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

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Supporting Information

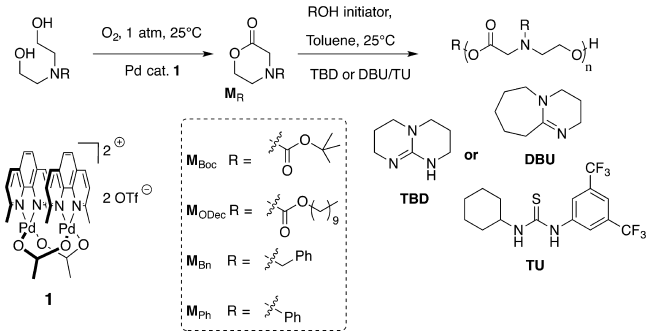
ABSTRACT: The oxidative lactonization of N-substituted diethanolamines with the Pd catalyst $[LPd(OAc)]_2^{2+}[OTf^-]_2$ generates N-substituted morpholin-2-ones. The organocatalytic ring-opening polymerization of *N*-acyl morpholin-2-ones occurs readily to generate functionalized poly(aminoesters) with *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 Au[21] 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 groups[32] 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 $\mathbf{M}_{Boc}$, 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 $\mathbf{M}_{Boc}$, but yielded narrower molecular weight distributions (Table 1, entries 1−4). The organocatalytic ring-opening polymerization of morpholinones $\mathbf{M}_{Boc}$ and $\mathbf{M}_{ODec}$ in toluene proceeded to 84%−90% conversion at rt, but the morpholinones $\mathbf{M}_{Bn}$ and $\mathbf{M}_{Ph}$ 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	$\mathbf{M}_{Boc}$	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_2Cl_2)	20	66%	5.9	1.32
5	$\mathbf{M}_{ODec}$	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	$\mathbf{M}_{Bn}$	TBD	100:1:1	1080	0%	–	–
8	$\mathbf{M}_{Ph}$	TBD	100:1:1	1080	0%	–	–

[a]Conditions: 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 $CHCl_3$ by PS calibrated GPC.

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

The ring-opening polymerization of the morpholinone $\mathbf{M}_{Boc}$ 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 (≤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 $\mathbf{M}_{Boc}$ 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 $\mathbf{M}_{Boc}$ in toluene at 25 °C. When the same experiments were carried out in dichloromethane, we measured $[M]_f = 0.35$ M for monomer $\mathbf{M}_{Boc}$, 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 $\mathbf{M}_{Boc}$ in C_6D_6. As the morpholin-2-ones $\mathbf{M}_{Bn}$ and $\mathbf{M}_{Ph}$ do not polymerize, we investigated the ring opening of $\mathbf{M}_{Bn}$ and $\mathbf{M}_{Ph}$ with CD_3OD to yield the corresponding methyl ester.[42] Thus, while the relative $\Delta H°$'s of $\mathbf{M}_{Boc}$ and $\mathbf{M}_{Bn}/\mathbf{M}_{Ph}$ 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 $\mathbf{M}_{Boc}$ ($\Delta H°_p = -4.8 \pm 0.3$ kcal/mol) is larger than the enthalpies for the ring opening of $\mathbf{M}_{Ph}$ ($\Delta H°_{ro}(\mathbf{M}_{Ph}) = -1.7 \pm 0.2$ kcal/mol) and $\mathbf{M}_{Bn}$ ($\Delta H°_{ro}(\mathbf{M}_{Bn}) = -1.1 \pm 0.1$ 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 $\mathbf{M}_{Bn}$ and $\mathbf{M}_{Ph}$ 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 $\mathbf{M}_{Boc}$, $\mathbf{M}_{OBut}$,[43] $\mathbf{M}_{Bn}$, and $\mathbf{M}_{Ph}$ revealed significant differences in the conformations of the lactone heterocycles. The N-atoms of *N*-alkyl or *N*-aryl $\mathbf{M}_{Bn}$ and $\mathbf{M}_{Ph}$ are pyramidalized (Figure 1, left), whereas those of the *N*-acyl $\mathbf{M}_{Boc}$ and $\mathbf{M}_{OBu}$ 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 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]

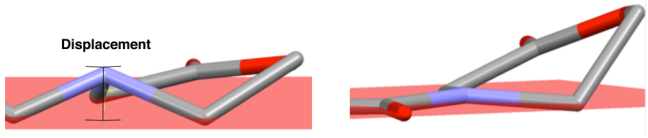
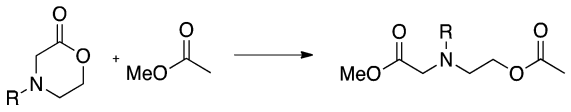


Figure 1. Geometry at N for $\mathbf{M}_{Bn}$ (left) and $\mathbf{M}_{Boc}$ (right).



(1)

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

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

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 $\mathbf{M}_{Boc}$ are soluble in organic solvents (THF, toluene, CH_2Cl_2, $CHCl_3$) 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 $\mathbf{M}_{ODec}$ were isolated in yields of 77%−83% as white solids and are soluble in DCM

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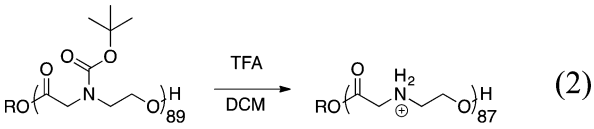
and toluene but were generally less soluble than $\mathbf{M}_{Boc}$ in THF. The acid-catalyzed deprotection of the polymer derived from $\mathbf{M}_{Boc}$ (p(M_{Boc}), (M_n = 10 800, M_n/M_w = 1.14, degree of polymerization = 89) was carried out with trifluoroacetic acid (TFA) in CH_2Cl_2 to afford the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



(2)

End group analysis by ^{1}H NMR before and after deprotection showed no degradation in molecular weight (degree of polymerization ~87, after deprotection). Furthermore, ^{1}H 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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