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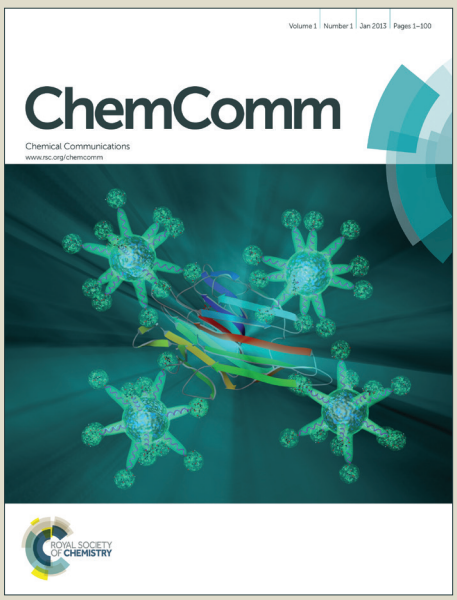

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ARTICLE

Tandem Catalysis: A New Approach to Polypeptides and Cyclic Carbonates

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A new tandem catalytic system mediates very efficiently and selectively at room temperature two sequential reactions to produce relevant derivatives in one pot. Remarkably, this new concept of catalysis allows the facile synthesis of polypeptides and provides direct access to cyclic carbonates in high yields, through the incorporation of the carbon dioxide released from the initial step, thus achieving full-atom economy.

Introduction

Amide bond formation is one of the most important reactions in organic chemistry. These linkages are not only the key chemical connections of proteins but also represent the basis for some of the most versatile and widely used synthetic polymers, pharmaceuticals and biologically active compounds.[1] In particular, amide-based polymers have a range of uses as commodity polymers and also in a variety of bioapplications as diverse as controlled drug release, gene therapy, regenerative medicine, or sensors. In 2007, the ACS Green Chemistry Institute proposed 'amide formation avoiding poor atom economy reagents' as one of the key research areas in organic chemistry.[2] Development of new methods for the synthesis of amide functionality, whether catalytic, waste-free or chemoselective, remains a considerable synthetic challenge. Notably, there has been recent interest in developing synthetic routes for preparation of polypeptides. An attractive method of designing polypeptides is to use the ring-opening polymerization (ROP) of α-aminoacid-*N*-carboxyanhydride (NCA) monomers.[3-7] NCAs typically polymerize in the presence of nucleophiles, bases or organometallic complexes to give polypeptides in good yield.[8-13] Successful controlled ROP of NCAs requires the elimination of side reactions in favour of the chain-growth process, thus relying on complex catalysts and/or drastic conditions.[14] Also, the polymerization process is accompanied by the release of carbon dioxide during the reaction. Although noteworthy successes were realized for the polymerization of NCAs since its discovery in 1906, use of easily accessible catalysts that exhibit high activities with high atom efficiency, have not been reported to date. To develop an atom economical polymerization of NCAs, we propose that catalysts capable of carbon dioxide functionalization might also exhibit polymerization activity. Therefore in order to suppress unwanted carbon dioxide release, we were interested in employing a single tandem catalyst to connect two independent catalytic cycles for the production of polypeptides and the formation of cyclic carbonates from carbon dioxide and epoxides (Figure 1). Tandem catalysis involves the sequential or concurrent action of two or more catalytic cycles in a single reactor to yield a product with minimum workup, or change in conditions.[15] These new catalytic schemes that take advantage of *in-situ* generated intermediates have several advantages over multistep syntheses, including time- and cost-savings, atom economy, waste reduction and energy consumption. To date, there is however only few examples in the literature in which a single metal complex is able to connect independent catalytic cycles for the production of polymers.[15,16]

In our search for new tandem catalysts, we focused on ligand/metal combinations known to effect both of the productive steps of polypeptide synthesis and carbonate formation.[17-26] Although salen catalysts[27] have essentially no precedent in NCA polymerization, recent reports documented the utility of discrete aluminium complexes in each of the vital steps of the tandem process.[28-32] Therefore, we hypothesized that commercially available metal complexes based on the specific tetradentate salen ligand would have the potential to act as tandem catalysts for the synthesis of cyclic carbonates and polypeptides (Figure 1).[24,33,34] Herein we report the use of tandem catalysts that exhibit excellent activity and selectivity for the atom-efficient production of two relevant compounds.

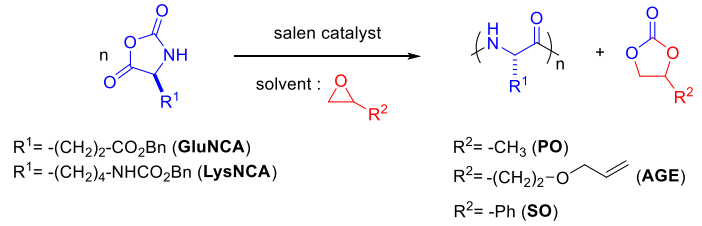

Figure 1. Tandem synthesis of polypeptides and cyclic carbonates.

Results and discussion

In order to develop a straightforward methodology to prepare polypeptides from NCA, we chose to target our initial efforts on the salen aluminium complex **1**. Indeed the use of (salen)Al(III) alkoxides has been explored for the ring-opening of NCAs, whereas Al hydroxides and carboxylates have been documented to form carbonates from epoxides in the presence of CO_2.[33-36] To evaluate the feasibility of the auto-tandem catalytic process depicted in Figure 1, we therefore conducted a preliminary experiment with the aluminium-based catalyst **1**, 50 equiv. of γ-benzyl-L glutamate *N*-carboxyanhydride (GluNCA) and an excess of propylene oxide (PO), which was used as a solvent.[37-39] Satisfyingly, the Al(salen) complex was an active initiator for the ROP of GluNCA to afford poly(γ-benzyl-L-glutamate) (PBLG) with high number-average molecular masses (M_n = 25000 g.mol^{-1}) and relatively broad molecular weight distribution (Table 1, entry 1). As already demonstrated by Bertrand,[40] this result demonstrates that the active species is an alkoxide complex resulting from the insertion of PO into an Al-Cl bond. To confirm the influence of the *in-situ* generated alkoxy ligand on the activity, a control experiment was carried out with the aluminium system **1** as initiator (Figure 2). Most interestingly, the results show that no polymer was formed, even after prolonged reaction times when the polymerization is carried out in different solvents. This is also in accordance with previous observations that described an aluminium alkoxide for the oligomerization of NCA.[33] Much to our dismay, the resulting catalytic system was not an effective catalyst for the overall tandem process. However, under the same reaction conditions cyclic propylene carbonate (PC) was synthesized in low yield in the presence of cocatalyst [PPN]Cl ([PPN]$^+$ = bis(triphenylphosphoranylidene)iminium) (entry 2). This result indicates that the aluminate complex derived from the (salen)Al(III) and iminium salt is the active species (Figure 2).[30,35] This type of Lewis base cocatalyst reversibly coordinates to the metal centre, increases the electron density on the metal, and labilizes the *trans* ligand to it.[36]

As a control experiment, the ROP of 25 eq. of GluNCA was performed using [PPN]Cl without a complex, and PBLG could be isolated. However the polymerization was not controlled as a too high experimental M_n was obtained (experimental 71300 g.mol^{-1} versus calculated M_n of 5500 g.mol^{-1}). In addition, no cyclic carbonate formation was observed. Also this observation precludes the possibility that the active species for the production of polypeptide is only the iminium salt, while the metal catalyst would account for the formation of the cyclic carbonate. Indeed the reactivity of [PPN]Cl alone is much lower than the one observed with our catalyst systems. In addition if more than one active species was active during the tandem process, we would obtain multimodal distributions. In our case, all polymerizations resulted in monomodal distributions, thus suggesting the presence of only one active site for the process. Finally as the formation of the anionic six coordinate species of the type *trans*-(salen)AlX_2^- occurs upon treating (salen)AlCl with [PPN]Cl, it seems that a more electron-rich metal centre is more efficient for this tandem reaction,[41] suggesting that the reaction pathway is influenced by the Lewis acidity and that weak Lewis acids are preferable for the coupling reaction.[42,43]

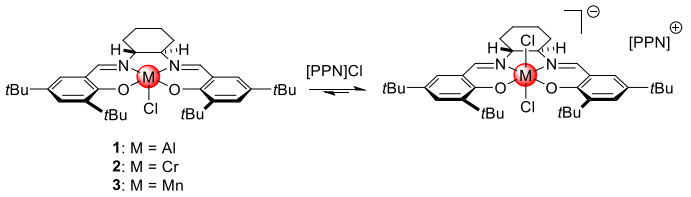

Figure 2. Formation of complex active species in the presence of salen catalyst and [PPN]Cl.

The optimization of the molar ratio between aluminium complex and [PPN]Cl was then explored and it was observed that the yield of PC was improved with an increased amount of [PPN]Cl for a constant reaction time of 1h (entries 1, 2, 5). Indeed, the highest activity was obtained with 5 equivalents of [PPN]Cl leading to an almost quantitative yield for PC (92%) (entry 5). This is in accordance with previous studies that demonstrated that the formation of the six coordinate anion *trans*-(salen)MX_2^- occurs more easily with at least 2 equivalents of PPNCl.[44] We also showed that the formation of PC grows linearly with increased reaction times. Indeed in the presence of 2 equivalents of [PPN]Cl propylene carbonate was produced in 47% after 5h (entry 3) *vs* 86% yield after 10h (entry 4). It is worth mentioning that the polymerization of GluNCA (200 equivalents) is still controlled with prolonged reaction times as PBLG exhibited similar M_n and polydispersity after 3.5 and 10h (entries 6 and 7). Chromium(III) and manganese(III) salen complexes **2** and **3** were then tested with 5 equivalents of [PPN]Cl and we observed that the two complexes also polymerize GluNCA to produce PBLG in the presence of PO (entries 8-9). Although no PC is formed in the presence of Mn(salen) complex (entries 8),[45] the screen did reveal that the chromium analogue catalysed the reaction very efficiently producing quantitative yield of PC with respect to GluNCA formation (entries 9-11). Also, when the amount of [PPN]Cl is lowered to 2 equivalents, 99% of PC were obtained in 1h with 2 (entry 10) *vs* 18% with the aluminium complex **1** (entry 2). Gratifyingly, the Cr(III) complex **2** was found to be as active when reaction time is reduced to 30 min as it still almost quantitatively converted PO to PC (entry 11). At the end of the tandem reaction, the remaining propylene oxide may be recovered under vacuum and may be used for the next batch. Then the residue was filtrated to separate propylene carbonate from the polymer. Interestingly, other monomers and epoxides, including *N*-benzyloxycarbonyl-L-lysine *N*-carboxyanhydride (LysNCA), allyl glycidyl ether (AGE) and styrene oxide (SO), are also viable for this tandem process. For instance, aluminium and chromium salen complexes **1** and **2** were tested with LysNCA instead of GluNCA in neat PO. With 5 equivalents of [PPN]Cl, the corresponding polymer was also formed in 100% yield in both cases after 1h at 20°C. With complex **1**, an experimental molecular weight of 13100 g.mol^{-1} was obtained ($M_{n,theo}$ = 13100 g.mol^{-1}) and PC was formed in 40% yield. In the presence of complex **2**, the polymer formed exhibited similar experimental molecular weight and polydispersity ($M_{n,exp}$ = 13800 g.mol^{-1}; M_w/M_n = 1.4). However, propylene carbonate was obtained with a higher yield of 58%.

Table 1. Ring-opening polymerization of GluNCA promoted by **1-3**.[a]

Entry	Initiator [I]	[PPNCl]/[I]	[NCA]/[I]	Time (h)[a]	Yields[b]	M_n (kg.mol^{-1})[c]	M_w/M_n[c]
1	**1**	-	50	1	29/0	24.9	2.4
2	**1**	2	50	1	100/18	10.3	1.3
3	**1**	2	50	5	100/47	10.0	1.5
4	**1**	2	50	10	100/86	8.0	1.5
5	**1**	5	50	1	100/92	7.0	1.3
6	**1**	5	200	3.5	100/38	51.5	1.2
7	**1**	5	200	10	100/83	55.8	1.2
8	**3**	5	50	1	100/0	52.9	1.1
9	**2**	5	50	1	100/99	8.5	1.4
10	**2**	2	50	1	100/99	10.2	1.5
11	**2**	5	50	0.5	100/97	7.3	1.3

[a] All reactions performed with [GluNCA] = 0.25 M at 20 °C in neat propylene oxide until completion as determined via integration of the benzyl resonances of GluNCA and polymer. Time was not necessarily optimized. [b] Y^1 = conversion in polymer, Y^2 = conversion in cyclic carbonate with respect to GluNCA conversion. [c] M_n and M_w/M_n of polymer determined by SEC-RI using PMMA standards at 60°C in DMF. $M_{n,theoritical}$ = [GluNCA]/[I] × %conv.(GluNCA) × M(GluNCA-CO_2)

When allyl glycidyl ether was used as a solvent instead of PO, in the same reaction conditions as above, quantitative and controlled polymerisation of 50 equivalents of GluNCA using complex **2** was also observed after 1h ($M_{n,exp}$ = 8100 g.mol^{-1}; M_w/M_n = 1.2). Moreover the corresponding cyclic carbonate was formed in 99% yield. In the case of a bulkier epoxide such as styrene oxide, formation of cyclic carbonate took place in a lower yield of 58% but the polymerization was still controlled as an experimental molecular weight of 10900 g.mol^{-1} and M_w/M_n of 1.1 were obtained. In addition, the controlled character of the polymerizations was further evidenced by the sequential polymerization of GluNCA, for which complete conversion was observed. Therefore 50 equivalents of GluNCA were polymerized in the presence of Al complex **1** and 2 equivalents of [PPN]Cl for 20 min before other 50 equivalents of GluNCA were added in the reaction mixture. The GPC of the resultant polymer revealed a monomodal distribution and a molecular weight of 15800 g.mol^{-1} was obtained (M_n = 10300 g.mol^{-1} after first addition of GluNCA) with M_w/M_n = 1.4. These results indicate that the polymerization is well controlled and living and that the tandem catalyst is active for the preparation of block copolymers.

To investigate the mechanism occurring during the tandem process, we carried out NMR-scale experiments in C_6D_6. These investigations were conducted with the chromium complex **2**. Several ^{1}H NMR spectra were recorded at regular intervals over a period of 7 h during the reaction of **2** with 45 equivalents of GluNCA and 9000 equivalents of PO (Figure S1). These *in-situ* ^{1}H NMR investigations are in full agreement with a two-steps sequential process: formation of the polypeptide occurs first, followed by the cycloaddition of carbon dioxide to epoxide. Presumably, the cyclization reaction begins when an epoxide co-monomer displaces a metal-bound polymeric chain. The epoxide is activated by a Lewis acidic metal centre, and undergoes nucleophilic attack by a suitable initiator present in the medium (such as chloride), allowing ring-opening. The alkoxide formed reacts with carbon dioxide to form a carbonate. Then, cyclic carbonate is generated by the backbiting of a metal-carbonate into an adjacent alkoxide linkage.[46]

Conclusions

In summary, we designed the first tandem catalytic system that allows the facile synthesis of polypeptides with well-defined sequences and provides direct access to cyclic carbonates in high yields, through the incorporation of the carbon dioxide released from the first step, thus achieving full-atom economy. This finding foreshadows new vistas in tandem catalysis. Studies focused on the elucidation of the mechanism of the polymerization, increasing the efficiency, and expanding the substrate scope are currently underway.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of all compounds, polymer characterization data, NMR spectroscopic analysis and polymerization details. See DOI: 10.1039/b000000x/

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