Organocatalytic Ring-opening Polymerization of N-Acylated-1,4-oxazepan-7-ones Towards Well-defined Poly(ester amide)s: Biodegradable Alternatives to Poly(2-oxazoline)s

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Experimental Details

Materials
All operations of air- and moisture-sensitive chemicals and materials were carried out in flamed Schlenk-type glassware under an argon atmosphere or in an argon-filled glovebox. 4-piperidone monohydrate hydrochloride (98.0%), acetyl chloride (98%), butyryl chloride (≥99.0%), phenylacetyl chloride (98.0%), benzoyl chloride (99.0%), potassium carbonate (≥99.0%), benzyl alcohol (BnOH, anhydrous, 99.8%) and m-chloroperoxybenzoic acid (m-CPBA, ≤77.0%) were supplied by the Aldrich Chemicals. 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, 98.0%, Aldrich) was purified by distillation over CaH₂ and then stored in the glovebox for use. 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD, 98.0%, Aldrich) was dried via vacuum oven under 40 °C for 24 h prior to use. 1-(3,5-Bis(trifluoromethyl)phenyl)-3-cyclohexyl thiourea (TU) was synthesized according to the literature method.² Chloroform-d (CDCl₃, "100%", 99.96 atom % D, contains 0.03 % (v/v) TMS, Aldrich) was dried over activated Davison 4 Å molecular sieves. ε-Caprolactone (ε-CL, 97.0%, Aldrich) and dichloromethane were distilled over CaH₂ and then stored in the glovebox for use. All other chemicals were purchased from Aldrich Chemicals and used as received unless otherwise stated.

Characterizations
Nuclear magnetic resonance (¹H NMR and ¹³C NMR) measurements were recorded on a Bruker AVANCE III-400 or 500 MHz instruments. All NMR spectra were taken in CDCl₃ unless otherwise stated. For POxPₚₚ, POxPₚᵦ, and PCL, size exclusion chromatography (SEC) analyses were performed using THF as an eluent at a flow rate of 1.0 mL min⁻¹ on a VISCOTEK VE2001 system equipped with PSS columns (Styragel HR 2 and 4). The number-average molecular weights (MₙSEC) and the molecular weight distribution (Mₘ/Mₙ, η) were obtained by conventional SEC analysis with a calibration curve constructed from polystyrene standards. For POxPₘₑᵦ, SEC was performed in DMF at a flow rate of 1.0 mL min⁻¹ on an Agilent liquid chromatography system fitted with refractive index (RID) and UV-Vis detectors, using two identical Agilent PLgel-M (5 µm) columns in connected series and an Agilent PLgel precolumn (10 µm). The column and flow path temperatures were controlled at 35°C. Data analysis was performed using SEC-Addon for ChemStation software from Agilent. Matrix-assisted laser desorption ionization time-of-flight
(MALDI-TOF) mass spectra were recorded in the linear mode by using trans-2-[3-(4-t-butyl-phenyl)-2-methyl2-phenylidene]malononitrile (DCTB) as the matrix in THF (sample/matrix: 1:10) and sodium trifluoroacetate (10 mg/ml in methanol) as an ionizing agent. Fourier transform infrared (FT-IR) spectra were recorded with a NICOLET iS10 FT-IR instrument. Differential scanning calorimetry (DSC) measurements were performed using a Mettler Toledo DSC1/TC100 IntraCooler system under an inert atmosphere (nitrogen). Scans were recorded at a heating and cooling rate of 10 °C min⁻¹ from -40 to +100 °C. The sample size was about 3-7 mg.

**General experimental procedures**

**Synthesis of monomers**

To a solution of 4-piperidone monohydrate hydrochloride (3.07 g, 20.0 mmol) in dichloromethane (DCM, 100 ml), potassium carbonate (8.08 g, 58.6 mmol) was added. After 5 minutes of stirring, the addition of acetyl chloride or butyryl chloride or phenylacetyl chloride or benzoyl chloride (39.04 mmol) proceeded at room temperature. The mixture was stirred for 16 h. The reaction was then quenched with 1M NaOH (60 ml) and then extracted with DCM (3 × 20 ml). The combined organic layers were dried over MgSO₄, filtered, and concentrated. The obtained yellow oil was used for the next step without purification. The resultant corresponding N-acylated-4-piperidone crude product (20.6 mmol) in 50 ml DCM was placed in a 250 mL round bottom flask with a stir bar. The m-CPBA (6.18 g, 30.9 mmol) was then slowly dropwise into the flask at 0 °C under stirring. The reaction was stirred for 24 hours at room temperature. The reaction solution was then washed with NaHCO₃, and NaCl saturated solution sequentially. The obtained solution was dried over anhydrous MgSO₄. After filtration, the solvent was concentrated by rotavapor. The crude product was purified by silica gel column chromatography (petroleum ether (PE): ethyl acetate (EA) = 5: 1).

**4-acetyl-1,4-oxazepan-7-one (OxPMe):** Yield: 1.2 g (37.5%); FTIR (v, cm⁻¹): 1735.76, 1642.71 (C=O); ¹H NMR (500 MHz, CDCl₃, δ, ppm): 2.15 and 2.18 (2s, 3H, -NCOCH₃), 2.80-2.87 (m, 2H, -CH₂COO-), 3.66-3.96 (m, 4H, -NCH₂-, -CH₂N-), 4.25-4.31 (m, 2H, -COOCH₂-); ¹³C NMR (126 MHz, CDCl₃, δ, ppm): 21.54, 21.88, 36.89, 37.91, 38.67, 43.66, 45.51, 50.23, 68.95, 69.52, 169.32, 169.39, 173.10 and 173.50. Because of restricted
rotation of the amide bond, the NMR signals appear as doublets, see Figure S2. MS (EI) m/z: [M]+
Calculated for C7H11NO3 157.074; Found 157.080.

4-butyryl-1,4-oxazepan-7-one (OxPPr): Yield: 1.4 g (37.8%); FTIR (ν, cm⁻¹): 1727.54, 1635.99 (C=O); ¹H NMR (500 MHz, CDCl₃, δ, ppm): 0.96 (t, 3H, -CH₃), 1.66 (m, 2H, -CH₂CH₃), 2.34 (m, 2H, -NCOCH₂-), 2.79-2.84 (m, 2H, -CH₂COO-), 3.66-3.95 (m, 4H, -NCH₂-, -CH₂N-), 4.24-4.28 (m, 2H, -COOCH₂-); ¹³C NMR (126 MHz, CDCl₃, δ, ppm): 13.75, 18.48, 34.88, 35.19, 36.63, 37.62, 38.37, 42.42, 45.27, 49.00, 68.78, 69.28, 171.63, 171.66, 173.12 and 173.49. Because of restricted rotation of the amide bond, some NMR signals appear as doublets, see Figure S4. MS (EI) m/z: [M]+ Calculated for C₉H₁₅NO₃ 185.105; Found 185.114.

4-benzoyl-1,4-oxazepan-7-one (OxPPh): Yield: 2.3 g (52.3%); FTIR (ν, cm⁻¹): 1716.22, 1620.86 (C=O); ¹H NMR (500 MHz, CDCl₃, δ, ppm): 2.76 (m, 2H, -CH₂COO-), 3.59-3.95 (m, 4H, -NCH₂-, -CH₂N-), 4.24 (m, 2H, -COOCH₂-); 7.31-7.40 (m, 5H, phenyl); ¹³C NMR (126 MHz, CDCl₃, δ, ppm): 37.07, 39.03, 44.29, 45.76, 50.88, 68.74, 126.79, 128.66, 130.11, 134.75, 170.90 and 173.24. Because of restricted rotation of the amide bond, some NMR signals appear as doublets, see Figure S6. MS (EI) m/z: [M]+ Calculated for C₁₂H₁₃NO₃ 219.090; Found 219.153.

4-(2-phenylacetyl)-1,4-oxazepan-7-one (OxPBn): Yield: 2.6 g (56.7%); FTIR (ν, cm⁻¹): 1714.65, 1633.15 (C=O); ¹H NMR (500 MHz, CDCl₃, δ, ppm): 2.39 and 2.73 (2t, 2H, -CH₂COO-), 3.62-4.19 (m, 6H, -NCH₂-, -CH₂Ph, -CH₂N-), 7.22-7.36 (m, 5H, phenyl); ¹³C NMR (126 MHz, CDCl₃, δ, ppm): 36.64, 37.18, 38.88, 41.26, 41.46, 43.27, 45.65, 49.80, 68.53, 69.18, 127.28, 128.39, 128.42, 128.71, 129.09, 134.35, 169.79, 169.91, 173.03 and 173.46. Because of restricted rotation of the amide bond, some NMR signals appear as doublets, see Figure S8. MS (EI) m/z: [M]+ Calculated for C₁₂H₁₃NO₃ 233.105; Found 233.121.

General procedure for organocatalytic ring-opening polymerization
A typical homopolymerization procedure (monomer OxPMe, Table 1, entry 5) is given below: In an argon-filled glovebox, TBD (8.4 mg, 0.06 mmol), TU (66.6 mg, 0.18 mmol) in 1.0 mL DCM and a stir bar were placed in a Schlenk tube. After 10 minutes, BnOH (6.2 µL, 0.06 mmol), and OxPMe (0.28 g, 1.8 mmol) in 1.0 mL DCM was added to the mixture to start the polymerization. The mixture was stirred for 1 h at room temperature under argon atmosphere. The polymerization
was quenched by the addition of an excess of acetic acid. The whole polymerization was monitored by $^1$H NMR. The quenched reaction mixture was concentrated to get the crude product. 2 mg of crude product was obtained in DMF and passed through a 0.22 µm filter to determine $M_n$, SEC and $D$ by SEC. The crude product was dissolved in 1 mL dichloromethane and dialyzed against MeOH overnight with a dialysis membrane (1 kDa MWCO, Spectra/Por® 7) to obtain the pure polymer.

**Kinetics Experiments**

In the argon-filled glovebox, TBD and TU in DCM were firstly added sequentially into a series of 6 mL vials. Then, BnOH and monomer in DCM were injected into the vials in turn, and the vials were sealed with screw caps. The vials were removed from the glovebox and stirred at room temperature. After specified time intervals, each vial was taken out and quenched with an excess of acetic acid for $^1$H NMR measurements and SEC analysis. Each reaction was used as one data point.

**Water Solubility Study**

20.1 mg of POxP$_{Me}$ ($M_{n,NMR} = 4.3$ kg mol$^{-1}$, $D = 1.11$, entry 5) and 10 µL CH$_3$CN were dissolved in 0.5 mL D$_2$O. This solution was transferred to a J-Young tube for $^1$H NMR recording. After 1 hour, a $^1$H NMR spectrum was acquired. The NMR spectrum was acquired again at 24 hours, then finally at 48 hours. Comparison of CH$_3$CN peak at 2.0 ppm (3H) with polymer peak at 4.21 ppm (2H) revealed a monomer unit concentration of 0.21 M in D$_2$O with no changing of chemical shifts after 48 hours.

**Hydrolytic degradation study**

10 mg of the polymer was dissolved by DCM (1 ml) in a series of 5 ml vials. Then, the DCM was removed by a vacuum oven to prepare a skinny polymer layer in vials. 1 ml of Phosphate buffered saline (PBS) (pH = 7.4) was added to the series of vials. The vials were sealed and incubated at 25 °C. After specified time intervals, each vial was taken out, freeze-dried, and analyzed by $^1$H NMR to monitor the degree of degradation.
Figure S1. FTIR spectrum of OxPMe monomer.

Figure S2. $^1$H NMR (CDCl$_3$, 25 °C, 500 MHz) and $^{13}$C NMR (CDCl$_3$, 25 °C, 125 MHz) spectra of OxPMe monomer.
Figure S3. FTIR spectrum of OxP$_{Pr}$ monomer.

Figure S4. $^1$H NMR (CDCl$_3$, 25 °C, 500 MHz) and $^{13}$C NMR (CDCl$_3$, 25 °C, 125 MHz) spectra of OxP$_{Pr}$ monomer.
Figure S5. FTIR spectrum of OxP$_{ph}$ monomer.

Figure S6. $^1$H NMR (CDCl$_3$, 25 °C, 500 MHz) and $^{13}$C NMR (CDCl$_3$, 25 °C, 125 MHz) spectra of OxP$_{ph}$ monomer.
Figure S7. FTIR spectrum of OxP$_{Bn}$ monomer.

Figure S8. $^1$H NMR (CDCl$_3$, 25 °C, 500 MHz) and $^{13}$C NMR (CDCl$_3$, 25 °C, 125 MHz) spectra of OxP$_{Bn}$ monomer.
Figure S9. (A) Plots of $\ln([M]_0/[M]_t)$ versus reaction time for the TBD/TU catalyzed ROPs of OxP$_{Me}$ (green line, entry 5), OxP$_{Pr}$ (red line, entry 8), OxP$_{Ph}$ (yellow line, entry 10) and OxP$_{Bn}$ (purple line, entry 12) at the ratios of $[M]_0/[BnOH]_0/[TBD]_0/[TU]_0 = 30/1/1/3$; (B) Plots of $M_{n,SEC}$ versus monomer conversion for TBD/TU catalyzed ROP of OxP$_{Me}$ (entry 5): (▼) $D$ ($M_w/M_n$ from SEC).

Figure S10. $^{13}$C NMR (CDCl$_3$, 125MHz, 25 °C) spectrum of the obtained POxP$_{Me}$ homopolymer (Table 1, entry 5).
Figure S11. $^1$H NMR (CDCl$_3$, 500 MHz, 25 °C) spectra of the obtained POxP$_r$ homopolymer (Table 1, entry 8).

Figure S12. $^{13}$C NMR (CDCl$_3$, 125 MHz, 25 °C) spectra of the obtained POxP$_r$ homopolymer (Table 1, entry 8).
Figure S13. MALDI-TOF MS spectra of the obtained POxP\textsubscript{Pr} homopolymer (Table 1, entry 9).

Figure S14. $^1$H NMR (CDCl$_3$, 500 MHz, 25 °C) spectra of the obtained POxP\textsubscript{Ph} homopolymer (Table 1, entry 10).
Figure S15. $^{13}$C NMR (CDCl$_3$, 125 MHz, 25 °C) spectra of the obtained POxP$_{Ph}$ homopolymer (Table 1, entry 10).

Figure S16. MALDI-TOF MS spectra of the obtained POxP$_{Ph}$ homopolymer (Table 1, entry 11).
Figure S17. $^1$H NMR (CDCl$_3$, 500 MHz, 25 °C) spectra of the obtained POxP$_{8n}$ homopolymer (Table 1, entry 12).

Figure S18. $^{13}$C NMR (CDCl$_3$, 125 MHz, 25 °C) spectra of the obtained POxP$_{8n}$ homopolymer (Table 1, entry 12).
Figure S19. MALDI-TOF MS spectra of the obtained POxP$_{\text{Bn}}$ homopolymer (Table 1, entry 13).

Figure S20. $^1$H NMR (CDCl$_3$, 500 MHz, 25 °C) spectra of the obtained PCL homopolymer (Table 1, entry 14).
Figure S21. $^{13}$C NMR (CDCl$_3$, 125 MHz, 25 $^\circ$C) spectra of the obtained PCL homopolymer (Table 1, entry 14).

Figure S22. MALDI-TOF MS spectra of the obtained PCL homopolymer (Table 1, entry 14).
Figure S23. $^1$H NMR spectra of the mixture of (a) TBD/3TU, (b) TU, and (c) TBD (CDCl$_3$, 500 MHz, 25 °C).

Figure S24. $^{13}$C NMR spectra of the mixture of (a) TBD/3TU/BnOH, (b) TBD/3TU, (c) TU, and (d) TBD (CDCl$_3$, 125 MHz, 25 °C).
Figure S25. $^1$H NMR spectra of the mixture of (a) BnOH/TBD/3TU, (b) BnOH/TBD, and (c) BnOH (CDCl$_3$, 500 MHz, 25 °C).

Figure S26. $^{13}$C NMR spectra of the mixture of (a) OxP$_{Me}$/TU and (b) OxP$_{Me}$ (Toluene-$d_8$, 125 MHz, 25 °C).
Scheme S1. A proposed plausible mechanism of TBD/TU catalyzed the ROP of OxPs.

Figure S27. $^1$H NMR spectra ($D_2O$, 500 MHz, 25 ºC) of water solubility study of POxP$_{Me}$ (Monomer unit concentration 0.21 M in $D_2O$; monomer unit concentration of full solubility 0.25 M in $D_2O$).
Figure S28. $^1$H NMR (CDCl$_3$, 500MHz, 25 °C) spectra of hydrolyzed PCL (entry 14) at 25 °C (PBS solution of pH 7.4) up to 70 days.

References