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Synthesis and antimicrobial applications of α-peptoid polymers

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The rapid evolution of drug-resistant pathogens and the lag in antibiotic development pose a severe threat to global public health. Host defense peptides (HDPs) have emerged as promising candidates due to their broad-spectrum antimicrobial activity and low resistance tendency. However, their practical application is hindered by poor proteolytic stability and high costs. Peptoids are ideal HDP mimics, as their characteristic side chain relocation from α-carbons to backbone nitrogen atoms confers superior proteolytic resistance. Nevertheless, their solid-phase synthesis remains inefficient and difficult to scale up. Recent advances in polymer chemistry enable the efficient synthesis of α-peptoid polymers, offering a promising platform for antimicrobial materials development. This perspective summarizes the progress in α-peptoid polymers research, focusing on monomer synthesis, polymerization reaction, and antimicrobial applications. We discuss their potential in the antimicrobial field and propose perspectives on current challenges and future directions, aiming to inspire further advances in the development of α-peptoid polymer-based antimicrobials with clinical application potential.

1. Introduction

The rapid evolution and widespread dissemination of drug-resistant pathogens, coupled with the scarcity of novel antibiotics, have created therapeutic challenges for numerous common infectious diseases, posing a significant threat to global public health security.[1,2] The World Health Organization predicted that without effective interventions, annual deaths from drug-resistant microbial infections could reach 10 million by 2050.[3] Host defense peptides, which are important components of the innate immune system in organisms, have been widely studied as promising candidates in the post-antibiotic era due to their broad-spectrum antimicrobial activity and low propensity to induce microbial resistance.[4–6] However, the inherent limitations of HDPs such as

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susceptibility to hydrolysis by proteases, poor *in vivo* stability, and high production costs have hindered their clinical application.[5,7,8]

To overcome the inherent shortcomings of natural peptides, researchers have developed a series of HDP mimics.[9–19] Among them, peptoids are considered ideal HDP mimics as they fundamentally eliminate the enzymatic cleavage site of the peptide bond by relocating the side-chain modification site from the α-carbon of the conventional peptide to the backbone amide nitrogen atom,[20–22] thereby exhibiting remarkable proteolytic stability.[23,24] This structural alteration also abolishes inter- and intramolecular chain hydrogen bonding, simplifying peptoid properties to primarily depend on side-chain composition and sequence arrangement, which significantly reduces engineering and design complexity.[25–27] However, the preparation of peptoids typically requires stepwise solid-phase synthesis, which is cumbersome, time-consuming, costly, and difficult to scale up (limited to milligram-scale production) while also imposing constraints on repeat unit length (rarely exceeding 50 residues).[27–30] Recent advances in polymer chemistry have opened new avenues for peptoid preparation, as polymerization strategies enable the production of higher yields and higher-molecular-weight polypeptoids.[29,31] This facile synthetic approach establishes polypeptoids as a highly tunable platform for rapid polymer prototyping, demonstrating great potential for applications in antimicrobial materials, biomedicine, and other fields.[32–34]

In this perspective, we review recent advances in α-peptoid polymers research, with a focus on three core aspects, including monomer preparation, polymerization reaction, and antimicrobial design and applications (Fig. 1). Through in-depth discussion of these critical areas, we provide a further outlook on the current challenges and future research directions in the field. By reviewing the existing research results, this work aims to offer perspectives that may contribute to the development of novel antimicrobial materials with both efficient antimicrobial activity and clinical translation potential.

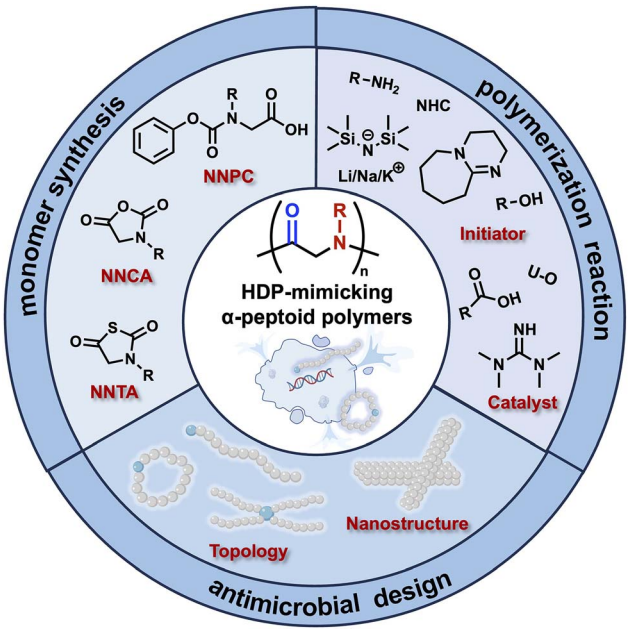

Fig. 1 This perspective summarizes the recent advances in α-peptoid polymers research, focusing on monomer synthesis, polymerization reaction, and antimicrobial application.

2. Synthesis of monomers

The monomer type determines the polymerization conditions, fundamental structures, and functions of α-peptoid polymers.

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Currently commonly used monomers include *N*-substituted *N*-carboxyanhydride (NNCA), *N*-substituted *N*-thiocarboxyanhydride (NNTA), and *N*-phenoxycarbonyl *N*-substituted glycines (NNPC), each possessing unique chemical structural characteristics (Fig. 2).

2.1 Synthesis of NNCA

The preparation of NNCAs predominantly is based on the synthetic methods for *N*-carboxyanhydrides (NCAs). Hermann Leuchs prepared NCA monomers in 1906 through the reaction of *N*-alkoxycarbonyl amino acids with halogenating agents (*e.g.*, PBr_3, PCl_3, PCl_5, or $SOCl_2$) under vacuum at 50–70 °C.[35] Notably, this classic Leuchs method is also one of the most popular synthetic approaches for NNCA monomers (Fig. 3).

The Fuchs–Farthing route represents an alternative method for the synthesis of NNCA monomers.[36,37] This approach involves the reaction of *N*-substituted glycines with phosgene or non-gaseous phosgene substitutes, such as diphosgene or triphosgene, under heating conditions. Specifically, triphosgene first reacts with nucleophiles to generate phosgene *in situ*, which then reacts with the *N*-substituted glycine to form a highly reactive chloride intermediate. Subsequently, this intermediate undergoes an intramolecular cyclization to yield the NNCA monomer (Fig. 3). The phosgene generated during the reaction is rapidly consumed. However, this method is limited by the inevitable generation of hydrogen chloride (HCl) as a byproduct and incompatibility with acid-sensitive functional groups.

Acid scavengers such as triethylamine, (+)-limonene,[38] and α-pinene[39] can be employed to neutralize HCl generated during NNCA synthesis, thereby mitigating monomer decomposition

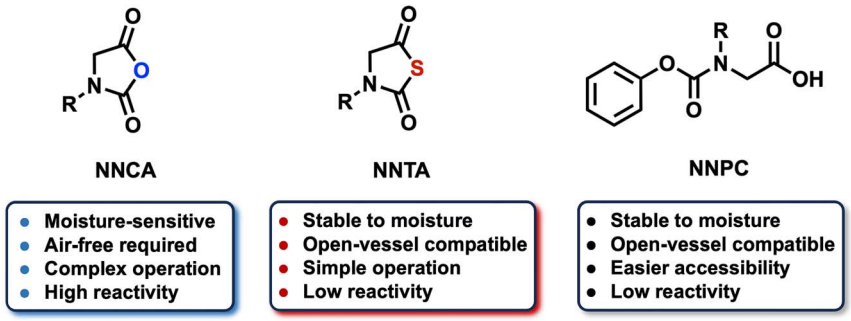


Fig. 2 Types of monomers for α-peptoid polymers.

and suppressing side reactions. However, these scavengers still exhibit limitations; for instance, the neutralization reactions of α-pinene are slow and incomplete.[40] In recent years, advances have been made in HCl scavenging strategies. Barz and co-workers developed an efficient approach utilizing triethyloxonium tetrafluoroborate to covalently incorporate chloride into volatile byproducts, enabling effective chloride removal upon a single step.[41] On the other hand, Lu *et al.* employed propylene oxide or epichlorohydrin as cost-effective HCl scavengers.[40] This strategy not only prevents acid-catalyzed decomposition of NCAs and NNCAs under humid conditions but also facilitates ring closure by lowering the reaction energy barrier.

However, the use of highly toxic phosgene and its derivatives to synthesize NNCA has been mostly limited to laboratory-scale production. Additionally, NNCA monomers generally exhibit pronounced moisture sensitivity, necessitating rigorously anhydrous conditions throughout the synthesis process. Purification prior to use and storage is also essential, as impurities can significantly compromise the storage stability and polymerization reactivity of NNCA. Consequently, there is an urgent demand for more stable monomers and more facile synthetic approaches.

2.2 Synthesis of NNTA

NNTA is a thio analog of NNCA, where the oxygen in the five-membered ring is replaced by sulfur. The synthetic methodology developed by Kricheldorf *et al.* is the most commonly used approach in NNTA preparation, owing to its high yields and low requirement for toxic reagents such as the avoidance of phosgene derivatives.[42] In this method, *N*-substituted glycines react with *S*-ethoxythiocarbonyl mercaptoacetic acid (XAA) in an alkaline aqueous solution to form the intermediate *S*-ethoxythiocarbonyl *N*-substituted glycines. Subsequently, in the presence of phosphine halides, the intermediates were further cyclized to yield the corresponding NNTA monomers (Fig. 4).

Compared with NNCA monomers, NNTA monomers are more stable, relatively insensitive to water, and easy to store. Furthermore, the synthesis and purification of NNTA monomers do not require strict anhydrous or oxygen-free operation, and can be performed in an open environment.[43] The enhanced stability of NNTA arises from two factors: first, the sulfur atom in NNTA has lower electronegativity than the oxygen atom in NNCA, resulting in reduced nucleophilicity of the C5 carboxyl carbon; second, compared to CO_2, carbonyl sulfide (COS) is more difficult to be released during the polymerization process.[44]

2.3 Synthesis of NNPC

NNPC are a class of protected amino acid derivatives that can be used in the synthesis of polypeptoids. Compared with NNCA and NNTA, NNPC offers the advantage of easier accessibility.

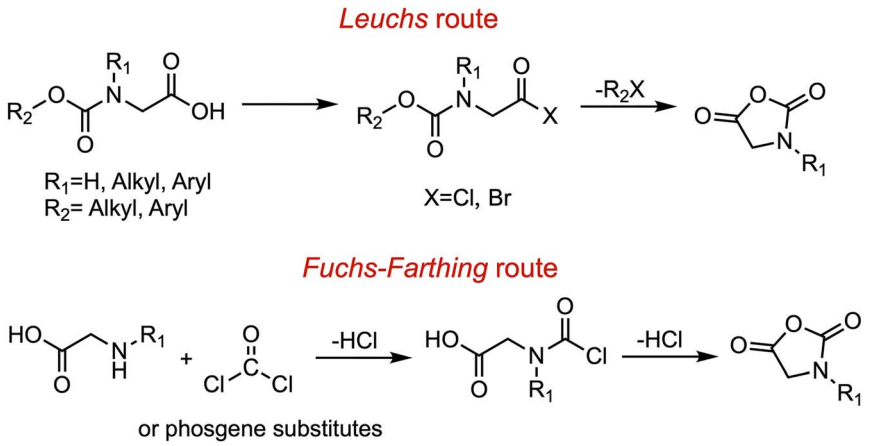


Fig. 3 Synthesis of *N*-substituted *N*-carboxyanhydrides.

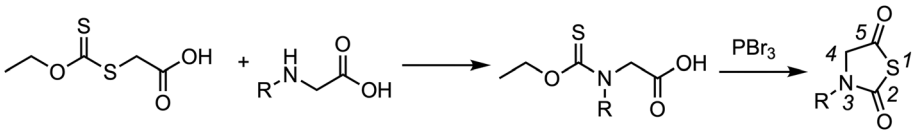


Fig. 4 Synthesis of *N*-substituted *N*-thiocarboxyanhydride according to the method developed by Kricheldorf.

This monomer can be prepared, purified, and stored long-term under ambient conditions while exhibiting good tolerance toward nucleophiles such as water and hydroxyl groups during polymerization.[45]

Schlaad *et al.* extended the NPC synthesis approach to *N*-alkylglycines, synthesizing *N*-phenoxycarbonyl-sarcosine by a two-step reaction of sarcosine with tetrabutylammonium hydroxide and diphenyl carbonate (DPC) (Fig. 5A).[46] Recently, Liu *et al.* reported a two-phase reaction system using methyl *tert*-butyl ether (MTBE) and water as solvents, which effectively avoids side reactions and enables the efficient synthesis of NPC and NNPC monomers.[47] A variety of NNPC monomers have been prepared using this synthetic approach, including Sar-NPC, *N*-ethylglycine NPC (NEG-NPC), and *N*-butylglycine NPC (NBG-NPC) (Fig. 5B).[45]

3. Polymerization of α-peptoid polymers

3.1 NNCA polymerization

NNCA ring-opening polymerization (ROP) is a facile and widely used method for synthesizing α-peptoid polymers, enabling the preparation of high-molecular-weight α-peptoid polymers with diverse structures and functionalities (Table 1). In this polymerization, primary amines are the most commonly employed nucleophilic initiators. Additionally, other initiators such as *N*-heterocyclic carbenes (NHCs), 1,8-diazabicycloundec-7-ene (DBU), and lithium hexamethyldisilazide (LiHMDS) can also be utilized for NNCA polymerization.

3.1.1 Primary amine-initiated polymerization. The most commonly used initiators for NNCA polymerization are primary amines, which typically follow the "normal amine mechanism (NAM)".[48] Specifically, the mechanism of primary amine-initiated ring-opening polymerization of NNCA proceeds *via* nucleophilic attack on the electrophilic 5-position carbonyl carbon (5-CO) of the NNCA ring. Upon nucleophilic attack, the NNCA undergoes ring-opening, accompanied by proton transfer to form an unstable carbamic acid intermediate, which is subsequently decarboxylated by the release of CO_2. The newly generated secondary amine then serves as the active center to sustain the polymerization reaction (Fig. 6).

Luxenhofer *et al.* demonstrated that the amine-initiated nucleophilic ROP of NNCAs follows pseudo-first-order kinetics, allowing precise control over the degree of polymerization by adjusting the monomer-to-initiator ratio while maintaining a narrow molar mass distribution.[38] The remarkable robustness of NNCA living polymerization was confirmed by ≥10 repeated chain extensions without evidence of chain termination or chain transfer.[49] Furthermore, well controlled block copolypeptoids such as poly(*N*-methylglycine)-*b*-poly(*N*-butylglycine) (PNMG-*b*-PNBG) can be prepared by sequential addition of monomers. This mechanism enables the synthesis of polymers with controlled molecular weights and predictable end groups.

The chemical structure of *N*-alkyl substituents in NNCA monomers directly affects their polymerization reactivity. To systematically investigate their relationship, Bonduelle *et al.* designed and synthesized 12 NNCA monomers with different *N*-alkyl groups, focusing on the steric and electronic effects of substituents on the ring-opening polymerization process.[50] Their study revealed that bulky substituents slowed down ROP kinetics, whereas electron-donating groups accelerated the polymerization rate. These findings may provide new ideas for developing catalytic systems to further improve the preparation of peptoid polymers.

Conventional ring-opening polymerization of NNCA is typically constrained by monomer hydrolysis susceptibility. The presence of water or other trace impurities in monomers or solvents may lead to various side reactions, such as deactivation of the reactive end groups or the formation of cyclic structures, thereby significantly reducing reaction efficiency.[51] Lu *et al.* developed an acetonitrile–water mixed solvent system that transforms water from a traditional limiting factor into a key promoter of polymerization and may provide a new strategy for

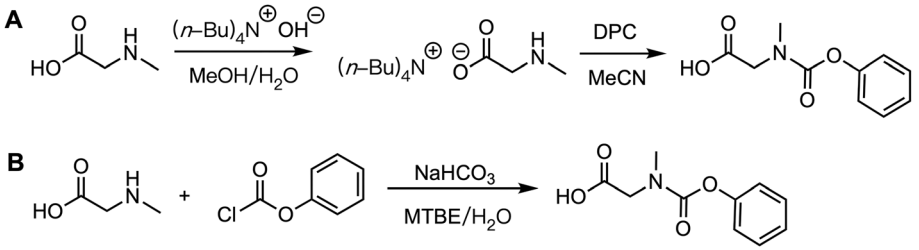


Fig. 5 (A) The synthesis route of Sar-NPC used by Schlaad *et al.* (B) The synthesis route of Sar-NPC used by Liu *et al.*

Table 1 Summary of polymerization strategies for the synthesis of α-peptoid polymers

Monomer	Initiator	Catalyst	Topological structure	Characteristics
NNCA	Primary amine		Linear	The polymerization proceeds *via* the normal amine mechanism (NAM) mechanism, exhibiting characteristics of living polymerization and enabling controlled synthesis of α-peptoid polymers. Polymerization requires purified monomers and anhydrous conditions
		Carboxylic acid		Carboxylic acid promotes proton transfer by acting as hydrogen bond donors and acceptors, thereby accelerating the polymerization rate and enabling the preparation of ultra-high molecular weight polysarcosine (chain lengths up to 8000)
		1,3-Bis[3,5-bis(trifluoromethyl)phenyl] urea (U–O)		U–O activates the carbonyl group on the NNCA ring through hydrogen-bonding interactions, thereby significantly accelerating the ROP rate of NNCAs. This catalytic strategy is particularly suitable for inactive NNCAs bearing bulky side chains
	Alcohol	1,1,3,3-Tetramethylguanidine (TMG)		TMG interacts with alcohols *via* hydrogen bonding, enhancing the nucleophilicity of the alcohol toward the ring-opening addition of NNCA monomers and thereby initiating chain growth
	Li/Na/KHMDS[a]			Liner α-peptoid polymers were generated by ROP of NNCAs in THF. The rate of polymerization significantly increased compared to that initiated by primary amines, especially for NNCAs with bulky *N*-substitution group
	NHC		Cyclic	In low dielectric constant solvents (such as THF and toluene), the quasi-living polymerization behavior is achieved by the ZROP mechanism. In polar solvents (such as DMF and DMSO), the polymerization is severely affected by side reactions
	DBU			The polymerization proceeds *via* a ZROP mechanism to produce cyclic α-peptoid polymers. DBU has excellent robustness and availability
	LiHMDS[b]			Cyclic α-peptoid polymers were generated by ring-expansion polymerization (REP) of NNCAs in DMF solvent
NNTA	Primary amine		Linear	By optimizing the polymerization conditions, controlled polymerization of NNTA can be achieved to obtain α-peptoid polymers
		Carboxylic acid		Controlled polymerization of NNTAs is achieved in polar amide solvents (DMAP, DMF and NMP) using acetic acid as catalyst
	Rare earth borohydrides			Controlled ROP of NNTAs was achieved to prepare α-peptoid polymers
	DBU		Cyclic	The polymerization proceeds *via* a ZROP mechanism with controlled molecular weight and narrow dispersion
NNPC	Primary/secondary amines	Tertiary amine base	Linear	Tertiary amine base accelerates the intramolecular condensation of NNPC and subsequent polymerization of NNCA

[a] In THF solvent, Li/Na/KHMDS can initiate the ROP of NNCAs to generate linear α-peptoid polymers. [b] In DMF solvent, LiHMDS can initiate the REP of NNCAs to generate cyclic α-peptoid polymers.

overcoming the strict anhydrous requirements for NNCA polymerization (Fig. 7A).[52] This system significantly enhances the efficiency and controllability of proline NCA (Pro-NCA) polymerization, enabling the synthesis of polyproline with a degree of polymerization up to 200 within merely 5 minutes. The resulting polymers possess well-defined end groups, predictable molecular weights, and narrow dispersity (Fig. 7B and C). Mechanistic studies revealed that water molecules serve as "proton carriers" that accelerate the proton shift in rate-determining step, substantially lowering the reaction energy barrier by 7.1 kcal mol^{-1} and thereby achieving exceptional polymerization efficiency (Fig. 7D).

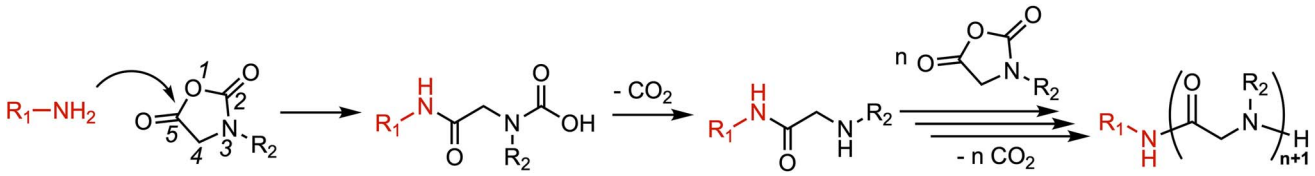


Fig. 6 Mechanism of primary amine-initiated NNCA polymerization.

In addition to developing novel initiators, researchers are also dedicated to exploring catalytic polymerization strategies to achieve efficient and rapid polymerization of NNCAs. This approach can significantly enhance the preparation efficiency of α-peptoid polymers while utilizing existing initiators, even enabling the synthesis of ultra-high molecular weight polymers. Therefore, investigating catalytic NNCA polymerization is of significant importance for broadening its application scope.

Lu *et al.* proposed a polymerization strategy based on carboxylic acid catalysis, which successfully achieved the efficient synthesis of polysarcosine with ultra-high molecular weight and narrow distribution.[53] Benzoic acid catalysis enabled full monomer conversion in 2.5 hours in a polymerization system with a monomer-to-initiator ratio of 2000 : 1, with the apparent rate constant increasing by 15-fold compared to the catalyst-free group. Furthermore, employing pivalic acid as the catalyst facilitated rapid polymerization of *N*-*n*Bu glycine NCA and enabled controlled synthesis of multiblock copolypeptoids. The authors proposed a possible catalytic mechanism wherein the carboxylic acid simultaneously interacts *via* hydrogen bonds with both the departing hydroxyl hydrogen and the leaving carboxyl oxygen in the rate-limiting transition state. This interaction avoids charge separation and high-tension conformations, thereby lowering the activation free energy and accelerating the polymerization process, ultimately achieving controlled synthesis of ultrahigh-molecular-weight polymers (Fig. 8).

NNCA monomers bearing bulky substituents typically exhibit slow reactivity, which severely limits the synthesis of α-peptoid polymers with diverse structures. Liu *et al.* found that

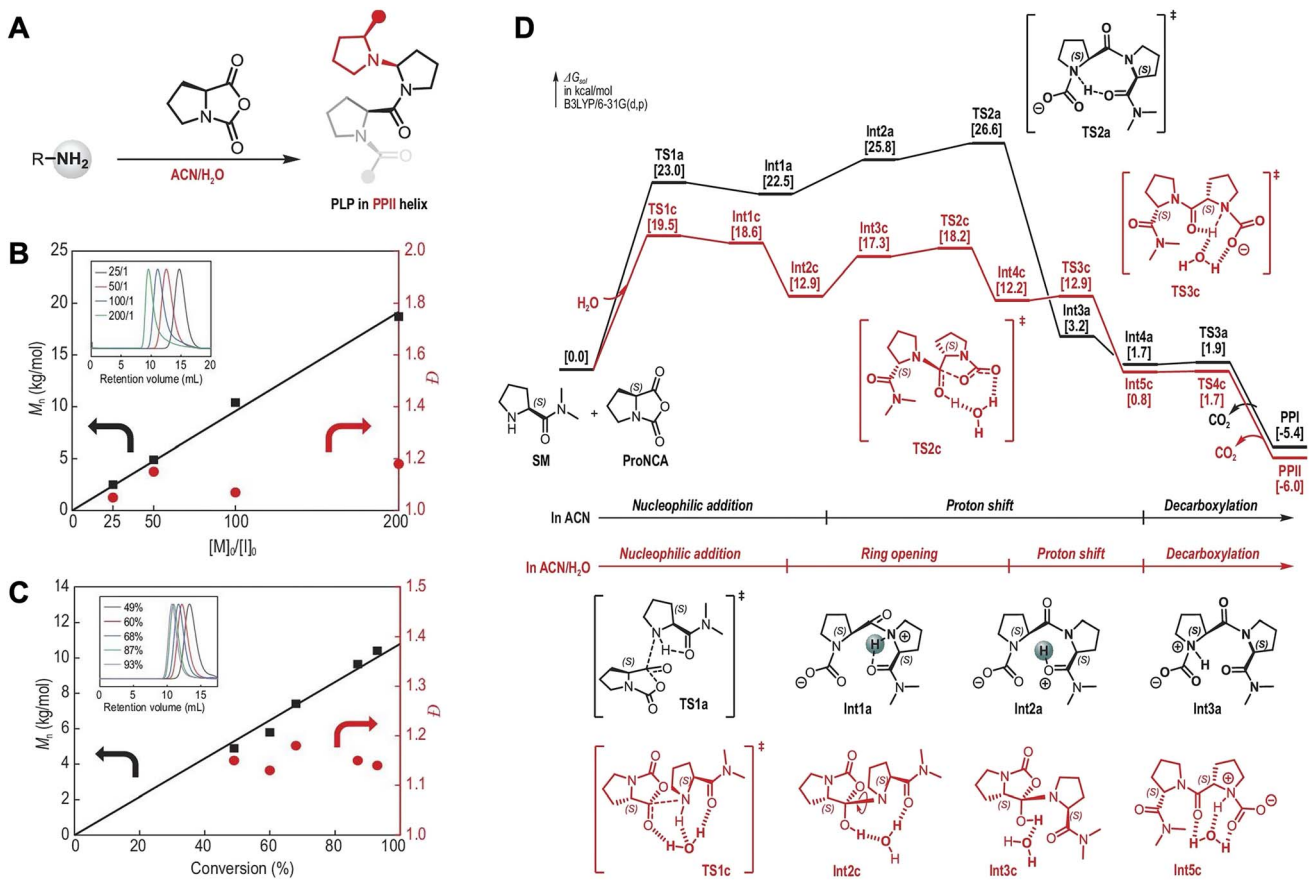


Fig. 7 (A) ROP of Pro-NCA in mixed acetonitrile/H_2O; (B) M_n and $Đ$ of polyproline as a function of $[Pro\text{-}NCA]_0/[I]_0$ ratio; (C) conversion of Pro NCA ($[Pro\text{-}NCA]_0/[I]_0 = 100/1$); (D) plausible pathways for the ROP of Pro-NCA in dry acetonitrile (black) and mixed acetonitrile/H_2O (red) revealed by density functional theory (DFT) calculations. Reproduced with permission from ref. 52. Copyright 2022, Oxford University Press.

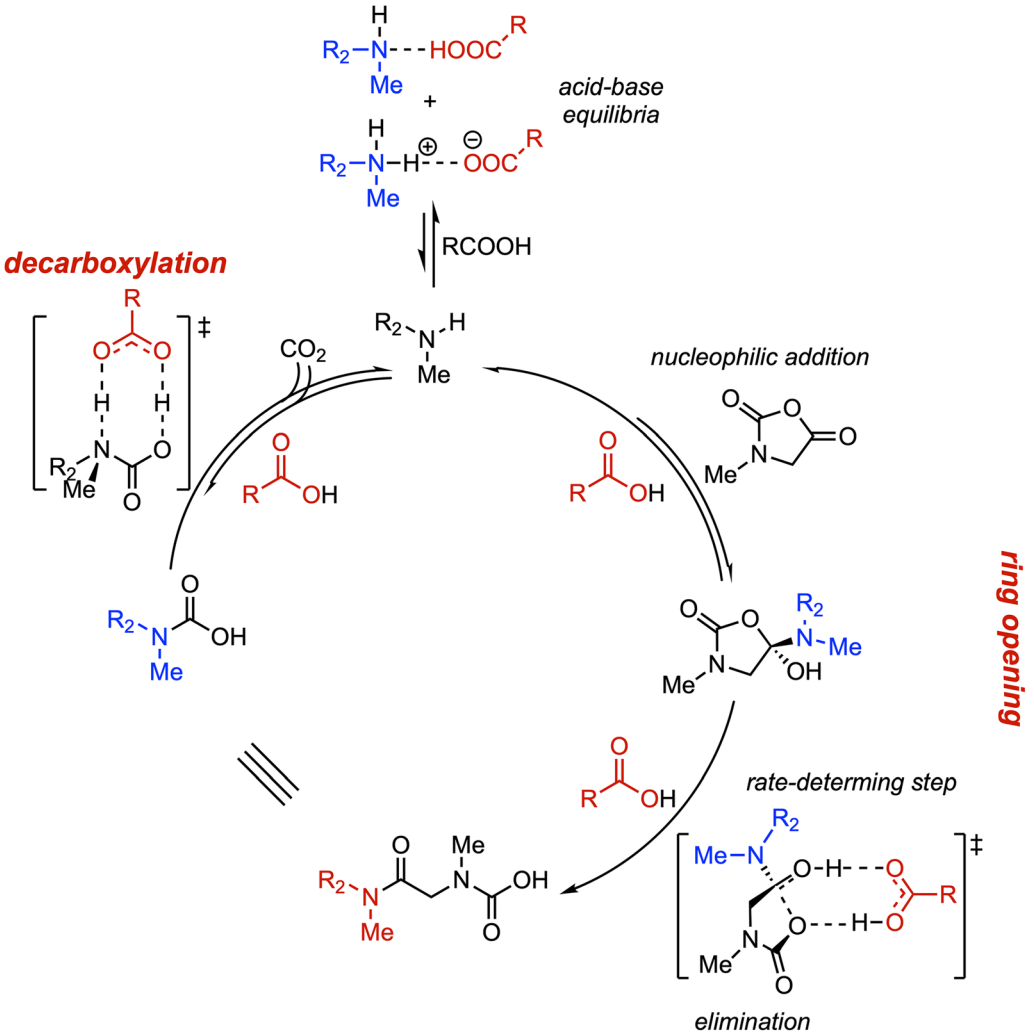


Fig. 8 Proposed mechanism for ROP of Sar-NCA catalyzed by carboxylic acids. Adapted with permission from ref. 53. Copyright 2024, American Chemical Society.

1,3-bis[3,5-bis(trifluoromethyl)phenyl]urea can activate the carbonyl group on the NNCA ring through hydrogen-bonding interactions, thereby significantly accelerating the ROP rate of NNCAs initiated by primary amines (Fig. 9).54 This urea-based catalytic system demonstrates broad compatibility with various NNCA monomers, enabling the efficient preparation of α-peptoid polymers with controlled molecular weights and narrow dispersity. Notably, it is particularly suitable for inactive NNCAs bearing bulky side chains, such as cyclohexyl-NNCA. This catalytic strategy provides a novel approach to expand

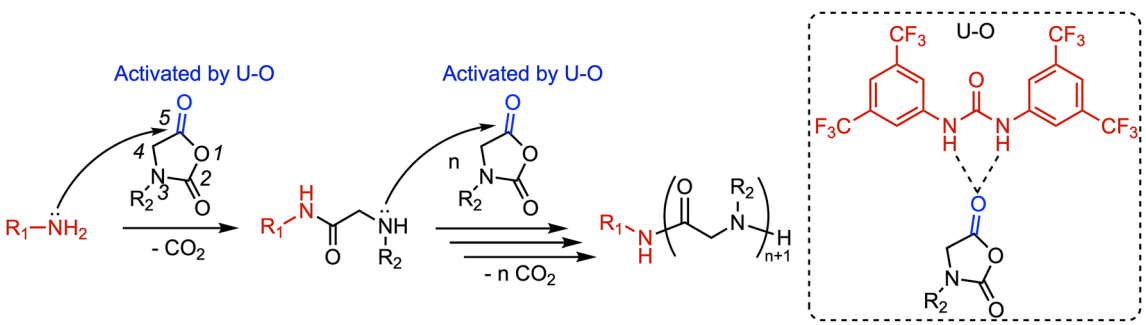


Fig. 9 Mechanism of primary amine-initiated ROP of NNCA catalyzed by U–O. Reproduced from ref. 54 with permission from the Royal Society of Chemistry.

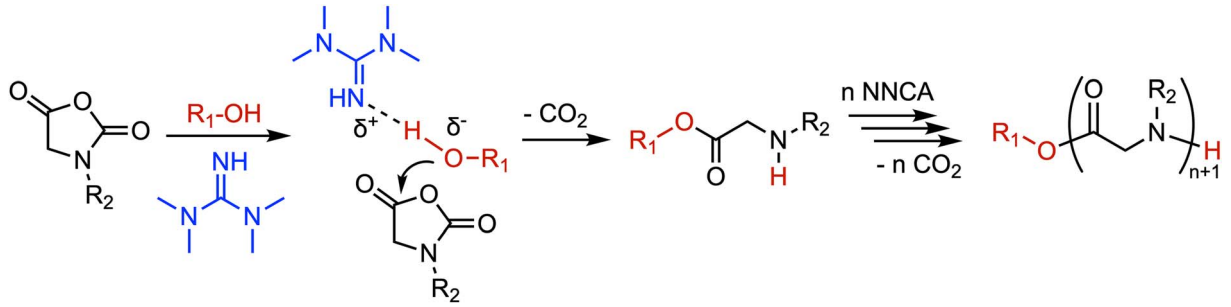


Fig. 10 Mechanisms of alcohol-initiated ROP of NNCA catalyzed by TMG.

the structural diversity of α-peptoid polymers and advance their functional exploration.

3.1.2 Alcohol-initiated polymerization in the presence of TMG. Zhang *et al.* successfully achieved the ROP of *N*-butyl *N*-carboxyanhydride (Bu-NCA) using appropriate alcohols as the initiator in combination with 1,1,3,3-tetramethylguanidine as the catalyst.[55] In these reactions, TMG interacts with alcohols *via* hydrogen bonding, enhancing the nucleophilicity of the alcohol toward the ring-opening addition of Bu-NCA monomers and thereby initiating chain growth (Fig. 10). Moreover, hydroxyl-terminated poly(ethylene glycol) (PEG) macro-initiators, in combination with TMG, could also be employed to synthesize PEG-poly(α-peptoid)s block copolymers.

3.1.3 Li/Na/KHMDS-initiated polymerization in THF solvent. Liu *et al.* recently discovered that lithium/sodium/potassium hexamethyldisilazide (Li/Na/KHMDS) can serve as initiators for the rapid polymerization of NNCAs, enabling efficient α-peptoid polymers synthesis (Fig. 11).[56] Mechanistic studies revealed that Li/Na/KHMDS initiates NNCA polymerization by deprotonating the CH on the NNCA ring, followed by nucleophilic attack of the resulting carbanion to the carbonyl carbon on the new NNCA ring, triggering ring-opening and generating a terminal *N*-carbamate as the reactive center for further propagation. This mechanism offers unique advantages in polymerizing inactive NNCAs bearing bulky *N*-substitution group compared to the classical normal amine mechanism. In primary amine-initiated polymerizations, the secondary amine terminus serving as the propagating species is highly susceptible to bulky *N*-substituents, resulting in low nucleophilicity and hence slow propagation kinetics (Fig. 6). In contrast, the nucleophilic attack by terminal *N*-carbamate on new NNCAs in Li/Na/KHMDS-initiated polymerization is much less affected by the *N*-substituents groups, and thus has a much faster polymerization rate (Fig. 11). For instance, the polymerization reaction time for cyclohexyl-NNCA was significantly reduced from 6 days, required when using primary amine initiators, to 20 hours.

3.1.4 NHCs-initiated polymerization. While the ROP of NNCAs initiated by primary amines, alcohols or Li/Na/KHMDS yields linear α-peptoid polymers, the zwitterionic ring-opening polymerization (ZROP) strategy enables the synthesis of cyclic α-peptoid polymers.

Kricheldorf *et al.* observed that base initiators including pyridine, tertiary amines, and imidazole, could initiate the polymerization of sarcosine NCA to yield cyclic PSRs.[57,58] Zhang *et al.* selected NHCs as nucleophilic initiators to trigger the ROP of NNCAs, yielding cyclic α-peptoid polymers with controllable molecular weight and narrow distribution.[59,60] Further studies revealed that the polymerization propagation rate strongly depended on the structure of the NHC and the choice of solvent.[61] Kinetic studies have shown that in low dielectric constant solvents such as tetrahydrofuran (THF) and toluene, the propagating intermediate maintaining a cyclic structure with two chain ends in close contact due to coulombic attraction (Fig. 12). Moreover, the positively charged NHC chain end in the progating zwitterions could reduce the nucleophilicity and basicity of the anionic carbamate chain end through coulombic interactions, suppressing side reactions and thereby enabling quasi-living polymerization behavior. In contrast, in polar solvents such as *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), the polymerization was significantly affected by extensive side reactions. In addition, the cyclic α-peptoid polymers could be converted into linear polymers through the addition of electrophiles.

3.1.5 DBU-initiated polymerization. 1,8-Diazabicycloundec-7-ene, a bicyclic amidine, is generally regarded as a strong base with weak nucleophilicity. However, recent studies have shown that DBU can act as a competent nucleophile, capable of

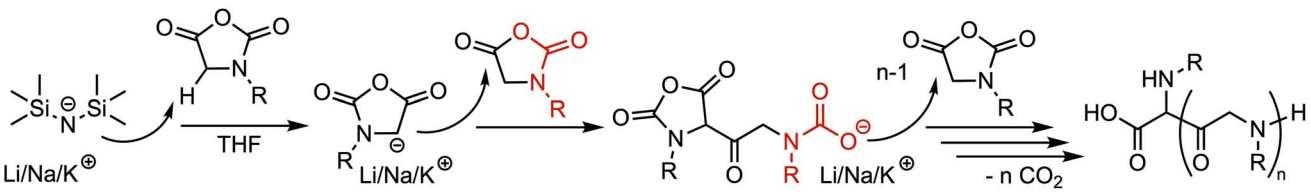


Fig. 11 The Li/Na/KHMDS-initiated ring-opening polymerization of NNCA in THF.

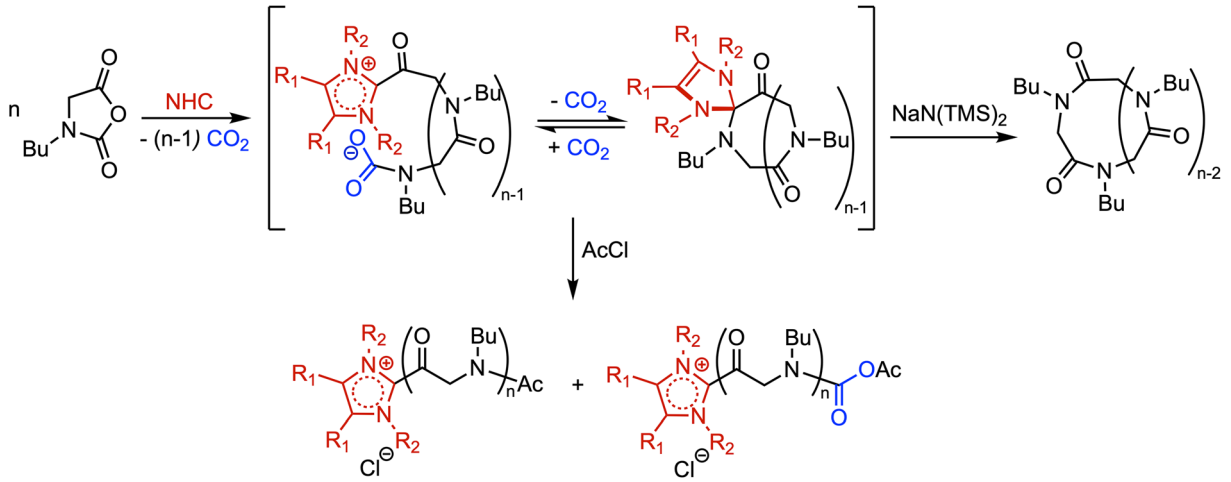


Fig. 12 Mechanism of NHC-initiated NNCA polymerization. Adapted with permission from ref. 61. Copyright 2012, American Chemical Society.

undergoing nucleophilic addition reactions with dimethyl carbonate and chloroformate.[62,63] Inspired by this, Zhang *et al.* investigated the ZROP of Bu-NCAs using DBU as the initiator, and found that the polymerization proceeded efficiently in a controlled manner, yielding cyclic poly(*N*-butylglycines) with controllable molecular weights and narrow dispersities (Fig. 13).[64] Kinetic studies showed that the initiation rate was comparable to the propagation rate in DBU-mediated ZROP, which was slightly faster than the previously reported NHC-mediated ZROP. Due to its excellent robustness and availability, as well as the good control over R-NCA polymerization, DBU represents an attractive strategy for producing well-defined cyclic α-peptoid polymers with tunable ring sizes.

3.1.6 LiHMDS-initiated polymerization in DMF solvent. Bonduelle *et al.* proposed an alternative approach for the synthesis of cyclic α-peptoid polymers—ring-expansion

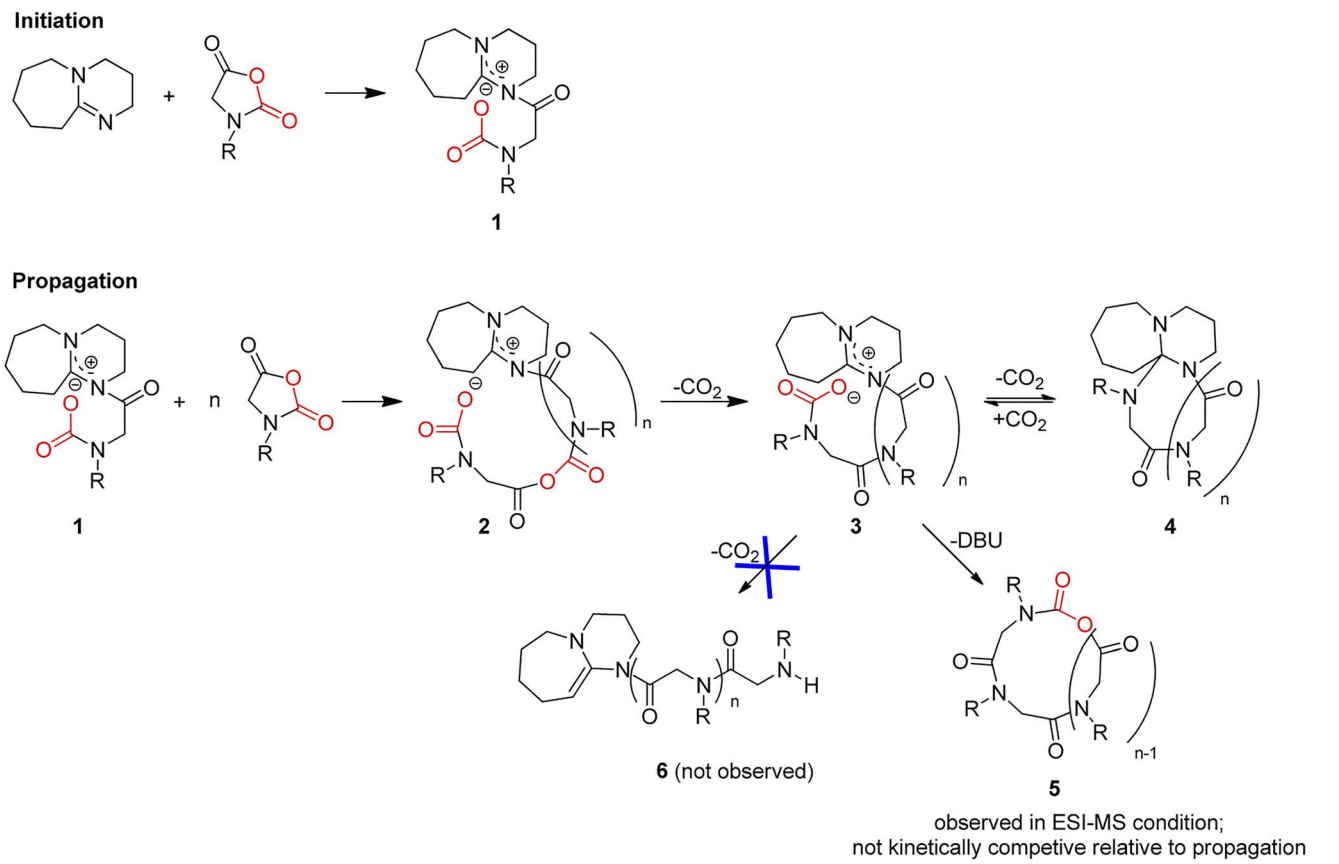


Fig. 13 Mechanism of DBU-initiated NNCA polymerization. Adapted with permission from ref. 64. Copyright 2016, American Chemical Society.

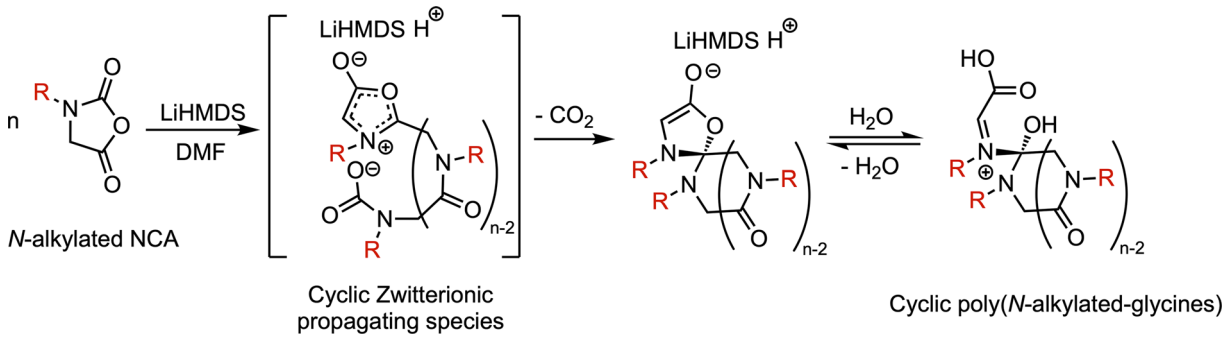


Fig. 14 The LiHMDS-mediated REP of NNCA in DMF.

polymerization of NNCAs—which can be conducted in more polar media such as DMF (Fig. 14).[65] This method employs lithium bis(trimethylsilyl)amide as the initiator to trigger NNCA polymerization, yielding cyclic α-peptoid polymers. Mechanistic studies indicated that reactions involves the formation of a cyclic zwitterionic propagating intermediate through the interaction between the anionic carbamoyl extremity and the positive charge of Münchnone moiety. Notably, this strategy allows the incorporation of lysine-like monomers in REP for the first time.

3.2 NNTA polymerization

NNTA, the thio-analogue of NNCA, exhibits enhanced monomer stability but reduced polymerization reactivity compared to NNCA. Due to their low reactivity, NNTAs have traditionally been employed in the stepwise solid-phase synthesis of peptoids, with their polymerization studies very limited.[42,66]

3.2.1 Primary amine-initiated polymerization. In 2008, Kricheldorf *et al.* examined Sar NTA polymerization in dioxane using *n*-hexylamine as initiator. While MALDI-TOF MS verified the isolated products had the anticipated structure featuring active amino terminus, the reaction achieved only low conversion.[67] Complete conversion was only observed at a monomer-to-initiator ratio (M/I) of 20. As the M/I ratio increased, the conversion rate progressively decreased, falling well below 100% at M/I ratios of 60 or 100. In 2016, Ling and Kricheldorf *et al.* achieved controlled polymerization of *N*-ethyl glycine NTA (NEG-NTA) using THF as the solvent and small molecule primary amines (*e.g.*, benzylamine and hexylamine, *etc.*) as initiators under heating at 60 °C, successfully synthesizing α-peptoid polymers with a high degree of polymerization up to 287 and a narrow dispersity (*Đ*) of 1.14 (Fig. 15).[68] Kinetic study and the synthesis of block copolypeptoids further confirmed the controllability of primary amine-initiated NNTA polymerization. This study demonstrated that through optimization of polymerization conditions, controlled polymerization of NNTA monomers can be achieved despite their relatively low reactivity, enabling the production of α-peptoid polymers with well-controlled molecular weights.

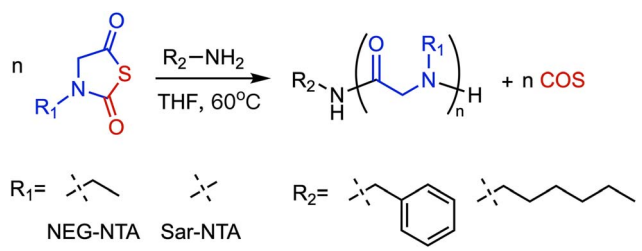


Fig. 15 Polymerization of NNTA initiated by primary amines.

NNTA ring-opening polymerization initiated by primary amines is tolerant to small amounts of water and does not require strict anhydrous conditions. For this property, Ling *et al.* explored the relationship between water content and polymerization controllability by investigating the ROP of NNTA in systems with varying water content using benzylamine as the initiator.[69,70] The study found that in the presence of small amounts of water (approximately 100–600 μg g^{-1}), the polymerization exhibited excellent controllability. In contrast, in high-water-content systems (approximately 6000–14 000 μg g^{-1}), the degree of polymerization gradually deviated from the feed ratio. Mechanistic studies demonstrated that hydrogen sulfide (H_2S), generated *via* hydrolysis of COS, was identified as the key factor suppressing both the yield and molar mass of the resulting polymers.[70] Based on this finding, side reactions can be effectively prevented by simply purging the reaction solution with an inert gas such as argon to remove COS and H_2S.

However, limited solvent compatibility is one of the major challenges in NNTA polymerization. Amide solvents such as *N*,*N*-dimethylacetamide (DMAc), DMF, and *N*-methylpyrrolidone (NMP) are commonly used solvents for biomacromolecules and poly(amino acid)s, but NNTA typically cannot achieve controlled polymerization in these solvents. Ling *et al.* addressed this issue by introducing stoichiometric acetic acid as a reaction promoter.[71] In the presence of acetic acid, controlled polymerizations of NEG-NTA, Sar-NTA, and *N*-butyl glycine NTA (NBG-NTA) were successfully achieved in polar amide solvents (including DMAc, DMF, and NMP). Mechanism study revealed that acetic acid not only accelerates polymerization kinetics but also suppresses side reactions by decreasing the concentration of H_2S dissolved in polar solvents. This work expands the solvent options for NNTA polymerization.

3.2.2 Rare earth borohydrides-initiated polymerization. Ling *et al.* reported the use of rare earth borohydrides

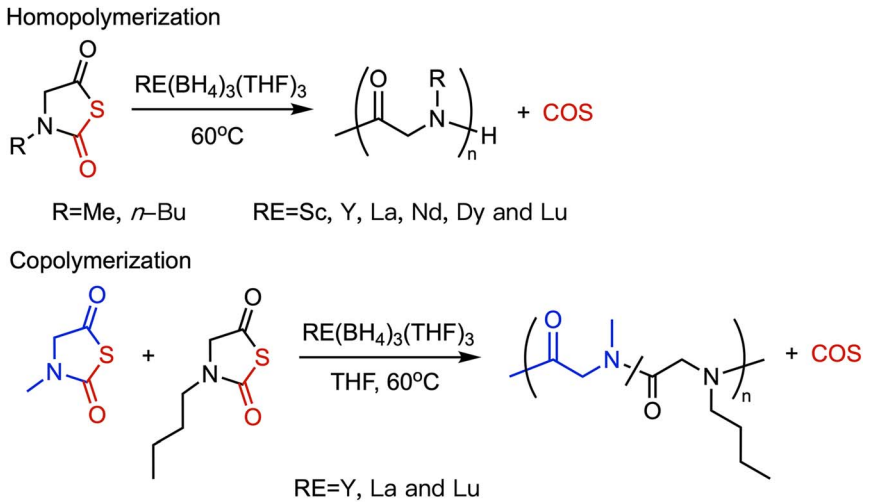


Fig. 16 Polymerization of NNTA Initiated by $RE(BH_4)_3(THF)_3$. Adapted with permission from ref. 72. Copyright 2014, American Chemical Society.

$[RE(BH_4)_3(THF)_3$, RE = Sc, Y, La, Nd, Dy, and Lu] as initiators for the controlled polymerization of NNTA monomers (Fig. 16).[72] Using $(BH_4)_3(THF)_3$ as the initiators in acetonitrile, they successfully synthesized polysarcosine with a molecular weight of up to 27.7 kDa, achieving a chain length comparable to that obtained *via* Sar-NCA polymerization. Additionally, the copolymer P(Sar-r-NBG) can be obtained by copolymerizing Sar-NTA with NBG-NTA in THF.

3.2.3 DBU-initiated polymerization. Lin *et al.* demonstrated that DBU can also initiate the ROP of NNTA, yielding cyclic α-peptoid polymers.[73] The polymerization proceeds *via* a ZROP mechanism, exhibiting excellent controllability, tunable molecular weights, and narrow dispersity.

3.3 NNPC polymerization

Schlaad *et al.* synthesized a series of polysarcosines with varying chain lengths using Sar-NPC as the precursor.[46] The number-average molar mass of the obtained products closely matched the theoretical value with narrow molar mass distributions ($Đ \approx 1.1$), indicating that the polymerization reaction proceeded in a controlled manner. The process specifically involved *in situ* conversion of Sar-NPC to Sar-NCA in DMSO solution at 60 °C, catalyzed by 2 vol% of tertiary amine base (DIPEA or TEA), followed by polymerization initiated by the primary amine. Mechanistic studies revealed that the tertiary amine base accelerates the intramolecular condensation of Sar-NPC and subsequent polymerization of Sar-NCA owing to the deprotonation of the Sar-NPC and the shift of the ammonium–amine equilibrium toward the amine (Fig. 17).

Ling *et al.* successfully achieved well-controlled polymerization of NEG-NPC and NBG-NPC under acetic acid catalysis, yielding α-peptoid polymers with tunable molecular weights and low dispersity ($Đ < 1.11$) (Fig. 18A).[45] In addition, kinetic studies and density DFT calculations confirmed that the side reaction during polymerization involves the backbiting reaction of oligomers to generate 1,4-dialkylpyrazine-2,5-diones (DAPs) (Fig. 18B).

4. Antimicrobial applications of α-peptoid polymers

The antimicrobial activity of HDPs is closely related to their structural characteristics. Cationic groups or net positive

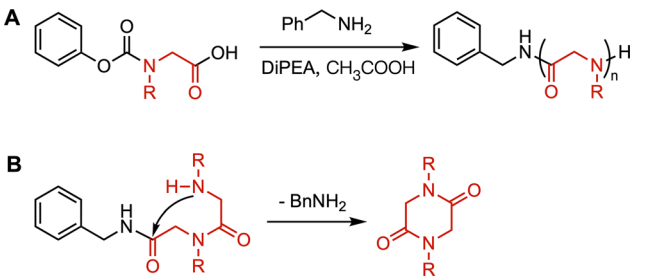


Fig. 18 (A) NNPC polymerization in the presence of acetic acid. (B) Backbiting reaction of oligomer to form DAP.

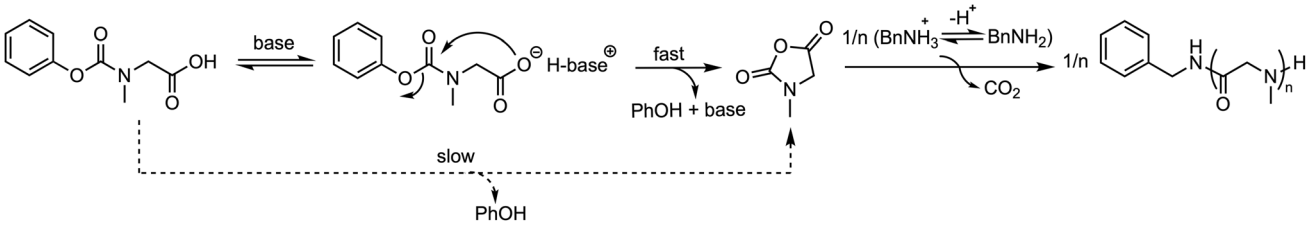


Fig. 17 Polysarcosine were prepared by Sar-NPC polymerization in the presence of tertiary amine bases and primary amine initiators.

Table 2 Structure and biological activities of HDP-mimicking α-peptoid polymers

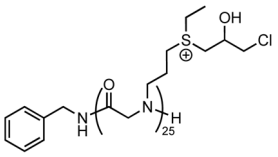
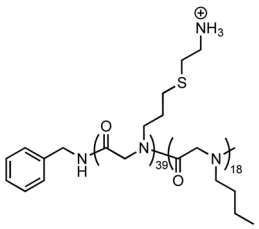
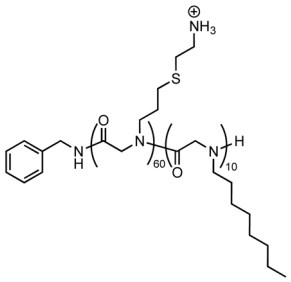
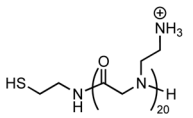
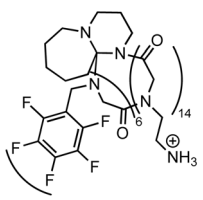
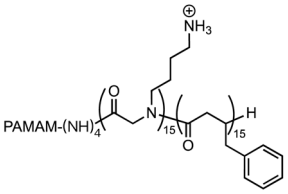
Polypeptoids structure	Antimicrobial activity: Tested strains	MIC[a] (μg mL^{-1})	Biocompatibility: Hemolysis[a]	Cytotoxicity[a]	Ref.
 PNAG$_{25}$-ET-Cl	*S. aureus* ATCC6538 *E. coli* ATCC25922	3.9 15.6	HC$_{10}$ > 1000 μg mL^{-1}	N/A	17
 AG$_{39}$-BG$_{18}$-NH$_2$	*S. aureus* ATCC6538 *P. aeruginosa* ATCC9027 *E. coli* ATCC25922	2 7.8 7.8	HC$_{50}$ = 250 μg mL^{-1}	N/A	85
 (PNAG$_{60}$-*g*-NH$_2$)-*b*-PNOG$_{10}$ (Fiber-like micelles)	*S. aureus* ATCC6538 *P. aeruginosa* ATCC9027 *E. coli* ATCC25922	7.8 64 256	HC$_{50}$ > 1000 μg mL^{-1}	N/A	86
 HS(Naeg)$_{20}$	*S. aureus* strains *S. haemolyticus* strains *S. epidermidis* strains *E. faecium* strains	6.25–12.5 1.56–25 3.13–6.25 6.25–25	HC$_{50}$ > 10 000 μg mL^{-1}	IC$_{50}$ = 400 μg mL^{-1}	18
 poly(Naeg$_{0.7}$Npfbg$_{0.3}$)$_{20}$	*S. epidermidis* ATCC 49134 *S. aureus* USA300 LAC *E. coli* ATCC25922 *P. aeruginosa* O1 *A. baumannii* BAA747	12.5 12.5 50 25 100	HC$_{50}$ > 200 μg mL^{-1}	IC$_{50}$ > 200 μg mL^{-1}	87

Table 2 (*Contd.*)

Polypeptoids structure	Antimicrobial activity: Tested strains	Antimicrobial activity: MIC[a] (μg mL^{-1})	Biocompatibility: Hemolysis[a]	Biocompatibility: Cytotoxicity[a]	Ref.
 S-P(Nlys-Nphe) 1 	*C. difficile*	62.5	N/A	CC_{50} = 79 μg mL^{-1}	88
	S. aureus	31.25–62.5			
	L. monocytogenes	15.6			
	B. fragilis	7.8			
	E. faecalis	31.25–62.5			
	E. coli	62.5			
	P. aeruginosa	31.25–62.5			
	A. baumannii	31.25			
	H. pylori	31.25			

[a] The MIC, hemolysis, and cytotoxicity values in this table are derived from literature, which are assay protocol dependent. The MIC is the minimum concentration of a compound to inhibit microbial growth. The HC_{50} is the concentration of a compound that causes 50% hemolysis. The IC_{50} is the concentration of a compound that causes 50% reduction in cell viability. N/A represents that no relevant data was reported in the literature.

charges serve as the critical element for exerting antimicrobial function, since the initial interaction between the HDPs and the negatively charged microbial cell membranes is primarily driven by electrostatic attraction.[74,75] Meanwhile, the hydrophobic ratio plays a vital role in modulating both activity and selectivity:[76,77] insufficient hydrophobicity weakens membrane interactions,[78] whereas excessive hydrophobic content may induce mammalian cell cytotoxicity,[79] or polymer aggregation, thereby reducing antibacterial efficacy.[80] Additionally, the chain length also significantly affects their activity and cytotoxicity. Within a certain range, the antimicrobial efficacy increases with chain length, but excessively chain length may instead elevate hemolytic activity and cytotoxicity.[81,82] In summary, the design of HDP mimics needs to synergistically modulate factors such as positive charge, hydrophobicity ratio, and chain length to achieve high antimicrobial efficacy while minimizing nonspecific damage to host cells.[31,83,84]

Currently, by mimicking the critical amphiphilic structural features of HDPs, researchers have successfully designed and synthesized a variety of antimicrobial α-peptoid polymers. These polymers overcame the limitations of natural peptides, such as enzymatic degradation, poor stability, and high synthesis costs, while retaining potent antimicrobial activity (Table 2). Notably, some antimicrobial α-peptoid polymers have demonstrated excellent *in vivo* efficacy in animal infection models, including both localized and systemic infections, highlighting their great potential for treating drug-resistant microbial infections (Table 3).

4.1 Sulfonium-ion-bearing antibacterial α-peptoid polymers

Chen *et al.* employed a post-polymerization functionalization strategy to introduce cationic groups into α-peptoid polymers, thereby mimicking the key amphiphilic structure of HDPs with positive charge and hydrophobicity. Specifically, they synthesized α-peptoid polymers *via* ROP of *N*-allyl NCA using $BnNH_2$ or methoxypolyethylene glycol amine as the initiators, followed by modification with ethyl thioalcohol and subsequent alkylation with functional epoxides to form antimicrobial polysulfonium derivatives (Fig. 19A).[17] By optimizing the hydrophilic/hydrophobic balance, the chlorohydroxypropane-modified polysulfoniums demonstrated high antibacterial activity and selectivity against both *E. coli* and *S. aureus* (Fig. 19B). Furthermore, the poly(α-peptoid)s sulfoniums effectively inhibited biofilm formation, eradicated mature biofilms, and demonstrated excellent bactericidal efficacy and wound healing capacity in a MRSA mouse wound infection model (Fig. 19C and D).

4.2 Copolypeptoids with antibiofilm activity

Sun *et al.* designed a novel cationic copolypeptoid antimicrobial agent by mimicking natural HDPs, synthesized *via* NNCA ring-opening polymerization followed by click chemistry modification (Fig. 20A).[85] Specifically, the ROP of a variety of NNCA monomers was initiated by benzylamine, where the incorporation of allyl or propargyl groups allowed for the acquisition of positively charged structures through post-modification with the thiol-terminated amine, and other fragments provided hydrophobic groups. Through modulation of the hydrophilic/hydrophobic balance, the copolypeptoids exhibited broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria (Fig. 20B), effectively inhibiting biofilm formation and eradicating mature biofilms while outperforming conventional antibiotics (Fig. 20C). Due to a membrane disruption mechanism similar to that of HDPs, resistance does not develop even with repeated use of the polymer (Fig. 20D). Moreover, the copolypeptoids exhibited excellent *in vivo* antibacterial efficacy, effectively eliminating bacteria and promoting wound

Table 3 *In vivo* therapeutic efficacy of HDP-mimicking α-peptoid polymers

Polypeptoids	Infection model	Microbial species	Therapeutic doses	Therapeutic efficacy	Ref
$PNAG_{25}$-ET-Cl	Rat full-thickness wound infection model	MRSA	4 h after infection 15 μL, 1 mg mL^{-1}	Reduces bacterial load by ~3 log, promotes wound healing, and reduces inflammatory infiltrate	17
PG_{42}-BG_{10}-$(NH_2)_2$	Rat full-thickness wound infection model	MRSA	6 h after infection 15 μL, 2 mg mL^{-1}	Reduces bacterial load by ~2 log, promotes wound healing, and reduces inflammatory infiltrate	85
($PNAG_{60}$-*g*-NH_2)-*b*-$PNOG_{10}$ fiber-like micelles	Mice full-thickness wound infection model	*S. aureus*	24 h after infection 50 μL, 1 mg mL^{-1}	Reduces bacterial load by ~2.5 log, promotes wound healing, and reduces inflammatory infiltrate	86
$HS(Naeg)_{20}$	Mice full-thickness wound infection model	MRSA	24 h after infection The treatments (15 μL, 1.56 mg mL^{-1}) were applied every 4 h for a total of 3 times	Reduces bacterial load by ~2 log	18
	Mice full-thickness wound infection model	*S. epidermidis*	24 h after infection The treatments (15 μL, 3.13 mg mL^{-1}) were applied every 4 h for a total of 3 times	Reduces bacterial load by ~2 log	
	Mice full-thickness wound infection model	*S. haemolyticus*	24 h after infection The treatments (15 μL, 3.13 mg mL^{-1}) were applied every 4 h for a total of 3 times	Reduces bacterial load by ~2.4 log	
	Mice keratitis model	MRSA	24 h after infection The treatments (10 μL, 1.56 mg mL^{-1}) were applied every 5 min during the first hour and every 30 min for the next 7 h	Reduces bacterial load by ~2.5 log	
	Mice peritonitis model	MRSA	1 h after infection A single-dose (20 mg kg^{-1}) was i.p. administered	Increases survival rate, reduces bacterial load for around 1.8 to 3.3 log CFU in all five organs, blood, and peritoneal fluid, and alleviates organ lesions	
	Mice peritonitis model	*S. epidermidis*	1 h after infection A single-dose (20 mg kg^{-1}) was i.p. administered	Increases survival rate, reduces bacterial load for around 2 to 3.7 log CFU in all five organs, blood, and peritoneal fluid	
	Mice peritonitis model	*S. haemolyticus*	1 h after infection A single-dose (20 mg kg^{-1}) was i.p. administered	Increases survival rate, reduces bacterial load for around 2.2 to 3.5 log CFU in all five organs, blood, and peritoneal fluid	

healing. Notably, when coated onto magnetic nanospheres, the copolypeptoids demonstrated recyclable properties and enhanced antimicrobial activity as combined with near-infrared-induced photothermal therapy (Fig. 20E).

4.3 Self-assembled copolypeptoids for effective biofilm eradication

Sun *et al.* further developed a novel self-assembled cationic antimicrobial polypeptoid.[86] Specifically, a cysteamine hydrochloride-modified diblock copolypeptoid, poly(*N*-allylglycine-*g*-NH_2)-*b*-poly(*N*-octylglycine) (PNAG-*g*-NH_2)-*b*-PNOG, was synthesized *via* ROP of NNCA and post-polymerization functionalization (Fig. 21A). This polymer could self-assemble into fiber-like and spherical micelles in aqueous solutions at different pH. The fiber-like micelles demonstrated high antimicrobial activity and selectivity, exhibiting superior efficacy to vancomycin in both inhibiting *S. aureus* biofilm formation and eradicating mature biofilms (Fig. 21B). Antimicrobial mechanism studies revealed that micelles exerted their bactericidal effects by disrupting bacterial cell membranes (Fig. 21C). Further *in vivo* experiments demonstrated that the polypeptoid micelles showed excellent antibacterial efficacy in a *S. aureus* infection mouse skin model (Fig. 21D).

4.4 HDP-mimicking α-peptoid polymers with potent *in vivo* efficacy

Liu *et al.* developed a novel strategy for the one-pot ring-opening polymerization of antibacterial α-peptoid polymers without requiring additional post-modification. They successfully synthesized an NNCA monomer with amino groups on its side

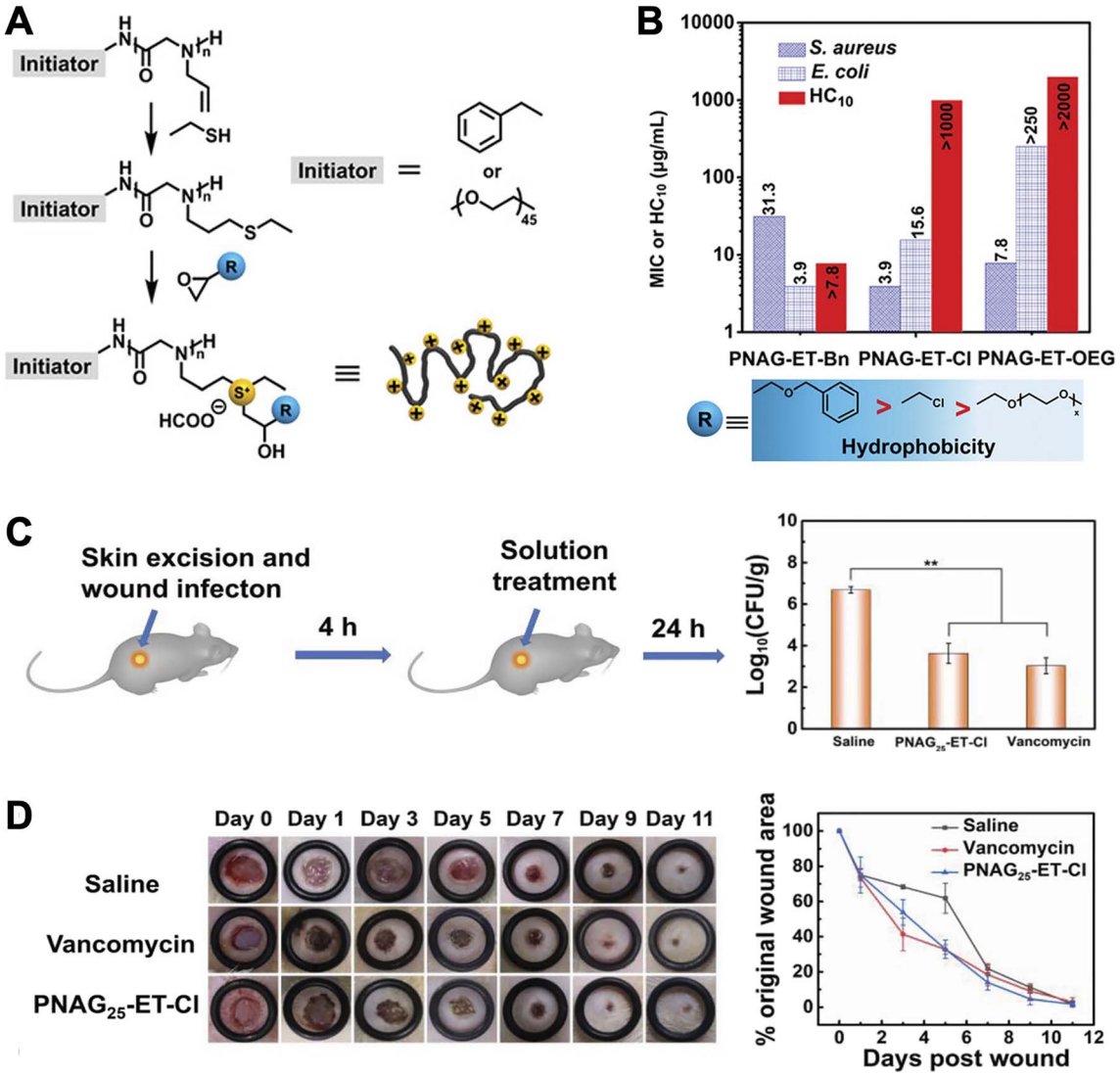


Fig. 19 The antibacterial sulfonium-ion-bearing α-peptoid polymers. (A) Synthesis of the cationic poly(α-peptoid)s sulfoniums. (B) The MIC values against *S. aureus* and *E. coli*, as well as the HC_{10} values of poly(α-peptoid)s sulfoniums. (C) Schematic representation of the mouse skin MRSA infection model and *in vivo* antimicrobial activity. (D) Digital images and size changes of mouse skin wounds treated with saline, vancomycin and poly(α-peptoid)s sulfoniums at different time points. Adapted with permission from ref. 17. Copyright 2021, John Wiley and Sons.

chain (N^{β}-Cbz-aminoethyl-NCA) for the first time and prepared a library of α-peptoid polymers with various C-terminal functional groups *via* one-pot polymerization (Fig. 22A).[18] The optimal α-peptoid polymer exhibited potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA) planktonic bacteria, persister cells, and biofilm. Moreover, *S. aureus* didn't acquire resistance upon polymer even after continuous treatment with polymer for 834 passages. The preferred molecule exhibited effective *in vivo* anti-infectious performance in the mouse wound model, the mouse keratitis model, and the mouse peritonitis model induced by MRSA (Fig. 22B). In addition, the α-peptoid polymers also displayed potent *in vitro* and *in vivo* antibacterial activity against various other drug-resistant Gram-positive bacteria.

This study designed a NNCA monomer bearing side-chain amino, overcoming the previous technical limitation in antimicrobial α-peptoid polymers synthesis that required post-polymerization functionalization to introduce cationic groups and providing a simplified route to obtain structurally controllable amphiphilic α-peptoid polymers. Furthermore, it also demonstrated the significant potential of HDP-mimicking α-peptoid polymers in the treatment of drug-resistant microbial infections through various animal models, especially systemic infection models.

4.5 HDP-mimicking cyclic α-peptoid polymers with broad-spectrum activity

Liu *et al.* further synthesized a series of amphiphilic cyclic α-peptoid polymers *via* copolymerization of cationic monomer N^{β}-Cbz-aminoethyl-NCA and hydrophobic monomer *N*-pentafluorobenzyl-NCA, using DBU as the initiator.[87] The optimal cyclic α-peptoid polymers, poly$(Naeg_{0.7}Npfbg_{0.3})_{20}$,

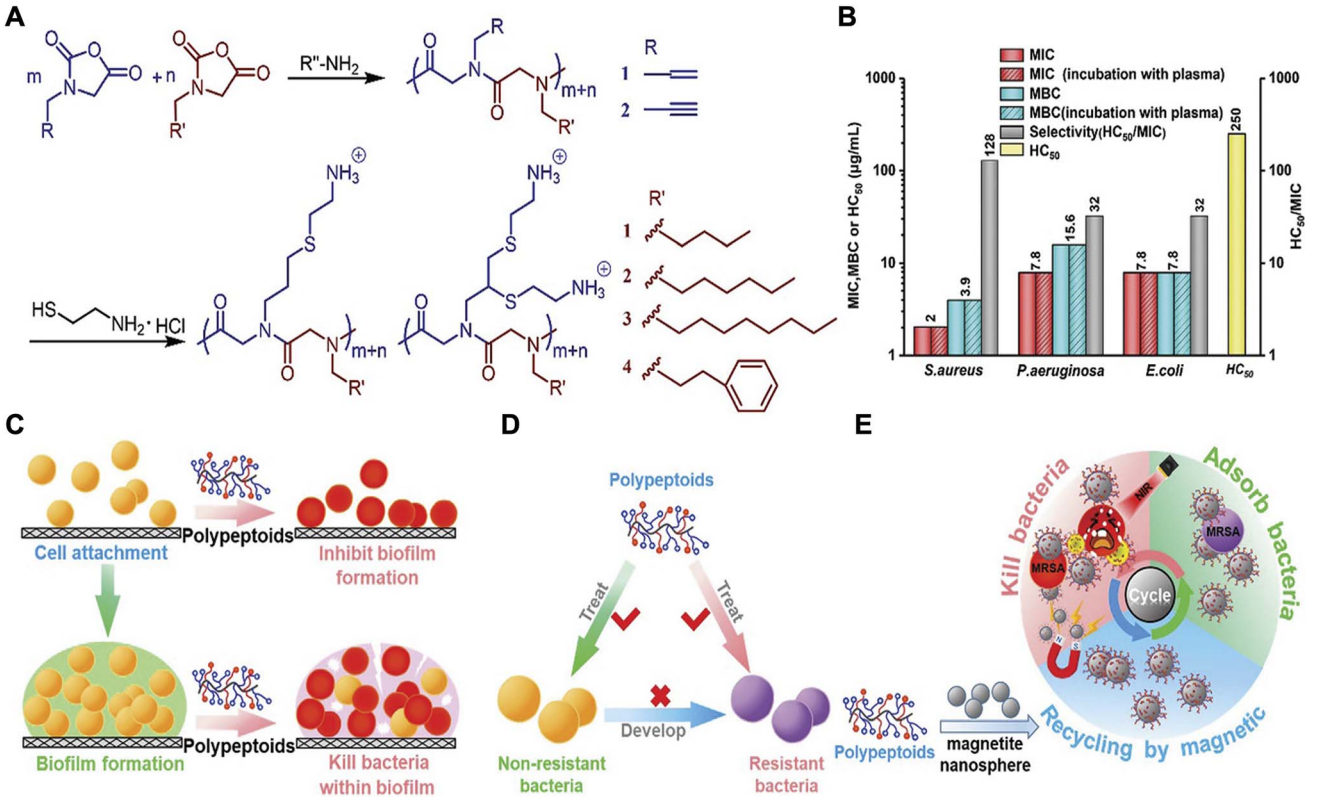


Fig. 20 Antimicrobial copolypeptoids with potent activity against drug-resistant bacteria and biofilms. (A) Synthesis of the cationic copolypeptoids. (B) The MIC/MBC values against *S. aureus*, *P. aeruginosa*, and *E. coli*, as well as the HC_{50} values of polypeptoids. (C) Antibiofilm activity of polypeptoids. (D) Potent activity against drug-resistant bacteria without visible resistance and cross-resistance after repeated usage. (E) Schematic representation of recycling antibacterial of polypeptoids coated FS nanospheres. Reproduced with permission from ref. 85. Copyright 2022, John Wiley and Sons.

exhibited broad-spectrum antimicrobial activity against drug-resistant bacteria, but low hemolysis and cytotoxicity (Fig. 23). The mode-of-action study revealed that its antibacterial activity was closely associated with bacterial membrane interaction. This study demonstrated the potential application of cyclic α-peptoids polymers in the antimicrobial field.

4.6 Star-like antibacterial α-peptoid polymers

Bonduelle *et al.* employed a dendritic macroinitiator (PAMAM) to synthesize star-like topology α-peptoid copolymers *via* ROP of *N*-protected-lysine-like NNCA and phenylalanine-like NNCA monomers.[88] The star-like α-peptoid polymers featured cationic side chains and broad-spectrum antimicrobial activity against multiple bacterial strains, including *Clostridium difficile*, *S. aureus*, *Listeria monocytogenes*, and *Enterococcus faecalis*, with MIC values ranging from 7.8–62.5 μg mL^{-1} (Fig. 24). Furthermore, structure–activity relationship studies revealed that their antibacterial performance could be modulated by fine-tuning hydrophobic content and the number of arms.

5. Current challenges and future directions

HDP-mimicking peptoids represent a promising class of antimicrobial agents, offering a potential alternative to conventional antibiotics for treating drug-resistant microbial infections. However, peptoids are typically prepared by stepwise solid-phase synthesis, which is time-consuming, cumbersome, difficult to scale up, and expensive. The development of polymerization chemistry has opened up new avenues for the preparation of peptoid polymers, and a variety of HDP-mimicking polymers have been synthesized by solution polymerization. These antimicrobial α-peptoid polymers exhibit potent activity against bacteria, especially drug-resistant bacteria, and demonstrate excellent *in vivo* therapeutic efficacy in multiple animal infection models. Despite significant progress in the development of HDP-mimicking α-peptoid polymers, their clinical applications still face several key challenges, including:

Currently, the diversity of monomers available for synthesizing HDP-mimicking α-peptoid polymers remains limited, with a particularly short of positively charged monomers. The existing cationic monomers are predominantly restricted to lysine-like structure,[18,88] and this structural limit severely constrains the molecular diversity of antimicrobial α-peptoid polymers. To address this limitation, future research should pay attention the development of positively charged monomers, such as those introducing secondary amines, tertiary amines, or imidazole in their side chain, to diversify the structure of α-peptoid polymers and thus obtain antimicrobial agents with

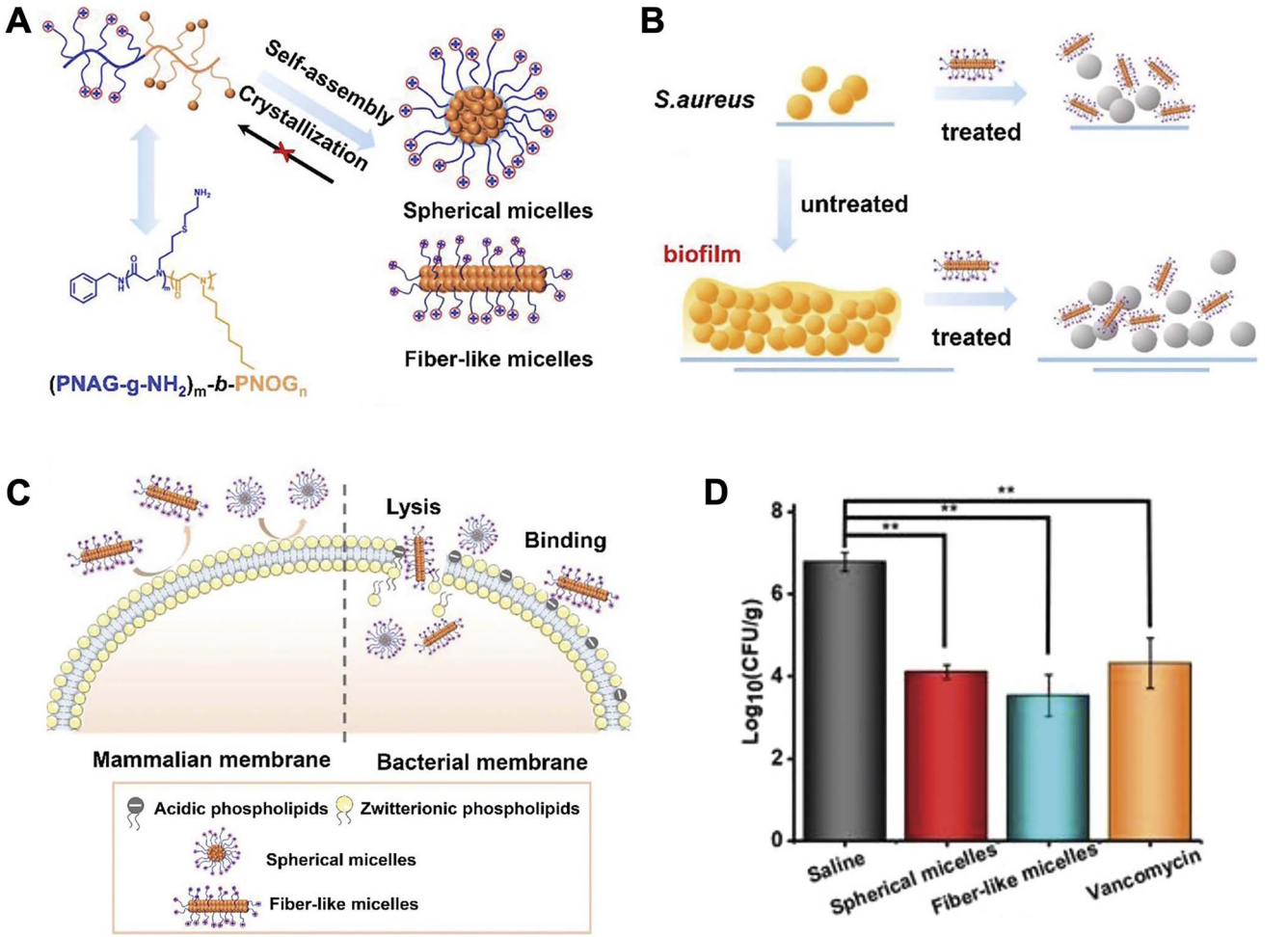


Fig. 21 The antimicrobial copolypeptoid assemblies. (A) Self-assembly of the cationic micelles. (B) Antibiofilm activity of the fiber-like micelles. (C) Illustration of the proposed antibacterial mechanism. (D) The bacteria load in infected tissues after treatment with fiber-like micelles, spherical micelles and vancomycin. Reproduced with permission from ref. 86. Copyright 2022, John Wiley and Sons.

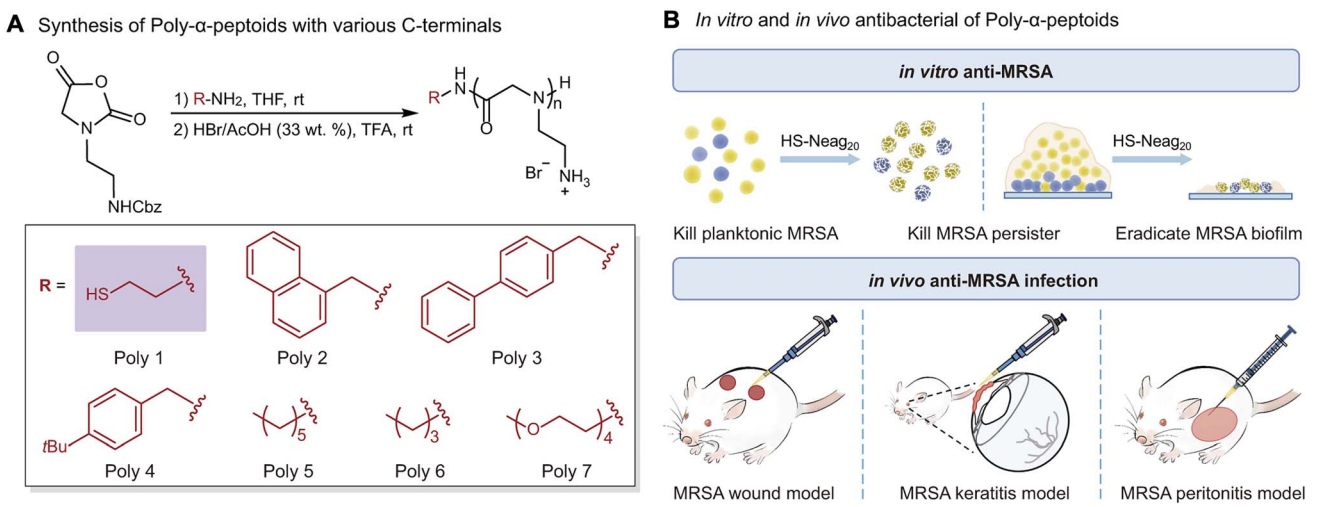


Fig. 22 Design and synthesis of α-peptoid polymers with anti-MRSA activity. (A) Design and synthesis of antibacterial α-peptoid polymers with various C-terminal functional groups. (B) Schematic illustration on the antibacterial performance of α-peptoid polymers, *in vitro* and *in vivo*. Reproduced with permission from ref. 18. Copyright 2021, Springer Nature.

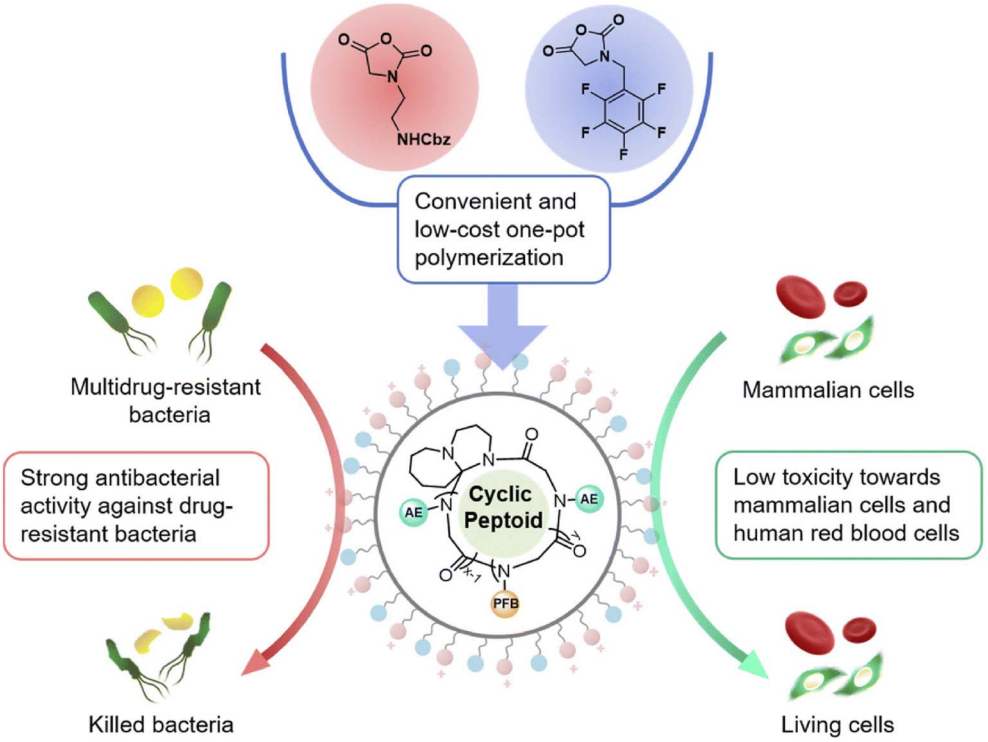


Fig. 23 Cyclic α-peptoid polymers displays potent activity against drug-resistant bacteria and low mammalian cell toxicity. Reproduced from ref. 87 with permission from the Royal Society of Chemistry.

potent activity and high selectivity. Notably, while α-peptoid polymers have demonstrated considerable potential as antibacterial agents, their application in antifungal therapy remains largely unreported. The expansion of structural diversity will promote the development of antifungals and even broad-spectrum antimicrobials.

Although the polymerization strategy of α-peptoid polymers offers advantages over solid-phase synthesis in terms of yield and chain length, several aspects warrant further investigation, including the optimization of reaction condition and large-scale production processes. Future breakthroughs may arise from the development of novel controlled polymerization, such as exploring novel initiators and catalysts, to enable efficient and rapid synthesis of high-molecular-weight α-peptoid polymers under mild conditions.

In vivo studies on antimicrobial α-peptoid polymers are limited, with their biosafety, immunogenicity, pharmacokinetics, and antibacterial mechanisms in complex physiological environments still unclear, hindering clinical translation. The systematic investigation on the *in vivo* therapeutic potential of α-peptoid polymers need to be carried out in the future to promote their translation from laboratory research to clinical applications. Furthermore, innovative *in vivo* application strategies could be explored to enhance therapeutic efficacy against drug-resistant microbial infections, including investigating synergistic effects between α-peptoid polymers and existing antibiotics and optimizing targeted delivery systems to infection sites by utilizing nanoparticle-based drug delivery platforms or stimuli-responsive antimicrobial materials.[89–91]

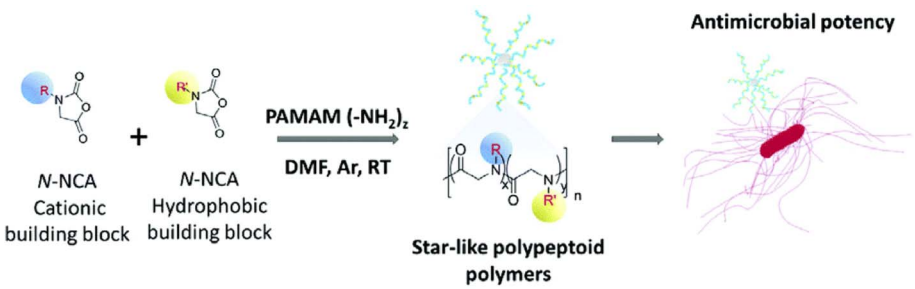


Fig. 24 Design and synthesis of antibacterial star-like α-peptoid polymers. Reproduced from ref. 88 with permission from the Royal Society of Chemistry.

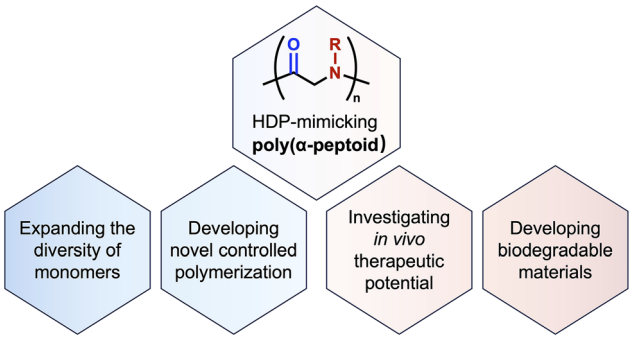


Fig. 25 Outlook on future developments of antimicrobial α-peptoid polymers.

Biodegradable antibacterial polymers represent promising materials for medical applications such as stents, implants, and wound dressings.[92–95] Future research could focus on the development of degradation-tunable design strategies, such as constructing peptide/peptoid hybrid polymers with tunable degradation rates or incorporating chemically labile bonds into peptoid backbones that can be specifically cleaved by the infection microenvironment.[96,97] By developing synthetic strategies and applications for biodegradable α-peptoid polymers, it is expected to maintain their antimicrobial activity while further improving other properties such as biocompatibility, thereby enhancing their potential for applications in medical devices and biomedicine.

It must be emphasized that the above challenges do not diminish the scientific value of antimicrobial α-peptoid polymers, but reveal the key scientific issues and technical bottlenecks that need to be address in this field (Fig. 25). α-Peptoid polymers, as representative natural peptide mimics, not only demonstrate unique advantages in terms of resistance to proteolysis, but also provide an expansive polymer prototype platform for developing novel antimicrobial agents with exceptional therapeutic potential. With continuous development of materials science, polymerization chemistry, and other disciplines, these biomimetic antimicrobial compounds are poised to achieve transformative breakthroughs across multiple fields, including novel antimicrobial materials and biomedical applications, thereby offering innovative solutions to address the global antibiotic resistance crisis.

Abbreviations

HDP	Host defense peptide
NNCA	*N*-Substituted *N*-carboxyanhydride
NNTA	*N*-Substituted *N*-thiocarboxyanhydride
NNPC	*N*-Phenoxycarbonyl *N*-substituted glycine
NCA	*N*-Carboxyanhydride
HCl	Hydrogen chloride
XAA	*S*-Ethoxythiocarbonyl mercaptoacetic acid
COS	Carbonyl sulfide
DPC	Diphenyl carbonate
MTBE	Methyl *tert*-butyl ether
ROP	Ring-opening polymerization
NHC	N-Heterocyclic carbene
DBU	1,8-Diazabicycloundec-7-ene
LiHMDS	Lithium hexamethyldisilazide
NAM	Normal amine mechanism
REP	Ring-expansion polymerization
DFT	Density functional theory
TMG	1,1,3,3-Tetramethylguanidine
PEG	Poly(ethylene glycol)
ZROP	Zwitterionic ring-opening polymerization
THF	Tetrahydrofuran
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
H_2S	Hydrogen sulfide
DMAc	*N*,*N*-Dimethylacetamide
NMP	*N*-Methylpyrrolidone
DAP	1,4-Dialkylpyrazine-2,5-diones
S. aureus	*Staphylococcus aureus*
E. coli	*Escherichia coli*
P. aeruginosa	*Pseudomonas aeruginosa*
S. haemolyticus	*Staphylococcus haemolyticus*
S. epidermidis	*Staphylococcus epidermidis*
E. faecium	*Enterococcus faecium*
A. baumannii	*Acinetobacter baumannii*
C. difficile	*Clostridium difficile*
L. monocytogenes	*Listeria Monocytogenes*
B. fragilis	*Bacteroides fragilis*
E. faecalis	*Enterococcus faecalis*
H. pylori	*Helicobacter pylori*
MRSA	Methicillin-resistant *Staphylococcus aureus*

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Author contributions

J. X.: visualization, investigation, writing – original draft, review & editing. W. H.: investigation. X. F.: investigation. Z. L.: investigation. M. Z.: investigation, writing – original draft, review & editing. R. L.: supervision, resources, funding acquisition, writing – review & editing, project administration.

Conflicts of interest

The authors declare that they have no competing interests.

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