introduction of bio-relevant handles to the polycarbonate backbone, including targeting agents, drugs, imaging tools, and hydrophilic arms. Specifically, the development of efficient and simple chemistries for post-polymerization modifications has allowed this functionalization to be separated from the synthesis making the whole process simpler to achieve. Put simply, the aliphatic polycarbonate scaffold is versatile and easy to access, which makes it potentially useful for a wide range of applications in the biomaterials field: from nanoparticles with different morphologies as drug delivery vehicles, to 3D printed scaffolds for tissue regeneration, and hydrogels for both cell encapsulation and tissue healing.

The application of APCs for the synthesis of nanoparticles for drug delivery has been widely explored, generating spherical micelles and vesicles that are not only able to target the desired tissue, but can also disassemble under a specific trigger and selectively deliver the cargo to the site of action, limiting the side effects on healthy tissues. On the other hand, while the chemistry of polycarbonate-based hydrogels has been widely investigated, their application in the biomaterials field is currently limited. As such, tailoring

their chemistries to expand the range of biomedical applications to which these materials can be directed, represents an exciting route for future investigations. Moreover, the biocompatibility and biodegradability of polycarbonates can be further exploited in the fabrication of solid materials for tissue healing and regeneration. This route offers application of the tunable degradation and mechanical properties of APCs, as well as their high functional group tolerance, that can be used to attach biological handles that promote cell adhesion, proliferation, and even stem cell differentiation. Particularly in this field, the use of 3D printing to design personalized materials that are able to address each patient's needs, can significantly open the doors for the use of polycarbonate-based scaffolds as biomedical implants.[451] Although significant advances have been achieved in the design of functional APCs for biomedical applications, some challenges still remain. To date, PTMC is the only aliphatic polycarbonate that has been widely investigated in biomedical devices - functional APCs have not yet been translated from the laboratory bench to clinical trials. The introduction of functionalities into the polycarbonate backbone allows to afford materials with different physicochemical and mechanical properties that can be further functionalized to tailor the desired biological application. Therefore, a deeper exploitation of the in vivo fate and biosafety of functional APCs, along with an in-depth understanding of the *in vivo* degradation of these materials, is essential to pave the way to the introduction of functional APCs into the clinic.

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