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·综述·

酶促环碳酸酯开环聚合

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摘 要 酶促环状单体开环聚合(ROP)是制备生物降解聚合物的绿色合成途径. 脂肪族聚碳酸酯展现出良好的生物相容性、生物降解性和结构可设计性，已成为组织工程、药物递送、电子材料和包装材料等领域的研究热点. 近年来，以酶为催化剂、醇为引发剂，通过开环聚合制备了一系列不同结构的功能化生物降解聚碳酸酯. 本综述以三亚甲基碳酸酯、三亚甲基碳酸酯衍生物、四亚甲基碳酸酯、大环碳酸酯单体分类，总结了酶促环碳酸酯开环聚合的研究进展、机遇与挑战，希望对生物合成高分子和生物降解材料等相关领域提供借鉴.

关键词 酶；环碳酸酯；开环聚合；引发剂；生物降解

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在可持续发展日益成为共识的背景下，生物降解材料为解决传统塑料污染和满足特殊应用场景要求提供了理想方案[1~3]. 目前，主要的生物降解材料种类包括脂肪族聚酯[4~12]、脂肪族聚碳酸酯[13~15]、聚磷酸酯[16,17]、聚氨基酸[18,19]、聚磷腈[20~22]、聚酯酰胺[23,24]等. 其中，脂肪族聚碳酸酯展示出优异的生物相容性、生物降解性和结构可设计性[25]，在组织工程、药物递送、电子材料、包装材料等领域具有重要的应用价值[14,26]. 醇引发环碳酸酯开环聚合是制备脂肪族聚碳酸酯的重要方法之一[27]，具有聚合过程可控、分子量高、分子量分布窄等优势[28]，催化体系有金属催化[29]、有机催化[30,31]和酶催化[32]，机理不同，各具特色，共同促进了开环聚合制备生物降解材料的发展[33]. 金属催化体系在活性和聚合可控性方面具有优势，但金属残留可能限制其在生物医用材料中的应用[29]；有机催化体系可避免金属残留，并可通过有机碱催化、氢键活化或催化−引发协同作用等方式实现环碳酸酯的快速可控聚合，得到高分子量聚碳酸酯[30,31,34]；酶催化的优势则体现在底物识别、官能团耐受和低残留合成方面，适用于功能化脂肪族聚碳酸酯的绿色制备[32,35,36]. 环氧化物和二氧化碳开环共聚也是合成聚碳酸酯的重要方法[13,37~40]，已在多篇综述中进行了全面总结，不在本文讨论范围.

酶作为一种无毒[35,36,41]、高效[35,42]、高选择性[35,43~45]、条件温和[46]的生物催化剂[47]，在药物分子、精细化学品和高分子合成等方面应用广泛. 特别是酶工程[48,49]、蛋白质工程[50,51]、固定化技术[52,53]和计算生物学[54]等领域的发展，增强了酶的稳定性、提高了催化效率、扩大了底物范围，使酶变为可定制、高性能的催化工具[48,50,52,54~57]. 已报道的面向开环聚合的酶包括南极假丝酵母脂肪酶 B (CALB)[58~60]、猪胰脂肪酶(PPL) [61]、洋

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葱假单胞菌脂肪酶(PC)[62]等，其催化的开环聚合反应通常遵循活化单体机理(图1(a))[63~72]. 其中，市售的Novozym 435 (N435)是固定于大孔聚丙烯酸树脂的CALB，具有优异的催化能力和稳定性，对其在开环聚合领域的研究最为深入[73,74]. 根据环大小，单体分为六元环(三亚甲基碳酸酯(TMC)、三亚甲基碳酸酯衍生物)、七元环(四亚甲基碳酸酯(TeMC))和大环碳酸酯(图1(b)). 醇作为引发剂(图1(c))，可以赋予聚合产物特定的端基和不同的链结构，进一步与可控自由基聚合[75~78]、开环易位聚合[79]、电聚合[80]“点击”反应[81]等过程耦合，制备出系列新型功能化聚碳酸酯共聚材料.

本文聚焦酶促环碳酸酯开环聚合，以三亚甲

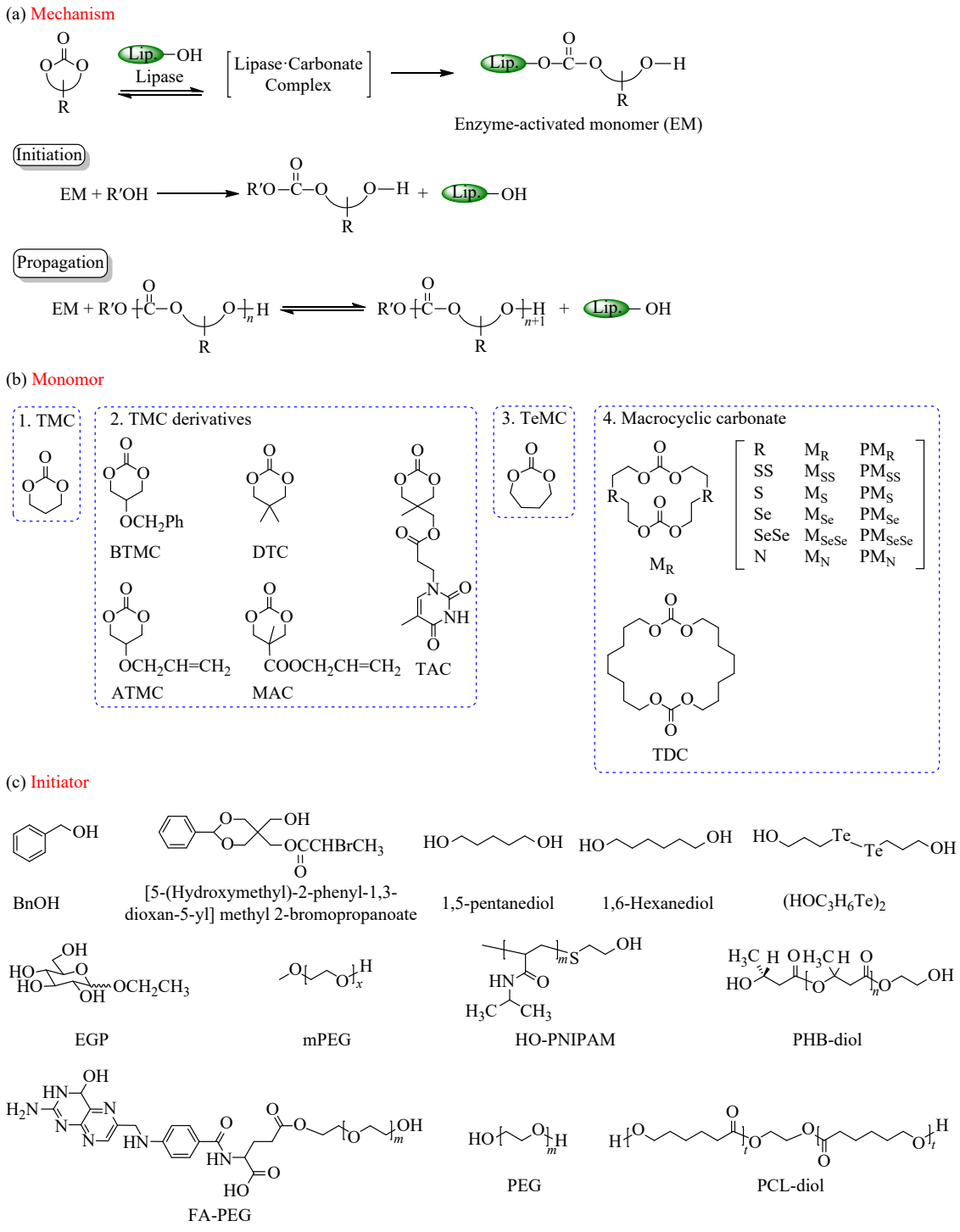

Fig. 1 (a) Mechanism of enzymatic ROP of TMC[63,64]; (b) Cyclic carbonate monomers; (c) Hydroxyl initiators.

基碳酸酯、三亚甲基碳酸酯衍生物、四亚甲基碳酸酯、大环碳酸酯单体分类，总结了酶催化醇引发开环聚合以及聚合−聚合耦合制备功能化聚碳酸酯的研究进展，对本领域存在的挑战与机遇进行了探讨和展望，希望助推生物合成高分子和生物降解材料等相关领域的发展.

1 三亚甲基碳酸酯

三亚甲基碳酸酯(TMC)是六元环脂肪族碳酸酯单体，聚三亚甲基碳酸酯(PTMC)是脂肪族聚碳酸酯家族中最具代表性的成员之一，是一种疏水性无定形聚合物，其玻璃化转变温度(T_g)约为−20 ℃，常被用作两亲性嵌段共聚物中的疏水段，以及作为软链段实现共聚物改性[82,83]. PTMC在纯水中稳定性高，其降解遵循酶促表面侵蚀机制，这对开发长期植入体和研究药物释放动力学极具价值[84~86]. 为赋予PTMC基材料定制化的功能特性与精准可控的链结构，一系列单羟基和多羟基(大分子)化合物被用于引发TMC的酶促ROP，将特定的功能基团、聚合物链段引入聚合物链末端，从而高效构建功能化均聚物和结构明确的嵌段共聚物等高性能材料.

碳纳米管(CNT)是具有高强度、轻量化、高表面积、优异的热稳定性和化学稳定性的一维量子材料[87,88]. Socka和Brzeziński等[89]制备了载体为多壁碳纳米管(MWCNTs)的固定化CALB (CALB-MWCNTs)，这种生物纳米催化剂酶负载量高、稳定性强、传质效率高、易于分离回收. 将1,5-戊二醇(1,5-pentanediol)作为引发剂，其2个伯羟基均能引发TMC开环聚合，生成两端带有羟基的遥爪型聚碳酸酯. ε-CL与TMC无规共聚得到了数均分子量$M_{n,SEC}$范围在5.0~50.0 kg/mol的系列共聚物(图2(a)). 由于PTMC为无定形链段，TMC投料的增加导致PCL结晶度(X_c)由65.5%下降至1.8%，熔融温度(T_m)由58.5 ℃降低至51.6 ℃.

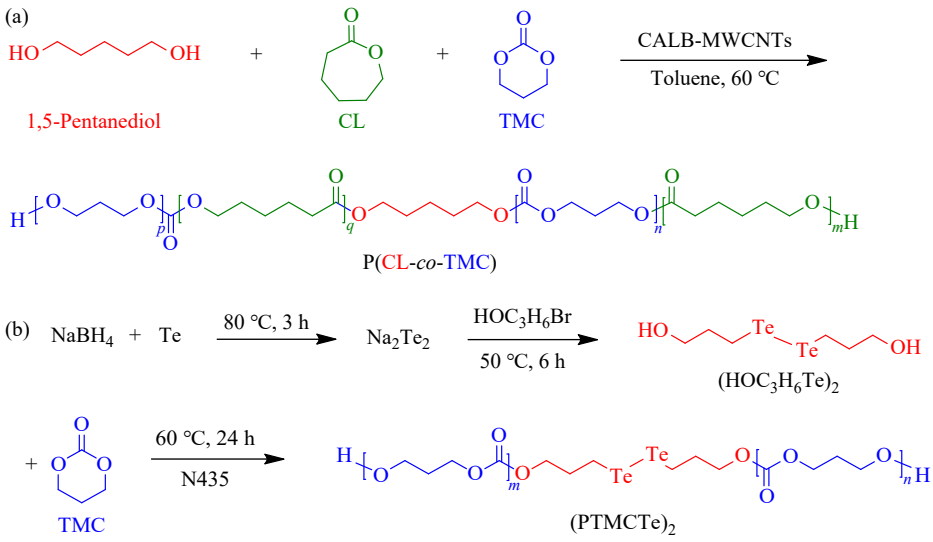

Fig. 2 (a) CALB-MWCNTs-catalyzed ring-opening copolymerization of ε-CL and TMC initiated by 1,5-pentanediol; (b) Synthesis of ditelluride compound ($(HOC_3H_6Te)_2$) and its use as an initiator for enzymatic ROP of TMC.

动态共价聚合物(DCP)具有动态共价键(如亚胺键、酰腙键、二硫键、二硒键、硼酸酯键、脲键)，能在外界刺激(如光、热、pH、催化剂、机械力、超声)下发生可逆断裂和重组，具有自修复、形状记忆、刺激响应、可回收等特性，在自修复材料、生物医学、智能涂层等领域应用前景广阔[90,91]. 相比之下，双碲键(Te-Te)的键能更低，可用于开发在室温、无刺激下即可实现键交换的动态聚合物. Lang等[92]合成了双羟基功能化的双碲化合物2,2′-二碲二丙醇($(HOC_3H_6Te)_2$)，并使其引发TMC本体聚合，成功制备了含Te-Te的聚碳酸酯$(PTMCTe)_2$ (图2(b)，$M_{n,GPC}$=2.94×10⁴ g/mol). $(PTMCTe)_2$在避光、室温、无外界刺激条件下即可发生动态交换反应. 当$(PTMCTe)_2$与含双碲键的聚己内酯$(PCLTe)_2$共混时，可原位生成嵌段共聚物PCLTeTePTMC，该共聚物作为高效增容剂，显著改善了$(PTMCTe)_2$/$(PCLTe)_2$共混体系的相容性，使共混物的微观界面趋于模糊. 相较于

1,6-己二醇(1,6-hexanediol)引发的PCL/PTMC (断裂伸长率ε_b=38.26%)，(PTMCTe)$_2$/(PCLTe)$_2$共混薄膜的ε_b大幅提升至80.51%.

酶促ROP与原子转移自由基聚合(ATRP)的级联反应是制备结构明确的功能嵌段共聚物的有效策略. 该策略通常依赖于含有羟基和ATRP活性基团(如卤素原子)的双功能引发剂，其羟基引发ROP，生成保留有ATRP活性位点的大分子引发剂，该活性位点则负责引发乙烯基单体的ATRP. Heise等[77,93]、Howdle等[94,95]、Tang等[96,97]、Wang等[98,99]及Chen等[99]基于此策略，合成了一系列聚己内酯-嵌段-乙烯基聚合物. Wang等[100]首先合成了含有羟基和溴原子的双功能引发剂[5-(羟甲基)-2-苯基-1,3-二氧六环-5-基]甲基2-溴丙酸酯 ([5-(Hydroxymethyl)-2-phenyl-1, 3-dioxan-5-yl] methyl 2-bromopropanoate)来引发TMC在N435催化下的开环聚合，得到大分子引发剂PTMC-Br ($M_{n,GPC}$=2.3×10^3 g/mol，$Đ$≈1.88). 随后向反应体系中加入2,2′-联吡啶(bpy)、CuCl和苯乙烯(St)，并将温度升至110 ℃，PTMC-Br的碳-溴键(C—Br)作为活性位点成功引发St的ATRP，制备了PTMC-*b*-PSt (图3).

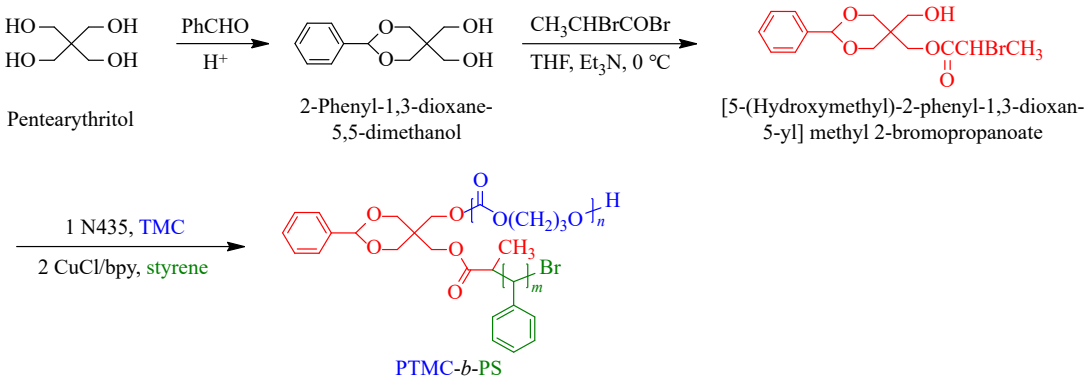

Fig. 3 Synthesis of bifunctional initiators and preparation of PTMC-*b*-PSt diblock copolymers *via* cascade enzymatic ROP and ATRP[100].

酶的高区域选择性决定了只有空间位阻最小的伯羟基和小空间位阻的仲羟基能够进入脂肪酶的催化口袋来引发反应，大空间位阻的羟基则保持惰性[44,101~104]. 与具有等效伯羟基的对称线性二醇(1,5-戊二醇、2,2′-二碲二丙醇和1,6-己二醇)引发体系不同，Gross等[105]选用亲水性糖类分子乙基吡喃葡萄糖苷(EGP)作为功能性引发剂，旨在利用酶的区域选择性精准构建两亲性结构(图4(a)). 研究考察了7种脂肪酶对TMC开环聚合的催化效果：N435的催化效率最高，TMC的转化率高达97%；来自荧光假单胞菌的脂肪酶(AK)和猪胰脂肪酶(PPL)的催化效率次之，TMC的转化率>78%；来自洋葱假单胞菌的脂肪酶(PS-30)、念珠菌脂肪酶(CCL)、来自米黑毛霉的脂肪酶(IM)和来自爪哇毛霉的脂肪酶(MAP-10)的催化效率低，TMC的转化率≤20%. 由于酶的区域选择性，仅EGP分子上的C-6位伯羟基引发聚合，最终制备了由亲水性EGP头基和疏水性PTMC链组成的两亲性低聚物($M_{n,GPC}$=7.2×10^3 g/mol，$Đ$=2.5)，其在可降解表面活性剂、洗涤剂和功能高分子材料等领域具有应用潜力.

利用端羟基聚合物作为大分子引发剂，是实现嵌段共聚物精准合成的一种高效策略. 聚羟基丁酸酯(PHB)脆性大、硬度高，难以直接作为热塑性材料使用[107]. 为此，Li等[106]以端羟基聚[(R)-3-羟基丁酸酯] (PHB-diol, $M_{n,NMR}$=2.2×10^3 g/mol)引发TMC开环聚合，N435为催化剂(图4(b$_1$)). 由于N435的区域选择性，仅PHB-diol末端的伯羟基引发聚合，而仲羟基保持惰性，从而构建了结构明确的二嵌段共聚物poly(HB-*co*-TMC) ($M_{n,NMR}$=4.4×10^3~8.7×10^3 g/mol，$Đ$=1.26~1.69). 与1,4-二氧六环(1,4-dioxane)相比，甲苯是酶促ROP的良溶剂，poly(HB-*co*-TMC)的产率由57%~71%提升至81%~89%. Poly(HB-*co*-TMC)的T_g (−24~−20 ℃)略高于纯PTMC (水为引发剂)的T_g (−27 ℃)，熔融温度(T_m=149~154 ℃)较PHB-diol (T_m=143 ℃)有所升高. 当聚己内酯二醇(PCL-diol, $M_{n,NMR}$=3.0×10^3 g/mol)作为引发剂时，可获得ABA型三嵌段共聚物poly(TMC-*co*-CL-*co*-TMC) ($M_{n,NMR}$=7.7×10^3~1.06×10^4 g/mol，$Đ$=1.58~1.64) (图4(b$_2$)).

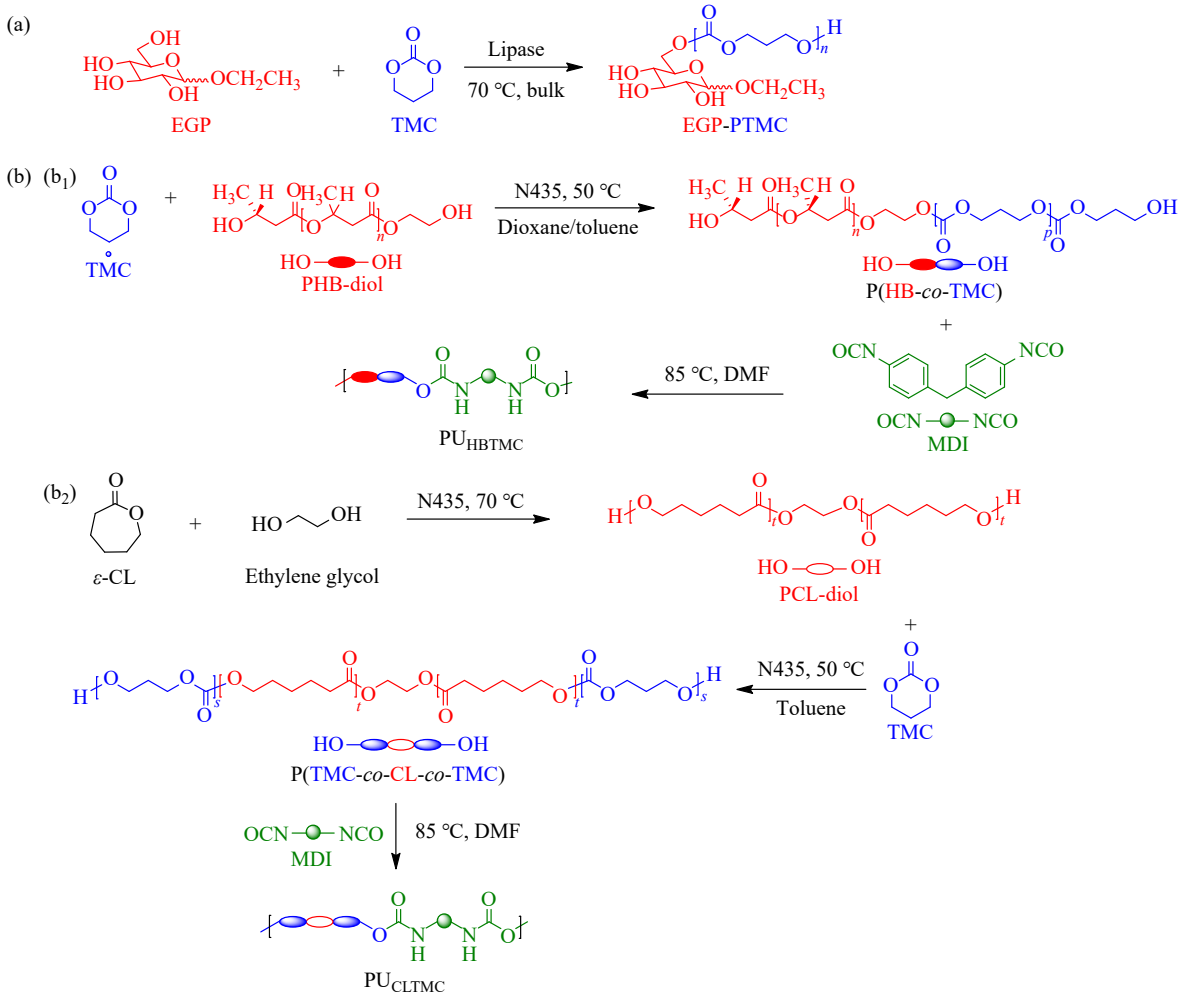

Fig. 4 (a) Enzymatic ROP of TMC initiated by EGP for the preparation of PTMC bearing hydrophilic head groups; (b) Enzymatic ROP of TMC initiated by macro-initiators (PHB-diol (b_1)/PCL-diol (b_2)) to fabricate block copolymers, followed by reaction with MDI to obtain thermoplastic polyurethanes[106].

Poly(HB-*co*-TMC) 和 poly(TMC-*co*-CL-*co*-TMC)可作为软段与二苯基甲烷-4,4′-二异氰酸酯(MDI)反应，制备高分子量的热塑性聚氨酯. 其中，以poly(HB-*co*-TMC)为软段合成的聚氨酯表现出优异的力学性能(ε_b=252%，杨氏模量 E=23 MPa). 此类兼具生物降解性与力学韧性的功能材料，在可生物降解软组织工程领域具有广阔的应用前景.

与传统的间歇式反应器相比，微反应器(MR)具有较高的表面积/体积比，其微尺度通道能够显著缩短热量和物质的传递路径，减小局部温度梯度与浓度梯度，从而提高传热/传质效率[108,109]；稳定的层流状态和可控的停留时间有助于减少返混及局部过热[110,111]；微反应器便于连续化操作，具有安全性高、参数可调等特点，因此可用于高效制备结构明确、性能可控的聚合物材料[110,112]. 微流控技术在开环聚合[79,112~119]、阴/阳离子聚合[120,121]、可逆失活自由基聚合[122,123]等领域得到了广泛而深入的研究. Zhu 和 Guo 等[124]构建了固定化酶(N435)微反应器平台，以苯甲醇(BnOH)引发TMC开环聚合. 与间歇式反应器相比，微反应器在提升表观速率常数(k_{app}=0.489 min^{-1} versus k_{app}=0.019 min^{-1})的同时，更好地控制了聚合过程，所得 PTMC 的分子量分布更窄($Đ$=1.12 versus $Đ$=1.20). 由于 N435 无法在较短时间内催化 L-丙交酯(LLA)开环聚合，而有机催化剂1,5,7-三氮杂双环[4.4.0]癸-5-烯(TBD)对 ε-CL 的催化活性较差，传统的单一催化体系难以合成包含聚酯、聚碳酸酯和聚丙交酯链段的嵌段共聚物. 为了解决这个问题，他们构建了酶-有机催化集成微反应器系统，成功实现了 ε-CL、δ-戊内酯(δ-VL)、TMC、和 LLA 的连续流开环共聚，高效制备了结构明确、窄分布($Đ$<1.3)的二嵌段和三嵌段共聚物(图5).

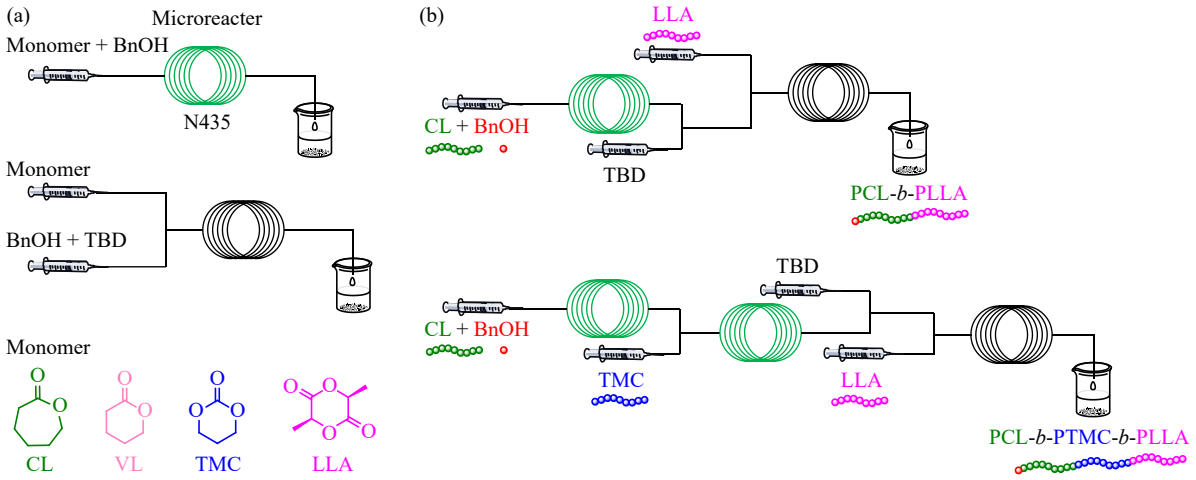

Fig. 5 (a) Schematic of an enzyme/organo-catalyzed microreactor for BnOH-initiated ROP of cyclic monomers. (b) Integrated enzyme-organocatalytic microreactor system for the synthesis of block copolymers[124].

Table 1 Enzymatic ROP of TMC for the synthesis of PTMC.

Initiator	Enzyme	Feed ratio [M]/[I]	Medium	T (℃)	t (h)	Conv. (%)	$M_{n,GPC}$ (g/mol)	$Đ$	Ref
1,5-Pentanediol	CALB-MWCNTs	43.5:1	Toluene	60	15−210 min	13.4−99.1	600−4.8×10^3 [c]	1.1−1.4	[89]
1,6-Hexanediol	N435	−	In bulk	60	24	−	−	−	[92]
$(HOC_3H_6Te)_2$	N435	300:1	In bulk	60	24	−	2.94×10^4	−	
[5-(Hydroxymethyl)-2-phenyl-1,3-dioxan-5-yl] methyl 2-bromopropanoate	N435	60:1	Toluene	55	18	−	2.30×10^3	1.88	[100]
EGP	PS-30	7:1	In bulk	70	96	20	−	−	[105]
	CCL	7:1	In bulk	70	96	5	−	−	
	IM	7:1	In bulk	70	96	<2	−	−	
	MAP-10	7:1	In bulk	70	96	15	−	−	
	AK	7:1	In bulk	70	96	>78	−	−	
	N435	7:1	In bulk	70	96	97	7.20×10^3	2.5	
	PPL	7:1	In bulk	70	96	>78	−	−	
$PHB\text{-}diol_{2200}$ [d]	N435	75:1−100:1	1,4-Dioxane	50	8	57−71 [b]	4.50×10^3−5.50×10^3	1.26−1.36	[106]
	N435	50:1−100:1	Toluene	RT-70	8	81−89 [b]	5.40×10^3−8.70×10^3	1.43−1.69	
$PCL\text{-}diol_{3000}$ [d]	N435	100:1−200:1	Toluene	50−70	8	54−67 [b]	7.70×10^3−1.06×10^4	1.58−1.64	[106]
BnOH	N435	10:1	Toluene	60	8 min [a]	98	1.20×10^3 [d]	1.12	[124]
					170 min	96	1.20×10^3 [d]	1.20	

[a] Reactor: MR; [b] Yield; [c] Measured by SEC; [d] Calculated by ^{1}H-NMR.

2 三亚甲基碳酸酯衍生物

为了赋予聚碳酸酯更大的结构可设计性，合成了一系列侧基带有苄氧基、丙烯酰氧基、烯丙基和生物活性基团的TMC衍生物[125]，酶促ROP对复杂官能团具有较好的耐受性，可在保留侧链功能基团的同时实现环碳酸酯开环聚合[126,127]. 这主要源于脂肪酶活性中心的底物识别能力、化学

选择性[44]以及相对温和的反应条件：环碳酸酯的碳酸酯羰基可被选择性活化并参与链增长，而侧链上的烯丙基、苄氧基、杂环和生物活性基团通常难以参与该催化过程[128]. 同时，酶催化体系可避免强酸、强碱或金属催化剂引起的交联、脱保护等副反应，从而有利于侧链功能基团的保留[125]. 利用这一特性，制备出了多种侧链功能化聚碳酸酯，尤其是以聚乙二醇(PEG)等作为大分子引发剂，高效合成了功能化两亲性嵌段共聚物(表2). 这些聚合物自组装形成的纳米胶束对细胞无毒，可高效负载药物，并且其侧基对pH、温度等微环境信号的智能响应实现了药物的控制释放.

Table 2 Enzymatic ROP of TMC derivatives for fabrication of side-chain functionalized polycarbonates.

Monomer	Initiator	Enzyme	Feed ratio [M]/[I]	Medium	T (℃)	t (h)	Conv. (%)	$M_{n,GPC}$ (g/mol)	$Đ$	Ref
BTMC	PEG_{6000} [c]	IPPL	136:1–545:1 [e]	In bulk	150	12	–	3.43×10^4–9.15×10^4 [b]	1.26–1.29	[131]
TAC	$mPEG_{2000}$ [d]	IPPL	5:1	Toluene	120	24	69 [a]	5.2×10^3	1.30	[133]
DTC	$mPEG_{2000}$ [d]	IPPL	5:1	Toluene	120	24	75 [a]	4.6×10^3	1.28	[133]

[a] Yield; [b] Calculated by ^{1}H-NMR; [c] PEG (M_W=6000) were purchased Shanghai Chemical Reagent Co.; [d] mPEG (M_n=2000) were purchased from Sigma-Aldrich; [e] The feed ratio was converted from the reported [BTMC]/[EO] ratio based on PEG with M_w=6000.

携带苄氧基侧基的5-苄氧基三亚甲基碳酸酯(BTMC)既能增强聚合物的疏水性，又可作为羟基保护基，通过脱除苄基原位释放羟基，为聚合物后续修饰提供反应位点[129,130]. Wang等[131]以固定化猪胰脂肪酶(IPPL)为催化剂，以PEG (重均分子量M_W=6.0×10^3 g/mol)为引发剂，使BTMC在150 ℃下本体聚合，成功合成了含苄氧基侧基的两亲性三嵌段共聚物PBTMC-*b*-PEG-*b*-PBTMC ($M_{n,NMR}$=3.43×10^4~9.15×10^4 g/mol) (图6(a)). 该共聚物能通过透析法在水中自组装成结构规整的球形胶束，其粒径约为50 nm.

为构建具有智能响应性及功能化潜力的药物递送系统，He等[132]合成了具有亲水性及温敏性的端羟基聚*N*-异丙基丙烯酰胺(HO-PNIPAM)，并将其作为大分子引发剂，使侧基携带烯丙基的5-甲基-5-烯丙氧羰基-三亚甲基碳酸酯(MAC)与

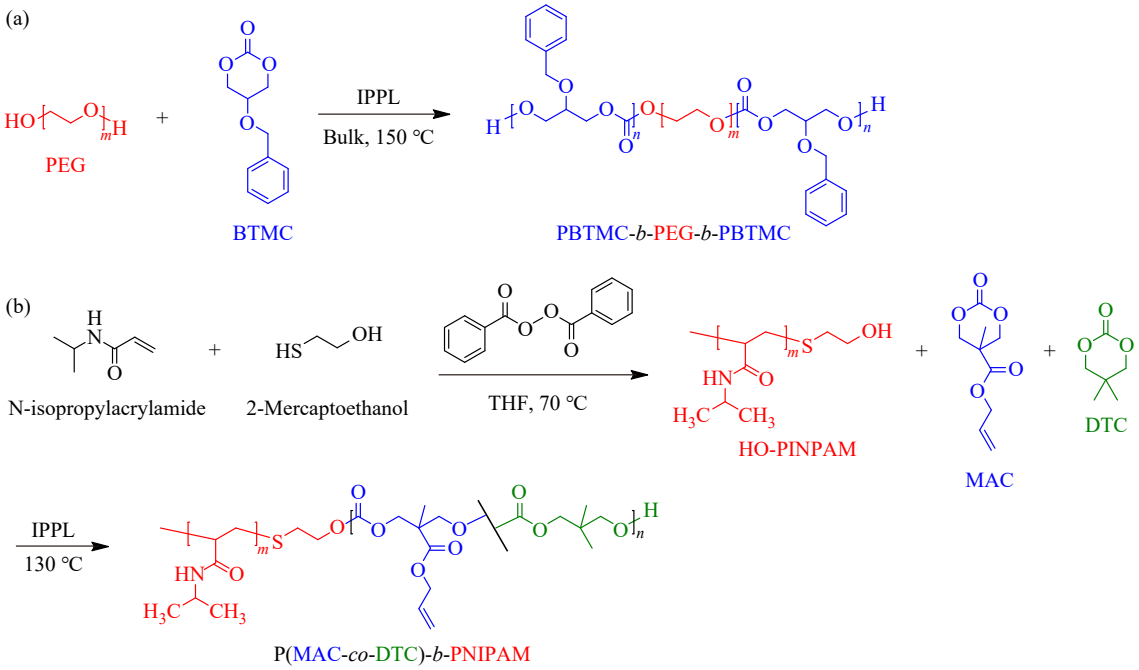

Fig. 6 (a) Enzymatic ROP of BTMC initiated by PEG for the preparation of ampHipHilic triblock copolymer PBTMC-*b*-PEG-*b*-PBTMC; (b) Synthetic routes to the macro-initiator HO-PNIPAM and ampHipHilic block copolymer P(MAC-*co*-DTC)-*b*-PNIPAM[132].

可调节疏水性的5,5-二甲基三亚甲基碳酸酯(DTC)在IPPL的催化下开环共聚，合成了温敏性两亲性嵌段共聚物P(MAC-*co*-DTC)-*b*-PNIPAM (图6(b)). 该共聚物在水中自组装成以聚碳酸酯为核、PNIPAM为壳的球形纳米胶束，其粒径在20~70 nm之间，且临界胶束浓度(CMC：20~60 mg/L)较低. 胶束受PNIPAM链段驱动展现出显著的温敏行为，其最低临界溶解温度(LCST)可随组分比例在38~43 ℃范围内进行调控. 作为药物载体，其负载的模型药物醋酸泼尼松在生理温度(37 ℃)的释放速率显著快于低温条件(4 ℃)，这源于温度升高导致PNIPAM (LCST：32~33 ℃)壳层由亲水伸展态转变为疏水塌缩态，产生的物理挤压效应加速了药物释放.

以含有胸腺嘧啶(thymine)侧基的六元环状碳酸酯单体(TAC)为核心，He等[133]构建了一种基于互补多重氢键作用的高效药物负载与pH响应性释放系统. 胸腺嘧啶与丙烯酰碳酸酯(AC)通过迈克尔加成反应生成功能单体TAC，以甲氧基聚乙二醇(mPEG，M_n=2.0×10^3 g/mol)为引发剂，TAC或(和)DTC为(共聚)单体，成功制备了两亲性嵌段共聚物mPEG-*b*-PTAC、mPEG-*b*-P(TAC-*co*-DTC)和mPEG-*b*-PDTC (图7). mPEG-*b*-PTAC疏水段上暴露的胸腺嘧啶基团能与模型药物甲氨蝶呤(MTX)分子中的2,6-二氨基吡啶(DAP)结构域形成特异性的互补多重氢键，这种非共价相互作用极大地提升了药物的负载能力，使载药量达到13.8 wt%. 在模拟肿瘤微环境的酸性条件(pH=5.0)下，MTX氨基的质子化削弱了多重氢键作用，使药物释放速率显著快于中性生理环境(pH=7.4)(前12 h内的累积释放量：60% versus 35%). 体外细胞实验表明，该胶束载体生物相容性良好；载药后对HeLa细胞的毒性与游离MTX相当，展现出优异的抗癌药物递送潜力.

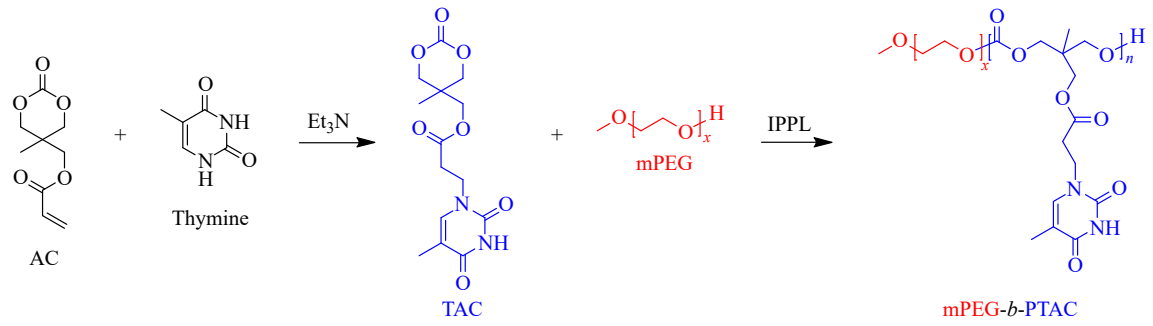

Fig. 7 Synthesis of TAC and the ampHipHilic block copolymer mPEG-*b*-PTAC.

尽管阿霉素(DOX)是一种广谱抗癌药物[134~136]，但其水溶性差、半衰期短及毒副作用大，极大的限制了其应用[137,138]. 构建基于pH敏感化学键的高分子前药胶束，利用肿瘤微环境触发药物释放，是克服上述缺陷的有效策略. He等[139]以mPEG (M_n=5.0×10^3 g/mol)为引发剂，利用IPPL催化侧基含烯丙基的5-烯丙氧基-1,3-二恶烷-2-酮(ATMC)和疏水单体DTC开环共聚，合成了两亲性嵌段共聚物mPEG-*b*-P(ATMC-*co*-DTC). 利用间氯过氧苯甲酸(*m*-CPBA)将ATMC单元侧链的烯丙基环氧化，再与水合肼开环引入肼基，最后通过酸敏感的腙键将DOX共价键合于聚合物侧链上，成功制备了目标前药mPEG-*b*-P(ATMC-*co*-DTC)-*g*-DOX ($M_{n,GPC}$=1.44×10^4~1.53×10^4 g/mol，$Đ$=1.29~1.33) (图8). 该前药在水中可自组装成粒径约90~140 nm的纳米胶束，载药量为9.9 wt%~12.5 wt%. 体外释放实验证实了腙键的pH响应断裂特性：在模拟肿瘤细胞内涵体/溶酶体的酸性环境(pH=5.0)下，72 h内DOX累积释放率超过84%；而在生理环境(pH=7.4)下，同期释放率仅为42%左右. 该前药胶束能通过胞吞作用高效进入HeLa细胞，在胞内酸性环境触发下释放DOX并作用于细胞核，表现出显著的细胞毒性，产生50%细胞死亡的抑制浓度(IC_{50})为10.9~16.1 mg/L.

叶酸(FA)受体在多种肿瘤细胞表面过度表达，利用FA作为配体修饰药物递送系统是实现肿瘤主动靶向的经典策略. He等[140]将酶促ROP与主动靶向设计相结合，报道了一种靶向纳米药物载体的构建方法. 首先利用1,1-羰基二咪唑(CDI)介导的酯化反应合成大分子引发剂FA-PEG，在IPPL的催化下，MAC与DTC分别被FA-PEG (100 ℃，48 h)和mPEG (90 ℃，8 h)引发共聚，

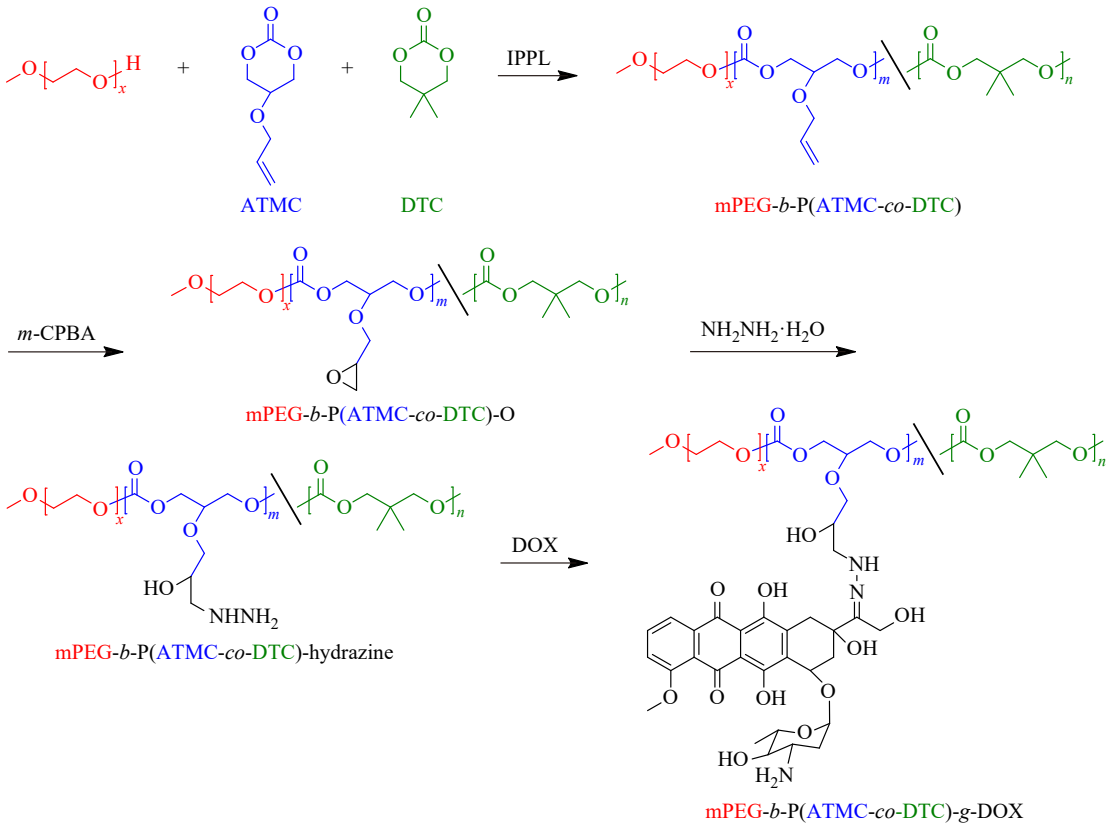

Fig. 8 Synthesis of the pH-responsive DOX prodrug mPEG-*b*-P(ATMC-*co*-DTC)-*g*-DOX *via* mPEG-initiated enzymatic ROP of ATMC and DTC[139].

成功制备了具有主动靶向功能的两亲性嵌段共聚物FA-PEG-*b*-P(MAC-*co*-DTC)及其非靶向对照物mPEG-*b*-P(MAC-*co*-DTC) (图9). 该共聚物在水中自组装成核-壳结构胶束，并通过物理包埋方式高效负载DOX. 与非靶向胶束相比，FA修饰的载药胶束能通过受体介导的内吞作用被HeLa细胞更高效地摄取. 载药后的FA靶向胶束(IC_{50}=0.58 mg/L)对HeLa细胞的细胞毒性显著优于非靶向胶束(IC_{50}=1.88 mg/L)，且疗效与游离DOX相当.

3 四亚甲基碳酸酯

四亚甲基碳酸酯(TeMC)是七元环状碳酸酯单体. 与无定形且力学强度较低的PTMC不同，聚四亚甲基碳酸酯(PTeMC)因其链段规整性而易于结晶，且疏水性更强，具有比PTMC更慢的降解速率、更高的结晶度及更优异的机械强度和热稳定性，因此在长效植入体、医药载体及组织工程支架等领域展现出独特优势[141,142]. 通过引入亲水性大分子引发剂，可构建两亲性嵌段共聚物，进而赋予材料自组装、药物递送等功能(表3).

Feng等[143]在30 ℃低温下，利用mPEG (M_n=2.0×10^3 g/mol)引发TeMC开环聚合，N435为催化剂，获得具有不同PTeMC链长的两亲性嵌段共聚物mPEG-PTeMC (图10(a)). 该共聚物可在水中自组装形成球形纳米胶束，临界胶束浓度(CMC)为1.6~9.3×10^{-7} mol/L，并随PTeMC链长增加而降低. 透射电子显微镜(TEM)结果显示，胶束呈球形且分散性较好，干态粒径约为25 nm，动态光散射(DLS)测得其水合粒径为120~180 nm (图10(b)). 胶束在磷酸盐缓冲液(PBS，pH 7.4)中放置5天后粒径无明显变化，表明其具有较好的胶体稳定性. 细胞毒性实验显示，mPEG-$PTeMC_2$在测试浓度范围内对人胚肾293T细胞无明显毒性(图10(c)). 该胶束对疏水模型药物布洛芬具有高包封率(约73%)和可控的缓释行为，释放速率随PTeMC链长的增加而降低(图10(d)).

4 大环碳酸酯

大环单体(环上原子数通常≥14个)，与小环单体在ROP的热力学机制上存在本质区别. 小环单体聚合主要表现为释放张力的焓驱动过程，而大环单体开环过程中的焓变较小，聚合过程更多

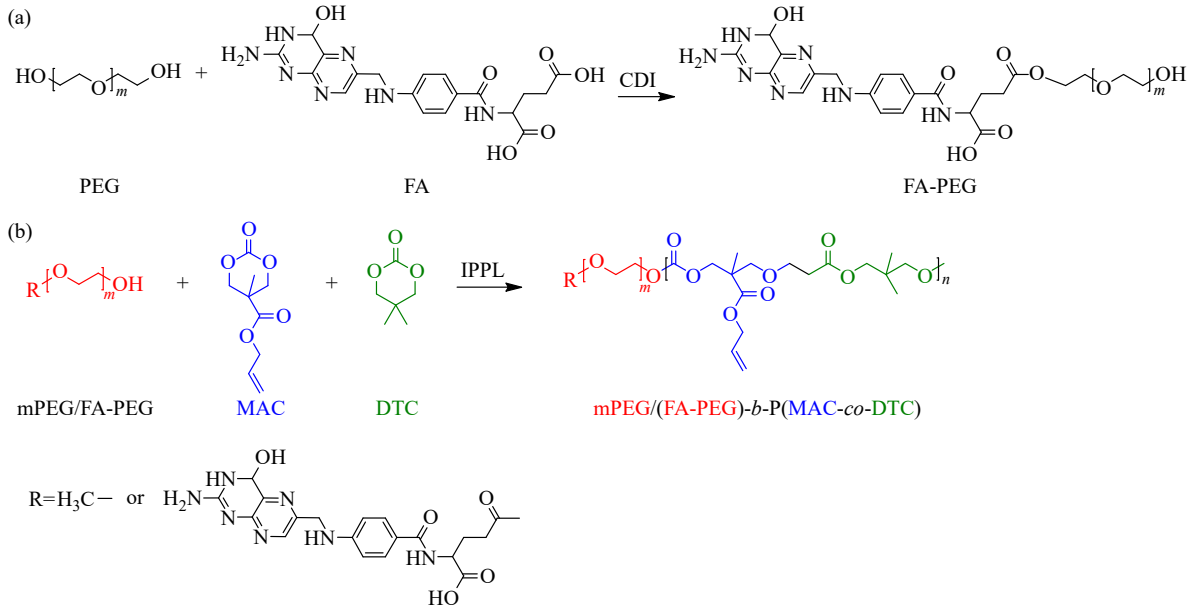

Fig. 9 (a) Synthesis of the macro-initiator FA-PEG; (b) Fabrication of ampHipHilic block copolymers, namely FA-PEG-*b*-P(MAC-*co*-DTC) and mPEG-*b*-P(MAC-*co*-DTC), *via* the ring-opening copolymerization of MAC and DTC monomers, using FA-PEG and mPEG as macro-initiators, respectively[140].

Table 3 Preparation of PTeMC *via* enzymatic ROP of TeMC.

Initiator	Enzyme	Feed ratio [M]/[I]	Medium	*T* (℃)	*t* (h)	Conv. (%)	$M_{n,NMR}$ (g/mol)	*Đ*	Ref
$mPEG_{2000}$ [a]	N435	1.7:1−17.2:1	Toluene	30	48	–	5.0×10^3−2.1×10^4	1.71−2.01	[143]

[a] mPEG (M_n=2.0×10^3) were purchased from Sigma-Aldrich.

依赖熵驱动[144~150]. 除了热力学机制的差异，大环单体众多的原子数为聚合物体系提供了结构多样性. 在大环单体的特定位点进行功能化修饰通常不会对其开环活性产生显著影响，这种独特的空间容忍性，使得多种官能团可被引入[145]. 酶催化尤其适用于大环单体的熵驱动ROP[151~155]. 近年来，利用这一优势，通过酶促ROP成功将硫、硒、氮等功能元素引入大环碳酸酯单体的主链结构中，从而直接赋予其氧化还原、pH响应等智能特性(表4). 由亲水性的大分子引发剂引发构建的两亲性共聚物通过自组装形成纳米胶束，其聚碳酸酯内核能够对肿瘤微环境中的特定信号(如活性氧、谷胱甘肽或酸性pH)产生快速响应.

为了构建响应速度快且生物安全性高的智能药物载体，Feng等[156]开发了一种主链含叔胺基团的阳离子聚碳酸酯递送系统. 大环碳酸酯6,14-二甲基-1,3,9,11-四恶杂-6,14-二氮杂-环己烷-2,10-二酮(M_N或ADMC)主链嵌入的叔胺基团具有pH敏感性，同时避免了传统阳离子聚合物合成中繁琐的保护/脱保护步骤，且PM_N的降解产物呈非酸性，可减轻聚酯降解引发的炎症并保护药物活性. 以N435为催化剂，通过mPEG (M_n=2.0×10^3 g/mol)引发M_N与ε-CL开环共聚，成功合成了两亲性二嵌段三元共聚物mPEG-*b*-poly(M_N-*co*-CL) (图11(a)). 该共聚物自组装形成纳米胶束具有pH响应特性(图11(b))：在模拟肿瘤微环境的酸性条件下(pH=6.0)，叔胺基团发生质子化，使核区电荷排斥增强，亲水性提升，导致胶束体积膨胀，结构变得松散，从而实现对布洛芬的快速释放，5 h内释放率达73%. 该共聚物对HeLa和COS7细胞均表现出极低的毒性[156].

主链功能化可降解聚合物的合成长期以来面临巨大挑战，其瓶颈在于主链含功能基团的环状单体难以高效制备. Lang和Zhang等[157]提出了一种合成主链功能化环状碳酸酯的通用策略：利用N435催化含硫/硒(S/Se)的功能二醇与碳酸二苯酯(DPC)在高度稀释的甲苯溶液中进行大环闭合反应，成功合成了含硫醚(M_S)、二硫键(M_{SS})、硒醚(M_{Se})及二硒键(M_{SeSe})的环状碳酸酯二聚体单体. 该策略具有优异的官能团耐受性，可扩展至

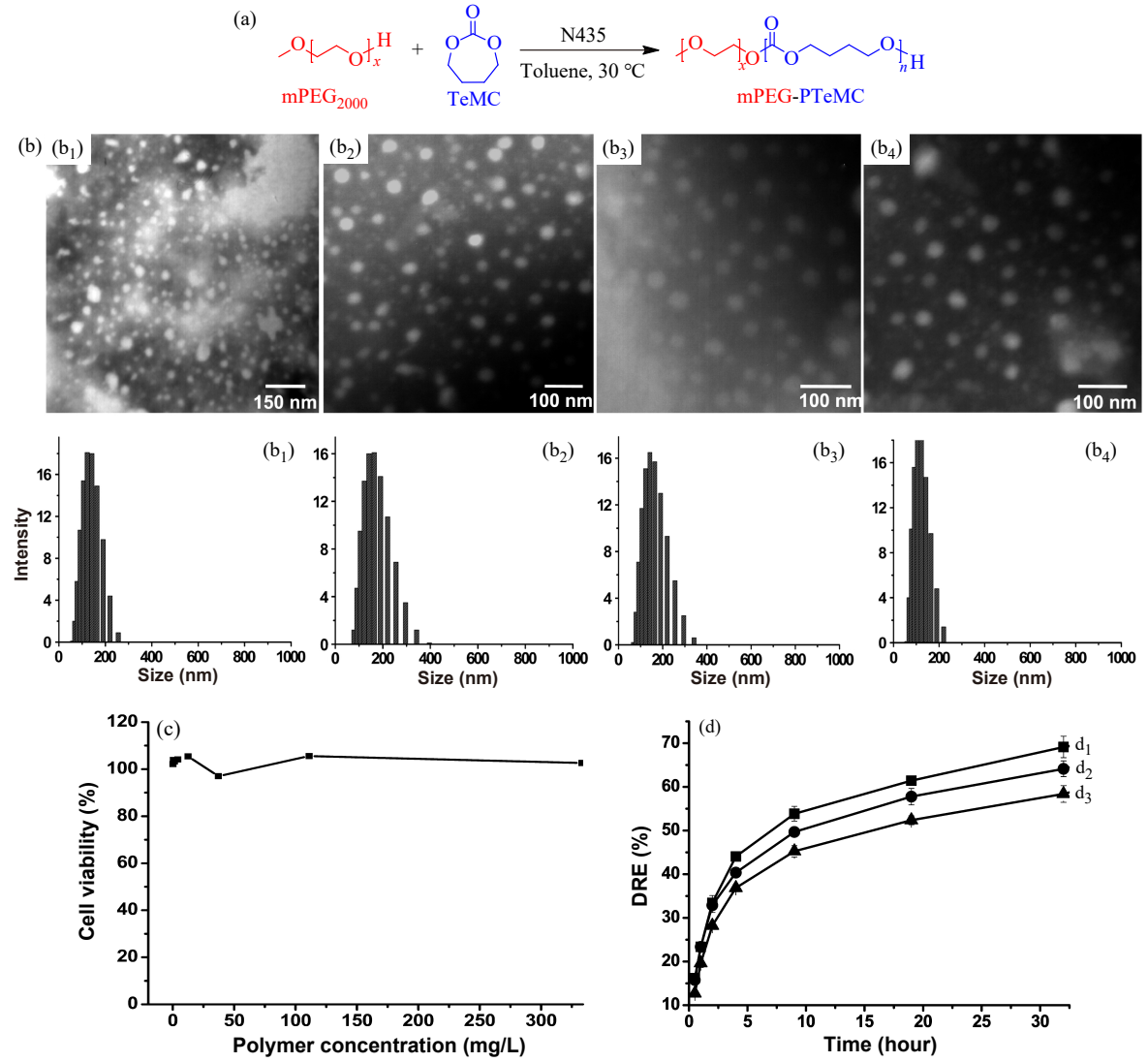

Fig. 10 (a) Synthesis of ampHipHilic block copolymer mPEG-PTeMC *via* mPEG-initiated enzymatic ROP of TeMC; (b) TEM images of micelles self-assembled from: (b_1) mPEG-PTeMC$_1$, (b_2) mPEG-PTeMC$_2$, (b_3) mPEG-PTeMC$_3$, and (b_4) mPEG-PTeMC$_4$ alongside their respective size distributions measured *via* DLS in distilled water; (c) *In vitro* cytotoxicity evaluation of mPEG-PTeMC$_2$ across a series of concentrations; (d) Cumulative drug release behaviors of the copolymers: (d_1) mPEG-PTeMC$_4$, (d_2) mPEG-PTeMC$_3$ and (d_3) mPEG-PTeMC$_1$ (Reprinted with permission from Ref. [143]; Copyright (2009) American Chemical Society).

N-取代等其他主链功能化体系. 以BnOH为引发剂，N435为催化剂，使上述单体在70 ℃的甲苯中开环聚合(图12). M_S、M_{SS}和M_{Se}的转化率均超过90%，所得聚碳酸酯(PM_S、PM_{SS}、PM_{Se})分子量可控且分布较窄($Đ$=1.26~1.55). 然而，由于PM_{SeSe}在甲苯中的溶解性极差，导致反应体系迅速变为非均相，M_{SeSe}的转化率仅为54%. 针对这个问题，他们利用“相似相溶”原理，先制备了具有良好溶解性的大分子引发剂PTMC-OH作为“可溶性载体”，从而有效改善了聚合过程中的溶解状态，使M_{SeSe}的转化率大幅提升至94%，并成功制备了嵌段共聚物PTMC-*b*-PM_{SeSe}. 主链中的硫族官能团赋予了聚碳酸酯氧化还原响应性，可对H_2O_2、二硫苏糖醇(DTT)、谷胱甘肽(GSH)等生物信号产生特异性响应. 这种可调控的刺激响应行为，结合聚碳酸酯优异的生物降解性，使得该类材料在炎症靶向、肿瘤治疗及智能药物递送等领域具有广阔的应用前景. 在之后的工作中，Lang和Wei等[158]分别用mPEG (M_n=2.0×10^3 g/mol)和PEG (M_n=2.0×10^3 g/mol)引发M_{SS}聚合，获得分子量分布较宽($Đ$=1.46，$Đ$=1.53)的两亲性嵌段共聚物.

Table 4 Synthesis of backbone-functionalized polycarbonates via enzymatic ROP.

Monomer	Initiator	Enzyme	Feed ratio [M]/[I]	Medium	T (℃)	t (h)	Conv. (%)	$M_{n,NMR}$ (g/mol)	$Đ$	Ref.
M_{SS}	BnOH	N435	20:1–100:1	Toluene	70	12	92~93	7.7×10^3–3.47×10^4	1.40–1.44	[157]
		N435	20:1–100:1	Toluene	70	12	93~94	6.9×10^3–3.36×10^4	1.38–1.45	[158]
	$mPEG_{2000}$	N435	20:1	Toluene	70	12	92	8.6×10^3	1.46	[158]
	PEG_{2000}	N435	20:1	Toluene	70	12	90	8.5×10^3	1.53	[158]
M_S	BnOH	N435	20:1–100:1	Toluene	70	10	97	6.0×10^3–2.91×10^4	1.31–1.55	[157]
	$mPEG_{2000}$	N435	5:1–50:1	Toluene	70	12	93–98	9.7×10^3–2.57×10^4[a]	1.26–1.48	[159]
M_{Se}	BnOH	N435	20:1–100:1	Toluene	70	6	97–98	8.7×10^3–3.53×10^4	1.26–1.48	[157]
			10:1–100:1	Toluene	70	12–48	–	5.6×10^3–3.59×10^4	1.30–1.36	[164]
	$mPEG_{45}$	N435	6:1–30:1	Toluene	70	24	–	4.0×10^3–1.37×10^4	1.13–1.26	[160]
	$mPEG_{2000}$	N435	10:1	Toluene	70	12	–	5.5×10^3	1.33	[164]
	PEG_{2000}	N435	10:1	Toluene	70	12	–	5.5×10^3	1.50	[164]
M_{SeSe}	BnOH	N435	20:1	Toluene	70	72	54–61	5.0×10^3	–	[157]
		N435	20:1	Thf	70	72	46	–	–	
		N435	20:1	1,4-Dioxane	70	72	71	–	–	
	$PTMC_{7800}$-OH	N435	20:1	Toluene	70	24	94	1.66×10^4	1.12	[157]
	$mPEG_{2000}$-OH	N435	20:1	Toluene	70	72	69	–	–	[157]

[a] Measured by GPC.

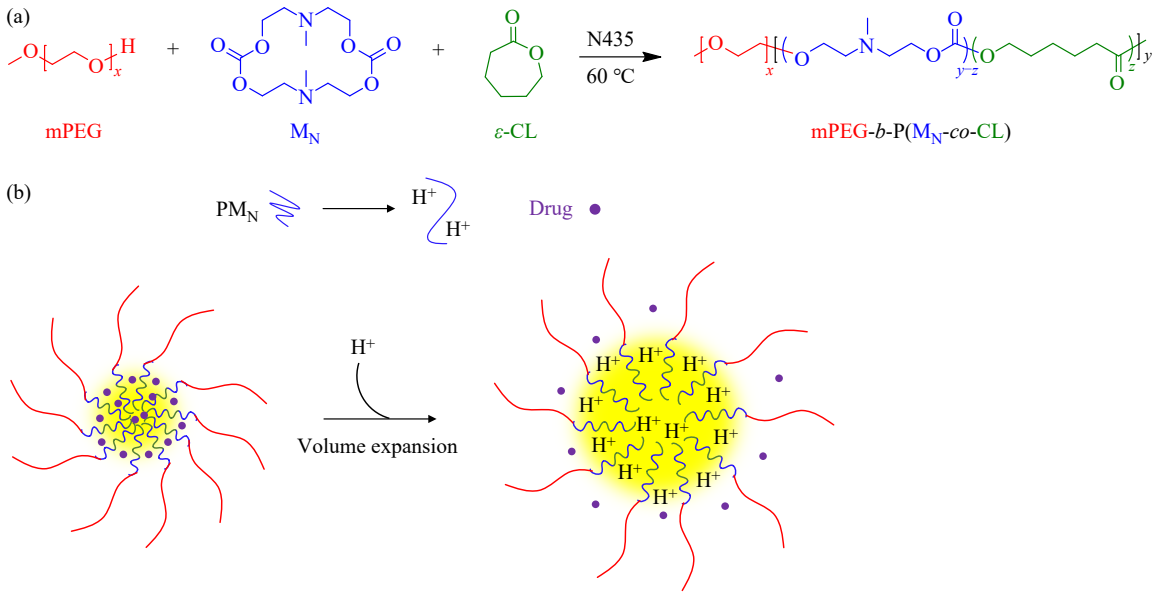

Fig. 11 (a) Synthesis of the ampHipHilic block copolymer mPEG-*b*-poly(M_N-*co*-CL) *via* mPEG-initiated enzymatic ring-opening copolymerization of M_N and ε-CL; (b) Schematic illustration depicting the pH-responsive morpHological transitions of micelles as well as the corresponding drug release behaviors[156].

在成功构建主链功能化大环单体的基础上，研究进一步聚焦于通过共聚策略集成多种响应基团，以模拟复杂的肿瘤微环境并实现更精准的药物控制释放. Zhang 等[159]用 N435 催化 M_S 开环聚合，mPEG (M_n=2.0×10³ g/mol)为引发剂，制备了两亲性嵌段共聚物 mPEG-*b*-PM_S ($M_{n,GPC}$=9.7×10³~2.53×10⁴ g/mol，$Đ$=1.26~1.48). 该共聚物在水中自组装成纳米胶束，主链中的硫醚官能团赋予材料显著的活性氧(ROS)响应性(图 13(a)). 在 H_2O_2 作用下，硫醚键被氧化为亲水性的亚砜和砜基，

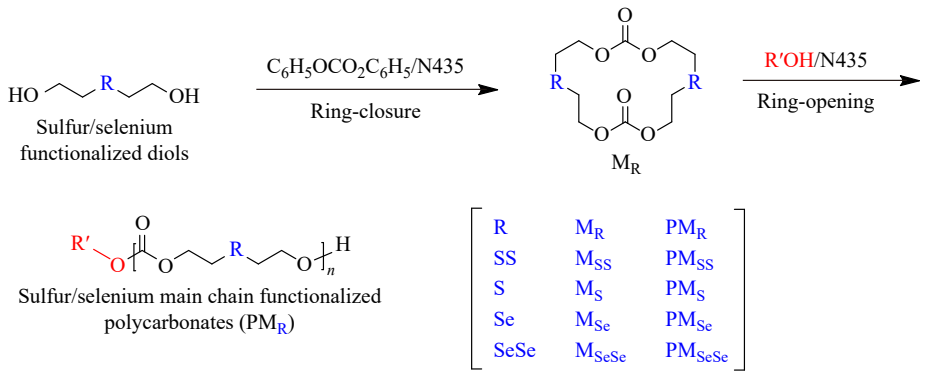

Fig. 12 General synthetic strategies for backbone-functionalized cyclic carbonates and their corresponding polymers[157].

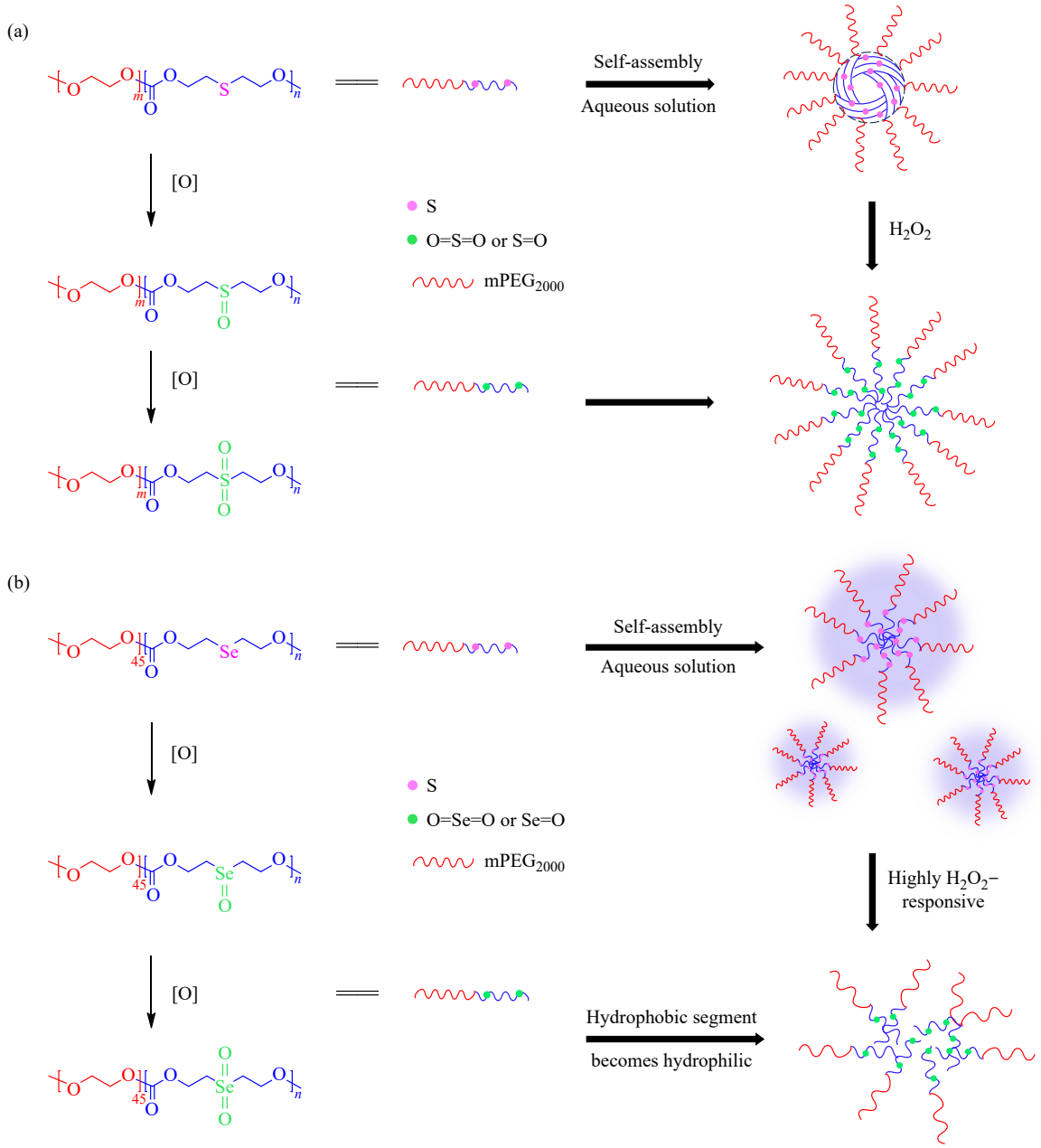

Fig. 13 (a) Self-assembly behaviors and oxidation properties of mPEG-*b*-PM$_S$ copolymers[159]; (b) Oxidation process and self-assembly characteristics of mPEG$_{45}$-*b*-PM$_{Se}$[160].

引发聚合物发生疏水−亲水转变，导致纳米结构解组装. 氧化过程未导致主链断裂，但由于分子链极性增加及柔性降低，聚合物的T_g升高，同时因引入亚砜和砜基，其热稳定性有所下降，热分解起始温度从270 ℃降至220 ℃. mPEG-*b*-PM_S及其氧化产物在高达250 μg/mL的浓度下对正常细胞(L929)和癌细胞(HeLa)均无显著毒性，展现了良好的生物相容性及其在ROS响应型药物递送领域的应用潜力. 为了进一步提升ROS响应的灵敏度，Zhang等[160]通过酶促ROP合成了主链含硒醚键的$mPEG_{45}$-*b*-PM_{Se} ($M_{n,NMR}$=4.0×10³~1.37×10⁴ g/mol，$Đ$=1.13~1.26). 该共聚物在水中自组装成的纳米胶束表现出增强的ROS响应性(图13(b))：疏水性的硒醚键在浓度低至5 mmol/L的H_2O_2作用下即可被快速氧化为亲水性的硒亚砜或硒砜，引发胶束溶胀及解体. 与此前的mPEG-*b*-PS相比，其最低响应浓度从100 mmol/L显著降低至5 mmol/L，完全响应时间从96 h大幅缩短至12 h以内. 此外，疏水段长度对响应速率有调控作用，疏水链段越长，胶束核越致密，氧化剂渗透越慢，导致初始响应出现延迟效应.

由于肿瘤微环境同时具有弱酸性和高GSH浓度的特征，Zhang等[161]制备了基于聚碳酸酯骨架构建的双重响应性自组装体系，为开发新型智能抗癌药物载体提供了新策略. 以BnOH引发pH敏感单体M_N与还原敏感单体M_{SS}开环共聚，合成了主链兼具叔胺与二硫键无规共聚物poly(M_N-*co*-M_{SS}). 由于叔胺基团的质子化能力提供亲水性，二硫键骨架提供疏水性，因此无需引入传统的PEG等亲水链段，该共聚物即可在水溶液中自组装成粒径约70 nm的纳米胶束. 该胶束在模拟肿瘤微环境中展现出显著的pH/还原双重响应性(图14(a))：在酸性条件(pH=5.5)下，叔胺质子化导致胶束壳层电荷斥力增大而溶胀，结构变得疏松；在高浓度GSH的还原环境中，二硫键断裂导致聚合物骨架降解及疏水核彻底崩解，实现胶束的解组装.

除了强还原性这一特征外，ROS水平异常升高也是肿瘤微环境的重要特征. Zhang等[162]以mPEG (M_n=2.0×10³ g/mol)引发M_N与M_{Se}开环共聚，合成了主链兼具叔胺与硒醚官能团的两亲性嵌段共聚物mPEG-*b*-poly(M_N-*co*-M_{Se}) ($M_{n,NMR}$=7.4×10³~8.1×10³ g/mol，$Đ$=1.36~1.49). 该共聚物自组装形成的纳米胶束表现出优异的ROS/pH双重响应性(图14(b))：硒醚基团可被H_2O_2迅速氧化为亲水性的硒亚砜或硒砜，其氧化响应速率较传统的硫醚聚合物体系提升了至少10倍，极大地提高了药物释放的灵敏度；而在酸性条件(pH=5.0)下，叔胺质子化引起的电荷斥力与亲水性增强导致胶束显著溶胀，粒径由约65 nm增至约320 nm. 这种双响应性胶束能有效负载抗癌药物DOX，并在模拟肿瘤微环境下实现药物的快速释放，12 h内释放近70%. 该共聚物及其氧化产物在测试浓度下(≤200 μg/mL)均表现出良好的生物相容性.

除了环状碳酸酯的共聚，Zhang等[163]还研究了内酯和碳酸酯的开环共聚. 以N435催化mPEG (M_n=2.0×10³ g/mol)引发ε-CL与M_{SeSe}开环共聚，合成了嵌段共聚物mPEG-*b*-poly(CL-*co*-M_{SeSe}) ($M_{n,NMR}$=5.5×10³~2.19×10⁴ g/mol，$Đ$=1.36~1.78). ε-CL的参与极大地改善了反应体系的均相性，将M_{SeSe}的转化率从均聚时的33%提升至共聚时的97%. PM_{SeSe}链段会使PCL结晶度下降，并且随着M_{SeSe}组分的增加，共聚物的T_g由−48.9 ℃升高至−10.7 ℃. 该共聚物能在水中自组装成粒径约50 nm的纳米胶束，主链中的二硒键赋予其ROS/GSH双重响应性：在H_2O_2氧化作用下二硒键转化为亲水的亚硒酸，在GSH还原作用下转化为硒醇.

为了优化酶促共聚过程的反应动力学并改善产物序列结构，Zhang等[32]利用结构匹配性更佳的大环单体进行共聚. 通过N435催化1,8-辛二醇与DPC闭环反应得到22元大环碳酸酯1,3,12,14-四氧杂环二十二烷-2,13-二酮(TDC)，在N435的催化下，$mPEG_{45}$ (M_n=2.0×10³ g/mol)引发M_{SeSe}与TMC (或TDC)无规共聚，制备了一系列两亲性无规共聚物 (图15(a)和15(b)). 在TMC/M_{SeSe}体系中，TMC表现出极高的反应活性(转化率为92%~98%)，M_{SeSe}转化率为82%~83%，所得共聚物mPEG-*b*-(PTMC-*co*-PM_{SeSe})的分子量分布较宽($Đ$=1.42~1.53). 而在TDC/M_{SeSe}双大环体系中，TDC与M_{SeSe}的转化率分别为78%~86%与68%~78%，所得共聚物mPEG-*b*-(PTDC-*co*-PM_{SeSe})的分子量分布变窄($Đ$=1.16~1.30). 动力学研究证实，由于TDC与M_{SeSe}均为大环结构，二者在酶催化活性位点上的竞争更为匹配，使得M_{SeSe}在TDC

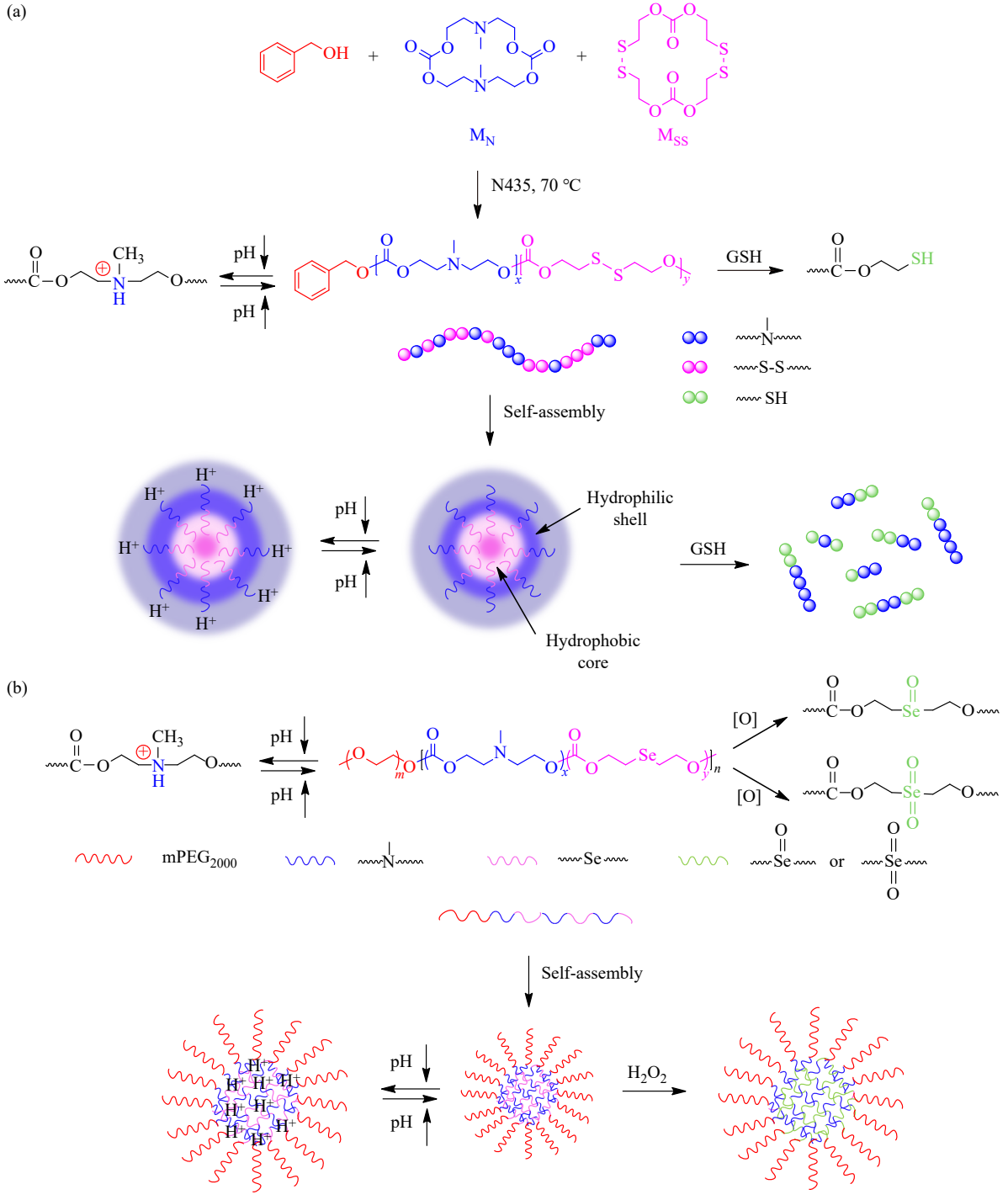

Fig. 14 (a) Synthesis of the poly(M_N-*co*-M_{SS}) copolymer *via* lipase-catalyzed ROP, along with its reductive and pH-responsive behaviors [161]. (b) Oxidative and pH-responsive behaviors of the mPEG-*b*-poly(M_N-*co*-M_{Se}) block copolymer: Micellar swelling is triggered by enhanced hydropHilicity derived from the oxidation of selenide groups to hydropHilic selenoxide or selenone, coupled with the protonation of tertiary amine groups [162].

体系中的相对聚合速率优于TMC体系，且更易形成无规共聚结构. mPEG-*b*-(PTDC-*co*-PM_{SeSe})在水中自组装成的纳米胶束具有显著的ROS响应性，在H_2O_2作用下发生解组装(图15(c)).

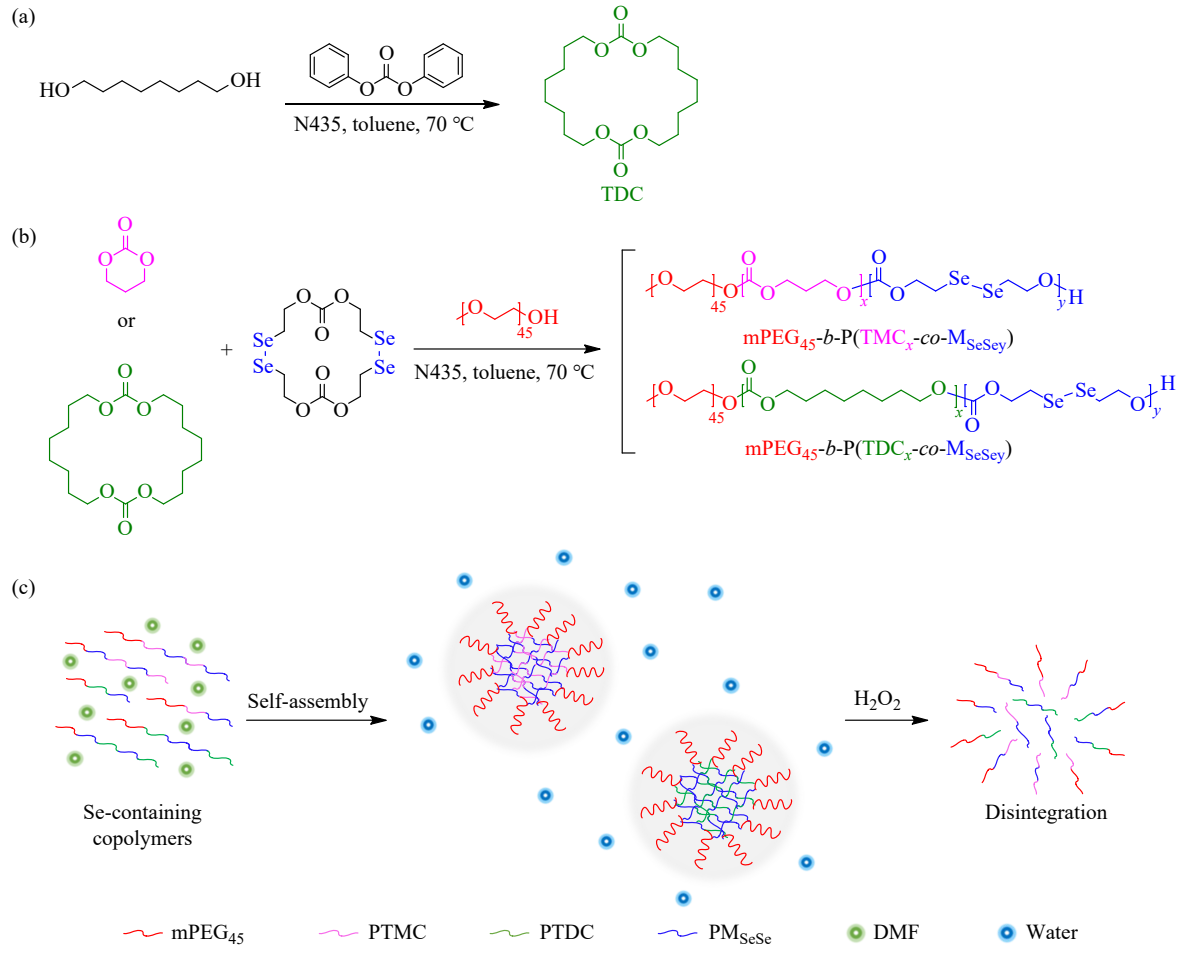

Fig. 15 (a) Synthetic route of macrocyclic carbonate TDC; (b) Enzymatic ring-opening copolymerization of M_{SeSe} with TMC or TDC; (c) Self-assembly behaviors and oxidation processes of ampHipHilic diselenide-containing copolymers[32].

5 结论与展望

酶促开环聚合日渐成为生物降解聚合物的重要绿色合成平台. 近年来，通过对单/多羟基(大分子)引发剂和环状碳酸酯的分子设计，在脂肪酶的催化下高效制备了兼具生物可降解性与功能性的脂肪族聚碳酸酯，在药物递送等领域展示出潜在的应用价值. 环状碳酸酯的酶促开环聚合受环尺寸、引发剂分子大小、单体的空间位阻与溶解性、酶催化效率、反应介质等因素共同影响. 相较于四氢呋喃和1,4-二氧六环，甲苯为更佳选择. 不同脂肪酶及固定化体系在底物适应性、催化效率和稳定性方面表现出差异. N435具有较好的稳定性和较宽的底物适用范围，是应用最广泛的催化剂；IPPL多用于TMC衍生物的开环聚合，并且能耐受较高温度，但相关研究未与N435进行比较；CALB-MWCNTs等新型固定化体系通过调控酶负载量、载体界面和传质环境，可改善催化剂回收及反应效率，但其制备复杂性、载体分散性和批次稳定性仍需进一步优化；AK、PS-30、CCL、IM和MAP-10等脂肪酶的催化效率较低. 小环碳酸酯和大环碳酸酯在热力学驱动力上存在显著差异. TMC及其衍生物和TeMC等中小环单体的聚合过程通常与环张力释放有关，研究多围绕不同羟基引发剂调控端基结构和制备嵌段共聚物展开，侧基修饰和引发剂的空间位阻会影响聚合速率和可控性；大环碳酸酯开环多依赖熵驱动，聚合过程对单体溶解性、体系均相性、单体−引发剂相容性更敏感，存在单体溶解性不足导致转化率低等挑战. 在功能应用方面，响应型聚碳酸酯的设计策略和响应机制存在差异. TMC衍生物通过功能侧链或大分子引发剂引入温敏链段、酸敏键或非共价作用位点，实现温度或pH单响应；而大环碳酸是将叔胺、硫/硒醚、二硫/二硒键等功能结构引入主链，构建pH、ROS或GSH响应体系. 响应灵敏度受响应基团类

型、链段亲疏水性、胶束核致密程度及刺激分子扩散能力共同影响，其中硒醚/二硒键通常较硫醚/二硫键表现出更高的氧化还原敏感性. 双响应体系可提高载体对复杂肿瘤微环境的适应性. 展望未来，酶促环碳酸酯开环建议关注以下方面：(1) 聚合物结构设计，通过创新环碳酸酯单体和引发剂结构，发挥生物催化和化学催化耦合优势，合成系列不同功能的聚碳酸酯，为相关研究奠定基础. (2) 酶促聚合过程强化，基于人工智能等手段开发活性更高、稳定性更好、底物适用范围更广的高效酶催化剂，利用微反应器技术进一步提升酶促反应效率，实现连续化高效制备. (3) 聚碳酸酯应用，全面评价不同结构聚碳酸酯的各项指标，阐明材料构效关系，深入挖掘不同结构和功能聚碳酸酯的潜力，拓展应用场景，为酶促合成提供指导.

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Review

Enzymatic Ring-opening Polymerizations of Cyclic Carbonates

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Abstract Enzymatic ring-opening polymerization (ROP) of cyclic monomers has emerged as a green and sustainable method for synthesizing biodegradable polymers. Among these materials, aliphatic polycarbonates have attracted considerable attention owing to their excellent biocompatibility, biodegradability, and diverse structures, with broad applications in tissue engineering, drug delivery, electronic materials, and packaging. Recently, a variety of

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functionalized biodegradable polycarbonates have been synthesized through the enzymatic ROP of cyclic carbonates in the presence of alcohol initiators. This review highlights the advances, challenges, and opportunities in the biocatalytic ROP of trimethylene carbonate (TMC), TMC derivatives, tetramethylene carbonate, and macrocyclic carbonates as monomers. This study provides guidance for the development of biosynthesis of polymers and biodegradable polymers.

Keywords Enzymatic; Cyclic carbonate; Ring-opening polymerization; Initiator; Biodegradable