Polymer Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Polym. Chem.*, 2022, **13**, 420

Facile synthesis of polypeptoids bearing bulky sidechains *via* urea accelerated ring-opening polymerization of α-amino acid *N*-substituted *N*-carboxyanhydrides†

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Received 2nd October 2021,
Accepted 6th December 2021

DOI: 10.1039/d1py01324f

rsc.li/polymers

Polypeptoids, as synthetic mimics of polypeptides, exhibit a variety of biological functions and excellent proteolytic stability. Polypeptoids can be synthesized by the ring-opening polymerization of α-amino acid *N*-substituted *N*-carboxyanhydrides (NNCAs); however, they suffer from the generally slow reactivity and poor stability of NNCAs, especially those with bulky substitutes. This long-standing challenge greatly limits the synthesis of polypeptoids with diverse structures. Herein, we found that commercially available 1,3-bis [3,5-bis(trifluoromethyl)phenyl]urea can greatly accelerate the primary amine-initiated ring-opening polymerization of NNCAs by activating the NNCA carbonyl *via* hydrogen bonding interactions. Urea-catalyzed NNCA polymerization is compatible with diverse NNCAs in preparing polypeptoids with variable polymer lengths and narrow dispersity and is especially suitable for inactive NNCAs bearing bulky *N*-substitutes, such as cyclohexyl-NNCA. This urea-catalyzed NNCA polymerization strategy will substantially increase the structural diversity and functional study of polypeptoids, implying wider and diverse applications of these polypeptide mimics.

Introduction

Polypeptoids represent a type of polypeptide mimics with a backbone composed of *N*-substituted glycine, which overcomes peptides' shortcoming of poor enzyme stability.[1] They have been actively studied in the fields of antibacterial agents,[2–4] drug and gene delivery,[5–7] tissue engineering,[8] antifouling,[9–11] and heat-responsive materials,[12,13] which exhibit their great potential in applications. Polypeptoids were prepared by the ring-opening polymerization of α-amino acid *N*-substituted *N*-carboxyanhydrides (NNCAs).[14–18] The functional study of polypeptoids involves the diverse functional groups of NNCAs.[19,20] In exploring host defense peptide mimicking antimicrobial polypeptides,[21–25] it was found that hydrophobic residues, such as the bulky cyclohexyl group, are critical in defining the antimicrobial activity and cytotoxicity of antimicrobial polypeptides.[26,27] However, currently only *N*-methyl glycine *N*-carboxyanhydride (sarcosine-NCA) is widely used to prepare polypeptoids using various polymerization strategies[28–31] due to the poor reactivity especially for NNCAs bearing bulky side chains like cyclohexyl.[32] To address this long-standing challenge, we recently reported the fast polymerization of NNCAs to prepare polypeptoids using Li/Na/KHMDS as the initiator.[32] Related advances have been used to initiate superfast and moisture-insensitive polymerization of α-amino acid *N*-carboxyanhydrides (NCAs) to prepare polypeptides.[33–35]

Among all strategies for polymerization of NNCAs, primary amines are the dominantly used initiators for ring-opening polymerization of NNCAs to prepare polypeptoids.[36–42] The merit of primary amine initiators lies in the easy introduction of diverse functional groups into the C-termini of polypeptoids *via* the initiators. Thus, we turn our attention to accelerating primary amine-initiated polymerization of NNCAs, especially for NNCAs bearing bulky side chains and with poor reactivity for polymerization. It has been reported that organocatalysts can accelerate polymerization reactions through hydrogen bonding interactions, thus enabling the preparation of polymers with controllable molecular weight and narrow distribution.[43–47] Specifically, this strategy has been used to activate NCAs to achieve fast polymerization using

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/d1py01324f

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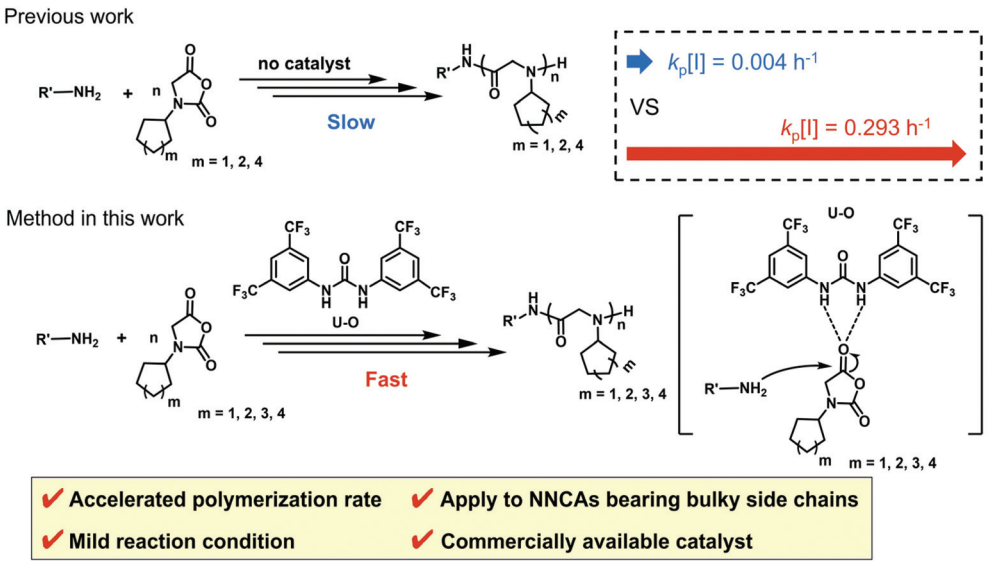
organocatalysts.[48,49] Inspired by these precedent studies, herein we explored commercially available 1,3-bis(3,5-bis(trifluoro-ethyl)phenyl)thiourea (TU–S) and 1,3-bis[3,5-bis(trifluoromethyl)phenyl]urea (U–O) as organocatalysts for primary amine-initiated NNCA polymerization and found that this strategy greatly accelerates the reaction *via* hydrogen bonding with the NNCA carbonyl and results in rapid ring-opening polymerization of NNCAs, even those bearing bulky side chains, to prepare polypeptoids efficiently (Scheme 1).

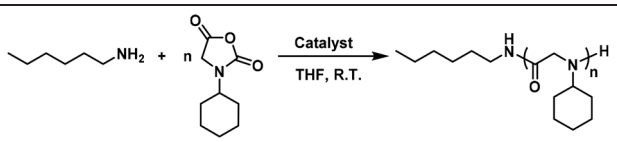
Results and discussion

Using *N*-cyclohexyl glycine *N*-carboxyanhydride (cyclohexyl-NNCA) as a model, we found that the ring-opening polymerization of NNCA was very slow using a primary amine, *n*-hexylamine, as the initiator. The polymerization took 7 days to prepare a polymer with a chain length of 20, and took a much longer time to prepare polypeptoids with longer chain lengths (Table 1, entry 1). Using TU–S as the organocatalyst at a concentration of 1/5 that of the NNCA monomer, the ring-opening polymerization of cyclohexyl-NNCA was greatly accelerated to complete within 22 hours and gave polypeptoids at about 20-mer in tetrahydrofuran (THF). However, the GPC trace of the resulting polypeptoid showed a shoulder (Table 1, entry 2, GPC trace in Fig. S1†). So, we continued to examine the urea catalyst U–O for its ability to accelerate the polymerization of NNCAs. We found that U–O, at a concentration of 1/5 that of the NNCA monomer, has superior performance in accelerating the polymerization of NNCA, and reduces the polymerization time from 7 days to 5 hours (Table 1, entry 3). In addition, using U–O as the catalyst, we obtained polypeptoids with



Scheme 1 Primary amine-initiated polymerization of NNCAs bearing bulky side chains, with and without using U–O as the catalyst.

Table 1 The *n*-hexylamine-initiated ring-opening polymerization of cyclohexyl-NNCA[a]



Entry	Catalyst	[M] : [I] : [Cat]	Time	$M_{n,calcd}$ (g mol^{-1})	$M_{n,SEC}$[b] (g mol^{-1})	$Đ$[b]
1	None	20/1/0	7 days	2900	2900	1.24
2[c]	TU–S	20/1/4	22 h	2900	3000	1.20
3	U–O	20/1/4	5 h	2900	3400	1.20
4	U–O	10/1/1	5 h	1500	1900	1.13
5	U–O	20/1/1	7 h	2900	3400	1.20
6	U–O	50/1/2.5	12 h	7100	6500	1.14
7	U–O	100/1/5	16 h	14 000	9700	1.22
8	U–O	200/1/10	21 h	27 900	14 000	1.20

[a] The *n*-hexylamine-initiated ring-opening polymerization of cyclohexyl-NNCA in THF catalyzed by TU–S or U–O ($[M]_0$ = 1 M). [b] All polypeptoids were characterized by gel permeation chromatography (GPC) using 0.01 M LiBr in DMF as the mobile phase at a flow rate of 1 mL min^{-1} at 50 °C. $M_{n,SEC}$ is the number-average molecular weight. $Đ$ is the dispersity index. [c] GPC curve indicates a shoulder.

expected polymer lengths, a narrow dispersity ($Đ$ = 1.20), and a monomodal distribution without shoulder (Fig. S2†). The observation that U–O showed better catalytic performance in NNCA polymerization than did TU–S is probably owing to the stronger electrophilicity of the oxygen atom in U–O than that of the sulfur atom in TU–S, resulting in a stronger hydrogen bonding interaction between U–O and the carbonyl in the NNCA ring.[50]

The catalytic performance of U–O in accelerating the ring-opening polymerization of cyclohexyl-NNCA was evaluated using polymerization kinetics obtained from HPLC analysis. The polymerization kinetics indicated a very slow ring-opening polymerization of cyclohexyl-NNCA initiated by *n*-hexylamine with M/I = 50 at an NNCA concentration of 1 M in THF, having the k_p[I] value of 0.004 h^{-1} (Fig. 1). Slow polymerization was due to the weak nucleophilicity of the reactive center, an *N*-cyclohexyl substituted secondary amine having steric hindrance for continuous nucleophilic addition. We also investigated how the equivalent of U–O relative to the NNCA monomer affects the polymerization rate. The addition of 5% U–O into the polymerization of cyclohexyl-NNCA accelerated the reaction substantially, with the k_p[I] value increasing from 0.004 h^{-1} (without catalyst) to 0.293 h^{-1}. Increasing the amount of U–O catalyst to 10% and 20% relative to the cyclohexyl-NNCA moderately increased the polymerization rate further to have a k_p[I] value of 0.362 h^{-1} and 0.403 h^{-1}, respectively (Fig. 1). These studies demonstrated that U–O has superior performance in catalyzing primary amine-initiated NNCA polymerization to greatly accelerate the polymerization rate of inactive NNCAs up to 100 fold.

U–O catalyzed ring-opening polymerization of cyclohexyl-NNCA using *n*-hexylamine as the initiator can prepare polypeptoids with variable chain lengths. With an NNCA-to-initiator ratio of 10, the cyclohexyl-NNCA monomers were completely converted to polypeptoids in 5 hours at room temperature with the desired molecular weight (M_n = 1900 g mol^{-1}) and narrow dispersity at $Đ$ = 1.13 (Table 1, entry 4). When the monomer-to-initiator ratio was gradually increased from 20 to 200, the obtained polypeptoids have incrementally increased molecular weight (M_n = 3400–14 000 g mol^{-1}) and narrow dispersities ($Đ$ = 1.14–1.22, Table 1, entries 5–8). All the obtained polypeptoids exhibited sharp and monomodal GPC traces (GPC traces in Fig. S3–S7†). This observation echoes the importance of exploring a new synthetic strategy to greatly accelerate the polymerization of NNCAs in preparing polypeptoids with variable molecular weights.[32] When monomer-to-initiator ratios of 100 and 200 were used, we observed a lower M_n than the theoretical value, possibly due to intramolecular transamidation in the polymerization process as reported in the precedent literature as a side reaction in the polymerization of NNCA.[14,51]

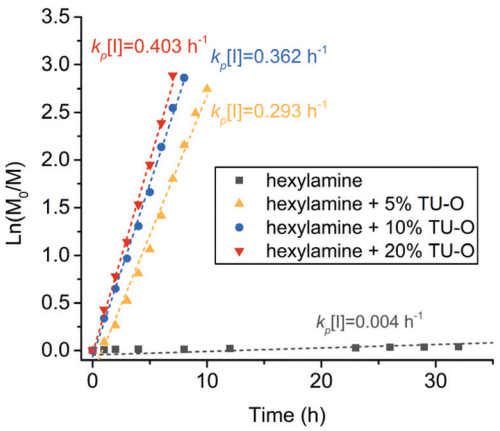


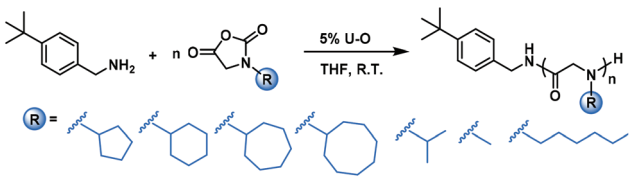
Fig. 1 Polymerization kinetics of *n*-hexylamine-initiated polymerization of cyclohexyl-NNCA catalyzed by different amounts of U–O in THF at room temperature ([M] : [I] = 50 : 1, $[M]_0$ = 1 M).

To test the substrate compatibility of this U–O catalyzed polymerization on NNCA, we further examined NNCAs bearing various side chain groups, such as *N*-cyclopentyl glycine *N*-carboxyanhydride (cyclopentyl-NNCA), *N*-cycloheptyl glycine *N*-carboxyanhydride (cycloheptyl-NNCA), *N*-cyclooctyl glycine *N*-carboxyanhydride (cyclooctyl-NNCA) and *N*-isopropyl glycine *N*-carboxyanhydride (isopropyl-NNCA). U–O substantially accelerated the polymerization of these NNCAs to complete within 9–12 hours (Table 2, entries 1–5, GPC traces in Fig. S8–S12†). For the polymerization of even more bulky *N*-*tert*-butyl glycine *N*-carboxyanhydride (*tert*-butyl-NNCA), only oligomers were obtained, which was likely because the great steric hindrance of the *tert*-butyl group substantially reduces the nucleophilicity of the secondary amine reactive center (Table S2 and Fig. S17†). We also tested U–O catalyzed polymerization of NNCAs bearing less bulky side chains, sarcosine-NCA and *N*-hexyl glycine *N*-carboxyanhydride (hexyl-NNCA), and observed very quick completion of polymerization within 10 min and 30 min for sarcosine-NCA and hexyl-NNCA, respectively (Table 2, entries 6 and 7, GPC traces in Fig. S13 and S14†). These studies indicated that U–O is compatible with NNCAs in preparing polypeptoids with diverse side chains.

The superior performance of U–O catalyzed NNCA polymerization to prepare polypeptoids encouraged us to explore the mechanism. We proposed that U–O activated the carbonyl group on the 5 position of the NNCA monomer *via* hydrogen bonding, which made NNCA more susceptible to be attacked by nucleophilic amines and realized the rapid ring-opening polymerization of NNCA (Scheme 2). In the chain initiation step, primary amine initiators nucleophilically attack the NNCA C5 carbonyl and generate the intermediate which is a secondary amine and act as the reactive center for continuous propagation. In the further chain propagation step, a secondary amine bearing a bulky cyclohexyl substituent acts as the reactive center and has significantly lower nucleophilicity to NNCAs than does the primary amine initiator (Scheme 2).

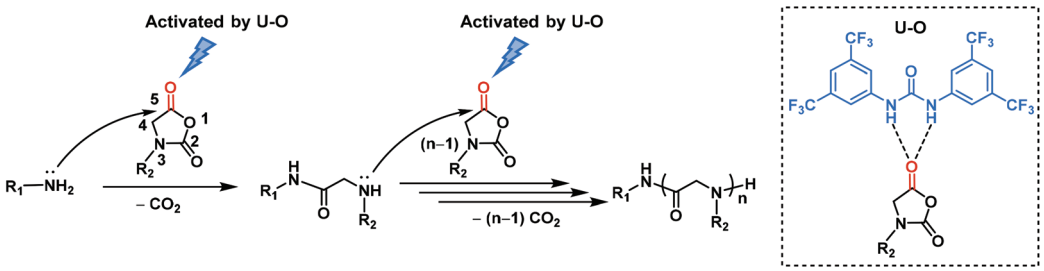
To explore the initiation step, we closely examined the 1 : 1 molar ratio mixture of an initiator *tert*-butylbenzylamine and cyclohexyl-NNCA. High resolution electrospray ionization mass spectroscopy (HRESI-MS) showed a characteristic peak at m/z 303.2432, referring to the active species in the initiation

Table 2 The *tert*-butylbenzylamine-initiated ring-opening polymerization of NNCAs bearing various *N*-substituted groups[a]



Entry	Monomer	[M] : [I] : [Cat]	Time	$M_{n,calcd}$ (g mol^{-1})	$M_{n,SEC}$[b] (g mol^{-1})	$Đ$[b]
1	Cyclopentyl-NNCA	20/1/1	10 h	2700	2500	1.27
2	Cyclohexyl-NNCA	20/1/1	10 h	2900	3400	1.21
3	Cycloheptyl-NNCA	20/1/1	11 h	3200	3400	1.21
4	Cyclooctyl-NNCA	20/1/1	12 h	3500	2700	1.25
5	Isopropyl-NNCA	20/1/1	9 h	2100	2700	1.14
6	Sarcosine-NCA	20/1/1	10 min	1600	1400	1.20
7	Hexyl-NNCA	20/1/1	30 min	3000	2900	1.21

[a] The ring-opening *tert*-butylbenzylamine-initiated polymerization of NNCAs bearing various *N*-substituted groups catalyzed by 5% U–O (molar ratio, $[M]_0$ = 1 M) in THF at room temperature. [b] All polypeptoids were characterized by GPC using 0.01 M LiBr in DMF as the mobile phase at a flow rate of 1 mL min^{-1} at 50 °C. $M_{n,SEC}$ is the number-average molecular weight. $Đ$ is the dispersity index.



Scheme 2 Proposed mechanism of primary amine-initiated ring-opening polymerization of NNCA catalyzed by U–O.

step, which supported our proposed mechanism in the chain initiation step (Fig. 2a). We also characterized the final polypeptoid obtained from the polymerization of cyclohexyl-NNCA using ^{1}H NMR spectroscopy, and found the characteristic peaks correlating to the *tert*-butylbenzyl group, which echoes the above conclusion that the polymerization is initiated *via* the nucleophilic addition of a primary amine initiator to the NNCA ring and incorporation of a C-terminal functional group by the primary amine (Fig. 2b). Moreover, the existence of *tert*-butylbenzyl terminal groups and cyclohexyl-NNCA residue repeating units was clearly identified in the characterization using matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectroscopy (Fig. 3). All these studies indicated that U–O catalyzed NNCA polymerization follows the normal amine mechanism (NAM).[52] We hypothesize that adding U–O into the NNCA polymerization reaction will not change the mechanism, but could activate NNCAs to facilitate the nucleophilic attack step and achieve rapid polymerization.

As aforementioned, the addition of U–O significantly increased the polymerization rate of NNCAs bearing bulky substituents, using primary amine as the initiator. This observation encouraged us to determine the catalytic mechanism of U–O using NMR spectroscopy and density functional theory (DFT) calculation. A close comparison of the ^{1}H NMR spectra of U–O and U–O/cyclohexyl-NNCA mixture revealed that the N–H on U–O shifts downfield from 7.67 ppm to 7.73 ppm due to the hydrogen bonding interaction between U–O and cyclohexyl-NNCA, as we proposed (Fig. 4). The ^{13}C NMR spectroscopy revealed that both carbon atoms on the NNCA C5 carbonyl and C2 carbonyl shift downfield slightly after adding U–O as the catalyst (Fig. S16†). This result indicates that U–O could activate both carbonyl groups on the NNCA monomer. Nevertheless, the NNCA C5 carbonyl is more easily attacked by nucleophiles than is the C2 carbonyl due to the higher electrophilicity of the C5 carbonyl. Furthermore, the geometry-optimized structure of U–O and cyclohexyl-NNCA in THF was obtained using DFT calculation, which suggested that U–O served as a hydrogen bond donor to form two hydrogen bonds with one cyclohexyl-NNCA C5 carbonyl with an average hydrogen bond length of 3.10 Å (Fig. 5). The structure also featured a prolongation of the C=O bond in cyclohexyl-NNCA induced by the hydrogen bonds. Furthermore, the binding energy of U–O and cyclohexyl-NNCA (ΔE = −7.26 kcal mol^{-1}) in THF suggested that the hydrogen bonds are medium strength hydrogen bonds.[53] These studies revealed that U–O activates the cyclohexyl-NNCA monomer through hydrogen bonding interaction to increase its reactivity as an electrophile and accelerate the polymerization of NNCA. DFT calculation also

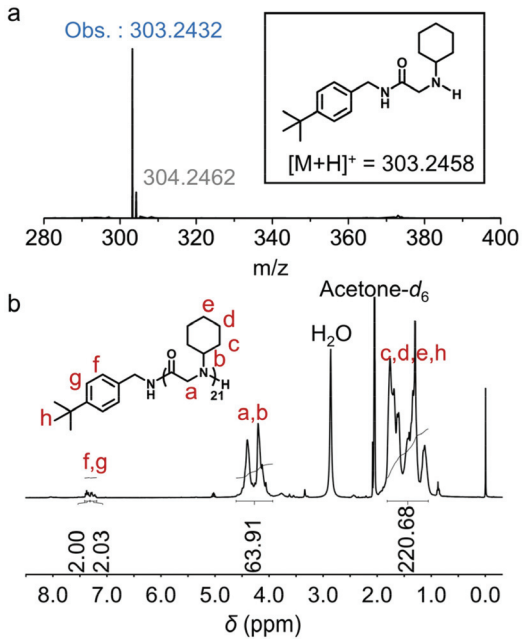


Fig. 2 (a) HRESI-MS analysis of cyclohexyl-NNCA and *tert*-butylbenzylamine at the molar ratio of 1 : 1 with 5% U–O (molar ratio) in THF ($[M]_0$ = 0.5 M). The peak of *m*/*z* = 304.2462 belongs to the isotope peak. (b) ^{1}H NMR spectrum of polypeptoid synthesized from *tert*-butylbenzylamine-initiated polymerization of cyclohexyl-NNCA catalyzed by 5% U–O in THF at room temperature ([M]/[I] = 20, $[M]_0$ = 1 M).

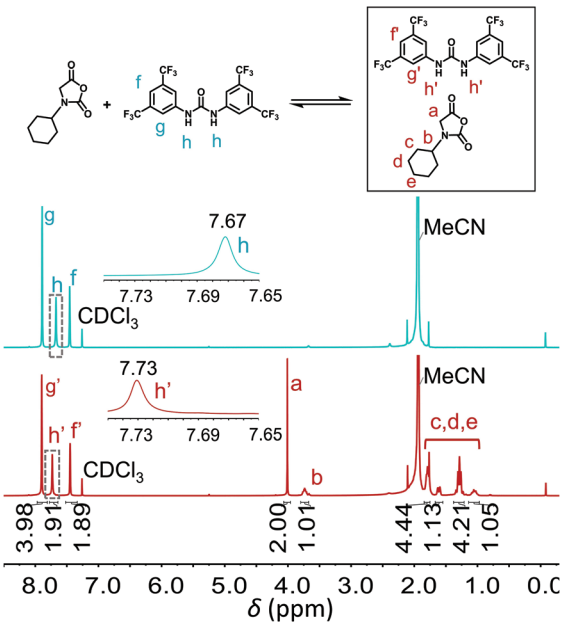


Fig. 4 Comparison of ^{1}H NMR spectra for U–O only and cyclohexyl-NNCA mixed with U–O (1 : 1, molar ratio), in $CDCl_3$/MeCN ($CDCl_3$: MeCN = 85 : 15, v/v).

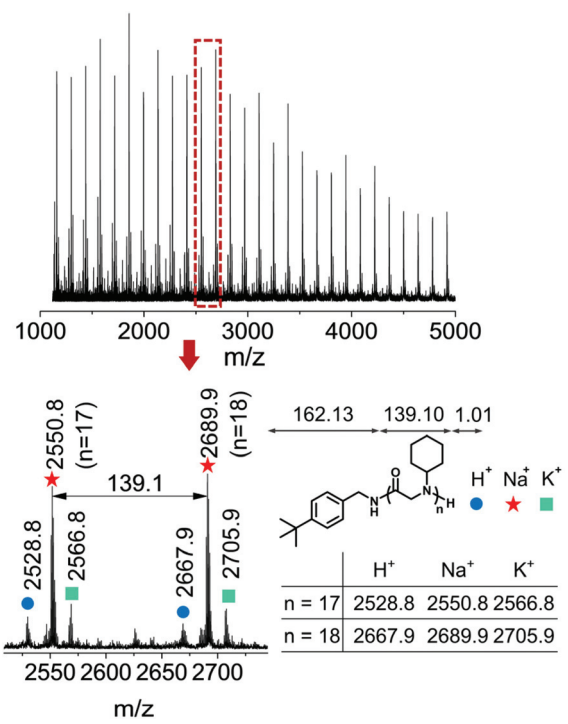


Fig. 3 MALDI-TOF-MS characterization of polypeptoid prepared from *tert*-butylbenzylamine-initiated polymerization of cyclohexyl-NNCA catalyzed by 5% U–O (molar ratio) in THF at room temperature ([M]/[I] = 20, $[M]_0$ = 1 M). Detailed analysis is shown in Fig. S15.†

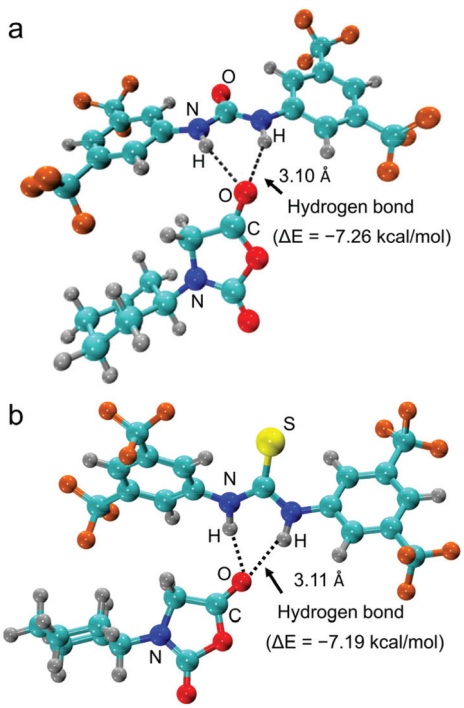


Fig. 5 The DFT-optimized geometry structure showing the hydrogen bonding interaction between (a) U–O and cyclohexyl-NNCA in THF (silver: H, cyan: C, blue: N, red: O, and brown: F), (b) TU–S and cyclohexyl-NNCA in THF (silver: H, cyan: C, blue: N, red: O, yellow: S and brown: F).

revealed that the hydrogen bonding interaction of TU–S and cyclohexyl-NNCA (ΔE = −7.19 kcal mol^{-1}) was slightly lower than that of U–O and cyclohexyl-NNCA (ΔE = −7.26 kcal mol^{-1}), which is probably caused by the oxygen atom in U–O being more electrophilic than the sulfur atom in TU–S. This result is consistent with the experiment wherein both TU–S and U–O exhibited excellent catalytic performance in speeding up NNCA polymerization and could reduce the polymerization time of cyclohexyl-NNCA ([M]/[I] = 20) from 7 days to 22 hours and 5 hours, respectively (Table 1, entries 2 and 3).

Conclusions

Polypeptoids have attracted more and more attention as a class of polypeptide mimics for diverse applications and are prepared from the ring-opening polymerization of NNCAs. The generally slow reactivity and poor stability of NNCAs greatly limit the synthesis of polypeptoids with diverse structures and applications. Currently, the *N*-methyl glycine *N*-carboxyanhydride (sarcosine-NCA) is dominantly used because sarcosine-NCA is the least bulky *N*-substitute NNCA to undergo easy polymerization. However, it is a long-standing challenge to prepare polypeptoids with diverse structures from NNCAs with bulky substitutes. In this study, we report a fast NNCA polymerization strategy using primary amine as the initiator and 1,3-bis[3,5-bis(trifluoromethyl)phenyl]urea as the catalyst. The use of urea catalyst greatly accelerates the reaction rate of the polymerization by activating the carbonyl in the NNCA ring *via* hydrogen bonding interactions, without changing the NAM mechanism for NNCA polymerization. This fast polymerization strategy is compatible with diverse NNCAs, including bulky *N*-substituted NNCAs, to prepare polypeptoids that are otherwise inaccessible without using the catalyst. The use of a commercially available urea catalyst and compatibility with diverse NNCAs together imply the great potential of this strategy in fast NNCA polymerization to prepare polypeptoids for a variety of applications.

Author contributions

K. C., Y. W. and R. L. conceived the idea, proposed the strategy, designed the experiments, evaluated the data, and wrote the manuscript together. K. C. performed the majority of the experiments. X. W. performed DFT calculation and evaluated the data. M. Z. participated in NNCA synthesis and initial polymerization tests. R. Z. participated in HPLC analysis. J. W. participated in NNCA synthesis. X. X. conducted the MALDI-TOF assay. Y. Y. participated in data analysis. All the authors proofread the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (No. 22075078, 21774031, 21861162010, 31800801), Program of Shanghai Academic/Technology Research Leader (20XD1421400), Research Program of State Key Laboratory of Bioreactor Engineering, and the Fundamental Research Funds for the Central Universities (JKD01211520). We also thank the staff members of the Mass Spectrometry System at the National Facility for Protein Science in Shanghai (NFPS), Zhangjiang Lab, China for providing technical support and assistance in data collection and analysis.

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