

Organocatalytic Ring-Opening Polymerization of Morpholinones: New Strategies to Functionalized Polyesters

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S Supporting Information

ABSTRACT: The oxidative lactonization of *N*-substituted diethanolamines with the Pd catalyst [LPd(OAc)]₂²⁺[OTf]₂ generates *N*-substituted morpholin-2-ones. The organocatalytic ring-opening polymerization of *N*-acyl morpholin-2-ones occurs readily to generate functionalized poly(aminoesters) with *N*-acylated amines in the polyester backbone. The thermodynamics of the ring-opening polymerization depends sensitively on the hybridization of the nitrogen of the heterocyclic lactone. *N*-Acyl morpholin-2-ones polymerize readily to generate polymorpholinones, but the *N*-aryl or *N*-alkyl substituted morpholin-2-ones do not polymerize. Experimental and theoretical studies reveal that the thermodynamics of ring opening correlates to the degree of pyramidalization of the endocyclic *N*-atom. Deprotection of the poly(*N*-Boc-morpholin-2-one) yields a water-soluble, cationic polymorpholinone.

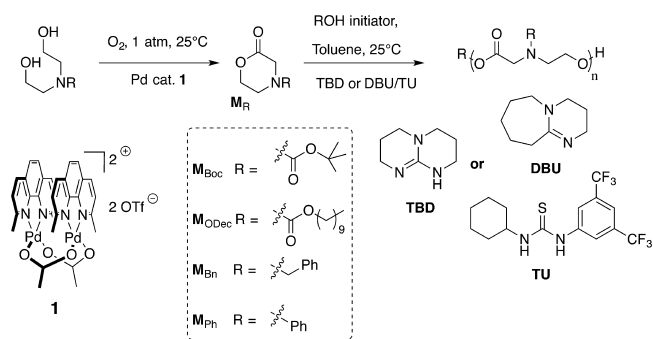
The synthesis of biodegradable synthetic polymers that mimic the rich functional diversity of natural polymers is a formidable challenge.^{1–3} Functionalized polyesters^{1–4} and polycarbonates^{5,6} are an attractive class of artificial biopolymers,⁷ biomedical materials,^{8,9} and functional materials that can readily degrade in the environment.^{10,11} The ring-opening polymerization of functional monomers is an attractive synthetic strategy for the synthesis of these materials,^{1–4} despite the challenges^{1,2,12} encountered in developing expedient synthetic methods^{6,13–16} to the requisite monomers.

We seek new catalytic strategies to generate functionalized lactones^{17–23} or carbonates.²⁴ The catalytic oxidative lactonization of diethylene glycol is one of the major strategies for generating dioxanone (1,4-dioxan-2-one, DX),¹⁷ an important monomer for the generation of degradable poly(etheresters).²⁵ The oxidative lactonization of substituted diethanolamines with Ru,^{18,19,22} Pd,²⁰ or Au²¹ catalysts provides an expedient synthesis of *N*-substituted morpholin-2-ones, but little is known regarding the ring-opening polymerization of these lactones. The ring-opening polymerization of the related 2,5-morpholinediones is known.²⁶ The organocatalytic ring-opening polymerization of *N*-substituted morpholin-2-ones would provide a general strategy to prepare a family of functionalized poly(aminoesters). Biodegradable poly(aminoesters) containing amines in the polymer backbone^{27–31} or as pendant groups³² are an attractive class of biomedical materials,³³ particularly for drug and gene delivery,^{28–30} or as antimicrobial agents.³⁴ Poly(aminoesters) are typically generated by step-

growth synthesis;^{28,29,31} herein we report the oxidative lactonization of substituted diethanolamines and the organocatalytic ring-opening polymerization of the resulting morpholin-2-ones to generate a new class of functionalized poly(aminoesters).

Diethanolamines are a readily available class of industrial chemicals.³⁵ The catalytic oxidative lactonization of diethanolamines with the cationic Pd complex [(neocuproine)Pd(OAc)]₂(OTf)₂ **1**^{20,36} affords the corresponding morpholin-2-ones in isolated yields of 54%–76%. The oxidative cyclization with **1** is tolerant of a variety of functionalized amines, and the oxidative lactonization of the *N*-Boc diethanolamine was carried out on a 2.0 g scale (Scheme 1).

Scheme 1. Synthesis and Oxidative Lactonization of Substituted Diethanolamines



The organocatalytic ring-opening polymerization of four morpholin-2-ones was investigated with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)³⁷ and the 1,8-diazabicycloundec-7-ene/thiourea (DBU/TU) catalyst systems^{38,39} (Scheme 1, Table 1). Polymerizations were carried out at rt in toluene solution with an alcohol initiator and catalyst loadings of 0.5–2 mol % (Table 1). Dichloromethane can also be used as a solvent for the polymerization of **M_{Boc}** but in this solvent the monomer conversions were lower. As previously observed,⁴⁰ the DBU/TU system was less active than the guanidine TBD for the ring-opening polymerization of **M_{Boc}** but yielded narrower molecular weight distributions (Table 1, entries 1–4). The organocatalytic ring-opening polymerization of morpholinones **M_{Boc}** and **M_{ODec}** in toluene proceeded to 84%–90% conversion at rt, but the morpholinones **M_{Bn}** and **M_{Ph}** did not

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Table 1. Organocatalytic Ring-Opening Polymerization of Morpholinones^a

entry	morpholinone	cat.	[M]:[I]:[C] ^b	time/min	conv.	M_n^c	M_w/M_n
1	M_{Boc}	DBU/TU	100:1:1	360	87%	14.2	1.07
2		DBU/TU	200:1:1	360	86%	22.6	1.07
3		TBD	100:1:1	5	86%	8.6	2.02
4		TBD	100:1:1 (CH ₂ Cl ₂)	20	66%	5.9	1.32
5	M_{ODec}	DBU/TU	100:1:1	1080	90%	10.8 ^d	1.26
6		TBD	100:1:1	20	88%	10.9 ^d	1.45
7	M_{Bn}	TBD	100:1:1	1080	0%	–	–
8	M_{Ph}	TBD	100:1:1	1080	0%	–	–

^aConditions: Monomer 1 M in toluene, 25 °C. ^b[Monomer]:[ROH]:[catalyst]. ^c M_n (kDa) determined in THF by PS calibrated GPC. ^d M_n determined in CHCl₃ by PS calibrated GPC.

polymerize at all under similar conditions, even with the more active TBD catalyst.

The ring-opening polymerization of the morpholinone M_{Boc} with DBU/TU in toluene exhibits the features of a living polymerization: the molecular weight increases linearly with conversion, the molecular weight distributions remain below $M_w/M_n \leq 1.12$ to high monomer conversion ($\leq 87\%$), and the decay in monomer concentration follows first-order kinetics. Nevertheless, in toluene at rt, we observed no further monomer conversion when the concentration of monomer approached 0.13 M (see Figures S7–S9, Supporting Information (SI)), indicative of an approach to equilibrium.

The equilibrium monomer concentration for the polymerization of M_{Boc} was determined from both polymerization and depolymerization experiments in the presence of TBD and resulted in a final monomer concentration of $[M]_f = 0.13$ M for M_{Boc} in toluene at 25 °C. When the same experiments were carried out in dichloromethane, we measured $[M]_f = 0.35$ M for monomer M_{Boc} indicating that the nature of the solvent has a significant influence on the thermodynamics of ring opening.⁴¹

The enthalpies of ring opening were determined for the ring-opening polymerization of M_{Boc} in C₆D₆. As the morpholin-2-ones M_{Bn} and M_{Ph} do not polymerize, we investigated the ring opening of M_{Bn} and M_{Ph} with CD₃OD to yield the corresponding methyl ester.⁴² Thus, while the relative ΔH° 's of M_{Boc} and $M_{\text{Bn}}/M_{\text{Ph}}$ cannot be directly compared, these experiments provide a means of comparing the relative thermodynamic preferences of the morpholinones to undergo ring opening in the presence of an alcohol.⁴²

The results of these experiments (see Table S2, SI) reveal that the enthalpy of polymerization for M_{Boc} ($\Delta H^\circ_p = -4.8 \pm 0.3$ kcal/mol) is larger than the enthalpies for the ring opening of M_{Ph} ($\Delta H^\circ_{\text{ro}}(M_{\text{Ph}}) = -1.7 \pm 0.2$ kcal/mol) and M_{Bn} ($\Delta H^\circ_{\text{ro}}(M_{\text{Bn}}) = -1.1 \pm 0.1$ kcal/mol) to give the methyl ester, indicating that these latter two morpholinones are less susceptible to ring opening. The low enthalpies of ring opening for M_{Bn} and M_{Ph} are consistent with the low reactivity observed for ring-opening polymerization.⁴¹

DFT calculations (Gaussian 09, M06-2X DFT hybrid functional, 6-311+G(d,p) basis set with the CPCM solvent model in toluene) provided further insights. Geometry optimizations of morpholinones M_{Boc} , M_{OBu} ,⁴³ M_{Bn} , and M_{Ph} revealed significant differences in the conformations of the lactone heterocycles. The N-atoms of *N*-alkyl or *N*-aryl M_{Bn} and M_{Ph} are pyramidalized (Figure 1, left), whereas those of the *N*-acyl M_{Boc} and M_{OBu} are typical of planar amides (Figure 1, right).

A significant result of these calculations was a correlation between the structure of the morpholin-2-ones, in particular the

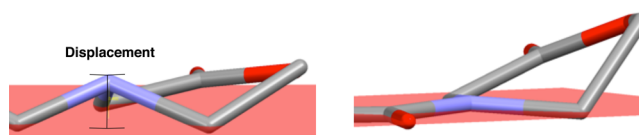
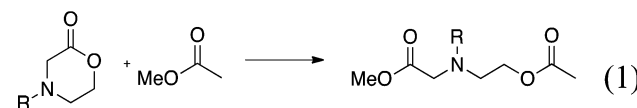


Figure 1. Geometry at N for M_{Bn} (left) and M_{Boc} (right).

degree of pyramidalization of the endocyclic N-atom, with the energetics of ring opening. The enthalpies of ring opening were calculated for a model ring-opening reaction with methyl acetate (eq 1).^{44,45}



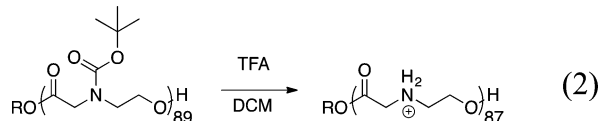
These calculations suggest that the enthalpies of ring opening of morpholin-2-ones containing acylated N-atoms, M_{Boc} ($\Delta H_{\text{calc}} = -9.3$ kcal/mol) and M_{OBu} ⁴³ ($\Delta H_{\text{calc}} = -9.4$ kcal/mol), are more negative than those containing aryl M_{Ph} ($\Delta H_{\text{calc}} = -8.7$ kcal/mol) or alkyl-substituted M_{Bn} ($\Delta H_{\text{calc}} = -4.9$ kcal/mol) N-atoms.

Notably, while the experimental estimate for the enthalpy of ring opening of the *N*-aryl morpholinone M_{Ph} with methanol to generate the methyl ester is only $\Delta H_{\text{ro,MeOH}} = -1.7$ kcal/mol, the calculated enthalpy of ring opening of M_{Ph} (eq 1) is intermediate to that of M_{Boc} and M_{Bn} . This suggested to us that M_{Ph} might be induced to copolymerize with the reactive M_{Boc} morpholinone. Copolymerization of M_{Boc} and M_{Ph} results in partial incorporation of M_{Ph} to yield a random polymer. In contrast, the attempted copolymerization of M_{Boc} and the *N*-alkyl M_{Bu} showed no incorporation of the alkyl-substituted morpholinone M_{Bu} (see Figures S1, S2, SI). This result is consistent with the intermediate pyramidalization and ring-opening enthalpy of M_{Ph} .

These findings provide important insights into the structural factors that contribute not only to the thermodynamics of ring opening polymerization reactions but also to lactonization and other cyclization reactions.⁴⁶ In particular, our experimental and theoretical studies suggest that the ring-opening polymerization of morpholin-2-ones is a general strategy to poly(aminoesters), provided that the nitrogen is acylated.

The poly(morpholin-2-ones) generated from monomer M_{Boc} are soluble in organic solvents (THF, toluene, CH₂Cl₂, CHCl₃) and were isolated in yields 74%–77% as white solids after dialysis in methanol to remove catalyst residues and the monomer. The polymers generated from M_{ODec} were isolated in yields of 77%–83% as white solids and are soluble in DCM

and toluene but were generally less soluble than M_{Boc} in THF. The acid-catalyzed deprotection of the polymer derived from M_{Boc} ($p(M_{\text{Boc}})$, ($M_n = 10\,800$, $M_n/M_w = 1.14$, degree of polymerization = 89) was carried out with trifluoroacetic acid (TFA) in CH_2Cl_2 to afford the cationic water-soluble poly(aminoester) (eq 2).



End group analysis by ^1H NMR before and after deprotection showed no degradation in molecular weight (degree of polymerization ~ 87 , after deprotection). Furthermore, ^1H NMR spectra show this polymer to have a solubility of >0.5 M in D_2O , with no evidence of decomposition after remaining in solution for 48 h at rt (see Figure S6, SI).

In summary, we have shown that the oxidative lactonization of diethanolamines and the organocatalytic ring-opening polymerization of *N*-acyl substituted morpholin-2-ones provide a general strategy to functionalized poly(aminoesters). Experimental and theoretical studies reveal that the thermodynamic polymerizability of the morpholin-2-ones depends sensitively on the substituents of the endocyclic N-atom: *N*-acyl morpholin-2-ones are readily polymerized, but those bearing pyramidalized endocyclic amines are not as readily polymerized due to their lower enthalpies of ring opening. The ring-opening polymerization of *N*-acyl morpholin-2-ones yields a new family of functionalized polyesters and water-soluble cationic poly(aminoesters).

■ ASSOCIATED CONTENT

Supporting Information

Synthetic details, characterization data, computational data, and supplementary procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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