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Perspective

Unveiling Proton Transfer as the Key Process to Understand and Promote the Ring-Opening Polymerization of *N*-Carboxyanhydrides

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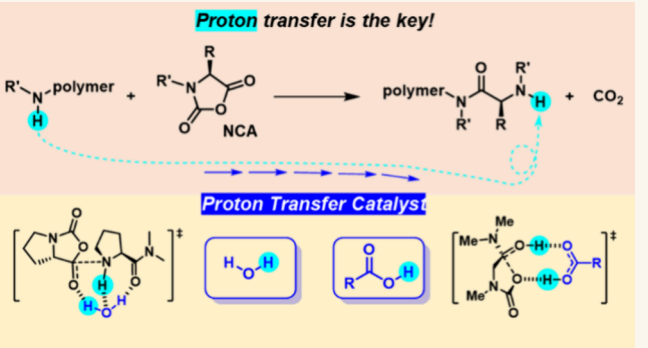
ABSTRACT: The ring-opening polymerization (ROP) of *N*-carboxyanhydrides (NCAs) holds great potential for the efficient preparation of versatile and biocompatible poly(amino acid)s, such as polypeptides and polypeptoids. This perspective highlights the pivotal role of proton transfer in NCA ROP, emphasizing the use of proton transfer catalysts (PTCs) such as carboxylic acids and water to enhance polymerization kinetics and achieve (unprecedented) polymers with high molecular weights. Further studies on the exploration and rational design of PTCs offers promising opportunities to further innovate NCA ROP chemistry and broaden its applications in material science.



KEYWORDS: *N-carboxyanhydride, ring-opening polymerization, proton transfer, catalyst, water, carboxylic acid*

INTRODUCTION

The ring-opening polymerization (ROP) of *N*-carboxyanhydrides (NCAs) is one of the most promising methods for the efficient preparation of versatile poly(amino acid)s (PAAs) such as polypeptides and polypeptoids (Figure 1A).[1,2] Research on the synthesis and ROP of NCAs, which dates back to the early 1900s, has expanded dramatically over the past two decades, with a particular focus on achieving faster and more controlled polymerizations under milder and ambient conditions. Toward this goal, considerable efforts have also been devoted to understanding the ROP mechanism of NCAs. In the classical narrative of the NCA polymerization mediated by primary amines, the reaction was typically divided by two steps: ring-opening aminolysis of NCA (typically the rate-determining step, RDS) followed by the decarboxylation of the carbamic acid intermediate, known as the normal amine mechanism (NAM).[3−5] Proton transfer, despite its important role in both steps of NAM, is often overlooked (Figure 1B). This perspective aims to discuss recent advances in understanding the proton transfer process in NCA ROP and to elucidate the pivotal roles of proton transfer catalysts (PTCs) in developing next-generation ROP methodologies.

PROTON TRANSFER IN AMINOLYSIS OF ESTERS AND ANHYDRIDES

Proton transfer is one of the most general and important reactions in chemistry, holding the key to understand many basic organic/inorganic transformations and enzymatic reactions.[6,7] An ideal proton transfer reaction follows a linear X---H---Y geometry, where X and Y are atoms with a relatively high electronegativity. Deviations from this optimal geometry usually increase the reaction energy barrier. Specifically, for nucleophilic substitution at the carbonyl of carboxylic derivatives, which typically proceeds via addition, followed by elimination, proton transfer is even more critical. Intramolecular proton transfer often results in an unfavorable bent geometry, necessitating a catalyst to facilitate a more favorable intermolecular proton transfer for acceleration. For instance, Zipse and Wang found that uncatalyzed aminolysis of esters involved highly strained four-membered transition states (TSs), with proton transfer geometries deviating significantly from linearity.[8] A bifunctional proton transfer catalyst (PTC) such as 2-hydroxypyridine, in contrast, facilitated the reaction by simultaneously accepting an external proton and donating its own proton to the substrate via an eight-membered TS, where proton transfer angles approached the optimal value of 180° (Figure 1C). Furthermore, in 2008, Leszczynski et al. reported a computational study of the aminolysis of succinic anhydride, attributing the autocatalytic nature of the reaction to the role of the carboxylic acid product as an efficient bifunctional PTC, similar to 2-hydroxypyridine in the aminolysis of esters (Figure 1D).[9]

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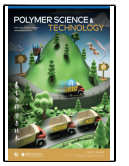

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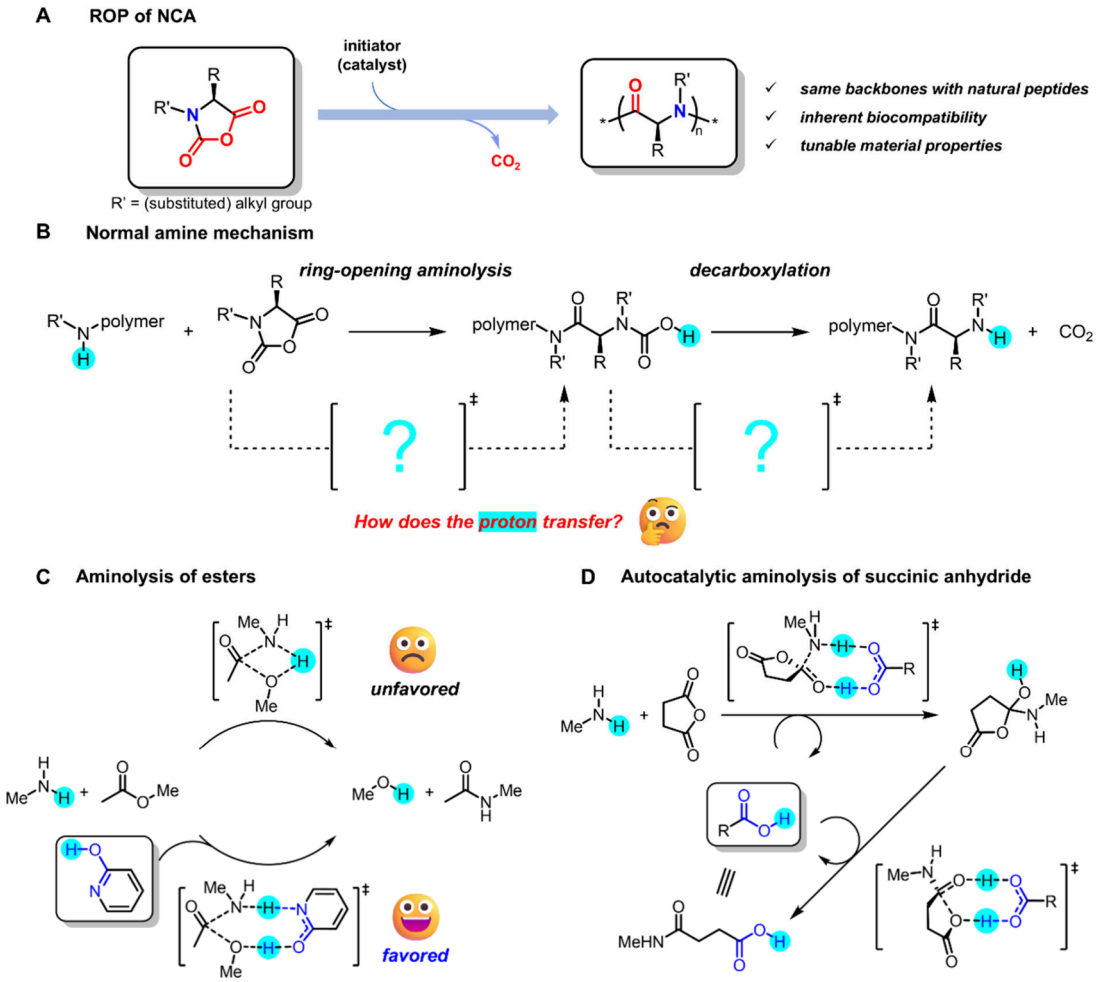

Figure 1. (A) ROP of NCA. (B) Normal amine mechanism and proton transfer. (C) Aminolysis of ester with or without catalysis of PTC. (D) Autocatalytic aminolysis of succinic anhydride.

Given the similar reactivities of NCA, succinic anhydride, and esters, it is not surprising that PTCs can also enhance the ROP kinetics of NCAs, as we discuss below.

WATER-ASSISTED ROP OF PROLINE NCA

Water is the most prevalent PTC. Beyond the proton transfer catalyzed by a single water molecule, water can facilitate the process through H-bond networks composed of multiple H_2O molecules.[10] Presumably, water can also act as a powerful PTC accelerating the ROP of NCAs. However, since NCAs are susceptible to hydrolysis under aqueous conditions, this potential is not realized until recently Lu and co-workers reported the first case of water-assisted, ultrafast, and controlled ROP of proline NCA (Pro-NCA) in 50%/50% mixed acetonitrile/water system.[11] This method produced narrowly dispersed polyproline with a well-defined polyproline II (PPII) helix in only 2−5 min and near-quantitative yields, in sharp contrast to the sluggish and uncontrolled polymerization of Pro-NCA in pure organic solvents. PPII helix features in all *trans* amide bonds in chemical structure and is water-soluble, distinctly different from the water-insoluble polyproline I (PPI) helix with all amide bonds in *cis* form. According to mechanism experiments and density functional theory (DFT) calculations, it was proposed that the intramolecular proton transfer reaction of the high-energy charge-separated intermediate, rather than the nucleophilic addition, was the RDS in pure acetonitrile (Figure 2A). The introduction of water, by contrast, significantly reshaped the whole reaction potential energy surface and efficiently lowered the free energy barriers of the nucleophilic addition, elimination, and decarboxylation steps by facilitating transfer of protons and minimizing charge separation (Figure 2A). More interestingly, water also favored the formation of *trans* amine bonds instead of *cis* bonds in pure acetonitrile, leading to PPII helix selectivity. It should be mentioned that the change in solvent polarity and/or dielectric constant in the 50%/50% mixed acetonitrile/water may also contribute to the acceleration. This notion, however, was not considered the primary factor, as a trace amount (1−2%) of H_2O was also found to accelerate the ROP significantly. Moreover, the isotope effect was seen as H_2O enhanced the rate of Pro-NCA ROP more than D_2O.[12,13] Overall, it was the ultrafast polymerization rate that overrode and suppressed the major side reaction, namely, the monomer hydrolysis, leading to the controlled ROP and excellent end group fidelity of the resulting polyproline. Nevertheless, this water-assisted ROP is currently limited to Pro-NCA and hydroxyproline NCA.[14] The strained bicyclic structure of these monomers likely contributes to their higher reactivity of them. Following works on accessing the generality of the chemistry are required.

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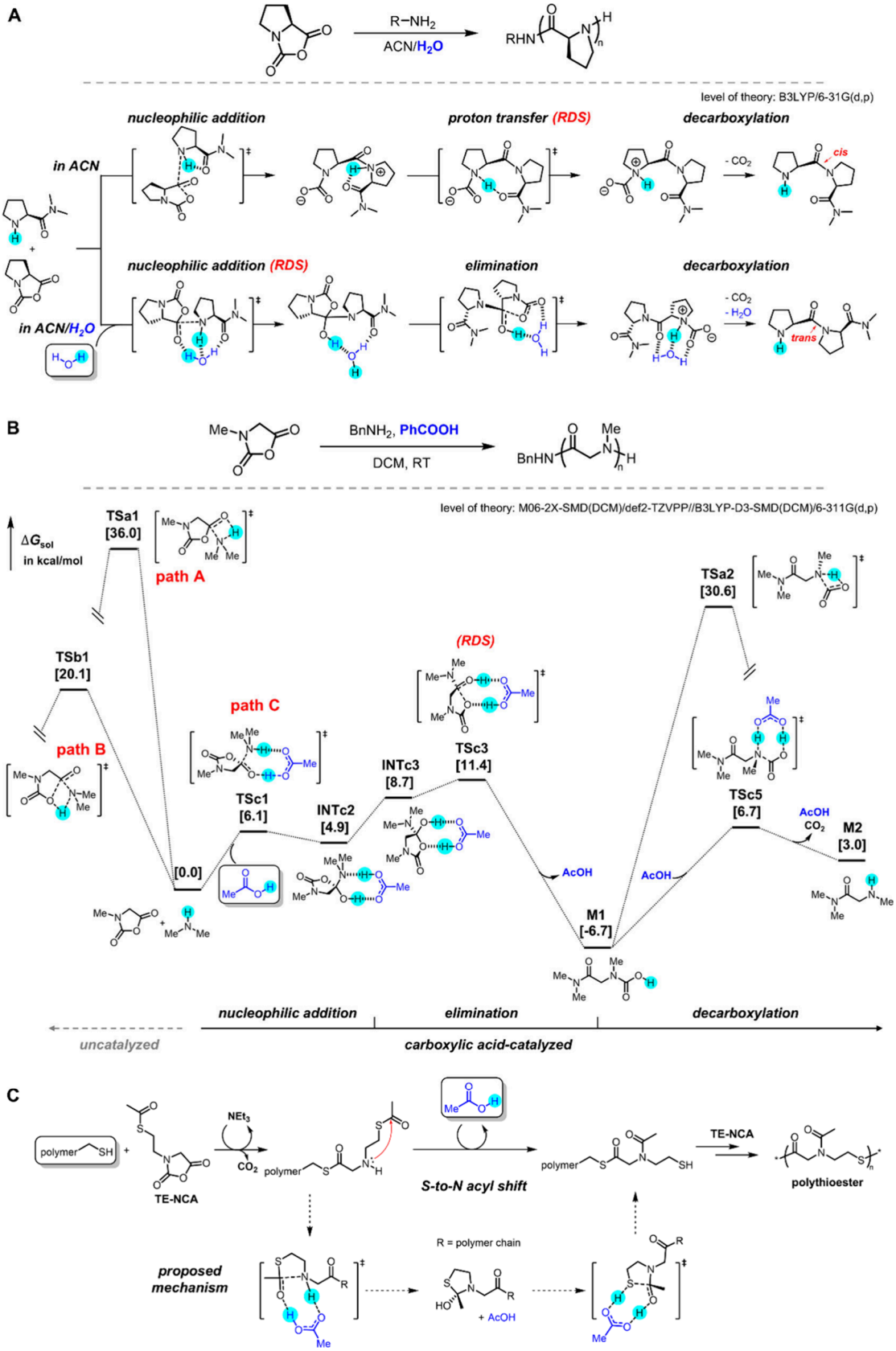

Figure 2. (A) Proposed mechanism for the ROP of proline NCA with or without the assistance of water. (B) Computed potential energy surface for carboxylic acid-catalyzed ROP of sarcosine NCA. (C) Ring-opening cascade polymerization of NCA facilitated by acetic acid.

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CARBOXYLIC ACIDS AS PTCS FOR ROP OF NCAS

Carboxylic acids are common and inexpensive PTCs that not only promote the aminolysis of anhydrides but also efficiently accelerate the keto-enol tautomerization.[9,15] Different from water, carboxylic acids are unique in proton transfer geometries for simultaneously donating their own acidic proton on hydroxy oxygen and accepting an external proton on the basic carbonyl oxygen atom. For ROP of NCAs, adding carboxylic acid as catalyst sounds counterintuitive as the chain propagation center is a primary amine, and acid−base equilibrium would reduce the reactivity of the propagating chain end. Early studies using ammonium chloride or ammonium tetrafluoroborate for NCA polymerization resulted in improved control, but at the cost of significantly reduced reactivity.[16,17] The first attempt on using carboxylic acid as a catalyst could date back to 1950s, when Ballard and Bamford first introduced pyridine-2-carboxylic acid to the ROP of sarcosine NCA (Sar-NCA), achieving a 0.5-fold rate enhancement.[18] However, this pioneering research did not gain much attention until Zhang and Ling recently utilized carboxylic acids as additives in the ROP of *N*-thiocarboxyanhydrides (NTAs), though the role of carboxylic acids as PTC was not explicitly discussed.[19,20] Lu and coworkers utilized carboxylic acids as an additive to not only enhance the ROP rate of D-penicillamine NCA (Pen-NCA) and inhibit rearrangement side reactions but also improve the selectivity of polymerization over isomerization side reactions.[21] The same group also reported the ROP of glutamic acid NCA (Glu-NCA) with all the side chain carboxylic acid unprotected.[22] All of these studies suggested that certain amounts of carboxylic acids played a catalytic role in enhancing both the control and rate of ROP of NCAs.

Standing on the shoulders of the above precedents, comprehensive studies of using carboxylic acids as PTCs for the fast and controlled ROP of sarcosine NCA (Sar-NCA) was carried out (Figure 2B).[5] For Sar-NCA, carboxylic acids accelerate the ROP by up to 50 times, producing polysarcosine (pSar) with ultrahigh molecular weights up to 586 kDa for the first time. The acidity of carboxylic acids and the Kamlet−Abboud−Taft basicity parameter β of solvents were found to reversely correlate with the rate of polymerization. DFT computations revealed that carboxylic acids efficiently lower the barrier of ring-opening aminolysis of NCAs by acting as bifunctional PTCs as proposed (Figure 2B, path C). Specifically, in the rate-determining TS (TSc3), acetic acid, the model catalyst, simultaneously activates the elimination-driven hydroxyl oxygen lone pair and the leaving carboxyl group via double hydrogen bonding, enabling low-barrier elimination of the tetrahedral intermediate and subsequent barrierless linear double proton transfer. Without carboxylic acids, however, the aminolysis likely undergoes highly strained four-membered TSs, similar to those observed in esters and succinic anhydride (Figure 2B, path A & B). DFT calculations also proposed the PTC role of carboxylic acids in the following decarboxylation step. Looking back, carboxylic acids are different with hydrogen chloride or hydrogen tetrafluoroboric acid in that the formers have appropriate acidities and, in the meantime, can function as both hydrogen bonding donor and acceptors to facilitate proton transfer. Unlike the water-assisted ROP that was currently limited to Pro-NCA, it is worth noting that the carboxylic acid-catalyzed ROP of NCAs offers a general solution for the fast and controlled ROP of many different (*N*-substituted) NCA monomers, allowing access to PAAs with unprecedented molecular weight and (multi)block sequences. Nearly at the same time, Zhang/Xuan and Cheng/Song research groups also independently reported the ROP of various NCA monomers catalyzed by carboxylic acids, echoing the generality of the above methodology.[23,24]

In addition to classic ROPs of NCA that produce PAAs, carboxylic acids also aid in the development of the first ring-opening cascade polymerization (ROCAP) of NCA (Figure 2C).[25] Specifically, acetic acid is used as a PTC to lower the energy barrier of an intramolecular *S*-to-*N* acyl shift reaction (aminolysis of thioester), which is then successfully integrated into the chain propagation of NCA, yielding recyclable polythioesters and unprecedent poly(thioester-*co*-peptoid)s.

OUTLOOK

In this perspective, we briefly discuss the critical role of the previously overlooked proton transfer in the ROP of NCAs and how different PTCs can enhance this process. Recent literature highlights carboxylic acids and water as effective PTCs that significantly boost polymerization kinetics, yielding (unprecedented) polymers with higher molecular weights and improved control. The simplicity, good control, and significant rate enhancement of the PTCs have encouraged many groups applied the above methods in their own researches.[26−30] Traditionally, catalyst design for NCA ROP has focused on activating the carbonyl group of the monomer or increasing the nucleophilicity of the living amine chain end. This perspective offers a valuable complement to these approaches, presenting new opportunities for designing and developing novel PTCs for NCA ROP. Future research could expand the range of catalysts to include other common PTCs used in organic synthesis, such as 2-hydroxypyridine derivatives, alcohols, phenols, and tertiary amines, to innovate NCA chemistry further.[31] Additionally, molecular engineering could enhance the activity and selectivity of PTCs. For instance, achieving stereoselective ROP of NCAs might be possible through a catalyst-controlled mechanism using highly efficient chiral PTCs, and sequence-controlled polymerizations of NCA mixtures are likely achieved by utilizing the difference in affinity for PTCs between various monomers. It should also be noted that the solvents for PTC-mediated ROP of NCA should be carefully considered as both the proton transfer processes and solubility of polypept(o)ides depend highly on the nature of solvents. Temperature is another key parameter that should be optimized to achieve both fast kinetics and high selectivity for chain propagation. Despite these promising prospects, research on PTCs for NCA ROP is still in its early stage, awaiting more work to be done. Beyond the polymerization practice, mechanistic experiments and theoretical calculations are also necessary for a deeper understanding of these processes. It would be of vital importance to capture the key intermediates and obtain more concrete evidence regarding the proton transfer process using advanced technologies such as ultrafast spectroscopy.[32] While kinetic isotopic effect (KIE) provides valuable information regarding the existence of the proton transfer process in the RDS of the polymerization experimentally, DFT calculations enable practical assessment of various possible reaction pathways to figure out the most plausible one. By continuing to explore and develop these catalysts both experimentally and theoretically, we can unlock new possibilities in polymer chemistry and expand the horizon of polypept(o)ides for versatile materials applications.

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Notes

The authors declare no competing financial interest.

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